

## 5.03 ENTRECTINIB, Capsule 200 mg, Rozlytrek<sup>®</sup>, Roche Products Pty Ltd.

### 1 Purpose of submission

- 1.1 The submission requested an Authority Required listing for entrectinib for the treatment of locally advanced (Stage IIIB) or metastatic (Stage IV) c-ros proto-oncogene 1 (ROS1)-positive non-squamous or not otherwise specified (NOS) non-small cell lung cancer (NSCLC). A streamlined co-dependent submission was lodged concurrently with the Medical Services Advisory Committee (MSAC) for a minor amendment to Medicare Benefits Schedule (MBS) item 73344, to allow testing for ROS1 gene rearrangement for access to either crizotinib or entrectinib on the Pharmaceutical Benefits Scheme (PBS). The co-dependent submission will be considered by MSAC at its April 2020 meeting.
- 1.2 A PBS listing was requested on the basis of a cost-minimisation analysis between entrectinib and crizotinib. The key components of the clinical issue addressed by the submission are summarised below.

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

Component	Description
Population	Patients with c-ros proto-oncogene 1 (ROS1) positive, locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC.
Intervention	Entrectinib 600 mg (three 200 mg capsules) daily until progression or unacceptable toxicity.
Comparator	Crizotinib 250 mg (one 250 mg capsule) twice daily until progression or unacceptable toxicity.
Outcomes	Objective response rate (ORR), progression free survival (PFS), overall survival (OS), Quality of life (QoL) and treatment-related adverse events CNS outcomes (including time to CNS nervous system progression, CNS objective response rate and CNS duration of response) have been presented for the entrectinib studies. Limited CNS ORR outcomes have been reported in the crizotinib studies.
Clinical claim	In patients with ROS1-positive, locally advanced or metastatic NSCLC, entrectinib is non-inferior to the main comparator crizotinib based on key systemic efficacy outcomes (ORR, PFS and OS). Entrectinib has demonstrated a non-inferior, but different safety profile relative to crizotinib.

Source: Table 1.1, p16 of the submission.

CNS = central nervous system; NSCLC = non-small cell lung cancer.

### 2 Background

#### **Registration status**

- 2.1 Therapeutic Goods Administration (TGA) status at the time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. The requested TGA indication was for the treatment of patients with ROS1-positive, locally advanced or metastatic NSCLC. The TGA Clinical Evaluation Report (CER) was received on 29

January 2020 and the TGA Delegate’s Overview was provided prior to the March 2020 PBAC Meeting.

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

### 3 Requested listing

3.1 The proposed restrictions are provided below.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ENTRECTINIB 200 mg capsule, 90	1	1	\$7,280.42 published price \$TBC <sup>a</sup> effective price	ROZLYTREK Roche Products Pty Ltd
Category/Program:	General Schedule			
PBS indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC			
Treatment phase:	Initial treatment			
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing			
Clinical criteria:	<ul style="list-style-type: none"> <li>The treatment must be as monotherapy, <b>AND</b></li> <li>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, <b>AND</b></li> <li>Patient must have a WHO performance status of 2 or less, <b>AND</b></li> <li>Patient must have evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, <b>AND</b></li> <li>Patient must not have received prior treatment with a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor for this condition, <b>OR</b></li> <li>Patient must have developed intolerance to a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor necessitating permanent treatment withdrawal.</li> </ul> <p>The authority application must be made in writing and must include:                      (1) a completed authority prescription form; and                      (2) a completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.</p>			
Treatment phase:	Continuing treatment			
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone			
Clinical criteria:	<ul style="list-style-type: none"> <li>The treatment must be as monotherapy, <b>AND</b></li> <li>Patient must have previously received PBS-subsidised treatment with this drug for this condition, <b>AND</b></li> <li>Patient must not develop disease progression whilst receiving PBS-subsidised treatment with this drug for this condition.</li> </ul>			
Treatment phase:	Grandfathering treatment			
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing			
Clinical criteria:	<ul style="list-style-type: none"> <li>Patient must have received treatment with entrectinib for this condition prior to [the PBS listing date], <b>AND</b></li> <li>The treatment must be as monotherapy, <b>AND</b></li> <li>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, <b>AND</b></li> <li>Patient must have a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with this drug for this condition, <b>AND</b></li> <li>Patient must not have progressive disease; <b>AND</b></li> </ul>			

	<ul style="list-style-type: none"> <li>• Patient must have evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, <b>AND</b></li> <li>• Patient must not have received prior treatment with a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor for this condition, <b>OR</b></li> <li>• Patient must have developed intolerance to a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor necessitating permanent treatment withdrawal.</li> </ul> <p>The authority application must be made in writing and must include:                  (1) a completed authority prescription form; and                  (2) a completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p>
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<sup>a</sup> TBC = to be confirmed.

3.2 The submission proposed a published dispensed price for maximum quantity (DPMQ) for entrectinib equal to the published DPMQ for crizotinib, which would result in the same cost per 30-days of treatment with either entrectinib or crizotinib. The submission also proposed that the effective price for entrectinib would be no higher than the cost-minimised effective price for crizotinib, based on their equi-effective doses.

