Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Augtyro

Active ingredient: Repotrectinib

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

January 2026

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing 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
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BID	Twice a day
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CI	Confidence interval
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Complete response
DLP	Data lock point
DOR	Duration of response
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMA SmPC	European Medicines Agency Summary of Product Characteristics
ER_{AUC}	Exposure ratio, area under the curve
ER_{BSA}	Exposure ratio, body surface area
ER_{Cmax}	Exposure ratio, maximal drug concentration
ERBB2 (HER2)	Human epidermal growth factor receptor 2
ESMO	European Society For Medical Oncology
FDA	Food and Drug Administration (USA)
FISH	Fluorescent in-situ hybridisation
IHC	Immunohistochemistry
KRAS	Kirsten rat sarcoma viral oncogene homolog
MATE1/2K	Multidrug and toxin extrusion proteins 1/2K
MET	Mesenchymal-epithelial transition factor
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NGS	Next-generation sequencing
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
OATP1B1	Organic anion transporting polypeptide 1B1
ORR	Objective response rate
PD	Pharmacodynamics
PD-L1	Programmed death-ligand 1
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetics
PR	Partial response
PSUR	Periodic safety update report
QD	Once a day
RET	Rearranged during transfection
RMP	Risk management plan
ROS1	ROS proto-oncogene 1
RT-PCR	Real-time polymerase chain reaction

SAE	Serious adverse event
SD	Stable disease
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TKI	Tyrosine kinase inhibitor
TRK	Tyrosine receptor kinase
UGT1A1	UDP-glucuronosyltransferase 1A1

Product submission

Submission details

Types of submission:	New chemical entity
Product name:	Augtyro
Active ingredient:	repotrectinib
Decision:	Approved
Date of decision:	23 July 2025
Date of entry onto ARTG:	25 July 2025
ARTG numbers:	Augtyro repotrectinib 40 mg capsule bottle (445679) Augtyro repotrectinib 160 mg capsule blister pack (445678)
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd, 4 Nexus Court, Mulgrave, Victoria 3170,
Dose form:	Hard capsules
Strengths:	40 mg, 160 mg
Containers:	**Augtyro 40 mg hard capsules** 120-cc and 200-cc, high-density polyethylene (HDPE) bottles with 2-piece child-resistant continuous thread (CRCT) polypropylene (PP) closures. **Augtyro 160 mg hard capsules** Polyvinyl chloride/Aclar (PVC/Aclar) clear blister with push through aluminium foil lidding. Aclar refers to polychlorotrifluoroethylene (PCTFE).
Pack sizes:	60 and 120 hard capsules
Approved therapeutic use for the current submission:	Augtyro, as monotherapy, is indicated for the treatment of adult patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).
Routes of administration:	Oral
Dosage:	160 mg orally once daily for 14 days, followed by 160 mg orally twice daily until disease progression or unacceptable toxicity. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	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.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database 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 Bristol-Myers Squibb Australia Pty Ltd (the Sponsor) to register Augtyro (repotrectinib) for the following proposed indication:[1]

> *Augtyro, as monotherapy, is indicated for the treatment of adult patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).*

Disease or condition

Non-small cell lung cancer

Based on Australian Institute of Health and Welfare estimates for 2021, the age-standardised annual incidence and mortality rates of lung cancer in Australia were 42.6 and 26.5 per 100,000 population, respectively.[2] The 5-year relative survival is around 20%; and lung cancer was predicted to be the leading cause of cancer-related deaths in both men and women for 2021. Around 40% of cases are metastatic at diagnosis.[3]

Lung cancer is the most common cancer diagnosed for Aboriginal and Torres Strait Islander people (based on data from 2012-2016).[4] Indigenous Australians are more than twice as likely to be diagnosed with lung cancer and have an approximate 5-year survival rate around 30% shorter, compared to non-Indigenous Australians.[5]

Most lung cancers (80-90%) are categorised as non-small cell lung cancer (NSCLC), which comprises both squamous and non-squamous (including adenocarcinoma) forms.[6] Adenocarcinomas are the most common subtype of NSCLC: they make up nearly half of all lung cancers.[7]

ROS1

The ROS proto-oncogene 1 (ROS1), located on chromosome 6, encodes an 'orphan' receptor tyrosine kinase (without a known ligand), whose physiological function remains unclear. ROS1

[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 in the Australian Register of Therapeutic Goods.
[2] Australian Institute of Health and Welfare (2021) Cancer in Australia 2021, Release date 1 Dec 2021 and Data tables: Cancer in Australia chapter 8 - Number of deaths (mortality data table). DOI: 10.25816/ye05-nm50. Accessed 28 April 2025
[3] Australian Institute of Health and Welfare (2019) Cancer in Australia 2019. Release date 21/03/2019.
[4] AIHW, 2021.
[5] AIHW, 2021.
[6] European Medicines Agency, Augtyro European public assessment report (EPAR), 2024. Accessed 24 April 2025.
[7] EMA, 2024.

shares sequence homology with the ALK gene, another proto-oncogene, and many ALK inhibitors also show ROS1 affinity.[8]

Physiologically, when bound by their respective ligands, receptor tyrosine kinases dimerise, autophosphorylate, and activate downstream signalling pathways, including those involved in cell growth and apoptosis.[9] Mutation of the genes that encode them can drive oncogenic transformation, often by interfering with key regulatory or functional domains resulting in constitutive kinase activation, overexpression, impaired autoinhibition, reduced turnover, or altered substrate affinity.[10]

In the case of ROS1-driven tumours, the causative mutation is a large-scale genetic rearrangement, in which a fusion event causes a region encoding the ROS1 kinase domain to be juxtaposed to a new genetic partner and resulting in expression of a novel, constitutively active fusion kinase.[11] ROS1 rearrangements are identified in around 1% or 2% of NSCLC;[12] 3% of adenocarcinomas.[13] Thus, of the 13810 predicted lung cancer diagnoses in Australia in 2021, 110-250 cases would be expected to be ROS1-positive.

Compared with other NSCLC, tumours harbouring ROS1 rearrangements are associated with younger age at diagnosis, female sex, Asian ethnicity, a minimal or never smoking history, and with adenocarcinoma histology.[14] Squamous cases do occur, however, two patients (1%) with ROS1-positive squamous NSCLC were included in trials submitted to the Australian Medical Services Advisory Committee (MSAC) in support of ROS1 test funding.[15] Based on the largest series studied (n=220), ROS1 rearrangements do not appear to co-occur with ALK mutations, but rarely co-occur with EGFR (0.5%) or KRAS (1.8%) mutations.[16]

Diagnostic testing for ROS1 rearrangements in NSCLC

As ROS1-positive tumours cannot be reliably identified from other lung adenocarcinomas based on histopathology or clinical features alone, their identification relies on molecular diagnostic techniques. Fluorescent in-situ hybridisation (FISH), immunohistochemistry (IHC), real-time polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS) can all be used (Appendix, Table A1), but NGS is preferable as it allows testing of a single sample for multiple actionable abnormalities with excellent sensitivity and specificity, identifying known and previously unknown variants.[17] Cost and speed are obstacles that generally reduce with technological advancements.

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[8] Lin JJ, Shaw AT. Recent Advances in Targeting ROS1 in Lung Cancer. J Thorac Oncol. 2017;12(11):1611–1625. doi:10.1016/j.jtho.2017.08.002

[9] Paul MK, Mukhopadhyay AK. Tyrosine kinase - Role and significance in Cancer. Int J Med Sci. 2004;1(2):101-115. doi: 10.7150/ijms.1.101. Epub 2004 Jun 1. PMID: 15912202; PMCID: PMC1074718.

[10] Cerrato, A., Visconti, R. & Celetti, A. The rationale for druggability of CCDC6-tyrosine kinase fusions in lung cancer. Mol Cancer 17, 46 (2018). https://doi.org/10.1186/s12943-018-0799-8

[11] Lin JJ, J Thorac Onco, 2017.

[12] Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30:863–870. doi: 10.1200/JCO.2011.35.6345.

[13] Zhu Q, Zhan P, Zhang X, Lv T, Song Y. Clinicopathologic characteristics of patients with ROS1 fusion gene in non-small cell lung cancer: a meta-analysis. Transl Lung Cancer Res. 2015 Jun;4(3):300-9. doi: 10.3978/j.issn.2218-6751.2015.05.01. PMID: 26207220; PMCID: PMC4483477.

[14] Bergethon K, 2012.

[15] Medical Services Advisory Committee (MSAC), 1454 – Diagnostic testing for ROS proto-oncogene 1 (ROS1) rearrangements in non-small cell lung cancer (NSCLC) to determine eligibility for crizotinib treatment. Public summary document for application number 1454. Accessed 06/01/2020.

[16] Lin JJ, Ritterhouse LL, Ali SM, Bailey M, Schrock AB, Gainor JF, Ferris LA, Mino-Kenudson M, Miller VA, Iafrate AJ, Lennerz JK, Shaw AT. ROS1 Fusions Rarely Overlap with Other Oncogenic Drivers in Non-Small Cell Lung Cancer. J Thorac Oncol. 2017 May;12(5):872-877. doi: 10.1016/j.jtho.2017.01.004. Epub 2017 Jan 11. PMID: 28088512; PMCID: PMC5403618.

[17] Lin, JJ, 2017.

Oncomine is an NGS test approved in Australia for use as a companion diagnostic with crizotinib for ROS1.[18] However, testing for ROS1 has become standard for NSCLC. Published best practice recommendations from the Royal College of Pathologists of Australasia in collaboration with the Thoracic Oncology Group of Australasia state that all advanced stage lung carcinomas with an adenocarcinoma component should undergo reflex testing, preferably by NGS for both RNA and DNA, for a panel of biomarkers that includes ROS1, EGFR, BRAF, KRAS, ERBB2 (HER2), ALK, ROS1, MET, RET and NTRK and PD-L1.[19] This position on molecular testing of NSCLC reflects that of major international guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society For Medical Oncology (ESMO).[20,21] Funding for such testing has been included on the Australian MBS since November 2023.[22]

Testing in TRIDENT-1, the pivotal trial submitted in the current application for registration of repotrectinib, used a variety of local testing approaches. Standard of care ROS1 testing in Australia is highly likely to be comparable to the testing used in the trial and is adequate to fulfil the need for companion testing for the proposed usage. Therefore, there is no need to require a specific plan regarding companion testing from the Sponsor for repotrectinib.

Twenty-four different ROS1 fusion partner genes have been described in NSCLC, all of which retain the entire ROS1 kinase domain.[23] Retention of this intact kinase domain appears to be sufficient to drive oncogenesis in any fusion gene product, regardless of fusion gene partner.[24,25] However, different fusion partner genes may result in different subcellular localization of the fusion product,[26] and could predict different responsiveness to tyrosine kinase inhibitor (TKI) therapy or clinical behaviour such as predilection for central nervous system metastasis.[27]

Current treatment options

Selection of a first line therapy for advanced (metastatic or locally advanced, inoperable) NSCLC crucially relies on testing for actionable driver mutations.[28]

[18] Search for "ROS1" in Companion Diagnostics (CDx) list | Therapeutic Goods Administration (TGA)

[19] Cooper WA, Amanuel B, Cooper C, Fox SB, Graftdyk JWA, Jessup P, Klebe S, Lam WS, Leong TY, Lwin Z, Roberts-Thomson R, Solomon BJ, Tay RY, Trowman R, Wale JL, Pavlakis N. Molecular testing of lung cancer in Australia: consensus best practice recommendations from the Royal College of Pathologists of Australasia in collaboration with the Thoracic Oncology Group of Australasia. Pathology. 2025 Feb 14:S0031-3025(25)00066-2. doi: 10.1016/j.pathol.2025.02.001. Epub ahead of print. PMID: 40102144.

[20] Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, Peters S, Planchard D, Smit EF, Solomon BJ, Veronesi G, Reck M; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Apr;34(4):339-357. doi: 10.1016/j.annonc.2022.12.009. Epub 2023 Jan 23. PMID: 36872130. Online tool accessed 6 MAY 2025 at: ESMO Interactive Guidelines

[21] National Comprehensive Cancer Network (NCCN) guidelines version 3.2025 for NSCLC. Dated 14 January 2025. Accessed 28 April 2025

[22] NGS panel including ROS1 MBS item for newly diagnosed NSCLC. Accessed 30 APR 2025 at: Item 73437 | Medicare Benefits Schedule

[23] Ou SI, Nagasaka M. A Catalog of 5' Fusion Partners in ROS1-Positive NSCLC Circa 2020. JTO Clin Res Rep. 2020 Apr 28;1(3):100048. doi: 10.1016/j.jtocrr.2020.100048. PMID: 34589944; PMCID: PMC8474457.

