5.06 REPOTRECTINIB, Capsule 40 mg, Capsule 160 mg, Augtyro®, Bristol-Myers Squibb Australia Proprietary Limited.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 85 (General Schedule) Authority Required Pharmaceutical Benefits Scheme (PBS) listing for repotrectinib for the treatment of adult patients with locally advanced (Stage IIIB) or metastatic (Stage IV) c-ROS proto-oncogene 1 (*ROS1*)-positive non-small cell lung cancer (NSCLC).

1.2 Listing was requested on the basis of a cost-minimisation analysis (CMA) versus entrectinib.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with c-ROS proto-oncogene 1 (*ROS1*), locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC
Intervention	Repotrectinib 160 mg (one 160mg capsule) daily for 14 days, then 160 mg twice daily until progression or unacceptable toxicity.
Comparator	Main: Entrectinib 600 mg (three 200mg capsules) daily until disease progression or unacceptable toxicity. Supplementary: Crizotinib 250 mg (one 250mg capsule) twice daily until progression or unacceptable toxicity.
Outcomes	Primary: objective response rate Secondary: progression-free survival, overall survival, duration of response, intracranial response rate (in patients with BL brain metastases), safety
Clinical claim	Compared to entrectinib and crizotinib, repotrectinib offers non-inferior comparative efficacy and non-inferior safety

Source: Table 2, p14 of the submission.
BL = baseline; NSCLC = non-small cell lung cancer; ROS1 = c-ROS proto-oncogene 1.

2 Background

Registration status

2.1 **TGA Status at time of PBAC consideration:** The submission was made under the TGA/PBAC parallel process. The proposed indication for TGA approval is: *Augtyro, as monotherapy, is indicated for the treatment of adult patients with ROS1-positive locally advanced or metastatic NSCLC.* At time of evaluation, the TGA Clinical Evaluation Report (Round 2) was available. The TGA Delegate's Overview was received prior to the May 2025 PBAC meeting. The Delegates Overview noted the clinical data supports approval of the proposed indication and further stated the results of

TRIDENT-3 should be assessed by TGA to confirm the clinical data supports line-agnostic use of repotrectinib.

2.2 The sponsor is currently recruiting participants for a randomised controlled trial comparing repotrectinib to crizotinib in patients with locally advanced or metastatic TKI-naïve *ROS1*-positive NSCLC. The results of the study known as TRIDENT-3/CA127-1030 will be submitted to TGA when feasible (anticipated to be available in 2029) for evaluation as a category 1 submission.

2.3 Repotrectinib was approved in the United States by the Food and Drug Administration (FDA) for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC on 15 November 2023.

2.4 Repotrectinib was granted conditional marketing authorisation in the European Union (EU) by the European Medicines Agency (EMA) for the treatment of adult patients with ROS1-positive locally advanced or metastatic NSCLC on 14 November 2024.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. The revisions proposed by the Secretariat were based on the first line listing proposed by the Sponsor and do not reflect the information that became available in the TGA Delegate's Overview and considered by the PBAC.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
REPOTRECTINIB					
repotrectinib 40 mg capsule, 120	NEW	1	120	3	Augtyro
repotrectinib 160 mg capsule, 60	NEW	1	60	3	Augtyro

Restriction Summary / Treatment of Concept:		
		Category / Program: GENERAL - General Schedule (Code GE)
		Prescriber type: Medical Practitioners
		Restriction type: Authority Required (in writing via post/HPOS upload or real time assessment via OPA)
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: **No increase in the maximum quantity or number of units may be authorised.*
		Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Indication: ~~Locally advanced or metastatic non-small cell lung cancer (NSCLC)~~ *Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)*	
	Treatment Phase: Initial treatment	
	Clinical criteria:	
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition,	

	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less,
	AND
	Clinical criteria:
	The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC,
	AND
	Clinical criteria:
	Patient must have evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing,
	AND
	Clinical criteria:
	Patient must not have received prior treatment with a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor for this condition; or
	Patient must have developed intolerance to a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor necessitating permanent treatment withdrawal.
	Prescribing Instructions: *Applications for authorisation of initial treatment must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail.* *If the application is submitted through HPOS form upload or mail, it must include:* *(a) details of the proposed prescription; and* *(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
	Prescribing Instructions: *The following must be documented in the patient's medical records:* *(a) evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material.*
	Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)* *Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

Restriction Summary / Treatment of Concept:	
	Indication: ~~Locally advanced or metastatic non-small cell lung cancer (NSCLC)~~ *Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)*
	Treatment Phase: Continuing treatment
	Clinical criteria:
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition

	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*
*(note will be added only to repotrectinib 160mg listings)	

3.2 The proposed PBS listings for the initiation and continuation of repotrectinib treatment are generally consistent with current listings for entrectinib and crizotinib.

3.3 The National Comprehensive Cancer Network (NCCN) treatment guidelines[1] places entrectinib and crizotinib alongside repotrectinib as the preferred first-line treatment for patients with *ROS1*-positive NSCLC, while subsequent therapy with *ROS1* inhibitors may be recommended for patients with disease progression after treatment with repotrectinib, entrectinib or crizotinib.

3.4 Both the TGA-proposed indication and TRIDENT-1 study specify that those treated with repotrectinib must be adult patients (or ≥18 years as the study inclusion criteria). This is not specified in the proposed PBS listing. The ESC noted the proposed indication is age agnostic and is similar to current listing for entrectinib and crizotinib and considered this was reasonable.

3.5 The proposed PBS listing specifies that the condition must be 'non-squamous type NSCLC', however a small proportion of patients (3%) in TRIDENT-1 had squamous histology and adenosquamous carcinoma. Additionally, the inclusion of 'not otherwise specified type NSCLC' in the proposed PBS listing has not been supported by adequate evidence, and is not mentioned in TRIDENT-1; however, this is consistent with the listings of entrectinib and crizotinib.

3.6 If repotrectinib is listed on the PBS, the submission flagged potential flow-on effects to 2 immunotherapies—nivolumab and atezolizumab—used as second-line (or later) treatments for patients with Stage IV (metastatic) NSCLC. Based on current PBS restrictions for nivolumab and atezolizumab, if patients have been pre-treated with repotrectinib, entrectinib or crizotinib, they are ineligible to access these immunotherapies as a second-line treatment. The submission requests that PBAC consider a flow-on change to the current PBS restriction for nivolumab (and atezolizumab) used in a second-line setting. This change would allow *ROS1*-positive NSCLC patients treated with repotrectinib (and entrectinib or crizotinib) as their first-

[1] National Comprehensive Cancer Network (Version 3.2025) – Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer

line therapy to access nivolumab (and atezolizumab) as a potential second-line treatment upon disease progression.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Lung cancer is a prevalent type of cancer in Australia, with an estimated 14,782 incident cases in 2023. NSCLC is the most common histological type of lung cancer, making up 86.6% of all lung cancers. This equates to approximately 12,801 incident cases of NSCLC in 2023.

4.2 At diagnosis, 65.5% of NSCLC are staged as locally advanced (Stage III: 14%) or metastatic (Stage IV: 51.5%), with a 5-year relative survival rate of 17.1% and 3.2%, respectively.

4.3 *ROS1* rearrangements occur in approximately 1–2% of patients with lung adenocarcinoma.

4.4 Risk factors for lung cancers vary; however, tobacco smoking is the most common cause of lung cancer. Other risk factors include exposure to asbestos, radiation, arsenic and non-tobacco-related polycyclic aromatic hydrocarbons.

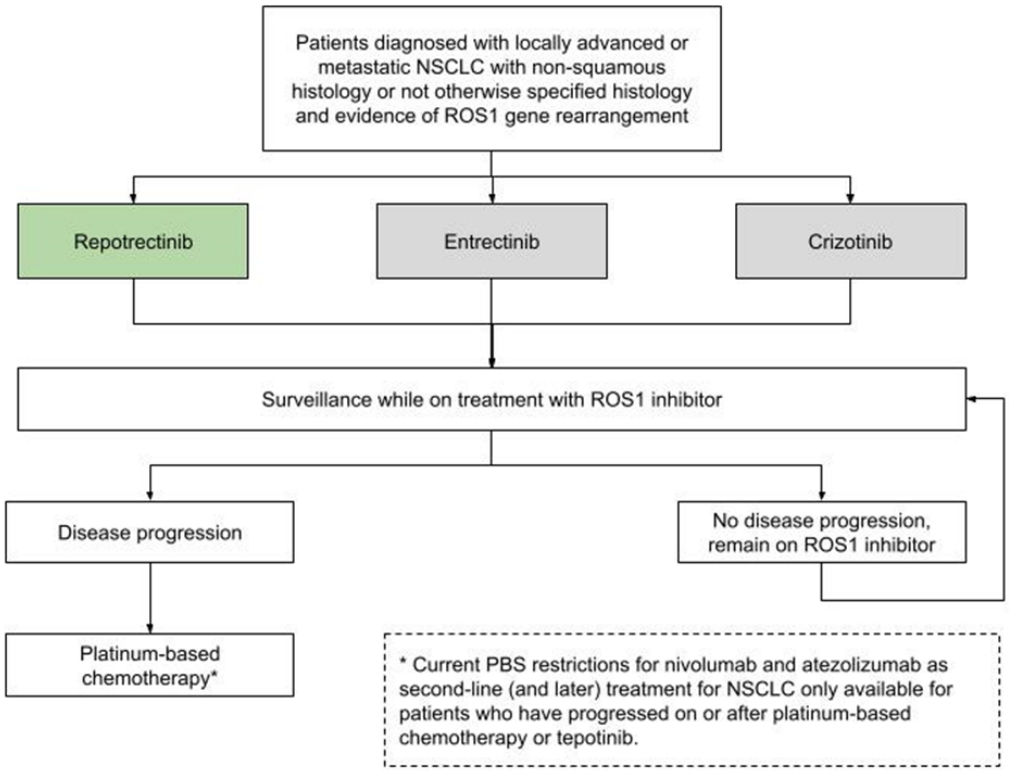
4.5 Early symptoms of lung cancer include chest discomfort or pain, a persistent cough that may worsen over time, difficulty breathing, blood in sputum, loss of appetite and unexplained weight loss.