3.3 The proposed PBS restrictions for initial and continuing entrectinib treatment were very similar to the current listing for crizotinib for this condition. The submission stated that an additional clinical criterion was specified, that would preclude the use of entrectinib following crizotinib (unless the patient had developed intolerance to crizotinib). This was to ensure the appropriate use of entrectinib, in line with the available clinical evidence. Two of the entrectinib studies presented in the submission (ALKA and STARTRK-1) permitted patients who had received prior treatment with crizotinib or ceritinib to enrol. The submission stated that an assessment of the clinical efficacy of entrectinib in the 25 patients with solid tumours (6 ROS1-positive and 19 anaplastic lymphoma kinase (ALK)-positive) in these studies who had received prior treatment with a ROS1 inhibitor (crizotinib) or an ALK inhibitor (crizotinib or ceritinib) showed no objective response (i.e. no clinical activity). Based on this evidence, the PBAC considered the inclusion of a criterion excluding the use of entrectinib in patients who have progressed on or following treatment with crizotinib to be appropriate. Further, the PBAC noted that FDA and the National Comprehensive Cancer Network (NCCN) treatment guidelines<sup>1</sup> places entrectinib alongside crizotinib as the preferred first-line treatment for patients with ROS-1 positive NSCLC, while subsequent therapy with other ROS1 inhibitors is not recommended for patients with disease progression after treatment with crizotinib or entrectinib.

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<sup>1</sup> National Comprehensive Cancer Network (Version 7.2019) – Clinical Practice Guidelines in Oncology

- 3.4 The submission suggested that similar changes to the clinical criteria for crizotinib for this indication would be appropriate. Ku et al (2019)<sup>2</sup> reported that entrectinib-resistant HCC78 cells exhibited cross-resistance to other ROS1 inhibitors (including crizotinib), and concluded that activation of the RAS signalling pathway can cause entrectinib resistance in ROS1-rearranged NSCLC, which was unlikely to be overcome by sequential single agent ROS1-targeting strategies against such tumours.
- 3.5 The submission estimated that approximately less than 10,000 patients from clinical trials and compassionate access programmes would require transfer to PBS eligible treatment. The PBAC considered the proposed clinical criteria specifying that ‘patients must not have received prior treatment with a ROS1 TKI’; OR ‘must have developed intolerance to a ROS1 receptor TKI necessitating permanent treatment withdrawal’ be redundant for the grandfather restriction.
- 3.6 The submission proposed an increase in the number of repeats that would allow patients more flexibility of follow-up with their clinicians. The ESC noted the PBAC has previously recommended an increase in the number of repeats for the alectinib, ceritinib and crizotinib ALK-positive NSCLC listings from 1 to 3 in both initial and continuing treatment phases<sup>3</sup>.
- 3.7 The submission stated that a streamlined co-dependent submission was lodged concurrently with MSAC, requesting a minor amendment to MBS item 73344 to allow testing for a ROS1 gene rearrangement for access to entrectinib. The current and proposed amendment to the MBS listing for ROS1 fluorescence in situ hybridisation (FISH) testing under Item 73344 are summarised below.

**Table 2: Current and proposed amendment to MBS listing for ROS1 FISH testing under item 73344**

Category 6 – PATHOLOGY SERVICES
MBS item: 73344
Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small-cell lung cancer (NSCLC), which is of non-squamous histology or histology not otherwise specified, with documented evidence of ROS proto-oncogene 1 (ROS1) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+; and with documented absence of both activating mutations of the epidermal growth factor receptor (EGFR) gene and anaplastic lymphoma kinase (ALK) immunoreactivity by IHC, requested by a specialist or consultant physician to determine if requirements relating to ROS1 gene rearrangement status for access to crizotinib or entrectinib under the Pharmaceutical Benefits Scheme are fulfilled.
Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00

Source: Table 1.8, p29 of the submission.

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

<sup>2</sup> Ku BM, Bae YH, et al. Entrectinib resistance mechanisms in ROS1-rearranged non-small cell lung cancer. Invest New Drugs. 2019.

<sup>3</sup><http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2019-11/other-matters-11-2019.docx.pdf>

## 4 Population and disease

- 4.1 Patients with ROS1-positive rearranged non-squamous or NOS NSCLC comprise approximately 1-2% of patients with NSCLC. The ROS1 gene fusion in NSCLC occurs predominantly in younger patients, females, patients who have never smoked and those of Asian ethnicity. For patients with advanced ROS1-positive NSCLC, reported central nervous system (CNS) metastasis incidence rates are high (36%) at diagnosis and associated with a poorer prognosis and quality of life.
- 4.2 Mutation detection, including ROS1, is standard of care for treatment selection in NSCLC patients. In Australia, immunohistochemistry (IHC) testing for ROS1 overexpression is performed sequentially after normal epidermal growth factor receptor test results and normal ALK test results. If ROS1 overexpression is detected by IHC, a MBS funded FISH test (MBS item 73344) is conducted to confirm ROS1-rearrangement status and enable access to targeted crizotinib therapy under the PBS.
- 4.3 The submission proposed entrectinib as an alternative treatment to crizotinib.
- 4.4 The submission claimed that there was an unmet need for an alternative ROS1 inhibitor with both systemic and demonstrated durable CNS activity, and that entrectinib has demonstrated both clinically meaningful systemic efficacy, and CNS activity, with durable intracranial objective responses. A key factor given in the submission for the rationale for listing entrectinib related to its CNS activity. While there was some data supporting the intracranial efficacy of entrectinib, in the absence of equivalent data for crizotinib, there was no comparative clinical evidence that entrectinib conferred any additional benefit over crizotinib in patients with CNS metastases. The ESC noted there was insufficient data to ascertain any magnitude of incremental benefit compared to crizotinib in relation to CNS metastases. However, the ESC noted the evidence presented for entrectinib may be suggestive of CNS activity and noted that CNS penetration of crizotinib is poor.