[24] Rossi G, Jocollé G, Conti A, et al. Detection of ROS1 rearrangement in non-small cell lung cancer: current and future perspectives. Lung Cancer (Auckl). 2017;8:45–55. Published 2017 Jul 7. doi:10.2147/LCTT.S120172

[25] Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. Ann Oncol. 2019;30(7):1121–1126. doi:10.1093/annonc/mdz131

[26] Neel D.S., Allegakoen D.V., Olivas V. Differential subcellular localization regulates oncogenic signaling by ROS1 kinase fusion proteins. Cancer Res. 2019;79:546–556. doi: 10.1158/0008-5472.CAN-18-1492.

[27] Li Z., Shen L., Ding D. Efficacy of crizotinib among different types of ROS1 fusion partners in patients with ROS1-rearranged non-small cell lung cancer. J Thorac Oncol. 2018;13:987–995. doi: 10.1016/j.jtho.2018.04.016.

[28] FDA initial Drug Approval Package for AUGTYRO (NDA 218213), 2023

In their absence, standard treatment is immunotherapy with a checkpoint inhibitor (unless contraindicated), with or without platinum-based chemotherapy depending on PD-L1 expression. However, there is currently very little evidence to support the use of combination immunotherapy and chemotherapy in ROS1-rearranged tumours.[29] They tend to show low tumour mutational burden and are unlikely to respond to immunotherapy as a monotherapy.[30]

The ESMO and NCCN guidelines for ROS1-rearranged NSCLC both recommend crizotinib, entrectinib or repotrectinib as preferred first line therapy for the treatment of ROS1-positive (rearranged) NSCLC, followed by repotrectinib or lorlatinib (if not received first line), or platinum-based chemotherapy as subsequent therapy options.[31,32] Of these, crizotinib and entrectinib (and chemotherapy) are approved in Australia. Lorlatinib is registered, but not for a ROS1-positive indication.

In Australia, entrectinib can be used for patients with CNS-only progression on crizotinib, but otherwise, for all patients who have progressed on an initial ROS1 TKI (i.e. all patients who start one), pemetrexed-based chemotherapy remains standard of care. Chemotherapy is certainly an active treatment option, and pemetrexed seems to have particular efficacy for ROS1-rearranged NSCLC:[33]

> The activity of chemotherapy has been systematically studied in patients with ROS1 fusion-positive NSCLCs. Pemetrexed, as monotherapy or in combination with a platinum-based agent (with or without bevacizumab), was predominantly used in these studies; objective response rates (ORRs) of 45–60% and median progression-free survival (PFS) durations of 5–23 months were observed with such treatments.[34]

In one study, amongst 19 patients with ROS1-positive NSCLC (5 of whom had previously received crizotinib), an objective response rates (ORRs) of 58% and a median PFS duration of 77.5 months was reported with pemetrexed-containing therapies, highlighting the difficulty with interpreting single arm time-to-event data.

Crizotinib and entrectinib were both approved based on clinically meaningful response rates and durations from single arm trials (Table 1).

[29] Choudhury NJ, Schneider JL, Patil T, Zhu VW, Goldman DA, Yang SR, Falcon CJ, Do A, Nie Y, Plodkowski AJ, Chaft JE, Digumarthy SR, Rekhtman N, Arcila ME, Iasonos A, Ou SI, Lin JJ, Drilon A. Response to Immune Checkpoint Inhibition as Monotherapy or in Combination With Chemotherapy in Metastatic ROS1-Rearranged Lung Cancers. JTO Clin Res Rep. 2021 May 18;2(7):100187. doi: 10.1016/j.jtocrr.2021.100187. PMID: 34590036; PMCID: PMC8474494.

[30] Choudhury, NJ, 2021.

[31] Hendriks LE, 2022.

[32] NCCN, 2025

[33] Drilon A, Jenkins C, Iyer S, Schoenfeld A, Keddy C, Davare MA. ROS1-dependent cancers - biology, diagnostics and therapeutics. Nat Rev Clin Oncol. 2021 Jan;18(1):35-55. doi: 10.1038/s41571-020-0408-9. Epub 2020 Aug 5. PMID: 32760015; PMCID: PMC8830365.

[34] Drilon, A 2020.

Table 1. Efficacy data for existing treatment options (compiled from the Product Information documents and literature publications)

	Crizotinib[35] (n=53) *Study 1001*	Entrectinib[36] (n=92) *ALKA/STARTRK-1/2*	Entrectinib[37] (n=168) *ALKA/STARTRK-1/2*
Objective response rate (95% CI)	72% (58, 83)	74% (64, 83)	68% (60, 75)
Duration of response, median (95% CI) in months	24.7 (15.2, 45.3)	NR	20.5 (14.8, 34.8)

The crizotinib results were assessed per investigator while entrectinib efficacy was assessed by blinded independent radiological review.

The approval of crizotinib was based on the clinical significance of the single arm findings.[38] A randomised study against chemotherapy (which was standard first-line treatment for NSCLC at that time) would not have been feasible, based on a loss of genuine equipoise due to the magnitude of response rate seen with crizotinib in the single arm studies, contextualised by the known natural history of the disease in the absence of treatment (which was incompatible with the observed response rate), and in line with strong mechanistic rationale, supported by non-clinical data. As it was first in class, no patient in the crizotinib study (PROFILE 1001) had previously received anti-ROS1 targeted therapy previously. Response rates were reasonably similar amongst patients who had received no prior systemic therapy (6/7 patients: 86% [42, 100]) and those who had received one or more prior systemic lines of therapy (32/46: 70% [54, 82]) according to supplementary materials published for the study.[39]

For entrectinib, whilst crizotinib had become a valid comparator, the evidence of intracranial activity supported approval. Intracranial responses to treatment with entrectinib for ROS1 positive NSCLC were seen in 7/10 patients in the dataset reviewed by the TGA,[40] and 19/24 (79%) of patients in the dataset reviewed by the European Medicines Agency (EMA).[41] While entrectinib can cross the blood-brain barrier, crizotinib is poorly CNS penetrant, and the CNS is a common site of progression on crizotinib. Whilst this was adequate evidence to justify regulatory approval despite the absence of randomised data, the clinical relevance of this in terms of time-to-event outcomes remains under study.[42]

[35] Therapeutic Goods Administration. Australian Product Information for crizotinib. Accessed 30 April 2025.
[36] Therapeutic Goods Administration. Australian Product Information for entrectinib. Accessed 30 April 2025.
[37] Drilon A, Chiu CH, Fan Y, Cho BC, 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, Siena S. Long-Term Efficacy and Safety of Entrectinib in ROS1 Fusion-Positive NSCLC. JTO Clin Res Rep. 2022 Apr 29;3(6):100332. doi: 10.1016/j.jtocrr.2022.100332. PMID: 35663414; PMCID: PMC9160474
[38] Therapeutic Goods Administration. Crizotinib Australian Public Assessment Report. 2018. Accessed 30 April 2025.
[39] Shaw, AT, 2019.
[40] Therapeutic Goods Administration. Australian Product Information for entrectinib. Accessed 30 April 2025.
[41] European Medicines Agency. European public assessment report (EPAR) for Augtyro. 2024. Accessed 24 April 2025
[42] Michels S, Massutí B, Vasyliv I, Stratmann J, Frank J, Adams A, Felip E, Grohé C, Rodriguez-Abreu D, Bischoff H, Carcereny I Costa E, Corral J, Pereira E, Fassunke J, Fischer RN, Insa A, Koleczko S, Nogova L, Reck M, Reutter T, Riedel R, Schaufler D, Scheffler M, Weisthoff M, Provencio M, Merkelbach-Bruse S, Hellmich M, Sebastian M, Büttner R, Persigehl T, Rosell R, Wolf J. Overall survival and central nervous system activity of crizotinib in ROS1-rearranged lung cancer-final results of the EUCROSS trial. ESMO Open. 2024 Feb;9(2):102237. doi: 10.1016/j.esmoop.2024.102237. Epub 2024 Feb 12. PMID: 38350336; PMCID: PMC10937203.

Progression does eventually inevitably occur despite treatment with crizotinib and/or entrectinib. Preclinical and clinical data describes secondary point mutations within the ROS1 kinase domain in 50−60% of crizotinib resistant tumours. These mutations include G2032R:[43]

> As more ROS1 inhibitors are developed, further research will be critical to defining the role of each TKI in the clinic. Paramount to addressing this question will be the rigorous evaluation of each agent's CNS activity, potency and clinical activity against resistant ROS1 mutant kinases, particularly G2032R, and toxicity profile. Current data suggest that G2032R is the most frequent ROS1 resistance mutation emerging post-crizotinib. Therefore, development of agents that effectively target the G2032R mutation and are safe/tolerable in patients should be of highest priority in the ROS1 field.

Entrectinib did not show activity against the L2026M or G2032R resistance mutations in preclinical study, or clinical activity in patients who received it after prior crizotinib in the ALKA or STARTRK-1 entrectinib studies (n=18; ORR 11%).[44]

Patients in STARTRK-2 could only enrol post crizotinib if they had CNS-only progression.[45] There has therefore been a need for development of TKIs with intracranial activity and activity against ROS1 resistance mutations.[46]

Of note, whilst head-to-head data are not currently available, there are ongoing randomised controlled trials of entrectinib against crizotinib and repotrectinib against crizotinib, which will hopefully address some of these key clinical questions about comparative clinical outcomes and possibly treatment sequencing.[47,48]

Clinical rationale

Repotrectinib is an oral, next-generation, potent, ATP-competitive small-molecule inhibitor of ROS1, TRK, and ALK. Repotrectinib was rationally designed as a differentiated compact macrocycle to allow for tight binding in the ATP-binding site while also minimizing steric interactions that lead to acquired, on-target resistance mutations.[49,50] To gain high binding affinity, most kinase inhibitors, including crizotinib and entrectinib, are large and have additional interactions with the kinase domain outside the ATP-binding pocket, which make these inhibitors vulnerable to acquired resistance mutations such as solvent front mutations that can sterically block drug binding.[51,52] The Sponsor proposes that repotrectinib-mediated

[43] Lin JJ, 2017.
[44] Drilon, A, 2022.
[45] Hoffmann-La Roche. Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions) (STARTRK-2). ClinicalTrials.gov identifier: NCT02568267. Updated 5 September 2025.
[46] Lin, JJ, 2017.
[47] Hoffmann-La Roche. A Study to Compare the Efficacy and Safety of Entrectinib and Crizotinib in Participants With Advanced or Metastatic ROS1 Non-small Cell Lung Cancer (NSCLC) With and Without Central Nervous System (CNS) Metastases. ClinicalTrials.gov identifier: NCT04603807. Updated 4 November 2025.
[48] Bristol-Myers Squibb. A Study of Repotrectinib Versus Crizotinib in Participants With Locally Advanced or Metastatic Tyrosine Kinase Inhibitor (TKI)-naïve ROS1-positive Non-Small Cell Lung Cancer (NSCLC) (TRIDENT-3). ClinicalTrials.gov identifier: NCT06140836. Updated 21 November 2025.
[49] Drilon A, Ou SI, Cho BC, et al. Repotrectinib (TPX-0005) Is a Next-Generation ROS1/TRK/ALK Inhibitor That Potently Inhibits ROS1/TRK/ALK Solvent- Front Mutations. Cancer Discov. 2018;8(10):1227-36.
[50] Murray BW, Rogers E, Zhai D, et al. Molecular Characteristics of Repotrectinib That Enable Potent Inhibition of TRK Fusion Proteins and Resistant Mutations. Mol Cancer Ther. 2021;20(12):2446-56.
[51] Awad MM, Katayama R, McTigue M, et al. Acquired resistance to crizotinib from a mutation in CD74-ROS1. N Engl J Med. 2013;368(25):2395-2401.
[52] Drilon A, Somwar R, Wagner JP, et al. A novel crizotinib-resistant solvent-front mutation responsive to cabozantinib therapy in a patient with ROS1-rearranged lung cancer. Clin Cancer Res. 2016;22(10):2351-2358.

inhibition of mutated ROS1 will provide a clinically meaningful response in patients with ROS1-positive NSCLC.