4.6 To confirm a diagnosis of lung cancer, a series of investigations including diagnostic work-up and staging of NSCLC may involve physical examination, complete medical history, tissue procurement for pathologic evaluation, laboratory examinations, diagnostic imaging studies and cardiopulmonary function studies.

4.7 The target population of the submission is adult patients diagnosed with locally advanced or metastatic *ROS1-positive* NSCLC.

4.8 Details of the proposed clinical management algorithm are presented in Figure 1.

Figure 1: Proposed clinical management algorithm



Source: Figure 5, p24 of the submission.
NSCLC = non-small cell lung cancer; PBS = Pharmaceutical Benefits Scheme; ROS1 = c-ROS proto-oncogene 1.

4.9 The submission proposed repotrectinib as an alternative treatment option to current PBS-listed *ROS1* inhibitors entrectinib and crizotinib.

4.10 Repotrectinib acts as an inhibitor of proto-oncogene tyrosine-protein kinase *ROS1* and of tropomyosin receptor tyrosine kinases (TRKs). Tyrosine kinase inhibitors (TKIs) can become less effective if patients develop acquired resistance due to mutations. Repotrectinib was designed to mitigate the effects of treatment-resistant mutations underlying acquired resistance. Repotrectinib binds to the adenine binding site of *ROS1* and TRK A-C, preventing the binding of ATP and thereby inhibiting tumour proliferation.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated entrectinib as the primary comparator, and crizotinib as a supplementary comparator. The main arguments provided in support of the nomination were:

- Entrectinib and crizotinib are *ROS1* inhibitors currently listed on the PBS for the treatment of patients with *ROS1*-positive NSCLC. In 2023, 69% of *ROS1* inhibitor PBS items were processed for entrectinib.

- Entrectinib and crizotinib approved TGA indications are similar to the proposed indication for repotrectinib.

5.2 The choice of entrectinib as the primary comparator is appropriate as the drug is approved for the treatment of *ROS1* NSCLC (para 5.03, Public Summary Document (PSD) entrectinib, March 2020).

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.4 For the requested population, the PBS-listed medicines entrectinib and crizotinib may be considered alternative therapies. The ESC advised it may be reasonable to not consider crizotinib an alternative therapy due to differences between repotrectinib and crizotinib, particularly with respect to their effectiveness in intracranial disease (with crizotinib being less effective in this context).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), family member or person directly caring for an individual (1), health care professionals (1), and organisations (4) via the Consumer Comments facility on the PBS website. The health care professional noted repotrectinib is a more potent *ROS1* inhibitor with good brain penetration, which prolongs disease response and avoids the need to treat brain metastases. Comments from individuals noted the need for additional therapies, as while their current treatment is effective, the disease eventually progresses, and an alternate option is required for the opportunity to prolong life. All consumer input was supportive of a PBS listing for repotrectinib.

6.3 The Lung Foundation Australia noted lung cancer is the leading cause of cancer deaths, the 4th leading cause of all death and the lowest survival rate compared to the most common cancers in Australia. It further noted the negative impact of lung cancer diagnosis on individuals' mental health and wellbeing and the importance of new treatment options to improve prognosis.

6.4 Rare Cancers Australia noted patients experience social, emotional and financial impacts due to their diagnosis and welcomes the PBS listing of repotrectinib.

6.5 The Thoracic Oncology Group of Australasia (TOGA) noted acquired resistance mutations develop in at least 50% of patients treated with entrectinib and crizotinib, limiting the durability of response. TOGA noted repotrectinib has clinical activity against *ROS1*–positive NSCLC, including the most common resistance mutations, detected in approximately a third of *ROS1* cases.

6.6 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the repotrectinib submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the TRIDENT-1 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) rating of 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement) [2].

Clinical studies

6.7 The submission was based on one non-comparative, open-label, multicentre phase 1/2 trial of repotrectinib, termed TRIDENT-1 (phase 2, n = 63 participants; phase 1 + phase 2, n = 71 participants); and two non-comparative studies of entrectinib, which consisted of an integrated analysis of the ALKA, STARTRK-1 and STARTRK-2 studies (n = 172 pooled participants) and the BFAST study (n = 55 participants).

6.8 Two efficacy analysis sets were reported from TRIDENT-1: n = 63 from the phase 2 component, and n = 71, which includes all 63 patients from the phase 2 component plus an additional 8 patients who received the recommended phase 2 dose during the phase 1 component.

6.9 Details of the trials presented in the submission are provided in Table 2.

[2] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol/publication title	Publication type; citation
Repotrectinib		
TRIDENT-1 (NCT03093166)	Bristol-Myers Squib. A phase 1/2, open-label, multi-center, first-in-human study of the safety, tolerability, pharmacokinetics, and anti-tumor activity of TPX-0005 in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements (TRIDENT-1), Addendum 01	CSR; 15 August 2023
	Bristol-Myers Squib. A phase 1/2, open-label, multi-center, first-in-human study of the safety, tolerability, pharmacokinetics, and anti-tumor activity of TPX-0005 in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements (TRIDENT-1), Addendum 02	CSR; 20 September 2024
	Drilon A, Camidge DR, Lin JJ, Kim SW, Solomon BJ, Dziadziuszko R, Besse B, Goto K, de Langen AJ, Wolf J and Lee KH, 2024. Repotrectinib in ROS1 fusion-positive non-small-cell lung cancer.	New England Journal of Medicine. 2024; 390(2), pp.118–131.
	Drilon et al., 2024. Repotrectinib in tyrosine kinase inhibitor (TKI)-naïve patients (pts) with advanced *ROS1* fusion-positive (*ROS1+)* NSCLC in the phase 1/2 TRIDENT-1 trial: Clinical update, treatment beyond progression and subsequent therapies.	Conference abstract; Journal Clinical Oncology 42, 8522–8522.
Entrectinib		
Integrated analysis of ALKA, STARTRK-1 and STARTRK-2	Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, De Braud F, Rolfo C, Ahn MJ, Wolf J and Seto T. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials.	The Lancet Oncology, 2020; 21(2), pp.261–270.
	Fan Y, Drilon A, Chiu CH, Loong HH, Siena S, Krzakowski M, Dziadziuszko R, Zeuner H, Xue C and Krebs MG. Brief report: updated efficacy and safety data from an integrated analysis of entrectinib in locally advanced/metastatic ROS1 fusion-positive non-small-cell lung cancer.	Clinical Lung Cancer,2024; 25(2), pp.e81–e86.
	Drilon A, Chi, CH, Fan Y, Cho B C, Lu S, Ahn MJ, Krebs MG, Liu SV, John T, Otterson GA, Tan DSW, Patil T, Dziadziuszko R, Massarelli E, Seto T, Doebele RC, Pitcher B, Kurtsikidze N, Heinzmann S and Siena S. 2022. Long-term efficacy and safety of entrectinib in ROS1 fusion-positive NSCLC.	*JTO clinical and research reports, 3(6), 100332.*
BFAST (NCT03178552)	Peters S, Gadgeel SM, Mok T, Nadal E, Kilickap S, Swalduz A, Cadranel J, Sugawara S, Chiu CH, Yu CJ and Moskovitz M. Entrectinib in ROS1-positive advanced non-small cell lung cancer: the phase 2/3 BFAST trial.	Nature Medicine, 2024; pp.1–10.

Source: Table 18 and Table 19, pp38-40 of the submission.
CSR = clinical study report; ID = identification.

6.10 The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Repotrectinib					
TRIDENT-1 EXP-1 cohort	P2: 63 P1+2: 71	Single arm, OL Median follow-up for patients analysed for efficacy: 33.9 (range: 24.0–76.5) months	High	Patients with advanced/metastatic solid tumours including the relevant prespecified subgroup of patients (expansion cohort EXP-1) with ROS1 fusion-positive NSCLC who had not previously received ROS1 TKI.	ORR, PFS, OS
Entrectinib					
ALKA	NR	Single arm, OL Trial-specific follow-up duration: NR	High	Patients with advanced/metastatic solid tumours with TRKA/B/C, ROS1 or ALK molecular alterations.	ORR, PFS, OS
STARTRK-1	NR	Single arm, OL Trial-specific follow-up duration: NR	High	Patients with any locally advanced or metastatic solid tumour preferably with NTRK1/2/3, ROS1 or ALK gene rearrangement	ORR, PFS, OS
STARTRK-2	NR	Single arm, OL Trial-specific follow-up duration: NR	High	Patients with locally advanced or metastatic solid tumours harbouring a NTRK1/2/3, ROS1 or ALK gene rearrangement.	ORR, PFS, OS
Pooled ALKA, STARTRK-1 and -2 data	172	ROS1 NSCLC Efficacy Evaluable Analysis Set including relevant subgroups from the above 3 entrectinib studies, defined as ROS1-positive TKI naïve NSCLC patients with measurable disease at BL and ≥12 months follow-up from onset of response or had discontinued study treatment at CCOD. Median follow-up for patients included in the integrated analysis: 37.8 months.			
BFAST Cohort D	55	Single arm, OL Median follow-up duration: 18.3 months	High	Patients with Stage IIIB/IV, ROS1-positive NSCLC who could have received previous systemic therapies (chemotherapy, immunotherapy), but no prior TKI treatment specifically targeting the ROS1 rearrangement.	ORR, PFS, OS

Source: Table 21, p46 of the submission.
ALK = anaplastic lymphoma kinase; BL = baseline; CCOD = clinical cutoff date; EXP-1 = prespecified expansion cohort 1; NR = not reported; NSCLC = non-small cell lung cancer; NTRK1/2/3 = neurotrophic tropomyosin receptor kinase 1, 2, 3; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; P2 = phase 2, P1+2 = phase 1 and phase 2; ROS1 = c-ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor; TRKA/B/C = tropomyosin receptor kinase A, B, C .