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

## 5 Comparator

- 5.1 The submission nominated crizotinib as the main comparator. The PBAC considered crizotinib to be the appropriate comparator.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (6) and organisations (4) via the Consumer Comments facility on the PBS website. The comments were supportive of a listing for entrectinib on the PBS and emphasised the need for alternative treatment options for patients with ROS1-positive NSCLC, particularly where patients are unsuitable or intolerant to current treatment. The comments described a range of benefits of targeted treatment with entrectinib, including prolonged survival, improved quality of life, reduced hospital visits due to more tolerable side effects compared to chemotherapy, and potential activity against CNS metastases.
- 6.3 The PBAC noted the correspondence received from Peter MacCallum Cancer Centre, Rare Cancers Australia and Lung Foundation Australia were supportive for entrectinib to be included on the PBS for patients with ROS1-positive NSCLC. The correspondence indicated that a treatment that can penetrate the CNS would be beneficial in this patient population noting that metastases often occur in the brain.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the entrectinib submission, categorising it as one of the therapies of “high priority for PBS listing” based on a published integrated analysis of the ALKA, STARTRK-1 and STARTRK-2 studies<sup>4</sup>. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale<sup>5</sup> (ESMO-MCBS) for entrectinib, which was limited to 3<sup>6</sup>(out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).

### **Clinical studies**

- 6.5 The submission was based on a naïve indirect comparison of pooled data from the relevant subgroup of patients from three single arm studies of entrectinib and four single arm studies of crizotinib.
- 6.6 The evidence for entrectinib was based on pooled data for the relevant subgroups of patients from the following three studies:
- ALKA: A phase 1, open-label, dose escalation study of entrectinib in patients with advanced/metastatic solid tumours with tropomyosin receptor kinase (TRK) A/B/C, ROS1 or ALK molecular alterations (N=58);
  - STARTRK-1: A phase 1, open-label study of entrectinib in-patient with any locally advanced or metastatic solid tumour (N=76). This study included a dose escalation segment and a dose expansion segment; and

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<sup>4</sup> Drlon A, Siena S, Dziadziuszko R, et al: Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials. *The Lancet Oncology*, 2019

<sup>5</sup> Chery NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

<sup>6</sup> ESMO MCBS Form 3 used (orphan drug where PFS/ORR are outcomes in trial)

- STARTRK-2: A phase 2, open-label study in patients with locally advanced or metastatic solid tumours harbouring a neurotrophic TRK1/2/3, ROS1, or ALK gene rearrangement (N=207).

The primary assessment of the efficacy of entrectinib was based on the ROS1 NSCLC Efficacy Evaluable Analysis Set (N=53), which included patients from all three studies (9 from ALKA, 7 from STARTRK-1, and 37 from STARTRK-2). This analysis set was defined as; ROS1-positive patients, ROS1 inhibitor-naïve NSCLC patients with measurable disease at baseline and who had  $\geq 12$  months of efficacy follow-up from onset of response, or patients who had discontinued treatment before the clinical cut-off date (CCOD)<sup>7</sup>. The decision to use this analysis set was initially made in consultation with the FDA when applying for FDA approval. This analysis set will henceforth be referred to as the entrectinib primary analysis set (PAS) throughout.

6.7 The evidence for crizotinib was based on four single arm studies:

- PROFILE 1001: A phase 1, open label, dose escalation study in patients with malignancies with c-MET amplification, c-MET activating mutations, or ALK/ROS1 molecular alterations. The total number of patients in the study could not be located. The submission presented results for the expansion cohort of patients with advanced ROS1-positive NSCLC (N=50/53)<sup>8</sup>.
- Wu 2018: A phase 2, open-label study in East Asian patients with advanced ROS1-positive NSCLC (N=127).
- EUCROSS: A phase 2, open-label study in European patients with advanced ROS1-positive NSCLC (N=34).
- METROS: A phase 2, open-label study in Italian patients with advanced NSCLC harbouring ROS1 molecular alterations, MET amplification or MET exon 14 mutations (N=52). Only data for the ROS1-positive subgroup of patients were presented in the submission (N=26).

PROFILE 1001 and Wu 2018 were presented as the primary evidence in the submission for crizotinib for the treatment of advanced ROS1-positive NSCLC considered by the PBAC at the November 2017 and July 2018 PBAC meetings, while preliminary data from EUCROSS was presented as supportive evidence.

6.8 The submission excluded one crizotinib study (AcSé study) on the basis that no full publications were identified in the literature search, noting that the PBAC had previously considered the results of this study as part of its recommendation to list

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<sup>7</sup> The submission defined this analysis set as ROS1-positive patients, and ROS1 inhibitor-naïve NSCLC patients with measurable disease at baseline and  $\geq 12$  months of follow-up from onset of response, but the TGA submission indicated that it included patients who had  $\geq 12$  months follow-up from onset of response, or had discontinued study treatment at the CCOD (p13, TGA Submission Section 2.7.3, Summary of clinical efficacy (CCOD 31 May 2018).

<sup>8</sup> 50 patients were included in the analysis set for the May 2014 data cut-off date. An additional 3 patients were included in the long-term follow-up data (data cut-off June 2018)

crizotinib for this indication. A full publication of this study was located during the evaluation (which had been published online subsequent to the date of the submission's literature search). AcSé study was a phase 2, single arm, open-label study of crizotinib in patients with MET or ROS1-positive NSCLC. Data for the ROS1-translocation cohort (N=37) are presented below, where feasible.

- 6.9 The ESC noted that the majority of patients for the entrectinib and crizotinib trials were treatment experienced at baseline, but the evidence presented in the submission was based on data mainly from the ROS1 inhibitor-naïve subgroup of patients across the studies.
- 6.10 Details of the studies presented in the submission are provided in the table below.