Regulatory status

Australian regulatory status

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

International regulatory status

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 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.

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 2 summarises these submissions and provides the indications where approved.

Table 2: International regulatory status at the time the TGA considered this submission

Country /Region	Submission date	Status	Indication
USA	27 March 2023	Approved 15 Nov 2023	Augtyro is indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). 40mg capsule only
EU	22 Nov 2023	Under Evaluation	Augtyro as monotherapy is indicated for the treatment of adult patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). Augtyro as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and • have received a prior TRK inhibitor, or • have not received a prior TRK inhibitor and have no satisfactory treatment options (see sections 4.4 and 5.1) 40mg and 160mg capsule

Canada	28 Feb 2024	Under Evaluation (ORBIS Type C)	Augtyro (repotrectinib capsules) is indicated for: Treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). 40mg and 160mg capsules
Switzerland	20 Dec 2023	Under Evaluation (ORBIS Type C)	Augtyro as monotherapy is indicated for the treatment of adult patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). Augtyro as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumors expressing neurotrophic tyrosine receptor kinase (NTRK) gene fusion that is locally advanced or metastatic or where surgical resection is likely to result in severe morbidity. 40mg and 160mg capsule
Singapore	Planned 30 Sep 2025	-	-
Brazil	Planned 31 Dec 2025	-	-
New Zealand	TBC	-	-

Registration timeline

Table 3 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 3: Timeline for Augtyro, submission PM-2024-01468-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2024
Evaluation completed	14 March 2025
Registration decision (Outcome)	23 July 2025
Registration in the ARTG completed	25 July 2025
Number of working days from submission dossier acceptance to registration decision*	245

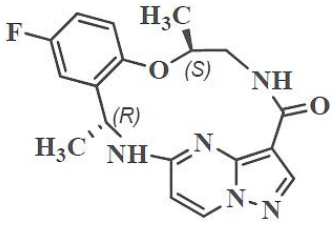
*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

Drug substance

Figure 1. The chemical structure of repotrectinib



Molecular Formula: $C_{18}H_{18}FN5O2$

Molecular weight: 355.37 g/mol

Repotrectinib (also known as TPX-0005) is a tyrosine kinase inhibitor with a lower molecular weight than other registered anti-ROS1 tyrosine kinase inhibitors (355.4 g/mol versus entrectinib at 560.6 g/mol).[53,54] Its small, macrocyclic structure was designed to overcome the steric interference caused by gatekeeper and solvent-front mutations in ROS1 (and ALK/TRK) that cause resistance to existing TKIs.[55,56] In vitro, it has significant inhibitory activity (inhibitory concentrations in the nM range) against the ROS1, ALK and TRK receptor tyrosine kinases, but particularly against ROS1, as summarised in Table 4.

Table 4. Reaction Biology *in vitro* HotSpot enzymatic kinase inhibitory assay of repotrectinib against wildtype (WT) and solvent-front mutations of ROS1, TRKA, TRKB, TRKC, and ALK.

Kinase IC_{50} (nM) at 10 µM ATP										
ROS1			**TRKA**		**TRKB**		**TRKC**		**ALK**	
WT	G2032R	D2033N	WT	G595R	WT	G639R	WT	G623R	WT	G1202R
0.0706	0.456	0.236	0.533	2.67	0.297	2.66	0.211	4.46	1.04	1.21

The identity of the drug substance including molecular structure and polymorphic form is adequately established. The company has adequately addressed genotoxic and nitrosamine impurities in the drug substance.

The drug substance-related impurities are controlled in accordance with ICH guideline Q3A[57]. The proposed limit for critical parameter, particle size distribution, is according to the batch results of the drug substance used to manufacture the phase 1/2 pivotal clinical and relative

[53] National Center for Biotechnology Information. PubChem Compound Summary for CID 135565923, Repotrectinib. https://pubchem.ncbi.nlm.nih.gov/compound/Repotrectinib.

[54] National Center for Biotechnology Information. PubChem Compound Summary for CID 25141092, Entrectinib. https://pubchem.ncbi.nlm.nih.gov/compound/Entrectinib.

[55] Cui JJ, Zhai D, Deng W, Huang Z, Rogers E, Ung J, Whitten J, Li Y. P3. 02a-009 TPX-0005: A Multi-Faceted Approach to Overcoming Clinical Resistances from Current ALK or ROS1 Inhibitor Treatment in Lung Cancer: Topic: ALK Biomarkers. Journal of thoracic oncology. 2017 Jan 1;12(1):S1164-5

[56] Drilon A, Ou SI, Cho BC, Kim DW, Lee J, Lin JJ, Zhu VW, Ahn MJ, Camidge DR, Nguyen J, Zhai D, Deng W, Huang Z, Rogers E, Liu J, Whitten J, Lim JK, Stopatschinskaja S, Hyman DM, Doebele RC, Cui JJ, Shaw AT. Repotrectinib (TPX-0005) Is a Next-Generation ROS1/TRK/ALK Inhibitor That Potently Inhibits ROS1/TRK/ALK Solvent- Front Mutations. Cancer Discov. 2018 Oct;8(10):1227-1236. doi: 10.1158/2159-8290.CD-18-0484. Epub 2018 Aug 9. PMID: 30093503.

[57] European Medicines Agency. ICH Q3A (R2) Impurities in new drug substances - Scientific guideline. 2006.

bioequivalence batches of the drug product. The specification applied for the drug substance is acceptable.

The analytical methods used to analyse the drug substance were adequately described and validated.

The stability data from 36-months support the proposed retest period of 48 months when stored at 25 °C.

Drug product

The appearance of the drug products is described as follows:

- 40 mg strength: Size 0, white opaque cap, white opaque body hard shell capsules filled with a white to off-white powder which may appear as a plug. The capsule cap is imprinted 'REP 40' in blue text.
- 160 mg strength: Size 0, blue opaque cap, blue opaque body hard shell capsules filled with a white to off-white powder which may appear as a plug. The capsule cap is imprinted 'REP 160' in white text.

The proposed product strengths are distinguishable by colour and marking.

The qualitative/quantitative compositions of the drug products and the manufacturing process are not the same. However, the company has provided data demonstrating the relative bioequivalence of the clinical 40 mg formulation (administered as 4 × 40 mg capsules) and 160 mg formulation (administered as 1 × 160 mg capsule) under fasted conditions. The clinical batches (unmarked for both strengths) are bridged to the marketing batches (marked) by in-vitro dissolution studies.

The specifications applied for the 40 mg and 160 mg strengths are adequate to ensure the quality of the proposed drug products. Impurities are adequately controlled, in accordance with ICH guideline Q3B[58]. Nitrosamine impurity risk assessment is adequate and acceptable. As per the risk assessment, the possibility for the presence of any nitrosamine impurities in the drug products is low.

The analytical methods used to analyse the drug product are adequately described and were acceptably validated.

The proposed container closures for 40 mg (child resistant HDPE bottle closure) and 160 mg (Blister) strengths comply with the relevant guidelines and are acceptable.

The stability data demonstrated that the drug products are stable for 36 months when stored below 25 °C.

Biopharmaceutics

The company has provided data demonstrating the relative bioequivalence of the clinical 40 mg formulation (administered as 4 × 40 mg capsules) and 160 mg formulation (administered as 1 × 160 mg capsule) under fasted conditions. However, the relative bioequivalence of the clinical 40 mg formulation (administered as 4 × 40 mg capsules) and 160 mg (administered as 1 × 160 mg capsule) under fed conditions has not been demonstrated. As per the quality evaluation, a bioequivalence study under fed conditions is deemed unnecessary.

[58] European Medicines Agency. ICH Q3B (R2) Impurities in new drug products - Scientific guideline. 2006.

Other information

The Product Information is considered acceptable from a pharmaceutical quality perspective.

The labelling is considered acceptable from a pharmaceutical quality perspective.

The provisional ARTG records are finalised.

There are no objections to registration from a pharmaceutical quality perspective.

Nonclinical evaluation summary

The review of the non-clinical aspects of the repotrectinib new chemical entity dossier by the TGA was based largely on the US FDA pharmacology review which is available in the public domain. The overall quality of the submitted nonclinical dossier was good.

In vitro, repotrectinib bound ROS1 with nanomolar affinity (K_d = 0.19 nM) and inhibited 26 kinases – including $ROS1^{WT}$ and $ROS1^{G2032R}$ – at concentrations below the clinical free C_{max} of 91 nM (Table 4). Effects against rat or monkey orthologues were not investigated.

Repotrectinib inhibited autophosphorylation of human $ROS1^{WT}$ and ROS1 oncogenes (CD74 and SDC4 fusion proteins) and similar effect was noted for ALK and TRKA/B. Antitumour activity was evaluated in subcutaneous xenograft models in athymic nude or SCID/Beige mice, transplanted with engineered cell lines expressing wild-type or mutant ROS1, ALK or TRKA oncogenes (fused SDC4, CD74, NMP, TPM3 or LMNA). Dose-dependent tumour growth inhibition ranging from 35% to 200% was observed in mice treated with orally administered repotrectinib (3 to 75 mg/kg BID). Neither NSCLC lines nor patient derived NSCLC cells were evaluated *in vivo* or *in vitro*. Consequently, the primary pharmacology program offers limited support for the proposed indications.

Based on the kinase inhibition panel, interactions in patients are considered likely, but with unknown clinical significance. Additionally, the drug inhibited LCK (lymphocyte cell-specific protein tyrosine kinase) at concentrations just above the clinical free C_{max} (IC_{50} = 110 nM), raising the possibility of immunosuppressive effects.

Safety pharmacology studies assessed effects on the cardiovascular, respiratory, gastrointestinal and central nervous systems (CNS). Repotrectinib had no toxicologically significant effects on cardiovascular function *in vivo* in monkeys or on hERG, hNaV1.5, or hCaV1.2 channels *in vitro*. Repotrectinib did not affect respiratory function in rats and monkeys. Severe CNS toxicity, such as ataxia and tremors, was observed in rats during 4- and 13-week repeat-dose studies at ER (exposure ratio)$_{Cmax}$ ≥ 2.8.

Overall, the pharmacokinetic profile in rats and monkeys was qualitatively similar to that of humans. T_{max} (2-4 h) was comparable across species. The half-life was ~ 4 h in rats and mice, 10h in dogs, and 29 h in monkeys. Plasma protein binding was high (92.07-95.41%) in all species including human. Tissue distribution was wide but penetration into brain and reproductive tissues was very limited. All metabolites formed in humans were also observed in rats and monkeys. No individual metabolite represented greater than 10% exposure to the parent compound. Drug-related material was excreted *via* faeces and urine with faeces as the predominant route of excretion in all species.

Based on *in vitro* studies, CYP3A4 inhibitors could affect repotrectinib's systemic exposure. Repotrectinib is a moderate inducer and might alter the exposure of co-administered drugs that are CYP2B6/C8/C9 or CYP3A4 substrates. Repotrectinib may reduce the exposure of co-administered drugs that are P-glycoprotein or BCRP substrates. Additionally, inhibition of OATPB1 is expected at clinically relevant concentrations. Interactions with OATPB3, MATE1,

MATE2K and UGT1A1 are considered possible as the ratio of the IC_{50} to the plasma C_{max} for unbound drug is ≤50.

Repotrectinib had a low order of acute oral toxicity in rats and monkeys.

Repeat-dose toxicity studies by the oral route were conducted in rats and cynomolgus monkeys (up to 13 weeks). Maximum exposures (AUC) were low in rats (with animal-to-clinical exposure ratios based on AUC [ER_{AUC}] of ≤3.7) and subclinical in monkeys (ER_{AUC} ≤0.6). Treatment-related mortality was observed in rats. In a 4-week study, two moderate dose (MD) males (ER_{AUC} ~2) and all high dose (HD) males and females either died or were euthanized *in extremis*. Increased mortality in HD animals (two males and eight females) in a 13-week study resulted in treatment break and a subsequent dose reduction (males: 50 → 40 mg/kg/day; females 40 → 30 mg/kg/day; surviving animals ER_{AUC} = 2.4). The cause of deaths was not determined but acute CNS effects (ataxia and tremors) were observed in moribund animals. CNS signs associated with early deaths generally abated after dosing holidays and dose reduction. In monkeys, sporadic deaths at ER_{AUC} ~0.33 were related to severe gastrointestinal (GI) toxicity. At ER_{AUC} ≥0.2 monkeys exhibited reversible GI toxicity (watery faeces, emesis, inflammation and mucosal gland hyperplasia). Both monkey and rat exhibited reversible hypocellularity in bone marrow, lymphoid tissues and thymus. Toxicities in rats also included reversible CNS effects (ataxia and tremors) at ER_{AUC} ≥2.4 as well as skin ulcers and scabs at ER_{AUC} ≥0.4.