6.11 The 3 entrectinib studies (ALKA, STARTRK-1 and STARTRK-2) that form the basis of the integrated analysis do not have published primary studies or associated publications (results reported on clinicaltrials.gov etc.) as these studies were pooled by the manufacturer prior to publication using individual patient-level data. Therefore, it is impossible to confirm the reported data of the integrated analysis or interrogate the number of patients that were enrolled in each of these 3 studies. The submission stated: 'Overall, while there is no apparent reason to doubt the integrity of the conduct of the 3 underlying entrectinib trials, or the full and proper selection of relevant data for inclusion in the integrated analysis, the lack of transparency in this aspect of the published data leave some unresolvable uncertainty.'

6.12 The submission reported the risk of bias of the included single arm trials as high. The submission stated that the main source of bias for the clinical evaluation is from the different distribution of confounding/prognostic factors due to the non-randomised treatment allocation in single arm trials. The submission did not appraise the included studies using a design-specific risk-of-bias tool nor provided adequate detail to support the individual domain assessment or overall judgement. As assessed during

evaluation (via the Institute of Health Economics Quality Appraisal Checklist), TRIDENT-1 and BFAST had a moderate level of bias. A moderate level of bias was assigned due to the lack of blinding of these single arm studies, along with insufficient/unclear details on co-interventions, whether patients were recruited consecutively, and if follow-up was long enough for important events to occur. As assessed during evaluation (via ROBINS-I[3]), the integrated analysis of ALKA, STARTRK-1 and STARTRK-2 studies had a critical level of bias. A critical level of bias[4,] was assigned as no methods were implemented to adjust for potential confounding, a lack of blinding, and it was unclear if methods of outcome assessment were comparable across the 3 studies.

6.13 There was considerable heterogeneity in terms of patient demographics, disease characteristics, and study follow-up durations, both between the repotrectinib and entrectinib studies, and between the entrectinib studies themselves, making an assessment of comparative effectiveness and safety difficult. Differences in patient characteristics included ECOG performance status, the number/type of prior lines of therapy, and the proportion of Asian patients, all of which are prognostic factors for *ROS1*-positive NSCLC. These characteristics and several others have also been identified as important differences between the repotrectinib trial setting and the Australian setting. The submission also flagged a high degree of heterogeneity in the duration of treatment and follow-up for data reported across the trials. The median follow-up duration of TRIDENT-1 was 28.4 months (phase 2) and 33.9 months (phase 1 and 2), whereas the integrated analysis of the ALKA, STARTRK-1 and STARTRK-2 studies had a median follow-up of 37.8 months; BFAST had a median follow-up of 18.3 months. Differences in follow-up timepoints of TRIDENT-1 compared to BFAST, and the integrated analysis (~10 months shorter or longer) likely impact results, making their comparability uncertain. The considerable heterogeneity in patient demographics, disease characteristics, and study follow-up durations are significant transitivity issues that introduce uncertainty to the presented comparisons. The ESC considered these issues introduced substantial uncertainty to the clinical comparisons, however considered that in the context of the rarity of *ROS1*-positive NSCLC and evidence previously presented for entrectinib being of similar quality, that the available evidence for repotrectinib, including the matching-adjusted indirect comparison (MAIC) presented alongside the submission, was likely adequate to assess the clinical claims. The Pre-PBAC Response agreed with ESC regarding the observed heterogeneity which made the assessment of comparative effectiveness and safety difficult, however, noted the ESC considered the level of evidence provided was likely adequate to assess the clinical claim of non-inferiority.

[3] Sterne J A, Hernán M A, Reeves B C, Savović J, Berkman N D, Viswanathan M et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions BMJ 2016; 355 :i4919 doi:10.1136/bmj.i4919

[4] A critical risk of bias was assigned for the domain of 'bias due to confounding', resulting in an overall risk of bias judgement of critical. Meaning that: "the study is too problematic to provide any useful evidence and should not be included in any synthesis"[3].

6.14 The submission took a non-standard approach to establishing a non-inferiority margin and assumed that a non-standard approach is acceptable to PBAC, given the established precedent in recommending PBS listing of entrectinib based on naïve comparisons to crizotinib (entrectinib PSD, March 2020). Therefore, the naïve comparative approach applied to the submission has been based on assumed similarities in effectiveness without direct statistical comparison of incremental benefit, due to the lack of comparator treatment arms. Based on published minimal clinically important differences (MCIDs), non-inferiority is supported if: (1) the percentage difference in 1-year survival rate reported among repotrectinib-treated patients is not more than 6% lower than for entrectinib-treated patients, (2) the difference in the point estimate of median overall survival (OS) among repotrectinib-treated patients is not more than 3.25 months less than for entrectinib-treated patients, (3) the difference in the point estimate of median progression-free survival (PFS) among repotrectinib-treated patients is not more than 4 months less than for entrectinib-treated patients.

Comparative effectiveness

6.15 The submission presented effectiveness results from the TRIDENT-1 study (patients treated with repotrectinib) and presented a naïve, unanchored, unadjusted comparison with an integrated analysis of the ALKA, STARTRK-1 and STARTRK-2 studies; and the BFAST study (patients treated with entrectinib) (**Table 4**). The submission also presented the results of an unanchored MAIC of repotrectinib and entrectinib (discussed further in paragraph 6.25). The ESC considered it was difficult to interpret the evidence given the nature of a naïve indirect comparison and considerable heterogeneity across the studies. However, on balance, did not believe it would preclude a comparative assessment of repotrectinib and entrectinib.

Table 4: **Summary of effectiveness results in TRIDENT-1; ALKA, STARTRK-1 & -2 integrated analysis; and BFAST**

	Repotrectinib (TRIDENT-1 phase 2) n=63	Repotrectinib (TRIDENT-1 phase 1 & 2) n=71	Entrectinib (ALKA, STARTRK-1 & 2 integrated analysis) n=172	Entrectinib (BFAST) n=55
Follow-up, median (months)	28.4	33.9	37.8	18.3
ORR				
ORR, n (%), (95% CI)	49 (78), (66, 87)	56 (79), (68, 88)	116 (68), (60, 74)	44 (82), (69, 91)
BOR				
CR, n (%)	9 (14)	9 (13)	23 (13)	3 (6)
PR, n (%)	40 (64)	47 (66)	93 (54)	41 (76)
SD, n (%)	11 (18)	11 (15)	16 (9)	7 (13)
PD, n (%)	2 (3)	2 (3)	16 (9)	1 (2)
Non-CR/non-PD	NR	NR	10 (6)	NR
Missing/not assessable [a]	1 (2)	NR	14 (8)	2(4)
Clinical benefit (CR, PR or SD)				
CBR, n (%), (95% CI)	60 (95), (87, 99)	67 (94), (86, 98)	NR	44 (82), (69, 91)
DOR				
DOR, median (95% CI) months	NE (28.7, NE)	–	20.4 (14.8, 34.8) [b]	16.7 (5.6, 24.0) [c]
DOR landmark analyses (survival probabilities by KM)				
≥6 months (95% CI)	92 (84, 99.5)	–	NR	NR
≥9 months (95% CI)	89 (81, 98)	–	NR	NR
≥12 months (95% CI)	85 (75, 95)	–	65 (56, 74) [b]	57 (NR) [c]
≥18 months (95% CI)	78 (66, 90)	–	52 (43, 32) [b]	NR
≥24 months (95% CI)	73 (60, 86)	–	NR	NR
PFS				
PFS, median (95% CI) months	37.1 (21.9, NE)	35.7 (24.6, NE)	16.8 (12.2, 22.4)	14.8 (7.2, 24.0)
PFS landmark analyses (survival probabilities by KM)				
≥6 months (95% CI)	90 (82, 98)	NR	NR	NR
≥9 months (95% CI)	81 (71, 91)	NR	NR	NR
≥12 months (95% CI)	76 (65, 87)	NR	58 (50, 65)	52 (NR)
≥18 months (95% CI)	68 (56, 81)	NR	47 (40, 55)	NR
≥24 months (95% CI)	62 (50, 75)	NR	NR	NR
OS				
OS, median (95% CI) months	NE (37.3, NE)	NR	44.1 (40.1, NE)	31.2 (20.2, NE)
OS landmark analyses (survival probabilities by KM)				
≥12 months (95% CI)	92 (85, 99)	91 (84, 98)	81 (75, 87)	NR
≥18 months (95% CI)	87 (78, 95)	86 (78, 95)	74 (67, 81)	NR
≥24 months (95% CI)	74 (63, 86)	75 (65, 86)	NR	NR
Intracranial ORR per BICR				
IC-ORR (CR + PR), n/N (%), (95% CI) [d]	–	8/9 (88.9), (52, 100) [e]	25/51 (49), (35, 63) [f]	–
IC-DOR, median (95% CI) months	–	NR	12.9 (7.6, 22.5)	–

Source: Table 30 (p63), Table 31 (p64), Table 32 (p66), Table 34 (p69), Table 36 (p72) of the submission.

BL = baseline; BOR = best objective response; BICR = blinded independent central review; CBR = clinical benefit rate (CR+PR+SD ≥ 6 weeks); CI = confidence interval; CR = complete response; DOR = duration of response; IC = intracranial; KM = Kaplan-Meier; NE = not evaluable; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

Notes: Absolute differences and hazard ratios were not calculated in the submission due to the naïve comparative approach implemented.