**Table 3: Studies and associated reports presented in the submission**

Study ID	Protocol title/ Publication title	Publication citation
<b>Entrectinib</b>		
ALKA	Clinical Study Report: A phase 1, dose escalation study of entrectinib (RXDX-101) in adult patients with advanced/metastatic solid tumors	October 2018
STARTRK-1	Clinical Study Report: a phase 1, multicentre, open-label study of oral entrectinib (RXDX-101) in adult patients with locally advanced or metastatic cancer confirmed to be positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK molecular alterations	October 2018
STARTRK-2	Interim Clinical Study Report: An open-label, multicenter, global phase II basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbor NTRK1/2/3, RSO1, or ALK gene rearrangements	November 2018
Integrated analysis of ALKA, STARTRK-1 and STARTRK-2	TGA submission Section 2.7.3: Summary of clinical efficacy (CCOD 31 May 2018) Section 2.7.4 Summary of clinical safety (CCOD 31 May 2018) Supplemental results report for entrectinib Section 2.7.3 Summary of clinical efficacy (CCOD 31 October 2018) Safety update report for entrectinib (CCOD 31 October 2018) Power point presentation: Entrectinib D75 Data summary (internal publication)	Date not provided    February 2019
<b>Crizotinib</b>		
PROFILE 1001	Shaw AT, Ou SHI, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer  Shaw AT, Riley GJ, Bang YJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001	New England Journal of Medicine 2014; 371(21): 1963-1971.  Annals of Oncology 2019; 30: 1121-1126.
Wu 2018	Wu Yi, Yang JCH, Kim DW, et al. Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small-cell lung cancer	Journal of Clinical Oncology 2018; 14(10): 1405-1411.
EUCROSS	Michels S, Massuti B, Schildhaus HU, et al. Safety and efficacy of crizotinib in patients with advanced or metastatic ROS1-rearranged lung cancer (EUCROSS): a European phase II clinical trial	Journal of Thoracic Oncology 2019; 14(7): 1266-1276.
METROS	Landi L, Chiari R, Tiseo M, et al. Crizotinib in MET-deregulated or ROS1-rearranged pretreated non-small cell lung cancer (METROS): a phase II, prospective, multicentre, two-arms trial	Clinical Cancer Research 2019; 25(24): 7312-7319.
AcSé <sup>a</sup>	Moro-Sibilot D, Cozic N, Perol M, et al. Crizotinib in c-MET- or ROS1-positive NSCLC: results of the AcSé phase II trial	Annals of Oncology: published online 4 October 2019.

Source: Table 2.2, pp40-41 of the submission

CCOD = clinical cut-off date.

<sup>a</sup> The submission did not present data from the AcSé study as only conference abstracts were publicly available when the literature search was performed (September 2019). A full publication of this study was located during the evaluation. Data for the ROS1-positive cohort have been presented where feasible.

6.11 The key features of the included evidence are summarised in the table below.

Table 4: Key features of the included evidence – indirect comparison

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Entrectinib</b>					
ALKA	58 PAS: 9 <sup>a</sup>	Single arm, OL <sup>b</sup>	High	Patients with advanced/metastatic solid tumours with TRKA/B/C, ROS1 or ALK molecular alterations.	ORR, PFS and OS
STARTRK-1	76 PAS: 7 <sup>a</sup>	Single arm, OL <sup>b</sup>	High	Patients with any locally advanced or metastatic solid tumour preferably with NTRK1/2/3, ROS1, or ALK molecular alterations.	ORR, PFS and OS
STARTRK-2	207 PAS: 37 <sup>a</sup>	Single arm, OL <sup>b</sup>	High	Patients with locally advanced or metastatic solid tumours harbouring a NTRK1/2/3, ROS1, or ALK gene rearrangement.	ORR, PFS and OS
Pooled data	53	ROS1 NSCLC Efficacy Evaluable Analysis Set <sup>c</sup> including relevant subgroups from the above three entrectinib studies. Median duration of follow-up 20.6 months (Oct 2018 data cut-off)			
<b>Crizotinib</b>					
PROFILE 1001	50/53 <sup>d</sup>	Single arm, OL, 62.6 mths	High	Patients with advanced ROS1-positive NSCLC.	ORR, PFS and OS
Wu 2018	127	Single arm, OL, 21.4 mths	High	East Asian patients with advanced ROS1-positive NSCLC.	ORR, PFS and OS
EUCROSS	34 <sup>e</sup>	Single arm, OL, 20.6 mths	High	European patients with advanced ROS1-positive NSCLC.	ORR, PFS and OS
METROS	52 ROS1: 26	Single arm, OL, 21.0 mths	High	Italian patients with advanced NSCLC harbouring ROS1 molecular alterations, MET amplification or MET exon 14 mutations. Data for the ROS1-positive subgroup of patients were presented in the submission.	ORR, PFS and OS
AcSé	90 ROS1: 37	Single arm, OL, NR	High	Patients with advanced c-MET or ROS1-positive NSCLC	ORR, PFS and OS

Source: Sections 2.3 and 2.4 of the submission.

NR = not reported; OL = open label; OS = overall survival; ORR = objective response rate; PFS = progression free survival.

<sup>a</sup> Number of patients in each study that were included in the entrectinib primary analysis set (PAS).

<sup>b</sup> The median duration of follow-up in the individual entrectinib studies has not been reported as the submission did not report results for the total study populations.

<sup>c</sup> The submission defined this analysis set as ROS1-positive patients, and ROS1 inhibitor-naïve NSCLC patients with measurable disease at baseline and ≥12 months of follow-up from onset of response, but the TGA submission indicated that it included patients who had ≥12 months follow-up from onset of response, or had discontinued study treatment at the CCOD (TGA Submission Section 2.7.3, Summary of clinical efficacy (CCOD 31 May 2018).