Repotrectinib was not mutagenic in the Ames assay but displayed aneugenic potential *in vitro* in a mammalian cell micronucleus assay (with and without metabolic activation) and *in vivo* in rats at ER_{Cmax} > 4. Aneugenic effects of repotrectinib in patients cannot be excluded.

In pregnant rats, oral repotrectinib led to increased, dose-dependent post-implantation loss at ER_{BSA} ≥0.18. Embryofetal toxicity included hind limb malformations at ER_{BSA} ≥0.37 and reduced fetal weight at ER_{BSA} = 0.61. No further embryofetal developmental studies were conducted. CNS effects in juvenile rats resulted in acute mortality and early euthanasia at lower ER_{BSA} levels (≥2.4) *cf.* adult animals (~3.6).

There are no impurities/degradants specified in the drug substance/drug product at limits above the applicable ICH Q3A/B qualification thresholds.

In summary:

- Nonclinical efficacy was demonstrated *in vivo* and *in vitro* against engineered cell lines expressing ROS1, ALK and TRKA oncogenes. The results were consistent with the drug's expected mode of action. However, the efficacy against patient-derived NSCLC cells was not demonstrated in animal models Consequently, the primary pharmacology program provides limited support for the proposed indications.
- Despite minimal brain penetration observed in rats, adverse effects on the central nervous system, such as ataxia and tremors, were noted. This has been noted in the PI. Similar effects are common with other drugs of the same class. Gastrointestinal effects (watery faeces, emesis, inflammation, mucosal gland hyperplasia) were observed in monkeys at subclinical exposures.
- Nonclinical data (LCK inhibition *in vitro* and lymphoid tissue hypocellularity observed *in vivo*) suggest immunosuppressive effects of repotrectinib and potentially increased susceptibility to infections.
- Repotrectinib might interfere with P-glycoprotein, BCRP and OATPB1 at clinically relevant concentrations. Interactions with OATP1B3, MATE1, MATE_2K and UGT1A1 are considered possible.
- Repotrectinib was not mutagenic; aneugenic effects cannot be ruled out.

- Repotrectinib was teratogenic in pregnant rats at subclinical exposures.
- Severe CNS toxicity was observed in juvenile rats at exposures lower than in adult animals. However, the drug is not indicated for paediatric use.

Considering the proposed indications and Pregnancy Category D, there are no nonclinical objections to the registration of repotrectinib in adults.

Clinical evaluation summary

Summary of clinical studies

The clinical dataset submitted in support of the registration of repotrectinib mainly comprised the study reports summarised in Table 5. Additional documents (bioanalytical reports, exploratory cross-trial comparisons, literature references) were also submitted.

Table 5. Clinical studies submitted to the TGA to support the repotrectinib submission

Study/reportID	Study description
Study TPX-0005-008	Phase 1 bioavailability study of repotrectinib oral suspension relative to repotrectinib capsules in healthy adult male subjects
Study TPX-0005-12	A Phase 1 Relative Bioavailability Study of repotrectinib (TPX-0005) Capsule Formulations in Healthy Adult Male Subjects
Study TPX-0005-14	A Phase 1, Open-Label, Randomized, Three-Period, Four-Treatment Crossover Study to Assess the Bioequivalence of repotrectinib (TPX-0005) Administered as the To Be Marketed Formulation Versus the Current Clinical Formulation and the Effect of Food in Healthy Adult Male Subjects
Study TPX-0005-09	A Phase 1 Study to Investigate the Mass Balance, Pharmacokinetics, and Metabolism of a Single Oral Dose and Pharmacokinetics of an Intravenous Tracer of [^{14}C]-repotrectinib in Healthy Male Subjects
Study TPX-0005-10	A Phase 1, Two-Part, Open-Label, Fixed-Sequence Study to Assess the Effects of Itraconazole and Rifampin on the Single Dose Pharmacokinetics of repotrectinib (TPX-0005) in Healthy Adult Male Subjects.
Study TPX-0005-11	A Phase 1, Open-Label, Randomized, Two-Period, Two-Treatment Crossover Study to Assess the Effect of Food on the Single-Dose Pharmacokinetics of repotrectinib (TPX-0005) in Healthy Adult Male Subjects.
PBPK	Physiologically based pharmacokinetic modelling report
PopPK (USA)	Population Pharmacokinetic Analysis Report - US
PopPK (EU)	Population Pharmacokinetic Analysis Report - EU
ER analysis	Exposure Response Analysis Report
QTcF report	Integrated Concentration-QTcF Analysis of Repotrectinib
Study 00515	Cardiac Safety Report

Study/reportID	Study description
Study TPX-0005-07	A Phase 1/2, Open-label, Safety, Tolerability, Pharmacokinetics, and Antitumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring ALK, *ROS1*, or NTRK1 3 Alterations (CARE).
Study TPX-0005-01	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)

TRIDENT-1 study

TRIDENT-1 was initiated in March 2017. Phase 2 commenced 28 June 2019. The primary analysis data cut-off (DCO) was June 2022, and the DCO for the clinical study report submitted to TGA (and EMA) was December 2023. Updated efficacy analyses, with a DCO of 15 October 2023, is described in the publicly available European public assessment report.[59]

The phase 1 component was conducted at 8 study centres in the USA (4 study centres), South Korea (3 study centres), and Australia (1 study centre). Phase 2 was conducted at 152 study sites across 19 countries (Australia, Belgium, Canada, China, Germany, Denmark, Spain, France, UK, Hong Kong, Hungary, Italy, Japan, South Korea, The Netherlands, Poland, Singapore, Taiwan, and USA).

Phase 1 of the study provided data supporting dose selection and food effect and included a midazolam substudy to inform potential for drug-drug interactions (DDI).

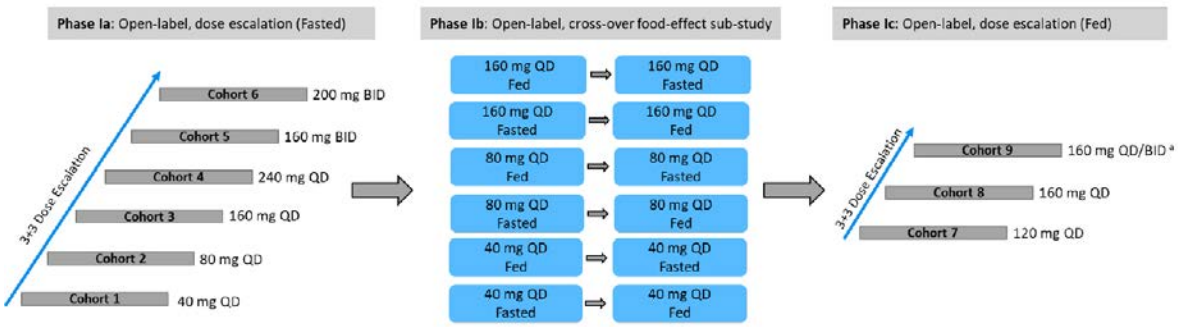
The key data supporting efficacy for the indication proposed for registration in Australia is sourced from phase 2 cohorts EXP-1, EXP-2, EXP-3 and EXP-4.

A detailed evaluation and description of the study design and findings (including sample size considerations, statistical methodology, protocol and amendments) conduct (including participant flow, protocol deviations) and outcomes (including study population baseline characteristics and results), can be found in the European public assessment report.

The study design is summarised in Figure 2.

Figure 2. A: Schema of Phase 1a, Phase 1b, and Phase 1c. B: Schema of Phase 1/2 Study TRIDENT-1.

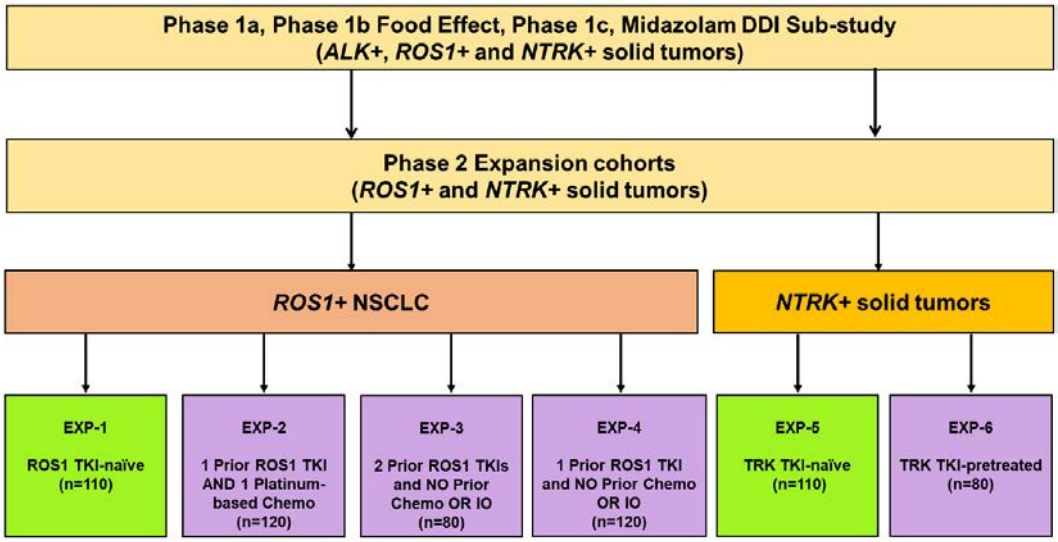
A.



BID=twice a day; QD=once a day. a 160 mg QD for 7 days followed by 160 mg BID

[59] European Medicine Agency. Augtyro Assessment Report. 2024

B.



Abbreviations: ALK+ = anaplastic lymphoma kinase-positive; chemo = chemotherapy; DDI = drug-drug interaction; EXP = expansion cohort; IO = immunotherapy; NSCLC = non-small cell lung cancer; NTRK+ = neurotrophin receptor kinase-positive; ROS1 = receptor tyrosine kinase encoded by the ROS/ gene; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.

Dose optimisation

Phase 1 of TRIDENT-1 included 93 subjects who received at least one dose (DCO 20 June 2022).

Dizziness (incidence of 61%) was the most common treatment-emergent adverse event (TEAE).

A formal "maximum tolerated dose" was not reached. However, dose-limiting toxicity occurred in three patients. In two cases dizziness was the dose-limiting toxicity and it occurred within 14 days of starting treatment at a relatively high dose (one at 240 mg daily, one at 160 mg BD). The third patient had grade 3 dyspnoea and hypoxia at 160 mg BD.

A preliminary efficacy analysis (DCO 4 March 2019) indicated clinical activity in ROS1- positive NSCLC across the studied dose range. Amongst ROS1-positive NSCLC subjects who had previously received anti-ROS1 targeted TKI, responses occurred in 55% (n=6/11) of patients receiving repotrectinib doses of at least 160 mg daily, and in 14% (n=1/7) of patients receiving doses of less than 160 mg daily. In TKI-naïve subjects, ORR was also highest (83%) at doses of at least 160 mg daily n = 5/6).

Dose titration from 160 mg daily to 160 mg BD to maximise PK/pharmacodynamic exposure was supported by additional PK/pharmacodynamic simulations.

Pharmacology

The pharmacokinetic (PK) properties of repotrectinib are described in detail in the publicly available EPAR and FDA multidisciplinary review,[60,61] and summarised in the approved product information for the USA (label) and the EU (SmPC); and in Table 6, below.[62,63] All data (except absolute bioavailability) refer to oral dosing.

[60] FDA, 2023

[61] EMA, 2024.

[62] Food and Drug Administration. Augtyro Full Prescribing Information. June 2024

[63] European Medicines Agency. Augtyro Summary of Product Characteristics.