[a] Missing or not assessable included patients with no post-BL scans available, missing subsets of scans, or patients who discontinued before obtaining adequate scans to assess or confirm response

[b] Median follow-up was 33.9 months for DOR and DOR landmark analysis
[c] Median follow-up was 37.8 months for DOR and DOR landmark analysis
[d] Of patients who had measurable brain metastases at BL
[e] Of patients with a response, 1/8 patients achieved a complete response and 7/8 patients achieved a partial response
[f] Of patients with a response, 8/25 patients achieved a complete response and 17/25 patients achieved a partial response

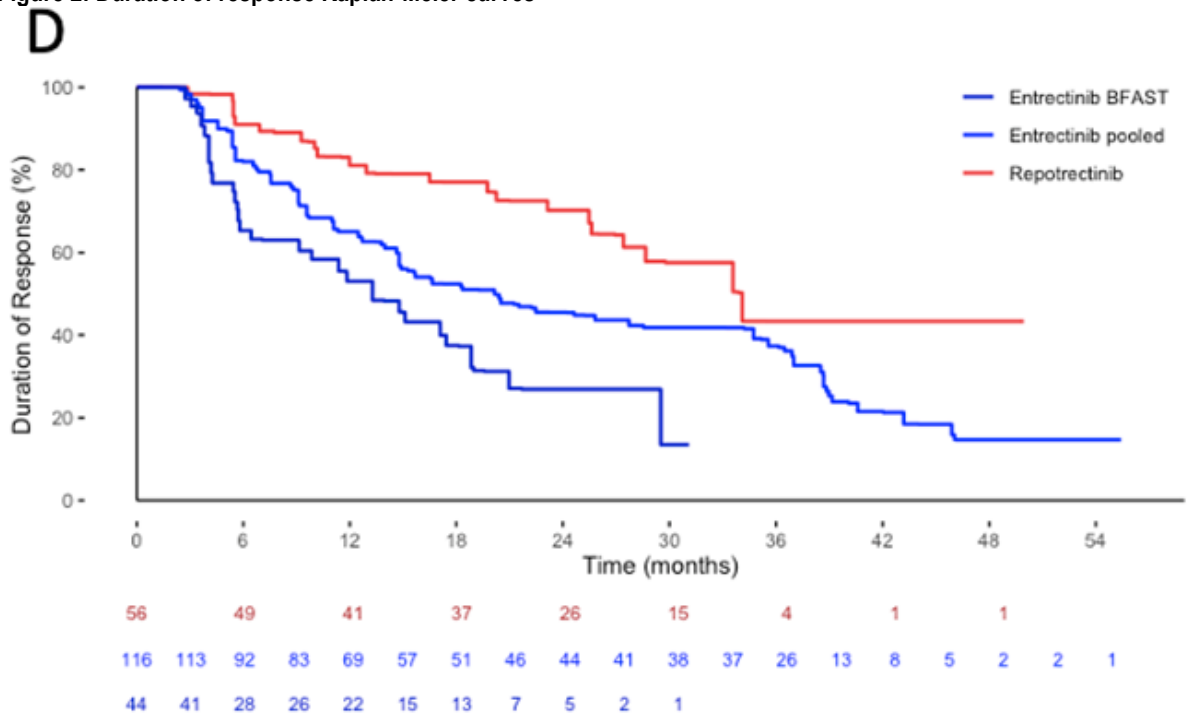
6.16 In TRIDENT-1, the objective response rate (ORR) to repotrectinib was 78% (49 of 63 patients) in the phase 2 component, 79% (56 of 71 patients) in the phase 1 and phase 2 component and 79% based on the data cut off period of 3 September 2024. ORR to entrectinib in the integrated analysis of the ALKA, STARTRK-1 and STARTRK-2 studies was ~67% (116 of 172 patients), and 82% (44 of 55 patients) in the BFAST study. As per the prespecified analysis plan, study investigators considered a clinically meaningful treatment effect to be 66% and 50% for ORR in TRIDENT-1 and the integrated analysis, respectively. Thus, an ORR of 78% and 79% in repotrectinib-treated patients and 67% in entrectinib-treated patients (from the integrated analysis) is considered to be a clinically meaningful treatment effect.[5] Results for ORR between repotrectinib and entrectinib are considered comparable.

6.17 The Pre-Sub Committee Response provided additional results from an updated analysis of TRIDENT-1 (September 2024 data cut), which showed similar results for repotrectinib in terms of objective response rate, complete response and partial response compared to the results presented in Table 4 above.

6.18 Analysis of survival probabilities by KM curves for the duration of response (DOR) at 12 months, demonstrated continued response in 85%, 65% and 57% of patients in TRIDENT-1 (phase 2), the integrated analysis of ALKA, STARTRK-1 and STARTRK-2, and BFAST, respectively. DOR combined KM curves are presented in Figure 2.

[5] For ORR, BFAST also met its primary endpoint which is stated to demonstrate a consistent ORR with that from the integrated analysis of entrectinib.

Figure 2: Duration of response Kaplan-Meier curves

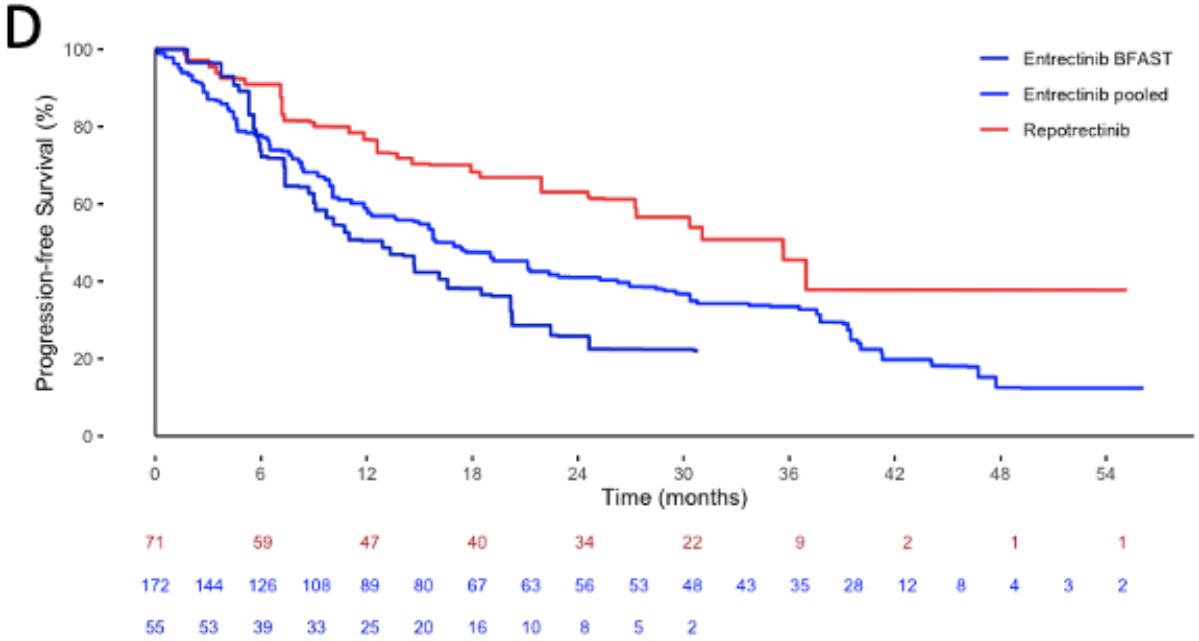


Source: Figure 14, p.65 of the submission.

6.19 In TRIDENT-1, median PFS in repotrectinib-treated patients was 37.1 months in the phase 2 component and 35.7 months in the phase 1 and phase 2 component. Median PFS in entrectinib-treated patients in the integrated analysis of ALKA, STARTRK-1 and STARTRK-2 was 16.8 months, and 14.8 months in BFAST. PFS combined KM curves are presented in Figure 3.

6.20 The submission argued that for the assessment of non-inferiority for PFS, the difference in the point estimate of median PFS among repotrectinib-treated patients is not more than 4 months less than for entrectinib-treated patients, therefore non-inferiority is supported. Given the lack of direct comparative evidence or supportive statistical analysis, time-to-event outcomes are difficult to interpret. The considerable heterogeneity in patient demographics, disease characteristics, and study follow-up durations must also be taken into consideration and are assumed to likely impact the results.

Figure 3: Progression-free survival Kaplan-Meier curves

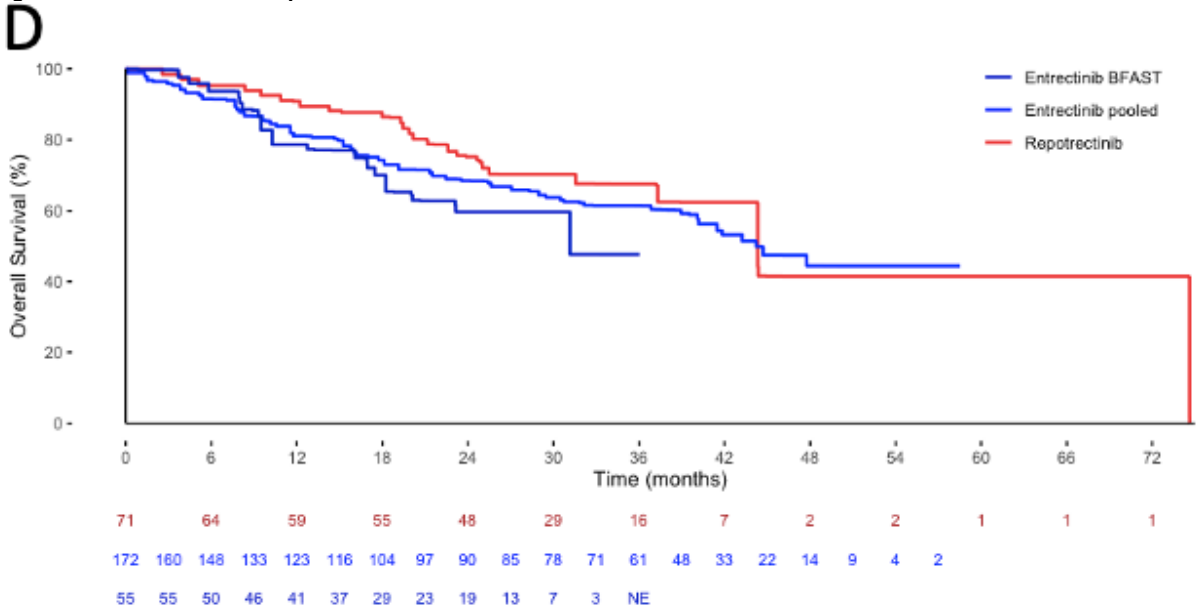


Source: Figure 15, p.68 of the submission.