<sup>d</sup> 50 patients with ROS1-positive NSCLC were included in the analysis set for the May 2014 data cut-off (median follow-up 16.4 months). An additional 3 patients were included in the long-term follow-up data (data cut-off June 2018, median follow-up 62.6 months).

<sup>e</sup> Only 30/34 (86%) of patients who received at least one dose of study treatment were included in the efficacy analyses: 3 were excluded for violation of eligibility criteria, and 1 was excluded due to inadequate baseline assessment.

6.12 The risk of bias in the included studies was high, given the single arm, open-label design of the studies.

6.13 As noted above, the evidence for entrectinib was based on an integrated efficacy analysis of pooled subgroups across the three clinical studies (ALKA, STARTRK-1 and STARTRK-2). Due to the inclusion of patients from ALKA and STARTRK-1, some patients in the PAS for entrectinib did not receive the dosing regimen outlined in the draft TGA Product information (600 mg once daily). The submission claimed that, as the majority (■%) of patients (N=■) in the entrectinib PAS received 600 mg once daily, the results

were considered to be suitable for the assessment of the efficacy of entrectinib at the dosing recommended in clinical practice. The Pre-Sub-Committee Response (PSCR) provided efficacy results for the subgroup of patients who did not receive the recommended dose of 600 mg daily. The ESC noted the results were based on small patient numbers (N=█, dose below 600 mg daily and N=█, above 600 mg daily respectively).

- 6.14 There was considerable heterogeneity in terms of patient demographic, disease characteristics, and study follow-up durations, both between individual crizotinib studies, and between the crizotinib studies and the entrectinib PAS, making an assessment of comparative efficacy and safety difficult. Differences in patient characteristics included (but were not restricted to) the Eastern Cooperative Oncology Group (ECOG) performance status, the number of prior lines of therapy, the proportion of patients with CNS metastases, and the proportion of Asian patients, all of which are prognostic factors for ROS1-positive NSCLC<sup>9</sup> (Table 5). The net direction and magnitude of any bias or confounding from this heterogeneity was not possible to determine. The PSCR acknowledged the inherent transitivity issues of a naïve indirect comparison but argued that the heterogeneity between the study populations was relatively less than that of the study populations previously considered for the PBS listing of crizotinib in ROS1-positive NSCLC. The ESC considered the heterogeneity in patient populations across the entrectinib and crizotinib studies should be interpreted in the light of the rarity of the patient population, while the ESC noted that this heterogeneity may have biased in favour of entrectinib in some studies and crizotinib in others. The ESC also noted that direct comparative clinical evidence was unlikely to be available for this patient population in the near future.

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<sup>9</sup> Doebele RC, Perez L, et al. Time-to-treatment discontinuation (TTD) and real-world progression free survival (rwPFS) as endpoints for comparative efficacy analysis between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients. *Journal of Clinical Oncology*. 2019; 37.

**Table 5: Heterogeneity across the entrectinib and crizotinib studies that may confound the naïve indirect comparison of efficacy and safety**

	Entrectinib evidence base (PAS)	Crizotinib studies	Direction of bias
Duration of follow-up, median	May 2018 data cut-off: 15.5 months Oct 2018 data cut-off: 20.6 months	PROFILE 1001: 16.4 and 62.6 months <sup>a</sup> Wu 2018: 21.4 months EUCROSS: 20.6 months METROS 21.0 months AcSé NR	Unclear
Duration of treatment, median	12.1 months in the entrectinib safety analysis set (N=134)	PROFILE 1001: 14.8 and 22.4 months <sup>a</sup> Wu 2018: 18.4 months EUCROSS: NR METROS 15.2 months AcSé 11.1 months	Potential bias in safety outcomes favouring entrectinib
Confounding factors in relation to study populations			
Age, median	53 years	Ranged from 52-68 across the studies	Unclear
Ethnicity, % Asian	36%	PROFILE 1001: 42% Wu 2018: 100% EUCROSS: 6% METROS, AcSé NR	Potentially favours studies with greater % of Asians <sup>b</sup>
ECOG PS = 2	11%	PROFILE 1001: 2% Wu 2018: 0% EUCROSS: 6% METROS 4% AcSé 25%	Potentially favours crizotinib in all studies except AcSé
Prior treatment, > 1 prior regimen for advanced disease	25%	PROFILE 1001: 44% Wu 2018: 39% EUCROSS: 44% METROS 23% AcSé NR	Potentially favours entrectinib
CNS metastases	43%	PROFILE 1001: NR Wu 2018: 18% EUCROSS: 21% METROS 23% AcSé 21%	Potentially favours crizotinib
Confounding factors in relation to treatment			
Dose	■% of patients in the PAS received the appropriate dose of entrectinib. <sup>c</sup>	All patients received the TGA-recommended dose of crizotinib.	Unclear

Source: Table 2.3 pp44-47, Table 2.4 pp49-52, Tables 2.5-2.8 pp54-56, and Table 2.11 p58 of the submission; PROFILE 1001 Protocol; AcSé Protocol.

ECOG PS = Eastern Cooperative Oncology Group performance status; NR = not reported; PAS = primary analysis set.

<sup>a</sup> For the May 2014 data cut-off and October 2018 data cut-off, respectively.

<sup>b</sup> Asian ethnicity is a favourable prognostic factor in patients with NSCLC.<sup>10</sup>

<sup>c</sup> ■% of patients received a lower dose intensity, and ■% received a higher dose intensity, than the recommended dose in the proposed PI.