PK data are available from studies in healthy volunteers, from patients with NTRK fusion-positive solid tumours, and from patients with ROS1-rearranged NSCLC.

Table 6. Brief summary of repotrectinib pharmacokinetics and pharmacodynamics

Property	Summary
Pharmacokinetic parameters	Dose proportional but less than linear exposure with single doses 40 mg – 240 mg. Steady-state PK is time-dependent due to autoinduction of CYP3A4: C_{avg} with a single 160 mg dose is similar to steady-state C_{avg} at recommended dose regimen. At recommended dose: estimated steady-state geometric mean (CV%) C_{max} = 572 ng/mL (38%); C_{min} = 158 ng/mL (58%); and C_{avg} ($AUC_{0\text{-}12h}$ divided by dosing interval) = 347 ng/mL (42%).
Absorption	Geometric mean (CV%) absolute bioavailability: 46% (20%) Food effect: increases exposure, but not enough to warrant mandating fasted dosing Tmax: 2-3 hours fasting, 4-6 hours fed.
Distribution	Plasma protein bound fraction: 95% Blood-to-plasma ratio: 0.56 in vitro 160 mg single oral dose geometric mean (CV%) volume of distribution (Vz/F) = 432 L (56%)
Metabolism	CYP3A4 to hydroxylated metabolites, then secondary glucuronidation. No metabolite exceeded 10% of total circulating drug-related radioactivity.
Excretion	Time-dependent elimination due to autoinduction of CYP3A4. Geometric mean (CV%) apparent oral clearance (CL/F) of single 160 mg dose: 16L/h (46%) Predominantly faecal excretion (89%; 51% as unchanged drug), with 5% urinary recovery of radiolabelled single 160 mg dose.

Property	Summary
Population pharmacokinetics	PopPK estimated mean (SD) terminal $T_{1/2}$ was 69 (30) hours (single dose) and 45 (21) hours after reaching steady state. No meaningful effect of mild or moderate renal impairment (not studied in severe), or mild hepatic impairment (not studied in moderate or severe), or gender, age (18-93 years), body weight (39.5 kg to 169 kg) or Asian compared to Caucasian ethnicity. Paediatric data (n=13) are limited; based on simulations, patients 12-18 years old are anticipated to have similar PK to adults. No paediatric indication is sought in the current application. Available paediatric PK data are summarised in the EMA documentation, noting that the NTRK indications approved by FDA and EMA specifically include paediatric patients.[64,65,66]
In vitro DDI data	Induces enzymes: CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2C9 Inhibits enzymes: CYP3A4/5 (GI tract), CYP2C8 and CYP2C9, and UGT1A1. Inhibits transporters: P-gp, BCRP, OATP1B1, MATE1 and MATE2-K. Is a substrate for: P-gp, and potentially MATE2-K and BCRP.
Exposure-response	Relationships and time course not fully characterised (data are limited for doses other than the recommended dose)
QT prolongation**Error! Bookmark not defined.**	Analysis of ECG data from 334 patients in the TRIDENT-1 phase 2 study, who received Augtyro at the recommended dose (non-controlled prandial state), demonstrated that the upper limit of 90% confidence interval (CI) of the mean QTcF change from baseline (ΔQTcF) exceeded 10 milliseconds (ms) for a few time point estimates but remained < 20 ms. Patients with increased risk of QTc prolongation were not enrolled in TRIDENT-1.

Efficacy

TRIDENT-1

The pivotal efficacy data with regard to the proposed ROS1-positive indication come from the following cohorts of TRIDENT-1:

- EXP-1 (ROS1 TKI-naïve)
- EXP-2 (one prior ROS1 TKI and one platinum-based chemotherapy)
- EXP-3 (two prior ROS1 TKIs)
- EXP-4 (one prior ROS1 TKI, no prior chemo or immunotherapy)
- Certain patients from phase 1 (see below)

[64] Food and Drug Administration. Augtyro Full Prescribing Information. June 2024
[65] European Medicines Agency. Augtyro Summary of Product Characteristics. Accessed 2 May 2025
[66] EMA, 2024.

Patients in the phase 2 cohorts were all adults with histological or cytological confirmation of locally advanced or metastatic MSCLC harbouring a ROS1 gene fusion, with repotrectinib-naïve, measurable disease per RECIST v1.1, and ECOG PS less than 2. Standard reproductive, cardiovascular and organ function exclusions applied, and patients with untreated or active CNS disease were also ineligible.

In phase 2, repotrectinib was administered orally 160 mg daily for the initial two weeks, with dose escalation to 160 mg BD thereafter for patients meeting the following criteria:

- No TEAEs higher than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1
- No dose interruptions
- No treatment-related laboratory abnormalities higher than Grade 1
- No clinically significant ECG abnormalities

Doses were to be taken at approximately the same time(s) each day. Treatment interruptions and dose reductions (first to 120 mg BD, subsequently to 80 mg BD) were permitted for management of adverse events.

The primary endpoint was ORR assessed by blinded independent central review (BICR) per RECIST v1.1 criteria. Key secondary endpoints included duration of response (DOR) and intracranial ORR. Time to event endpoints were reported but are unreliable due to the single-arm study setting. ORR and DOR were estimated using exact binomial confidence intervals. DoR was analysed using the Kaplan-Meier method to estimate median duration and associated confidence intervals. No multiplicity adjustments were planned, and each cohort was treated statistically as an independent single-arm trial. No interim analysis was planned. Only the primary endpoint was seen as inferential.

Clinically meaningful lower bounds for the primary endpoint (ORR) were nominated as part of justification presented for sample size calculations (Table 7).

Table 7. Clinically meaningful ORR lower bound used for sample size justifications for the ROS1 cohorts of TRIDENT-1

ROS1+ NSCLC cohort	Prespecified limit of ORR chosen to define a clinically meaningful result
EXP-1 ROS1 TKI-naïve	ORR (lower 95% CI bound) >66%, based on the ORR for crizotinib (66% [51, 79]).
EXP-2 1 prior ROS1 TKI AND 1 prior platinum-based chemo	ORR (lower 95% CI bound) >23% Based on the ORR reported for combination of docetaxel + ramucirumab for 2L+ NSCLC (not 'on-label' for ramucirumab in Australia), i.e. ORR 23% [20, 26].
EXP-3 2 Prior ROS1 TKI NO chemo or immunotherapy	ORR (lower 95% CI bound) >10% Based on ruling out chance regression.
EXP-4 1 Prior ROS1 TKI NO chemo or immunotherapy	ORR (lower 95% CI bound) >35% Based on superiority to first line chemotherapy in NSCLC. The ORR from platinum- based doublets or in combination with bevacizumab was in the range 25 – 35% (Abraxane® USPI, 2019; Alimta® USPI, 2019; Gemzar® USPI, 2019; Taxotere® USPI, 2019; Avastin USPI, 2009).

Several protocol amendments were enacted, many relating to eligibility criteria and prior therapies. These included:

- In amendment 6 leading to Version 7.0 (13 November 2019), enrolment was closed to patients with ALK+ tumours based on limited clinical evidence of efficacy.
- In amendment 9 leading to Version 10.0 (20 October 2020), EXP-3 inclusion criteria were modified to remove requirement for previous treatment with one line of platinum-based chemo/immuno-therapy due to the limited activity of repotrectinib being observed in the 4th line setting (2 prior TKIs + 1 line chemotherapy)
- In amendment 11 leading to Version 2.0 (14 January 2022), additional information was added: *"Clarified the statistical analysis language for EXP-4 that, assuming a target ORR of 50% with a sample size of 60, the lower bound of the 95% CI would be greater than 35%, which would show superiority to first line chemotherapy in NSCLC."*

The FDA report, which reflects a dataset submitted to FDA on March 27, 2023, did not identify any major concerns with protocol amendments (pages 109-110), study integrity or interpretability, and records the history of their regulatory interactions.[67]

Reported protocol deviations are also unlikely to have impacted interpretation of the study, and declarations of compliance with good clinical practice (GCP) were made.

Regulatory efficacy populations

FDA

The regulatory review that supported FDA's approval of repotrectinib in the USA was based on a pooling approach agreed to by FDA in a Type C meeting on 19 Aug 2020:**Error! Bookmark not defined.**

Written Responses Only (Clinical) Written Responses: Agreement with FDA that efficacy data from the Phase 1 and Phase 2 portions of the TRIDENT-1 study can be pooled for the primary analysis of efficacy to support registration in the targeted patient populations with ROS1+ advanced NSCLC (both TKI-naïve and TKI-pretreated)

The statistical analysis plan (SAP) version that was applicable to the FDA application was "Integrated SAP version 3.0", finalised 12 December 2022. Pooling criteria were as follows:

ROS1-positive TKI-naïve NSCLC cohort (Pooled EXP-1): includes all ROS1-positive NSCLC subjects in the Phase 1 and Phase 2 portions of TRIDENT-1 study who meet the following criteria:

- Confirmation by central laboratory test for ROS1 rearrangement per the requirement in each phase of TRIDENT-1 study protocol.
- No prior exposure to a ROS1 TKI.
- Started treatment at least 8 months prior to DCO date (6 months of follow-up for tumor assessment after first post-baseline scan).

ROS1-positive TKI-pretreated NSCLC cohort (Pooled EXP-4): includes all locally advanced or metastatic ROS1-positive NSCLC subjects in the Phase 1 and Phase 2 portions of TRIDENT-1 study who meet the following criteria:

- Confirmation by the central laboratory test for ROS1 rearrangement per the requirement in each phase of TRIDENT-1.
- Disease progression or intolerant to 1 prior line of ROS1 TKI treatment with no prior chemotherapy.

[67] FDA, 2023

- Started treatment at least 8 months prior to DCO date (6 months of follow-up for tumor assessment after first post-baseline scan).

The requirement for measurable disease at baseline was removed in this version of the SAP, and receipt of the recommended phase 2 dose was also not a requirement for inclusion in the pooled efficacy populations.

FDA also had the following comments regarding other efficacy data:

> *'FDA did not independently verify results from other cohorts (e.g., EXP-2 and EXP-3) from TRIDENT-1. FDA did not independently verify the results for time-to-event endpoints such as PFS and OS; time-to-event endpoints are not interpretable in non-comparative trials and are considered exploratory only. In addition, CBR is not considered to be a clinically relevant endpoint for efficacy evaluation. In response to an Information Request dated September 22, 2023, the Applicant clarified that the analysis of the secondary endpoints IC-ORR and IC-DOR in patients with measurable brain metastasis at baseline per BICR was performed in Phase 2 patients only, as per the BICR charter for mRECIST. In other words, the analysis was based on 63 TKI-naïve patients in EXP-1 and 53 TKI-pretreated patients in EXP-4.'*

EMA (and TGA)

EMA received the same initial dataset as TGA, but the EPAR reflects an updated dataset ('pooled expanded') with DCO of 15 Oct 2023. The assessments of efficacy summarised in the tables below, relate to the "ROS1 expanded pooled population" described by EMA in the EPAR.**Error! Bookmark not defined.** It is 'expanded' because enrolment continued and the cohorts are larger than at the two earlier DCOs/IAs (June 2022 and Dec 2022, respectively). It remains 'pooled' because it includes phase 1 and 2 patients in the same manner as the FDA dataset did.

The "ROS1 expanded pooled population" consisted of 15 patients from phase 1 and 308 patients from phase 2. Nineteen phase 2 patients and 25 phase 1 patients were excluded, mostly due to not meeting the prior lines of therapy requirements for the four ROS1 cohorts; a further 8 patients in the midazolam substudy were also excluded. Baseline characteristics (demographics and disease characteristics) of the efficacy population are described in detail in Table 15 of the EPAR.[68]

Briefly, amongst 323 patients, the median age was 56 years (range 27, 93), 63% were female, 52% were Asian, 64% had never smoked, 96% had adenocarcinoma histology, 34% had brain metastases at baseline, 77% had de novo metastatic disease, and 76% did not have a known TKI-resistant ROS1 mutation. Of 45 patients with a resistant ROS1 mutation at study entry, 35 were solvent front, 2 were gatekeeper, and 8 were 'other'.