6.21 In TRIDENT-1, median OS in repotrectinib-treated patients was not reached (not estimable [NE], 95% confidence interval [CI]: 37.3, NE) in the phase 2 component and not reported in the phase 1 and phase 2 component. Median OS in entrectinib-treated patients in the integrated analysis of ALKA, STARTRK-1 and STARTRK-2 was 44.1 months, and 31.2 months in BFAST. The submission stated that despite the median OS not being reached for repotrectinib (resulting in the inability to assess non-inferiority), the lower bound of the 95% CI of 37.3 months is greater than the median OS of 31.2 months reported in the BFAST trial. The applicant claimed this observation supports a conclusion that the median OS for repotrectinib will be greater than the median OS reported in at least one trial of entrectinib (BFAST).

6.22 Analysis of survival probabilities by KM curves for OS at 12 months demonstrated a survival rate of 92%, 91% and 81% in TRIDENT-1 (phase 2), TRIDENT-1 (phase 1 and 2) and the integrated analysis of the ALKA, STARTRK-1 and STARTRK-2 studies, respectively. BFAST did not report the OS rate at 12 months. According to the submission for the assessment of non-inferiority for OS, the percentage difference in 1-year survival rate reported among repotrectinib-treated patients is not more than 6% lower than for entrectinib-treated patients, therefore non-inferiority is supported. OS combined KM curves are presented in Figure 4. As discussed in paragraph 6.20, the OS data presented in Figure 4 is difficult to interpret for the same reasons and, leading to substantial uncertainty for the assessing the clinical claim.

Figure 4: Overall survival Kaplan-Meier curves



Source: Figure 16, p.71 of the submission.

6.23 For patients with measurable brain metastasis at baseline (BL), intracranial ORR (icORR) was 89% (8 of 9 patients) for repotrectinib-treated patients in TRIDENT-1 (phase 1 and phase 2; N = 9) and 49% (25 of 51 patients) for entrectinib-treated patients in the integrated analysis of the ALKA, STARTRK-1 and STARTRK-2 studies. Given the relatively small number of patients with brain metastases at BL it is difficult to determine whether this result is clinically meaningful. Due to the observed imbalance in prior treatment history between the repotrectinib and entrectinib trial populations, subgroup analyses stratified by prior treatment were conducted to allow for a more comparable assessment of treatment effects (Table 5).

6.24 When comparing the subgroup of patients without prior chemotherapy in TRIDENT-1 to the integrated analysis of ALKA, STARTRK-1 and STARTRK-2, the results show that ORR was higher in repotrectinib-treated patients (82%) than for entrectinib-treated patients (69%). Median PFS was longer in repotrectinib-treated patients (37.1 months) than in entrectinib-treated patients (17.7 months), and median DOR was comparable between repotrectinib-treated patients (33.6 months) and entrectinib-treated patients (35.6 months). The submission concludes that the results of the subgroup analysis suggest that repotrectinib demonstrates at least non-inferior efficacy compared with entrectinib. As discussed in paragraph 6.20, the subgroup analyses presented in Table 5 are difficult to interpret for the same reasons.

Table 5: Subgroup analysis: effectiveness results by prior systemic therapy

	Repotrectinib (TRIDENT-1 Phase 1 & 2) n=71	Entrectinib (ALKA, STARTRK-1 & 2 integrated analysis) n=172
Follow-up, median (months)	33.9	37.8
Prior chemotherapy, n (%)		
with prior chemotherapy	20	–
without prior chemotherapy	51	–
no prior systemic therapy	–	67
ORR, % (95% CI)		
with prior chemotherapy	70 (46, 88)	–
without prior chemotherapy	82 (69, 92)	–
no prior systemic therapy	–	69 (56, 79)
Median PFS, months (95% CI)		
with prior chemotherapy	35.7 (18.0, NE)	–
without prior chemotherapy	37.1 (22.0, NE)	–
no prior systemic therapy	–	17.7 (11.8, 39.4)
Median DOR, months (95% CI)		
with prior chemotherapy	34.1 (23.1, NE)	–
without prior chemotherapy	33.6 (25.6, NE)	–
no prior systemic therapy	–	35.6 (13.9, 38.8)

DOR = duration of response; NE = not evaluable; ORR = objective response rate; PFS = progression-free survival.

6.25 The submission reported additional results from an unanchored MAIC between repotrectinib and entrectinib[6]. This MAIC formed the basis of regulatory submissions to the FDA and EMA (BMS 2023[7]). The MAIC adjusted for imbalances in prespecified prognostic and effect-modifying factors, with the results indicating that repotrectinib was non-inferior and potentially superior to entrectinib for the outcome of PFS (weighted HR 0.52, 95% CI: 0.31, 0.87). On balance, the MAIC provides additional information for comparisons that have adjusted for imbalances in prognostic/effect modifying factors and generated weights using baseline characteristics and provides supportive evidence for the outcome of PFS.

6.26 The Pre-Sub-Committee Response (PSCR) presented the results of the MAIC and argued that adjusting for heterogeneity in baseline characteristics did not have a material impact on the repotrectinib PFS KM curve or PFS hazard ratio reported for repotrectinib vs entrectinib. The ESC agreed with the PSCR and considered the results for HR on PFS were similar for the MAIC and naïve comparison presented in the submission, and that the MAIC was informative to support the clinical effectiveness claim.

Comparative harms

6.27 The submission presented safety results from the TRIDENT-1 study (patients treated with repotrectinib) and compared them naïvely to the results of the integrated

[6] Wolf, J, Goring, S, et al. (2024). "147P Population-adjusted indirect comparisons of repotrectinib and entrectinib in ROS1+ locally advanced or metastatic non-small cell lung cancer (NSCLC)." ESMO open 9: 102734.

[7] BMS (2023). EMA abbreviated report. Indirect treatment comparisons of repotrectinib among patients with ROS1+ NSCLC. CA127-1036. Date: 6 October 2023.

analysis of the ALKA, STARTRK-1 and STARTRK-2 studies; and the BFAST study (patients treated with entrectinib) (Table 6).

6.28 The safety analysis set from TRIDENT-1 includes all patients who received ≥1 dose of repotrectinib in any phase 2 expansion cohort (n = 462), composed of 327 patients with *ROS-1*-positive NSCLC (TKI-naïve and TKI-pretreated) plus 135 patients with neurotrophic tropomyosin receptor kinase (NTRK)-positive tumours[8]. The included population in the safety analysis set is broader than the proposed PBS listing as it includes 135 patients with NTRK-positive tumours and includes approximately 264 patients who have received prior treatment with a ROS1 TKI for this condition. No ROS1 TKI-naïve subgroup population was presented and it is unclear if the whole-trial results are applicable to the TKI-naïve subgroup. The ESC acknowledged it was difficult to interpret the presented safety data given the pooled data includes NTRK-positive patients, as well as pre-treated ROS1 mutation patient and considered this limits the reliability of the safety claim.

6.29 The submission presented a variety of harms data associated with repotrectinib and entrectinib. The main harms reported included death, treatment-emergent adverse event (TEAE), treatment-related AE (TRAE), AE of special interest (AESI) and serious AE (SAE).

6.30 Harms data for entrectinib from different publications were not pooled. Statistical testing and effect measures (i.e. relative risk) between repotrectinib and entrectinib were not performed nor reported. An indirect comparison using MAIC (or similar) could have been performed.

6.31 In *ROS1*-positive NSCLC (TKI-naïve and TKI-pretreated) patients, repotrectinib (38%) and entrectinib (36%) had comparable total deaths at the end of follow-up. Death caused by TRAE between repotrectinib (*ROS1*-positive NSCLC patients) and entrectinib (integrated analysis) was comparable, at 0.3% and 0.4% respectively. Neither of the publications on entrectinib reported deaths that occurred within 28 days of the last dose, nor deaths from AESI.

6.32 *ROS1*-positive NSCLC (TKI-naïve and TKI-pretreated) patients on repotrectinib experienced a high rate of total TEAE (99%). Neither of the entrectinib publications reported total TEAE, including TEAEs that were serious, resulted in dose modification, or led to treatment discontinuation. *ROS1*-positive NSCLC patients on repotrectinib (57%) and entrectinib (56%) had comparable rates of grade ≥3 serious TEAE.

6.33 Patients on repotrectinib (any phase 2 expansion cohort) and entrectinib experienced comparable total rates of TRAEs (96% vs 93–95%). Both drugs had comparable TRAEs that were serious or led to treatment discontinuation. Regarding dose modification,

[8] The submission included 'All phase 2 subjects who were treated at the time of the data cutoff date in any expansion cohort' in the safety analyses, whilst the effectiveness data was based on 'efficacy evaluable subjects' and the 'efficacy analysis population' from TRIDENT-1

more *ROS-1* positive NSCLC patients on repotrectinib (36%) experienced drug interruption than those on entrectinib (20%).

6.34 Around 95% of *ROS-1* positive NSCLC patients on repotrectinib reported at least one AESI. One patient (0.3%) in the *ROS1-positive* NSCLC population of TRIDENT-1 experienced an AESI leading to death (a femur fracture, assessed as not treatment-related). Only a small portion of AESIs caused treatment discontinuation (4%) or SAEs (6%) in *ROS-1* positive NSCLC patients. A moderate amount of AESIs led to dose modification (37%) *ROS-1* positive NSCLC patients. The entrectinib publications did not report any AESIs.