6.15 In addition, there is considerable potential for confounding in any naïve indirect comparison due to both observed and unobserved factors, and such an approach cannot use the event rate in a common reference arm to assess and adjust for any

<sup>10</sup> Zhou W, Christiani DC. East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. *Chin J Cancer*. 2011; 30 (5):287-92.

imbalances that may exist, based on the assumption of a constant relative effect across baseline risks.

### Comparative effectiveness

6.16 The overall survival and progression free survival results in the single arm studies of entrectinib and crizotinib are summarised below.

**Table 6: Overall survival and progression free survival outcomes in the single arm studies**

	Entrectinib	Crizotinib				
	PAS N=53 <sup>a</sup>	PROFILE 1001 N=53 <sup>b</sup>	Wu 2018 N=127	EUCROSS N=30 <sup>c</sup>	METROS N=26	AcSé N=36
Median FU (months)	20.6	62.6	21.4	20.6	21.0	NR
<b>Overall survival</b>						
Patients with event, n (%)	■ (■%)	26 (49%)	NR	NR	10 (39%)	26 (72%) <sup>d</sup>
Median OS, months (95% CI)	NE (■, NE)	51.5 (29.3, NE)	32.5 (32.5, NE)	NE (17.1, NE)	NE	17.2 (6.8, 32.8)
OS rate, % (95% CI)						
6 months	92% (■%, ■%)	91% (79%, 96%)	92% (86%, 96%)	NR	96%	NR
12 months	85% (■%, ■%)	79% (65%, 88%)	83% (75%, 89%)	83% (69%, 97%)	79%	Approximately 60% <sup>e</sup>
<b>Progression free survival</b>						
Patients with event, n (%)	■ (■%)	36 (68%)	NR	16 (53%)	14 (54%)	NR
Median PFS, months (95% CI)	19.0 (12.2, ■)	19.3 (15.2, 39.1)	15.9 (12.9, 24.0)	20.0 (10.1, NE)	22.8 (15.2, 30.3)	5.5 (4.2, 9.1)

Source: Table 2.21, p72, Table 2.24, p74, Table 2.26, p76 and Table 2.28, p78 of the submission, Moro-Sibilot 2019

CI = confidence interval; FU = follow-up; NE = not evaluable; NR = not reported; OS = overall survival; PFS = progression free survival.

<sup>a</sup> October 2018 data cut-off

<sup>b</sup> June 2018 data cut-off

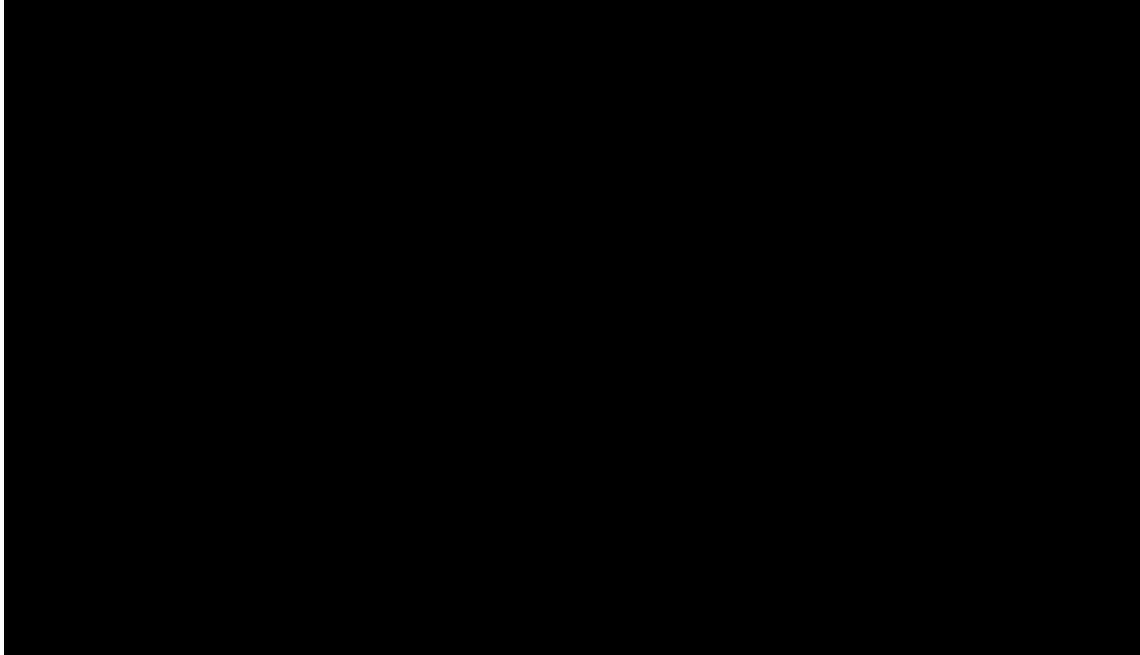
<sup>c</sup> Only 30/34 (86%) of patients who received at least one dose of study treatment were included in the efficacy analyses: 3 were excluded for violation of eligibility criteria, and 1 was excluded due to inadequate baseline assessment.

<sup>d</sup> Source: Moro-Sibilot 2019, Supplement, Figure S1 C

<sup>e</sup> Estimated from the Kaplan-Meier curves, Figure 2C, p6 Moro-Sibilot 2019.

6.17 The Kaplan-Meier (KM) plots for overall survival and progression free survival for the entrectinib PAS and the crizotinib studies, where provided, are presented below.