Main results of TRIDENT-1

Table 8. Overall summary of efficacy in TRIDENT-1 for ROS 1+ NSCLC - expanded pooled analysis set (DCO 15 October 2023), per the EPAR[69]

	TKI-naïve	TKI-pretreated			
	EXP-1	EXP-2	EXP-3	EXP-4	Pre-treated (pooled)

[68] EMA, 2024.

[69] EMA, 2024.

	TKI-naïve	TKI-pretreated			
	(N = 121)	(N = 53)	(N = 42)	(N = 107)	(N = 202)
Objective response rate (ORR)[1]					
ORR (95% CI)	77 (68, 84)	38 (25, 52)	31 (18, 47)	49 (39, 59)	42 (35, 49)
CR	*15 (12.4)*	*2 (3.8)*	*1 (2.4)*	*8 (7.5)*	*11 (5.4)*
PR	*78 (64.5)*	*18 (34.0)*	*12 (28.6)*	*44 (41.1)*	*74 (36.6)*
SD	*19 (15.7)*	*18 (34.0)*	*10 (23.8)*	*33 (30.8)*	*61 (30.2)*
PD	*4 (3.3)*	*11 (20.8)*	*15 (35.7)*	*17 (15.9)*	*43 (21.3)*
NE	*1 (0.8)*	*3 (5.7)*	*0 (0.0)*	*2 (1.9)*	*5 (2.5)*
Missing	*4 (3.3)*	*1 (1.9)*	*4 (9.5)*	*3 (2.8)*	*8 (4.0)*
Time to first response					
Median (range), months	1.8 (1.5, 7.4)	1.9 (1.0, 3.7)	1.9 (1.7, 5.6)	1.8 (1.6, 22.1)	1.8 (1.0, 22.1)
Duration of response (DoR)					
Median (95% CI), months	33.61 (25.46, NE)	9.30 (5.55, 12.91)	7.20 (3.71, NE)	14.75 (7.56, NE)	9.66 (7.46, 17.54)
Min, Max	1.4+, 49.7+	1.8+,38.5 +	3.5, 33.9	1.8+, 31.4	1.8+, 38.5+
KM estimated landmarks					
% (95% CI) of responses persisting ≥6 months	89 (82, 95)	63 (42, 85)	54 (27, 81)	72 (59, 84)	67 (57, 77)
% (95% CI) of responses persisting ≥12 months	76 (67, 85)	46 (22, 69)	27 (2, 52)	52 (37, 67)	47 (35, 58)
Intracranial response rate (IC-ORR)[2]	(N=14)	(N=10)	(N=6)	(N=23)	(N=39)
IC-ORR (95% CI)	86 (57, 98)	50 (19, 81)	0 (0, 46)	44 (23, 66)	39 (23, 55)
IC-CR	*3 (21.4)*	*0 (0.0)*	*0 (0.0)*	*2 (8.7)*	*2 (5.1)*
IC-PR	*9 (64.3)*	*5 (50.0)*	*0 (0.0)*	*8 (34.8)*	*13 (33.3)*
IC-SD	*1 (7.1)*	*3 (30.0)*	*2 (33.3)*	*9 (39.1)*	*14 (35.9)*

	TKI-naïve	TKI-pretreated			
IC-PD	*0 (0.0)*	*1 (10.0)*	*2 (33.3)*	*3 (13.0)*	*6 (15.4)*
IC-NE	*0 (0.0)*	*1 (10.0)*	*1 (16.7)*	*0 (0.0)*	*2 (5.1)*
IC response data missing	*1 (7.1)*	*0 (0.0)*	*1 (16.7)*	*1 (4.3)*	*2 (5.1)*
Time to first response					
Median (range), months	1.8 (1.6, 2.2)	1.8 (1.4, 10.9)	NA	1.9 (1.7, 5.5)	1.9 (1.4, 10.9)
Duration of IC response (IC-DoR)					
Median (95% CI), months	28 (23, NE)	NE (4, NE)	NA	NE (18, NE)	NE (18, NE)
Min, Max	1.9+, 35.1+	1.8+, 11.5+	NA	2.7, 26.0+	1.8+, 26.0+
KM estimated landmarks					
% of IC responses persisting ≥12 months	78	NE[3]	NA	80	75
% of IC responses persisting ≥24 months	62	NE	NA	53	50

CR= complete response; KM = Kaplan-Meier; NE = not estimable; PD; progressive disease; PR=partial response; SD=stable disease; + denotes ongoing response.

1 Confirmed responses

2 Confirmed responses. Expanded phase 2 set; phase 1 patients not pooled.

3 One of two IC-responses in EXP-2 was ongoing and had lasted more than 6 months at time of analysis.

Subgroups and sensitivity analyses

Subgroup analyses broadly showed similar efficacy amongst subgroups. Some particular groups of interest are described below.

Resistance mutations at baseline

Amongst patients with resistance mutations (n=45), 22 (49%) had an objective response, which is in line with the overall population ORR. Amongst patients with a *ROS1* G2032R mutation at baseline (n=17), ten had an objective response (59% (33, 82).

Efficacy after specific TKIs

Subgroup results for ORR by prior TKI (Table 9) does not identify a signal for differential treatment effect on this basis.

Table 9. ORR in TRIDENT-1 for subgroups based on prior ROS1 TKI (DCO 15 October 2023), per the EPAR[70]

	TKI-naïve	TKI-pretreated			
	EXP-1	EXP-2	EXP-3	EXP-4	Pre- treated (pooled)
	(N = 121)	(N = 53)	(N = 42)	(N = 107)	(N = 202)
Objective response rate (confirmed responses)		n/N % (95% CI)	n/N % (95% CI)	n/N % (95% CI)	n/N % (95% CI)
Prior crizotinib	n/a	16/41 39% (24, 56)	12/39 31% (17, 48)	40/82 49% (38, 60)	68/162 42% (34, 50)
Prior entrectinib	n/a	2/9 22% (3, 60)	6/11 55% (23, 83)	10/22 46% (24, 68)	18/42 43% (28, 59)

Patients who did not receive the recommended phase 2 dose

Amongst the dataset reviewed by FDA:[71]

- Patients treated at the recommended phase 2 dose (RP2D) accounted for 79% of the pooled EXP-1 cohort. Among the 8 patients who were treated with doses other than the RP2D, 4 demonstrated PRs, 3 demonstrated SD and one demonstrated PD.
- Patients treated at the RP2D accounted for 78.6% of the pooled EXP-4 cohort. Among the 3 patients included in the pooled EXP-4 cohort not treated at the RP2D, all patients demonstrated PRs.

Repotrectinib treatment-emergent resistance mutations

Whilst the data are of limited interpretability due to the sensitivity of ctDNA assays, serum samples were taken at baseline and again at progression for an exploratory analysis reported in the literature of paired samples with a view to investigating repotrectinib resistance mechanisms.[72]

In EXP-1 (the treatment-naïve cohort), there were 14 patients who experienced progression on repotrectinib. A *ROS1* resistance mutation was not detected for any of this group.

Amongst the other cohorts (EXP-2 -3, and -4; patients who'd all received at least one prior anti-ROS1 TKI), there were a total of 43 patients who experienced progression on repotrectinib. In this group, repotrectinib treatment-emergent resistance mutations in the *ROS1* gene were detected for six patients, as summarised in Table 10.

[70] EMA, 2024.
[71] FDA, 2023
[72] Drilon A, 2024.

The EMA notes in the EPAR that the Sponsor has committed to continuing to investigate the emergence of resistance.**Error! Bookmark not defined.**

Table 10. Emergent *ROS1* Mutations in TKI-Pretreated Patients Who Progressed on Repotrectinib.[73]

Patient	Baseline *ROS1* mutation	Emergent *ROS1* mutation	Emergent ROS1 Mutation Allele Frequency (%)	Best Overall Response
Patient 1	None	G2032R	0.2	Partial response
Patient 2	None	G2032R	0.26	Partial response
Patient 3	L2026M	G2032R	1.08	Stable disease
Patient 4	F2004I	G2032R	1.01	Stable disease
Patient 5	None	G2032R	0.82	Progressive disease
Patient 6	None	L2086F	0.32	Progressive disease

Safety

Safety analysis populations

FDA's Safety Analysis Set included all subjects who received any dose of repotrectinib in either the Phase 1 or Phase 2 portion of TRIDENT-1, and additional data were presented specific to patients who received the recommended phase 2 dose.

EMA's safety review was based on a larger data set, consisting of 565 patients who received at least one dose of repotrectinib in TRIDENT-1, including 367 patients with ROS1-positive NSCLC, 335 of whom had received the recommended phase 2 dose. EMA's safety set also included 38 paediatric patients who received at least one dose of repotrectinib in CARE.[74] The initial DCO for safety data matched the data submitted to TGA, but EMA reviewed additional safety data provided to them on request, with a DCO of 15 October 2023 (i.e. matching the DCO for the efficacy data reported above).

The CARE data are not relevant to the proposed Australian indications, and are very limited, as described in the EPAR.[75] These data do not contribute significantly to the current Australian regulatory decision.

ROS1 TKI class safety

Safety events of interest for repotrectinib, based on warnings and precautions for the two currently registered ROS1 TKI, are:[76]

- Hepatotoxicity
- Interstitial lung disease (pneumonitis)
- QT prolongation
- Bradycardia
- Vision disorders
- Congestive cardiac failure

[73] Drilon A, 2024, Supplementary Data, Table 10.
[74] EMA, 2024
[75] EMA, 2024
[76] Data from Therapeutic Goods Administration, Australian Product Information for crizotinib and Australian Product Information for entrectinib.

- Leukopenia
- Gastrointestinal perforation
- Central nervous system effects
- Including cognitive impairment, mood disorders, dizziness and sleep disturbances
- Bone effects and fracture
- Hyperuricaemia

Exposure

Amongst the 367 patients with ROS1-positive NSCLC described in the EPAR, the mean (SD) duration of exposure to repotrectinib was 12.7 (12.2) months, with a median of 9 months. A third had brain metastases at baseline according to BICR. Most (79%) were treated at the recommended phase 2 dose.

Adverse events

The adverse event profile in the study (though at different DCOs and potentially grouped differently) is summarised in the FDA label and EMA SmPC.[77,78] The most common TEAE overall was dizziness, which occurred in around 65% of patients.

The FDA summary of the safety profile is as follows:[79]

> Serious adverse reactions occurred in 35% of patients who received Augtyro. Serious adverse reactions in ≥2% of patients included pneumonia (6.3%), dyspnea (3.1%), pleural effusion (2.8%), and hypoxia (2.6%). Fatal adverse reactions occurred in 3.5% of patients who received Augtyro, including pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.
>
> Permanent discontinuation of Augtyro due to an adverse reaction occurred in 7% of patients. There were no specific adverse reactions that accounted for ≥1% of permanent discontinuations.
>
> Dosage interruptions of Augtyro due to an adverse reaction occurred in 50% of patients. Adverse reactions that required dosage interruption in ≥2% of patients were dizziness, dyspnea, muscular weakness, ataxia, pneumonia, peripheral neuropathy, anemia, and vomiting.
>
> Dose reductions of Augtyro due to an adverse reaction occurred in 38% of patients. Adverse reactions that required dosage reductions in ≥2% of patients included dizziness, ataxia, muscular weakness, peripheral neuropathy, and cognitive impairment.
>
> The most common (≥20%) adverse reactions that occurred in patients receiving Augtyro were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness and nausea.

At the latest 15 October 2023 cut-off, treatment emergent adverse events (TEAEs) had led to discontinuation in 11% of the 367 patients with ROS1-positive NSCLC; and to dose modification in 61% of patients, dose interruption in 55% of patients, and dose reduction in 38%. Serious

[77] Food and Drug Administration. Augtyro Full Prescribing Information. June 2024
[78] European Medicines Agency. Augtyro Summary of Product Characteristics.
[79] Food and Drug Administration. Augtyro Full Prescribing Information. June 2024

TEAEs were experienced by 58% of patients, and fatal TEAEs occurred in 7% of patients.[80] The FDA review concluded these were not unexpected in light of the population under study:[81]

> Overall, the deaths reported across the repotrectinib clinical program are consistent with the seriousness, complications and/or progression of the underlying malignancy (Nichols 2012), and life-threatening nature of disease under investigation.