6.35 The PSCR acknowledged safety data from a head-to-head trial repotrectinib vs entrectinib would provide more certainty regarding comparative safety claims, however argued the assessment of the totality of safety data presented in the submission reasonably supports the claim that repotrectinib is non-inferior in terms of safety compared with entrectinib.

Table 6: Summary of key harms in the TRIDENT-1; ALKA, STARTRK-1 & 2 integrated analysis; and BFAST

Trial ID	Repotrectinib (TRIDENT-1 Phase 2) n=462	Repotrectinib (TRIDENT-1 ROS1+ NSCLC) n=327	Entrectinib (ALKA, STARTRK-1 & 2 integrated analysis) n=247	Entrectinib (BFAST) n=55
Total deaths, n (%)	175 (39)	125 (38)	NR (NA)	20 (36) [a]
death within 28 days of last dose, n (%)	62 (13)	43 (13)	NR (NA)	NR (NA)
death from TEAE, n (%)	27 (6)	20 (6)	NR (NA)	2 (4)
death from TRAE, n (%)	2 (0.4)	1 (0.3)	1 (0.4)	0 (0)
death from AESI [b], n (%)	1 (0.2)	1 (0.3)	NR (NA)	NR (NA)
Any TEAE, n (%)	459 (99)	325 (99)	NR (NA)	NR (NA)
leading to discontinuation, n (%)	45 (10)	33 (10)	NR (NA)	NR (NA)
leading to dose modification, n (%)	283 (61)	200 (61)	NR (NA)	NR (NA)
dose reduction, n (%)	195 (42)	131 (40)	NR (NA)	NR (NA)
drug interruption, n (%)	255 (55)	181 (55)	NR (NA)	NR (NA)
SAE, n (%)	179 (39)	126 (39)	NR (NA)	NR (NA)
grade ≥3 [c], n (%)	262 (57)	185 (57)	NR (NA)	31 (56)
Any TRAE, n (%)	444 (96)	NR (NA)	234 (95)	51 (93)
leading to discontinuation, n (%)	20 (4)	15 (5)	NR (NA)	3 (6)
leading to dose modification, n (%)	217 (47)	144 (44)	NR (NA)	NR (NA)
dose reduction, n (%)	175 (38)	113 (35)	NR (NA)	20 (36)
drug interruption, n (%)	179 (39)	119 (36)	NR (NA)	11 (20)
SAE, n (%)	45 (10)	27 (8)	35 (14)	7 (13)
grade ≥3 [c], n (%)	149 (32)	100 (31)	NR (NA)	NR (NA)
At least 1 AESI, n (%)	312 (95)	440 (95)	NR (NA)	NR (NA)
leading to discontinuation, n (%)	13 (4)	17 (4)	NR (NA)	NR (NA)
cognitive disorders, n (%)	3 (0.6)	1 (0.3)	NR (NA)	NR (NA)
muscular weakness, n (%)	5 (1)	4 (1)	NR (NA)	NR (NA)
pneumonitis, n (%)	5 (1)	4 (1)	NR (NA)	NR (NA)
leading to dose modification, n (%)	115 (35)	172 (37)	NR (NA)	NR (NA)
dose reduction, n (%)	87 (27)	135 (29)	NR (NA)	NR (NA)
drug interruption, n (%)	88 (27)	130 (28)	NR (NA)	NR (NA)
SAE, n (%)	19 (6)	28 (6)	NR (NA)	NR (NA)
dizziness, n (%)	3 (0.6)	1 (0.3)	NR (NA)	NR (NA)
muscular weakness, n (%)	5 (1)	3 (0.9)	NR (NA)	NR (NA)
pneumonitis, n (%)	6 (1)	5 (2)	NR (NA)	NR (NA)
grade ≥3 [c], n (%)	46 (14)	66 (14)	NR (NA)	NR (NA)
dizziness, n (%)	13 (3)	6 (2)	NR (NA)	NR (NA)
muscular weakness, n (%)	10 (2)	7 (2)	NR (NA)	NR (NA)
pneumonitis, n (%)	5 (1)	4 (1)	NR (NA)	NR (NA)

Source: Table 41 (p79), Table 43 (p80), Table 44 (p82) of the submission.

AE = adverse events; AESI = adverse event of special interest; CTCAE = common terminology criteria for adverse events; n = number of participants reporting data; N = total participants in group; NA = not applicable; NR = not reported; NSCLC = non-small cell lung cancer; TEAE = treatment-emergent adverse event; TREA = treatment-related adverse events; SAE = serious adverse events.

Notes: Dose modification includes dose reduction or drug interruption.

[a] Adverse events of special interest discussed separately in this section

[b] Overall number of deaths were not reported as a safety statistic. This is reproduced from the number of patients with event from the overall survival data because the analysis set size is the same for safety and efficacy data reported from that trial.

[c] Classified using CTCAE grading

6.36 The ESC considered the comparative safety claim was very difficult to interpret due to the issues raised in paragraph 6.28 and the very limited available safety data for entrectinib (as demonstrated in the table above). However, the ESC considered the

available safety data did not raise any substantial concerns that the safety profile of repotrectinib was likely to be worse than that of entrectinib. The Pre-PBAC Response agreed with the assessment by ESC that the safety outcomes reported for *ROS1*-positive and TKI-naïve patients (PSCR, Table 3) treated with repotrectinib did not raise additional concerns regarding the safety in the population requested for PBS listing.

Benefits/harms

6.37 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.38 The submission described repotrectinib as non-inferior in terms of effectiveness compared to entrectinib and crizotinib. The evaluation considered the claim was uncertain and may not be adequately supported. The key issues were: (1) considerable heterogeneity in terms of patient demographics, disease characteristics, and study treatment/follow-up durations between studies; and (2) the naïve comparative approach lacks statistical testing to measure the magnitude of effect between repotrectinib and entrectinib. The ESC noted, however, that there was no suggestion from the data provided that repotrectinib was inferior to entrectinib or crizotinib.

6.39 The ESC also considered the claim of non-inferior comparative effectiveness to entrectinib was uncertain due to the inherent limitations of the available data, however considered on balance that the claim may be reasonable. The ESC further considered the available safety data was very difficult to interpret (as outlined in paragraph 6.36), however considered the available safety data did not raise any substantial concerns that repotrectinib was likely to have a worse safety profile than entrectinib.

6.40 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.41 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.42 The submission applied a cost minimisation approach (CMA) based on the clinical claim of non-inferior effectiveness and safety of repotrectinib and entrectinib. The ESC considered a CMA may be reasonable, given its view on the clinical claims.

6.43 The submission stated that the equi-effective doses was based on steady-state dosing, with 600 mg (once daily) for entrectinib and 320 mg (160 mg twice daily) for repotrectinib. The calculation was based on manufacturer recommended dosage, instead of trial-based dosage, due to data limitations. These doses are only correct for patients taking standard doses. The ESC noted an estimated 40.1% of patients in TRIDENT-1 experienced a dose modification due to AEs/intolerance, moving from 320 mg daily dose in what is referred to as the steady state to smaller dosing which

may occur in increments of 40 mg (to 120 mg or 80 mg, once or twice daily depending on titration status). The PSCR stated the entrectinib TGA Australian Public Assessment Report specified that 34.1% of patients experienced a dose reduction and that no data on the distribution of dose reduction levels was available.

6.44 Relative dose intensity (RDI) of entrectinib in ROS1-positive patients was unavailable, as was the proportion of patients with dose reductions of entrectinib. RDI and dose reductions were not considered for the CMA proposed in the submission. The exclusion of RDI may be reasonable and was consistent with the CMA accepted by the PBAC for entrectinib (to crizotinib). However, for dose reduction scenarios, the cost per day of treatment with entrectinib reduces substantially as opposed to the repotrectinib price per day increasing.

6.45 The submission assumed the effective price for entrectinib to be [redacted]% of the published price in its calculations. A daily cost of $[redacted] for entrectinib was calculated, also based on standard doses. All calculations and scenarios below are based on this assumed effective cost of entrectinib used in the submission. Aiming to match repotrectinib to the same cost, the submission calculated the dispensed price for maximum quantity (DPMQ) for 30 days (i.e. the 160 mg 60 pack) to be $[redacted], identical to the DPMQ of entrectinib (Table 7). The submission proposed a flat pricing approach for the 40 mg x 120 pack used for dose reductions. The ESC noted the proposed flat pricing structure for the two forms of repotrectinib; 160 mg x 60 capsules intended for the steady state (total of 9,600 mg) and 40 mg x 120 pack used for the estimated 40.1% of patients requiring a dose reduction (total of 4,800 mg) leads to an increased daily cost relative to entrectinib.

Table 7: Results of the economic evaluation (submission) – *steady state regimen*

Treatment	Mg/unit	Mg/day	Units/day	Units /script	Days /script	AEMP (effective)	DPMQ (effective)	Dispensed price/day
Entrectinib	200	600	3	90	30	$[redacted]	$[redacted]	$[redacted]
Repotrectinib	160	320	2	60	30	$[redacted]	$[redacted]	$[redacted]

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

6.46 The issues in 6.43 and 6.45 significantly underestimate the cost of repotrectinib for patients with dose reductions as the cost per day of entrectinib reduces in dose reduction scenarios, as illustrated in Table 8.

Table 8: Daily treatment costs with repotrectinib and entrectinib using sponsor-proposed price

Dose reduction	Entrectinib				Repotrectinib			
	Daily dose (pack)	Cost/ mg	Script duration	Dispensed price/day	Daily dose (pack)	Cost/ mg	Script duration	Dispensed price/day
None	600 mg (200 mg x 90)	$[redacted]	30 days	$[redacted]	320 mg (160 mg x 60)	$[redacted]	30 days	$[redacted]
First	400 mg (200 mg x 90)	$[redacted]	45 days	$[redacted]	240 mg (40 mg x 120)	$[redacted]	20 days	$[redacted]
Second	200 mg (200 mg x 90)	$[redacted]	90 days	$[redacted]	160 mg (40 mg x 120)	$[redacted]	30 days	$[redacted]

6.47 During the evaluation, two alternative approaches to the CMA were considered; (1) to consider the standard and dose reduction scenarios separately, with a weighted price for the 40 mg form of repotrectinib that is weighted between both dose

reduction regimens; or (2) to consider a single weighted cost per day scenario that accounts for dose reductions and weight the prices of both forms accordingly to achieve an average cost per day consistent with entrectinib across all dosage options.