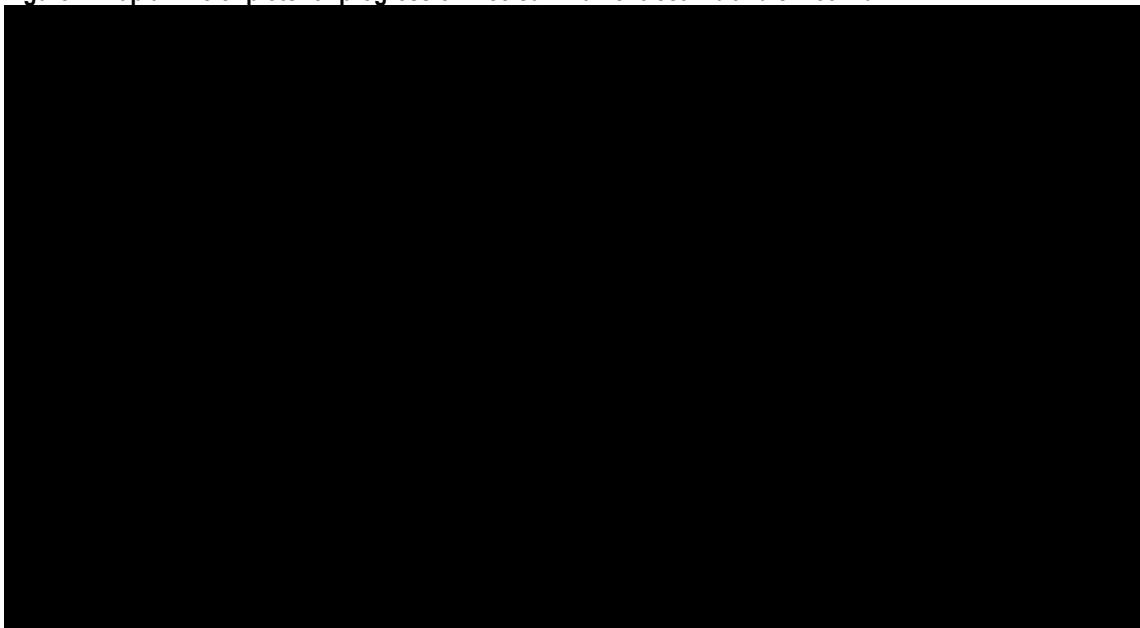
**Figure 1: Kaplan-Meier plots for overall survival: entrectinib and crizotinib**



Source: Figure 2.8, p77 of the submission; Excel workbook 'Attachment 2 ROS1 NSCLC Kaplan Meier Survival and HRQoL Plots'  
CCOD = clinical cut-off date; OS = overall survival.

Median follow-up: entrectinib integrated analysis 20.6 months, PROFILE 1001 62.6 months, EUCROSS 20.6 months, and METROS 21.0 months.

**Figure 2: Kaplan-Meier plots for progression free survival: entrectinib and crizotinib**



Source: Figure 2.7, p75 of the submission; Excel workbook 'Attachment 2 ROS1 NSCLC Kaplan Meier Survival and HRQoL Plots'  
CCOD = clinical cut-off date; PFS = progression free survival.

Median follow-up: entrectinib integrated analysis 20.6 months, PROFILE 1001 16.4 months, Wu 2018 21.4 months, EUCROSS 20.6 months, and METROS 21.0 months.

6.18 The median OS had not been reached for the entrectinib PAS. While the 12 month OS rate was similar across the entrectinib PAS and the crizotinib studies; PROFILE 1001,

EUCROSS and METROS, the duration of follow up in all studies other than PROFILE 1001, was not sufficient to reliably inform the longer-term efficacy of these treatments in terms of OS. The median survival in the entrectinib PAS, PROFILE 1001 and Wu 2018 was estimated to be greater than 30 months. The PSCR argued that the maturity of the data for clinical efficacy of entrectinib was at least consistent with that presented for crizotinib, which the PBAC had previously accepted and that the KM plots for OS and PFS showed a similar trend in survival probabilities that supports the claim of non-inferior efficacy for entrectinib. The ESC considered that based on the available evidence, it was reasonable to conclude that PFS between entrectinib and crizotinib was comparable. The ESC noted that although median OS was not reached in the entrectinib PAS, the data indicated a similar trend in the OS KM curve compared to the results for crizotinib.

- 6.19 Quality of life (QoL) data were collected in the entrectinib study STARTRK-2 and the crizotinib studies Wu 2018 and EUCROSS, using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30. In STARTRK-2 (N=37), the mean change from baseline in the global health status did not statistically differ from zero over the first 68 weeks; the results beyond this time-point were unreliable due to the small number of patients contributing to the data. In Wu 2018, while the mean change from baseline in the global health status for patients receiving crizotinib was above zero over the first 68 weeks, it was not clear whether this improvement was clinically meaningful. The change from baseline was not reported in EUCROSS. Any comparison of the QoL data across the studies should be interpreted with caution, given the considerable potential for attrition bias, the subjective nature of the outcome (and open label design of the studies), and the low number of patients contributing to the results in STARTRK-2 and EUCROSS, especially at the later time-points.

### ***Comparative harms***

- 6.20 The key adverse events (AEs) in the single arm studies are summarised below. It should be noted that in the tables of AEs in the submission, the data for Wu 2018 and METROS were AEs considered to be related to study treatment (treatment related AEs, TRAEs), while the data reported for the remaining studies were AEs regardless of causality. As Wu 2018 and METROS did not report AEs due to any cause to allow a comparison across the studies, AEs considered to be treatment-related have been reported below.