Amongst the 565 adults who received repotrectinib in TRIDENT-1 (whether for ROS1-positive NSCLC, NTRK solid tumour, or for other tumours), two of the fatal TEAEs were recorded as possibly treatment-related according to the investigators: one case of sudden death at 10 months after commencing treatment, and one case of cardiorespiratory arrest at 11 months after commencing treatment. The Sponsor considers these unlikely to be related to repotrectinib, based on the multiple risk factors and extensive medical history for these patients, and the time course of onset of the events (after many months on treatment).[82]

At 15 Oct 2023, Grade 3 or higher events with an incidence of at least 2% were dyspnoea (7.1%), anaemia (7.6%), pneumonia (5.7%%), pulmonary embolism (3.5%), hypoxia (3.5%), pleural effusion (3.0%), blood creatine phosphokinase increased (3.8%), weight increased (4.1%), aspartate aminotransferase increased (2.5%), neutrophil count decreased (2.7%), dizziness (2.2%), and syncope (2.7%).

At 15 Oct 2023, Grade 4 adverse events were dyspnoea (7 [1.2%]), blood creatine phosphokinase increased (6 [1.1%]), respiratory failure (4 [0.7%]), hypoxia (3 [0.5%]), sepsis (3 [0.5%]), hypertriglyceridaemia (2 [0.4%]), neutrophil count decreased (2 [0.4%]) and hyperuricaemia (2 [0.4%]).

Proposed Australian Product Information

The Sponsor has included in sequence 003 version 3.0 of the Australian draft Product Information (PI). Changes have been made from previous drafts in alignment with requests from the TGA evaluator. The current draft safety section is based on the recommended phase 2 dose safety set, at the earlier DCO of 19 DEC 2022, and is reproduced in Appendix 1 for reference. The summary of adverse events presented in the draft Australian PI is a good representation of the study data. Warning and precaution text in the draft Australian PI aligns with the approved US label and EU SmPC, with the following warnings covered:

- Central Nervous System (CNS) adverse reactions (including dizziness, ataxia, cognitive disorders)
- Interstitial Lung Disease (ILD)/Pneumonitis
- Hepatotoxicity
- Myalgia with creatinine phosphokinase (CPK) elevation
- Hyperuricemia
- Skeletal fractures
- Embryofetal toxicity
- Patients on a controlled sodium diet
- Paediatric population – efficacy and safety not established

[80] EMA, 2024
[81] FDA, 2023
[82] EMA, 2024

Companion diagnostic

The NCCN guideline makes the following observations about testing for ROS1:[83]

> FISH break-apart probe methodology can be deployed; however, it may under-detect the FIG-ROS1 variant.
>
> IHC approaches can be deployed; however, IHC for ROS1 fusions has low specificity, and follow-up confirmatory testing is a necessary component of utilizing ROS1 IHC as a screening modality.
>
> Numerous NGS methodologies can detect ROS1 fusions, although DNA-based NGS may under-detect ROS1 fusions.
>
> Targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.

The EPAR also contains the following information:[84]

> For study TRIDENT-1, a prototype CDx was developed, validated, and used as a Clinical Trial Assay (CTA) in Almac's CLIA/CAP accredited laboratory. This test is a qualitative in vitro diagnostic assay that uses targeted next-generation sequencing to detect fusions in ALK, ROS1, and NTRK1-3 genes. The assay profiles RNA isolated from FFPE solid tumour tissue. The analytically validated test was granted IDE approval in May 2019 (G190086) and IRB approval in May 2019. European Conformity (CE) marking was obtained in May 2019. Originally, Almac's test was developed to be used as a CDx for Augtyro. However, it was determined that this assay is no longer the best testing option for patients in the EU, and the Sponsor has now contracted with Foundation Medicine, Inc. for the validation of a CDx assay (F1CDx) for the identification of patients that are candidates for treatment with repotrectinib.
>
> Originally, prospective central confirmation testing with the Almac test was performed for all patients in TRIDENT-1 locally tested with either FISH, qPCR or an NGS. However, the protocol was later amended, and prospective confirmatory central testing was no longer required if the test was performed locally by qPCR or NGS. Later, also retrospective central testing was omitted for patients tested locally with qPCR and NGS. Approximately half of all patients included in TRIDENT-1 did not have a confirmation by central testing with the CTA after the change in testing strategy. Most of the local testing was performed with an NGS method. However, for ROS1+ NSCLC a large proportion of patients were also included in the Phase 2 part of the study based on local qPCR test (22%).
>
> All Phase 2 patients of TRIDENT-1 locally tested for ROS1 or NTRK1/2/3 fusions by FISH were prospectively confirmed by central CTA. The 6 patients in the pooled analysis included from Phase 1 who were locally tested with FISH, were retrospectively confirmed as ROS1+.
>
> The applicant has provided information on the agreement between the results of local NGS testing and prospective central testing with the CTA which shows acceptable agreement between the tests (PPA 92.9%). Based on information from all 26 patients with local qPCR test and central CTA test, a relatively low agreement between the tests (PPA 69.2%) was shown, thus, 30% of the qPCR tested patients without central confirmation were potentially ROS1 negative but received treatment with repotrectinib.

[83] NCCN, 2025.
[84] EMA, 2024.

In Australia, companion testing for the purposes of identifying patients for treatment could be conducted using any of these methodologies. Such testing reflects the testing used in the pivotal trial and deems the results likely to have adequate external validity for an Australian population.

In light of the current recommendations for the use of an NGS panel wherever possible,[85] and the corresponding MBS funding,[86] it is likely that this methodology will be used widely in Australia going forward. Based on the underlying mechanistic rationale, rational design, and the sum of the preclinical and clinical data, if anything, patients selected using an NGS-only methodology would be expected to have better outcomes than patients selected per the testing used in TRIDENT-1, i.e. by a range of local methodologies, therefore possibly including some patients who were, as EMA put it, "potentially ROS1-negative."

It is not rational to require the medicine Sponsor to nominate a particular IVD companion diagnostic in a companion testing plan for this medicine on that basis. If a Sponsor was to seek registration for a companion diagnostic for this repotrectinib indication, they would need to provide a justification based on clinical comparability between companion diagnostic testing the TRIDENT-1 trial testing.

Real world evidence/real world data

Real-world evidence (RWE) is clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD).[87]

RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.

This application did not include a formal submission of RWD/RWE but made reference to real-world data in justifying the representativeness of the pivotal study population with regard to demographics, and in considering the therapeutic context for the proposed usage (see Discussion).

Risk management plan

The European Union RMP version 0.3 (dated 26 September 2024; DLP 15 October 2023) and ASA version 2.0 (dated 19 February 2025) were submitted and evaluated. The summary of safety concerns is presented in Table 11. The summary of safety concerns in the ASA aligns with the EU-RMP.

Table 11. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Skeletal fractures	✓	–	✓	–
Important potential risks	None	–	–	–	–
Missing information	Safety in long-term use	✓	–	–	–

[85] Cooper WA, 2025.

[86] Department of Health, Disability and Ageing. Medicare Benefits Schedule - Item 73437

[87] Food and Drug Administration. Real-World Evidence. Updated 22 September 2025.

Risk-benefit analysis

In order to make a decision that repotrectinib should be registered in Australia, the efficacy, safety and quality of the goods for the intended usage need to be established. There is no explicit requirement for particular kinds of data or comparators; establishment is based on the objective strength of information, contextualised by the existing therapeutic landscape for an indication.

The intended usage in this case is for the treatment of adult patients with ROS1-positive NSCLC, in a line-agnostic fashion. Existing therapeutic options in this setting have limitations:

- Prior to the advent of targeted therapies, platinum-based chemotherapy for biomarker-agnostic NSCLC had been associated with a median OS of 10-11 months,[88] with an increase to around 14 months with the addition of pemetrexed. The associated toxicities are well described.
- Crizotinib elicits an anti-tumour response in a large proportion of patients (probably 70-80%) in the first-line setting when used to treat ROS1-positive NSCLC, and has been associated – based on real-world data – with median OS of 40 months.[89] The magnitude of effect on response rates was such that in context of the scientific rationale and preclinical data, randomisation against chemotherapy was very challenging. A small randomised trial was conducted, and indicated further randomisation should not be undertaken, with a larger ORR and longer PFS with crizotinib than first-line platinum-pemetrexed (PFS with crizotinib 18.4 months [95% CI: 6.4, 30.3] versus PFS with platinum-pemetrexed chemotherapy 8.6 months [95% CI: 6.9-10.3] P < .001).[90] OS was confounded by crossover.
- Despite the success of crizotinib as an initial anti-ROS1 TKI, it does not cross the blood brain barrier, and CNS progression comprises a large proportion of progression on crizotinib. Also notable is the development of mutations in ROS1 that confer crizotinib resistance.
- Entrectinib is another TKI that has been registered based on similar data to crizotinib for treatment of ROS1-positive NSCLC, in large part because in being able cross the blood-brain barrier, entrectinib was able to address the need for intracranial efficacy. For patients with CNS-only progression on crizotinib entrectinib provides a treatment option. However, nonclinical data predicted it would have poor activity against ROS1 mutations known to confer crizotinib resistance including G2032R and L2026M.[91] In keeping with this, disappointing efficacy was seen amongst patients with non-CNS progression on crizotinib (with an ORR around 11%).[92]

For patients who progress on crizotinib or entrectinib, platinum-pemetrexed chemotherapy remains a valid treatment option. However, despite the lack of a direct randomised comparison, it is highly likely that repotrectinib represents at least a reasonable treatment option compared to platinum-pemetrexed chemotherapy after the failure of first-line crizotinib or entrectinib. The evidence for this includes the following:

[88] Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002;346:92-8.
[89] Nadal E, Rifi N, Kane S, Mbacke S, Starkman L, Suero B, Le H, Samjoo IA. Efficacy and safety of crizotinib in the treatment of advanced non-small cell lung cancer with ROS1 gene fusion: a systematic literature review and meta-analysis of real-world evidence. Lung Cancer. 2024 Jun;192:107816. doi: 10.1016/j.lungcan.2024.107816. Epub 2024 May 9. PMID: 38749072.
[90] Shen L, Qiang T, Li Z, Ding D, Yu Y, Lu S. First-line crizotinib versus platinum-pemetrexed chemotherapy in patients with advanced ROS1-rearranged non-small-cell lung cancer. Cancer Med. 2020 May;9(10):3310-3318. doi: 10.1002/cam4.2972. Epub 2020 Mar 13. PMID: 32167664; PMCID: PMC7221427.
[91] Chong CR, Bahcall M, Capelletti M, et al. Identification of existing drugs that effectively target NTRK1 and ROS1 rearrangements in lung cancer. Clin Cancer Res. 2017;23:204–213. doi: 10.1158/1078-0432.CCR-15-1601.
[92] Drilon, A, 2022.

- TKIs appear to have superior efficacy to chemotherapy when used in the first-line setting, as outlined above.
- The safety profile of repotrectinib is different, if not favourable, from chemotherapy.
- The proportion of patients likely to experience tumour regression with repotrectinib after one prior TKI is clinically meaningful (49% [39, 59]) and is probably similar regardless of whether crizotinib or entrectinib was used first.
- The duration of responses in the post-TKI setting (EXP-4) is clinically meaningful with a median of close to 15 months.

Therefore, the efficacy of repotrectinib for the treatment of ROS1-positive NSCLC after failure of first-line TKI is established. Whilst the proposed dose for registration (the recommended phase 2 dose/RP2D) was not a requirement for inclusion in the efficacy population, durable responses were seen in a meaningful proportion of patients who did not receive the RP2D. Whilst a source of additional uncertainty, this is not a barrier to decision.

The establishment of efficacy in the treatment-naïve setting is partially supported by the establishment of efficacy in the ROS1 TKI pre-treated setting.

The use of crizotinib or entrectinib for the treatment of TKI-naïve ROS1 fusion-positive NSCLC results in response rates around 65-80%, depending on who is conducting the assessment (BICR versus investigator) and how precise an estimate the study is powered for. The response rate seen with repotrectinib in TRIDENT-1 in treatment-naïve ROS1-positive NSCLC appears to be at least similar to these. Contextualised by the biological rationale, rational molecular design, and preclinical data, inferior effectiveness is highly unlikely (though uncertainty persists in the absence of an internal control). Despite the uncertainty inherent in cross-trial comparison, the duration of response does appear to probably be longer with repotrectinib (median DOR 34 months) than with either crizotinib (median DOR 25 months)[93] or entrectinib (median DOR 21 months).[94] It is important to acknowledge that the absence of direct comparative data at this time poses difficulties in truly understanding the relative clinical benefit of crizotinib, entrectinib and repotrectinib. However, direct comparison is currently being conducted between crizotinib and entrectinib,[95] as well as between crizotinib and repotrectinib in the first-line setting,[96] providing reassurance that uncertainties over comparative benefit are unlikely to be persistent.