6.48 The PSCR argued the CMA scenario analyses (Scenarios 1 and 2) undertaken during the evaluation were unreasonable, as repotrectinib and entrectinib are unique molecules with different dosing and adverse event profiles. Furthermore, the PSCR also argued the approaches presented in the evaluation are at high risk of confounding as they assume that dose reductions are applicable from Day 1 of a patient treatment course, and that important data to inform any such comparisons including distribution of dose reduction levels and mean duration of entrectinib treatment were not available.

6.49 The ESC considered the proposed flat pricing approach for the standard and dose reduction packs of repotrectinib was unlikely to be reasonable, as the cost per patient per day was substantially higher across the dose reduction scenarios than for the standard dose pack and that a substantial proportion of the population (~40%) was likely to require dose reduction, as observed in the pivotal trial. The ESC acknowledged the arguments in the PSCR that information to establish equi-effective doses to entrectinib in multiple dose reduction scenarios is not available. However, the ESC considered it may be reasonable to consider alternative approaches to link the price of the dose reduction pack of repotrectinib to the standard pack, such as on a cost per milligram basis or to maintain the same cost per day weighted across the two dose reduction options. These are explored further in ESC Scenarios 1 and 2 below. The scenarios proposed by the ESC, which do not rely on assumptions about dose reductions for entrectinib, are presented below.

ESC Scenario 1: CMA prices based on a weighted cost per day, maintain price parity with the standard dose

6.50 Based on the sponsored calculated cost per day of $[redacted] (Table 7) and a weighted equi-effective dose for the dose reductions of 200 mg (Table 9), a revised AEMP is calculated to be $[redacted] and DPMQ to be $[redacted].

6.51 The cost per day calculations for the dose reduction scenarios were calculated as outlined in the table below:

Table 9: Repotrectinib dose reduction pack to maintain cost per day with standard pack (published prices)

Scenario	Percentage of REPO dose reduction use	REPO dose (mg)	DPMQ price/day
1st dose reduction	50.00%	240	$[redacted]
2nd dose reduction	50.00%	160	$[redacted]
Weighted dose	50:50 split	200	**$**[redacted]
		Dispensed price/DPMQ	$[redacted]
		Approved Ex-manufacturer price (back-calculated)	$[redacted]

Footnotes: Ex-manufacturer price back-calculated based on 1 July 2024 markups, valid at 1 April 2025.
Abbreviations: REPO = repotrectinib; mg = milligram; DPMQ = dispensed price for maximum quantity

6.52 The Pre-PBAC response considered this scenario may be reasonable as it ensures the cost per day in the dose reduction scenarios is equivalent to the standard dose.

ESC Scenario 2: Price per milligram (mg)

6.53 The sponsored calculated the cost per day of $[redacted] and an AEMP for the 160 mg x 60 pack of $[redacted] (Table 7). This equates to a price per mg $[redacted]. Applying the cost per mg to the smaller pack size of 40 mg x 120 capsules calculates an AEMP of $[redacted] and DPMQ of $[redacted].

6.54 The cost per day calculations for the dose reduction scenarios were calculated as outlined in the table below:

Table 10: Repotrectinib price per milligram approach (published price)

Standard pack		
Pack size	9,600 mg	Cost per mg: $[redacted]
AEMP	$[redacted]	
Dose reduction pack		
Pack size	4,800 mg	Cost per mg: $[redacted]
AEMP	$[redacted]	
DPMQ	$[redacted]	

Footnotes: Ex-manufacturer price back-calculated based on 1 July 2024 markups, valid at 8 April 2025.
Abbreviations: mg = milligram; AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

6.55 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with repotrectinib would be no more than the cost per patient of the entrectinib and the alternative therapies. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Repotrectinib cost per patient

6.56 The submission proposed the cost per patient to be $[redacted] per day, $[redacted] per course (course length assumption: 9.2 months). This is based on the cost of standard dose only. The overall daily cost per patient of repotrectinib is $[redacted], when accounting for the cost per day in dose reduction scenarios and the proposed flat pricing structure. The ESC noted that the proposed flat pricing structure for the steady state and dose reduction packs would result in the cost per patient per day being higher than that of entrectinib and considered this was inappropriate.

Estimated PBS usage and financial implications

6.57 This submission was not considered by DUSC.

6.58 The budgetary impact analysis (BIA) of the submission used a market-share approach to estimate the utilisation and financial impacts associated with a PBS listing of repotrectinib for the treatment of *ROS1*-positive adult patients with locally advanced or metastatic NSCLC.

6.59 The proposed effective approved ex-manufacturer price (AEMP) $[redacted] (DPMQ $[redacted]) calculated in the economic analysis was used for 2 individual packs of repotrectinib (120 mg, 60 pack; 40 mg, 120 pack).

6.60 Key inputs used to derive the financial estimates are presented in Table 11.

Table 11: Key inputs for financial estimates

Parameter	Value applied and source	Comment
PBS script volume	611 total scripts per year (153 crizotinib and 439 entrectinib). Medicare PBS item statistics for crizotinib (11589Y and 11594F) and entrectinib (12092K), Jan–Dec 2023	The input is prevalence data. Since patients already prescribed ROS1-inhibitor would not be switched to a new one unless severe intolerance occurred, this input is not appropriate.
Annual rate of growth of ROS1-positive NSCLC market	0% Assumed that the ROS1-positive NSCLC market has reached maturity. Sensitivity analysis conducted to apply growth rate of 18% (increase in scripts seen between 2022–2023)	Likely underestimated. Scripts show high growth rate each year (48% growth compared to previous year in 2021, then decline to 18% growth in 2023).
Uptake of repotrectinib	[redacted]% Clinician survey (presented within Utilisation and Cost workbook, Attachment 6)	Market share of all 3 treatments before/after repotrectinib listing were surveyed; however, market changes were only applied to repotrectinib, not to entrectinib and crizotinib (assumed same percentage changes in the submission).
Script equivalence	1 entrectinib/crizotinib: 0.975 repotrectinib Calculation to account for repotrectinib titration period using median duration of therapy of ROS1 patients in the TRIDENT-1 clinical trial	This is only a titration factor. For a titration factor, the assumption is reasonable given the available data; however, the limitation of the data introduces uncertainty
Substitution rate	<table><tr><td></td><td>Crizotinib 200 mg, 60</td><td>Crizotinib 250 mg, 60</td><td>Entrectinib 600 mg, 90</td></tr><tr><td>Repotrectinib 40 mg,120</td><td>100%</td><td>0%</td><td>40.1%</td></tr><tr><td>Repotrectinib 160 mg, 60</td><td>0%</td><td>100%</td><td>59.9%</td></tr></table>Calculation based on proportion of ROS1 patients requiring dose adjustment in the TRIDENT-1 clinical trial on median duration therapy of repotrectinib in the TRIDENT-1 clinical trial.	The figure of 40.1% is the percentage of patients requiring dose reduction in clinical trials, not the percentage of - script volume. Script equivalence should have been considered here, as for 1 script, the days it can last for entrectinib vs. repotrectinib are 30 vs 30 at standard dose, 45 vs 20 at first reduction and 90 vs 30 at second dose reduction (Table 8). This step underestimated the cost of repotrectinib.
Patient co-payment	PBS: $25.54, RPBS: $6.60 Medicare PBS item statistics for crizotinib (11589Y and 11594F) and entrectinib (12092K), Jan–Dec 2023	Reasonable
PBS/RPBS split	PBS: 96.83%; RPBS: 3.17% Medicare PBS item statistics for crizotinib (11589Y and 11594F) and entrectinib (12092K), Jan–Dec 2023	Reasonable

Source: Table 51 of the submission.
NSCLC = non-small cell lung cancer; ROS1 = c-ROS proto-oncogene 1.

6.61 The estimated use and financial implications of repotrectinib are shown in Table 12. Total net save to PBS/RPBS over 6 years was estimated to be net cost saving.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
number of patients treated	NA	NA	NA	NA	NA	NA
number of scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of repotrectinib						
cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for entrectinib and crizotinib						
cost to PBS/RPBS less copayments	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net financial implications						
net cost to PBS/RPBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
net impact to prescriptions processed	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
net cost to MBS	$0	$0	$0	$0	$0	$0
net cost to PBS/RPBS/MBS/Services Australia	NA	NA	NA	NA	NA	NA

Source: Table 60, 62, 65, 68 of the submission.

Notes: The submission did not calculate the net cost to Service Australia, but presented a net impact to prescriptions processed.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *net cost saving*

6.62 A major issue of the estimates is that they unreasonably substituted entrectinib 600 mg, 90 pack, with repotrectinib 40 mg, 120 pack, in 40.1% of patients who need a dose reduction, thereby significantly underestimating the cost of repotrectinib based on the proposed flat pricing across forms. Based on the ratios of script duration, one entrectinib 600 mg, 90 pack should be substituted with 2.25 repotrectinib 40 mg, 120 pack for the first dose reduction and 3 for the second dose reduction. The ESC considered the entrectinib prescriptions should be substituted with repotrectinib at 4:9 in the first dose reduction, then 1:3 in the second dose reduction.

6.63 This issue of a 1:1 substitution ration is that it creates a false negative net cost, as due to the proposed flat pricing structure in the submission, repotrectinib is more costly than entrectinib in dose reduction scenarios. Given it was estimated that ~40% of patients treated with repotrectinib would require dose reductions, the financial implications of this may be substantial, but are unable to be estimated, as entrectinib dose reductions are achieved by taking fewer capsules (and extending how long a prescription lasts) and no specific dose reduction form is separately listed on the PBS).

Quality Use of Medicines

6.64 Repotrectinib is a TKI, and with TKIs already PBS-listed for *ROS1*-positive NSCLC, Australian clinicians have extensive experience managing these patients.

6.65 Safety concerns for repotrectinib are intended to be managed via routine risk minimisation measures as presented in the Product Information and Consumer Medicines Information documents.

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule, Authority Required (written/online PBS authorities system) PBS listing of repotrectinib for the treatment of adult patients with locally advanced (Stage IIIB) or metastatic (Stage IV) c-ROS proto-oncogene 1 (*ROS1*) positive non-small cell lung cancer (NSCLC). The PBAC considered that, whilst there was considerable heterogeneity and the uncertainty associated with the clinical comparison, on balance it was likely repotrectinib provided similar health outcomes to entrectinib in the proposed population. The PBAC's recommendation was based on, among other matters, its assessment that the cost effectiveness of repotrectinib would be acceptable if it were cost minimised to entrectinib.

7.2 The PBAC considered the equi-effective doses for the standard dosing regimen were:

- Repotrectinib 320 mg daily (given as 2 x 160 mg doses); and
- Entrectinib 600 mg (once daily).

The PBAC considered it was reasonable for the cost of the repotrectinib dose reduction pack to not exceed that of the standard dose pack on a cost per day basis.

7.3 For the purposes of Section 101(3B) of the *National Health Act 1953*, the PBAC considered crizotinib was not an alternative therapy to repotrectinib. The PBAC noted the nominated comparator, entrectinib, was listed on a cost minimisation basis with crizotinib, however considered that clinical guidelines have evolved and crizotinib is no longer considered a standard therapy. In addition, the Committee considered that there are differences between repotrectinib and crizotinib, particularly with respect to their effectiveness in intracranial disease (with crizotinib being less effective in this context), and there is a high risk of *ROS1* NSCLC spreading to the central nervous system.

7.4 The PBAC noted the rarity of *ROS1* positive NSCLC and considered there remained a moderate clinical need for additional effective therapies, which was supported by the consumer comments received.

7.5 The PBAC noted the TGA Delegate's Overview was received after the ESC had provided its advice, and noted the Delegate considered that as a package, the available data supports approval of an indication that is line agnostic (i.e. can be used after progression with another *ROS-1* tyrosine kinase inhibitor (TKI)). On that basis, the PBAC considered it was reasonable to recommend a line agnostic listing for repotrectinib for *ROS-1* NSCLC, which would allow patients to use repotrectinib either as a first line option, or after progression with entrectinib or crizotinib, and acknowledged this would add an additional line of therapy for some patients. The Committee also noted a line agnostic listing would be consistent with the NCCN clinical guidelines. However, the PBAC noted this recommendation was based on the Delegate's Overview and may not reflect the final conditions of TGA registration and considered that a first line listing of repotrectinib (as currently exists for crizotinib and entrectinib) was acceptable if the finalised TGA indication is limited in such a manner.

Hence the restrictions upon implementation will reflect the final TGA registration of either first line treatment or line agnostic listing.

7.6 The PBAC noted the submission nominated entrectinib as the main comparator and considered this was reasonable.

7.7 The PBAC noted the clinical evidence for repotrectinib was based on a non-comparative, open-label, multicentre phase 1/2 trial, (TRIDENT-1 - phase 2, n = 63 participants; phase 1 + phase 2, n = 71 participants). The PBAC noted the primary endpoint was objective response rate, resulting in 79% based on the data cut off of 3 September 2024. It was further noted the sponsor is currently recruiting participants for a randomised controlled trial comparing repotrectinib to crizotinib in patients with locally advanced or metastatic TKI-naïve ROS1-positive NSCLC, named TRIDENT-3.

7.8 The PBAC noted the considerable heterogeneity in terms of patient demographics, disease characteristics, and study follow-up durations, both between the repotrectinib and entrectinib studies, and between the entrectinib studies themselves, making an assessment of comparative effectiveness and safety difficult. The PBAC considered these issues introduced substantial uncertainty to the clinical comparisons, however considered that in the context of the rarity of *ROS1*-positive NSCLC and evidence previously presented for entrectinib being of similar quality, that the available evidence for repotrectinib, including the matching-adjusted indirect comparison (MAIC) presented alongside the submission, whilst uncertain were adequate to assess the clinical claims in the context of the rarity of *ROS-1* NSCLC. The PBAC considered the available data from the unanchored, unadjusted comparison of repotrectinib and entrectinib (Table 4) suggested similar outcomes in terms of objective response rate (ORR), with repotrectinib achieving an ORR of 79% (TRIDENT-1 phase 1&2) and entrectinib achieving ORRs of 68% (integrated analysis) and 82% (BFAST analysis). The PBAC noted progression free survival (PFS) and overall survival (OS) results were more variable but also more uncertain, with 95% confidence intervals not estimable in many cases. The PBAC considered the matching-adjusted analyses presented in the submission and discussed in the PSCR (paragraph 6.25-6.26) were additionally supportive for the assessing the clinical claim. Overall, the PBAC considered it was reasonable to conclude that repotrectinib and entrectinib, on balance, are likely of non-inferior comparative effectiveness.

7.9 The PBAC considered it was difficult to assess the comparative safety of repotrectinib and entrectinib. However, the PBAC considered the limited data provided did not raise any substantial concerns that the safety profile for repotrectinib would be worse than that of entrectinib and considered the claim of non-inferior to entrectinib was, on balance, likely to be reasonable.

7.10 The PBAC considered the submission cost minimisation approach (CMA) of repotrectinib and entrectinib, based on an equivalent cost per day compared to entrectinib for the steady-state dosing of 600 mg (once daily) for entrectinib and 320 mg (160 mg twice daily) for repotrectinib was reasonable. In addition, the PBAC

noted the dose reduction requirements for repotrectinib (which the clinical trials suggest may occur in ~40% of patients) and considered the original submission proposal of a flat pricing arrangement for the dose reduction pack was not reasonable, given such an approach resulted in a substantially higher treatment cost per day in dose reduction scenarios and a substantial proportion of the population was expected to require a dose reduction. The PBAC considered it was reasonable for the dose reduction pack to be priced based on a weighted cost per day, equally applied across two dose reductions to achieve price parity with the standard dose on a cost per day basis (as discussed in 6.50).

7.11 The PBAC considered the estimated utilisation of repotrectinib provided in the submission required modification to accurately reflect the substitution rate. The PBAC noted the ESC advice and considered the entrectinib prescriptions should be substituted with repotrectinib at 4:9 in the first dose reduction, then 1:3 in the second dose reduction.

7.12 The PBAC noted that flow-on changes to the immunotherapy listings would be required to allow *ROS1*-positive NSCLC patients treated with repotrectinib, entrectinib or crizotinib as their first-line therapy to access immunotherapies as a potential second (or later) line treatment upon disease progression. More information is outlined in the recommended listing in section 8. In addition, the PBAC recommended the line agnostic listing of repotrectinib be affected by not including the criteria that currently apply to the listings of crizotinib and entrectinib that the patient must not have received prior treatment with a ROS1 TKI or have developed intolerance necessitating permanent treatment withdrawal. The Committee further advised that it was appropriate for these criteria to be retained for crizotinib and entrectinib as they are registered as first line treatment.

7.13 The PBAC advised that, under Section 101(3BA) of the *National Health Act 1953*, that repotrectinib should not be treated as interchangeable with any other drugs.

7.14 The PBAC advised that repotrectinib is not suitable for prescribing by nurse practitioners.

7.15 The PBAC considered the Early Supply Rule should not apply to repotrectinib, as it does not apply to entrectinib or crizotinib.

7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because repotrectinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over entrectinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial & continuing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
REPOTRECTINIB					
repotrectinib 40 mg capsule, 120	NEW	1	120	3	Augtyro
repotrectinib 160 mg capsule, 60	NEW	1	60	3	Augtyro
Category / Program: ☒GENERAL - General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (in writing via post/HPOS upload or real time assessment via OPA)					
Prescribing rule level					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Restriction Summary / Treatment of Concept:					
Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)					
Treatment Phase: Initial treatment					
Clinical criteria:					
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition,					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 2 or less,					
AND					
Clinical criteria:					
The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC,					
AND					
Clinical criteria:					
Patient must have evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing,					
Prescribing Instructions: Applications for authorisation of initial treatment must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail. If the application is submitted through HPOS form upload or mail, it must include: (a) details of the proposed prescription; and					

(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Prescribing Instructions: The following must be documented in the patient's medical records: (a) evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material.
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary / Treatment of Concept:
Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment Phase: Continuing treatment
Clinical criteria:
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

*Pending the final TGA registration, the restrictions may change if repotrectinib is approved as first-line drug therapy only.

8.2 Flow-on changes to 1L and 2L immunotherapy PBS listings for Stage IIIB (locally advanced) or Stage IV (metastatic) non-small lung cancer (NSCLC) to allow access to patients who progressed after targeted treatment:

1- Amend the clinical criterion that currently exists in pembrolizumab (11492W, 12121Y, 12119W).

	Clinical criteria: The condition must have progressed after treatment with ~~only one of (i) tepotinib, (ii) selpercatinib~~ *any of the prior targeted therapies that is PBS listed for this condition.*

2- Amend the clinical criterion that currently exists in nivolumab (11158G, 11143L, 12315E, 12323N) and atezolizumab (11284X, 11309F, 11940K, 14250B, 14247W, 11792P, 11807K, 14266W, 14298M) and cemiplimab (13160P, 13169D).

	Clinical criteria: The condition must have progressed after treatment with ~~tepotinib~~ *any of the prior targeted therapies that is PBS listed for this condition.*

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The Sponsor welcomes the PBAC's recommendation of repotrectinib for the treatment of ROS1-positive non-small cell lung cancer.