Nevertheless, with crizotinib and entrectinib available in the first line setting, it could be considered contentious to accept single arm data as adequate to establish clinical benefit without direct randomised data. Whilst those therapies were both approved themselves based on single arm data, some limited randomised data comparing crizotinib and pemetrexed-platinum is available,[97] and an abundance of real-world data indicates that the observed clinical benefit in ORR and DOR translates to benefits on more traditional trial endpoints like PFS and OS. The potential for this to be contentious is mitigated, to my mind, by the presence of groups for whom existing options are severely limited, or non-existent. These groups are in keeping with the cohorts defined in TRIDENT-1, i.e.:

[93] Therapeutic Goods Administration. Australian Product Information for crizotinib. Accessed 30 April 2025
[94] Drilon, A, 2022.
[95] Hoffmann-La Roche. A Study to Compare the Efficacy and Safety of Entrectinib and Crizotinib in Participants With Advanced or Metastatic ROS1 Non-small Cell Lung Cancer (NSCLC) With and Without Central Nervous System (CNS) Metastases. ClinicalTrials.gov identifier: NCT04603807. Updated 4 November 2025.
[96] Bristol-Myers Squibb. A Study of Repotrectinib Versus Crizotinib in Participants With Locally Advanced or Metastatic Tyrosine Kinase Inhibitor (TKI)-naïve ROS1-positive Non-Small Cell Lung Cancer (NSCLC) (TRIDENT-3). ClinicalTrials.gov identifier: NCT06140836. Updated 21 November 2025.
[97] Shen, L. 2020.

- Patients with progression on either crizotinib or entrectinib, whose only option is chemotherapy (EXP-4)
- Patients who have received both a TKI and prior chemotherapy (EXP-2)
- Patients who have received two prior TKIs only (EXP-3)

Acknowledging that it is limited, there is objective evidence of clinically meaningful activity amongst these patient groups in the submitted dataset.

One important limitation relates to amendment 9 leading to Version 10.0 of the study protocol (20 OCT 2020), in which the EXP-3 inclusion criteria were modified to remove the requirement for previous treatment with one line of platinum-based chemo/immuno-therapy due to the limited activity of repotrectinib seen in the 4th line setting (2 prior TKIs + 1 line chemotherapy).

In terms of clinical safety, the toxicities of treatment with this molecule, whilst certainly not dismissible, differ to those of chemotherapy, and compare reasonably with toxicities seen for similar TKIs. CNS effects are prevalent, and account for most of the need for dose reduction or interruption. Hepatotoxicity, ILD, myalgia with CPK elevation, hyperuricaemia and skeletal fractures are proposed warnings, aligned with the US label. QT prolongation, bradycardia and congestive cardiac failure don't appear to be significant risks as for crizotinib/entrectinib, however, the potential for ocular toxicity/visual disorders with repotrectinib has been flagged as requiring additional follow-up, with an FDA post-marketing requirement issued for a study on this topic (PMR 4547-2; anticipated to be available around August 2028). The effects of moderate and severe hepatic impairment on PK are the subject of a second PMR (4547-3; anticipated to be available mid 2026). Leukopenia and gastrointestinal perforation are warnings in the crizotinib PI that have not been notable with entrectinib and repotrectinib data to date.

Additional FDA PMRs relate to clinical and PBPK DDI studies (in relation to CYP3a and P-gp inhibitors: PMR 4547-4, expected June 2026), and inhibitory effect on the PK of MATE2-K, P-gp, OATP1B1, and BCRP substrates (4547-5, expected July 2029). Additionally, post-marketing commitments are in place regarding updated data from TRIDENT-1 to improve precision of response rate and durability estimates (PMC 4547-6), application of the PBPK model to anticipate DDI with CYP3A inducers (PMC 4547-7), clinical PK trials to investigate effects on single dose PK of CYP2B6, CYP2C9, and CYP2C19 substrates (PMC 4547-8) and validation of an appropriate IVD diagnostic device (PMC 4547-9).

Fatal adverse events (7%) and permanent discontinuations due to adverse events (11%) were reported in the trial, but specific patterns of suspected treatment-related drug effects were not discernible. Deaths were for the most part in keeping with events common in an advanced NSCLC population, including a case of DIC. Thromboembolism, thrombotic microangiopathy and DIC are reported to be more common in patients with ROS-1 rearranged tumours than other NSCLC.[98]

Overall, this appears to be an adequately described safety profile for this rare condition, with a set of toxicities that are in keeping with the class and are likely to be acceptable in the context of this life-threatening condition.

Conclusions

The magnitude of response rate and durability of responses observed with repotrectinib treatment for patients with ROS1-positive NSCLC are clinically meaningful for this population with a poor prognosis. There is meaningful evidence of anti-tumour activity in patients who received one prior ROS1 TKI, two prior ROS1 TKIs or one prior ROS1 TKI and also prior

[98] Gendarme S, Bylicki O, Chouaid C, Guisier F. ROS-1 Fusions in Non-Small-Cell Lung Cancer: Evidence to Date. Curr Oncol. 2022 Jan 28;29(2):641-658. doi: 10.3390/curroncol29020057. PMID: 35200557; PMCID: PMC8870726

chemotherapy. There is meaningful evidence of anti-tumour activity in patients with intracranial disease, and there is meaningful evidence of anti-tumour activity in patients with mutations of ROS1 known to confer crizotinib resistance. This evidence supports repotrectinib as a therapeutic option for these patient subpopulations with no standard treatment options. The ORR observed in ROS1 TKI-naïve patients is comparable to the response rates observed in other approved therapies for this indication (crizotinib and entrectinib). As a package, the data supports approval of an indication that is line-agnostic

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Augtyro (repotrectinib) for the following indication:

> *Augtyro, as monotherapy, is indicated for the treatment of adult patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).*

Specific conditions of registration

Augtyro (repotrectinib) is to be included in the Black Triangle Scheme. The PI and CMI for Augtyro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The Augtyro EU-Risk Management Plan (RMP) (version 0.3, dated 26 September 2024, data lock point 15 October 2023), with Australia-Specific Annex (ASA) (version 2.0, dated 19 February 2025), included with submission PM-2024-01468-1-4, 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).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

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.

The final clinical study report from Study CA127-1030/ TRIDENT-3 should be submitted to the TGA as a Category 1 submission when available.

The final report from a prospective study to evaluate risk factors, manifestations, and outcomes associated with the signal of serious ocular toxicity with repotrectinib in patients with ROS1 positive NSCLC or solid tumours, should be submitted to the TGA as a Category 1 submission when available. (US-FDA commitment 4547-2)

The final study report from a clinical pharmacokinetic trial in non-cancer hepatically impaired subjects to evaluate the effect of moderate and severe hepatic impairment on the single dose pharmacokinetics and safety of repotrectinib, should be submitted to the TGA as a Category 1 submission when available. (US-FDA commitment 4547-3).

The final study report from a clinical pharmacokinetic trial to evaluate the effects of multiple doses of a specific strong CYP3A inhibitor and a specific P-gp inhibitor, respectively on the

single-dose pharmacokinetics and safety of repotrectinib, should be submitted to the TGA as a Category 1 submission when available (US-FDA commitment 4547-4).

The final study report from a clinical pharmacokinetic trial to evaluate the effect of multiple doses of repotrectinib on the single dose pharmacokinetics of a substrate of MATE2-K, P-gp, OATP1B1, and BCRP, should be submitted to the TGA as a Category 1 submission when available (US-FDA commitment 4547-5).

The final study report from a physiologically based pharmacokinetic (PBPK) modelling study, to assess the magnitude of decreased drug exposure with appropriate dosage recommendations of repotrectinib when concomitantly used with moderate CYP3A inducers, should be submitted to the TGA as a Category 1 submission when available (US-FDA Commitment 4547-7).

The final study report from a clinical pharmacokinetic trial to assess the magnitude of decreased drug exposure, with repeat doses of repotrectinib on the single dose pharmacokinetics of a substrate of CYP2B6, CYP2C9, and CYP2C19, should be submitted to the TGA as a Category 1 submission when available (US-FDA Commitment 4547-8).

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Appendix

Table A1. Comparison of methods of diagnostic testing for ROS1 gene mutation

	Test description	Strengths and limitations
FISH	Also known as 'break-apart' FISH. Fluorescent labels are attached to either end of the ROS1 gene (red at one end, green at the other – usually at the kinase end). Normal expression results in a yellow signal, as the two labels emit light from the same spot in the cell. Gene rearrangement results in separation of the signals in the genetic material, appearing as separate red and green dots, or in the case of a deletion as just a single coloured dot remaining.	Fast but provides limited information (what fusion partner, where the break is). High specificity. Good sensitivity, but: May not detect minimally-displaced changes, e.g. intrachromosomal deletion GOPC–ROS1 fusion variant;[99] and unable to detect other mutations or epigenetic mechanisms (e.g. rearrangements at transcriptional level, alternative transcript initiation).
IHC	Tissue slides are incubated with a monoclonal antibody that binds ROS1,[100] conjugated to a molecule that allows visualisation by staining. Staining intensity is used semi-quantitatively to estimate ROS1 expression. ROS1 is absent from normal lung tissue but reactive pneumocytes and osteoclasts may stain positive, so a positive tumour control is mandatory. [101] Sensitivity of IHC is reportedly 94% to 100% with specificity of 76% to 100%, but this is dependent on the cut-off for 'positive', which varies. Increasing the cut-off to 3+ increases specificity but reduces sensitivity.[102]	Fast Cheaper than FISH. Good sensitivity. Not as specific as FISH: prone to false positives, and results are subject to inter-observer variability.

[99] Savic S, Bubendorf L. Acta Cytol. 2012;56(6):611–621
[100] Sholl LM, Sun H, Butaney M, Zhang C, Lee C, Jänne PA, Rodig SJ. Am J Surg Pathol. 2013 Sep;37(9):1441-9. doi: 10.1097/PAS.0b013e3182960fa7. PMID: 23887156; PMCID: PMC3831351.
[101] Luk PP, Selinger CI, Mahar A and Cooper WA (2018) Archives of Pathology & Laboratory Medicine: August 2018, Vol. 142, No. 8, pp. 922-928. https://doi.org/10.5858/arpa.2017-0502-RA
[102] Luk PP, 2018.

	Test description	Strengths and limitations
RT-PCR	Quantitative RT-PCR estimates expression of a gene based on RNA in a sample. RNA is reverse-transcribed into complementary (cDNA), which is then amplified through a series of rounds of polymerase chain reaction using a heat-sensitive DNA polymerase and primers that flank the specific gene of choice. Incorporation of labelled probes at each round of amplification allows quantitation of the RNA of interest, proportional to the amount of RNA that was initially present. Multiplex designs may allow multiple analytes to be assessed in the one assay.	Slow, sequencing large amounts not feasible. More expensive than FISH and IHC. Good sensitivity but relies on primer selection (unknown fusions may not be identified). Good specificity. Limited by requiring high quality RNA – this is not always available, especially from formalin-fixed, paraffin-embedded samples.
NGS	DNA or RNA sample is directly sequenced. Large scale sequencing (e.g. whole gene, whole chromosome, or whole genome) is made faster by cutting up the DNA into small fragments, sequencing them all simultaneously (in parallel), and then reassembling the sequence by automated assembly of contiguous sequences. The genetic sequence of the tumour can be compared to a normal control and any differences can be assessed for meaning.	Fast but more expensive than other methods. Good sensitivity and specificity. Rare or undescribed mutations are not likely to be missed. One test on one sample may be used to test for multiple genetic alterations/potential oncogenic drivers. This is particularly salient in NSCLC where multiple 'druggable' targets are known and tissue samples may be difficult to obtain.

FISH = fluorescent in-situ hybridisation, IHC = immunohistochemistry, RT-PCR = reverse-transcription polymerase chain reaction, NGS = next-generation sequencing.

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Reference/Publication #