Table 7: Summary of key treatment-related adverse events in the single arm studies

	Entrectinib	Crizotinib			
	SAS <sup>a</sup> N=134	PROFILE 1001 N=53 <sup>b</sup>	Wu 2018 N=127	EUCROSS N=34	METROS N=26
Median duration of treatment, months (range)	( )	22.4 <sup>c</sup> (NR)	18.4 (0.1, 34.1)	NR	15.2 (NR)
Any TRAE, n (%)	( ) (%)	52 (98.1%)	122 (96.1%)	33 (97.0%)	26 (100%)
Grade 3-4 TRAE, n (%)	( ) (%)	16 (30.2%)	32 (25.2%)	8 (23.5%)	8 (30.8%)
Serious TRAE, n (%)	( ) (%)	2 (3.8%)	NR	5 (14.7%)	0
TRAE leading to treatment discontinuation, n (%)	( ) (%)	1 (1.9%)	1 (0.8%)	NR	3/52 (6%) <sup>d</sup>
TRAE leading to death, n (%)	( ) (%)	0	0	1 (2.9%)	0

Source: Table 2.32, p84 of the submission; Table 4, p21 Safety update report for entrectinib (CCOD 31 October 2018); Michels 2019; Table S5 and S6 Landi 2019 Supplement; European Public Assessment Report (EPAR) for crizotinib<sup>11</sup>.

NR = not reported; SAS = safety analysis set; TRAE = treatment-related adverse events

<sup>a</sup> The safety results for entrectinib were based on the ROS1-positive NSCLC analysis set (SAS), which included all patients from ALKA, STARTRK-1 and STARTRK-2 with ROS1-positive NSCLC (N=134).

<sup>b</sup> Source: Table 28, p45 EPAR for crizotinib (July 2016)

<sup>c</sup> Source: Shaw 2019

<sup>d</sup> Combined ROS1 and MET-positive cohorts (N=52)

Note: As only limited safety data were reported for AcSé (in graphical form) they have not been included in the Table.

6.21 The comparison of safety outcomes across the studies was confounded by the heterogeneity in the patient populations and differences in the duration of treatment. In addition, attribution of causality of AEs (i.e. treatment-related or otherwise) may be unreliable in single arm studies. Given these considerations, it was not possible to make any reliable conclusion regarding the comparative safety of entrectinib and crizotinib. However, the safety results suggest a numerically higher number of Grade 3-4 TRAE's for entrectinib and hence do not preclude the possibility that entrectinib may be associated with significantly more Grade 3-4 TRAEs compared with crizotinib.

6.22 In the ROS1-positive NSCLC safety analysis set (SAS) for entrectinib, the most frequent serious TRAEs (by system organ class) were: nervous system disorders ( ), cardiac disorders ( ), general disorders ( ) and vascular disorders ( ). The only serious TRAE that occurred in more than one patient in the ROS1 NSCLC SAS was pyrexia (n= , %).<sup>12</sup> The majority of deaths in the entrectinib studies were judged by the FDA reviewers as unlikely to be related to entrectinib, although the possibility of a causal relationship for entrectinib in some of the deaths could not be excluded given the single arm nature of the studies.<sup>13</sup> In the crizotinib studies, one death due to an AE in EUCROSS was considered by the investigator to be treatment-related (pulmonary embolism). Treatment-related serious AEs included bradycardia and gastrointestinal amyloidosis (each reported in one patient in PROFILE 1001), and eight events in 5 subjects in EUCROSS, including visual disturbance, diarrhoea (2 events), vomiting, pulmonary embolism, deep vein thrombosis, pneumonitis and complicated renal cyst. The ESC considered that while it was difficult to assess the comparative

<sup>11</sup> Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/xalkori#assessment-history-section>

<sup>12</sup> Source: pp177-8 Safety update report for entrectinib CCOD October 2018 - supporting data.

<sup>13</sup> Source: US Food and Drug Administration. Multi-disciplinary Review and Evaluation NDA 212725. 2019.

safety between entrectinib and crizotinib due to the issues noted in paragraph 6.21 above, it was reasonable to conclude that entrectinib has a different safety profile to crizotinib and overall, is likely to be similar to crizotinib in terms of safety.

### ***Clinical claim***

- 6.23 The submission described entrectinib as non-inferior in terms of both effectiveness and safety to crizotinib. The evaluation considered the claim was not adequately supported by the evidence presented in the submission, given the naïve indirect nature of the comparison provided, the considerable heterogeneity in the baseline characteristics between study populations, and differences in the duration of treatment and follow-up across the studies. The PSCR noted that the PBAC previously recommended the listing of crizotinib based on a naïve indirect comparison (paragraph 7.9, crizotinib, Public Summary Document (PSD), November 2017 PBAC meeting). As such, the PSCR argued that the claim of non-inferiority for efficacy and safety between entrectinib and crizotinib was adequately supported by the naïve side-by-side comparison of the clinical studies presented in the submission, given the limited capacity to conduct adequately powered head-to-head clinical trials in the context of this rare cancer.
- 6.24 The results for the main patient-relevant outcome, overall survival, were immature in a number of studies, including the entrectinib ROS1-positive NSCLC PAS from the pooled entrectinib studies.
- 6.25 The PBAC noted it was difficult to draw definitive conclusions regarding the comparative effectiveness of entrectinib and crizotinib from the available data due to the issues outlined in paragraph 6.23. However, the PBAC considered that, on balance, entrectinib and crizotinib would likely have similar efficacy overall.
- 6.26 The PBAC noted that entrectinib was associated with a numerically higher number of serious TRAEs compared with crizotinib however, considered the safety profile of entrectinib to be different to crizotinib which makes comparisons difficult. Overall, the PBAC considered that there are likely no substantive differences in safety between entrectinib and crizotinib.

### ***Economic analysis***

- 6.27 The submission presented a cost-minimisation analysis of entrectinib compared to crizotinib.
- 6.28 The submission assumed the duration of entrectinib treatment was the same as that of crizotinib and the equi-effective doses were estimated as entrectinib 600mg daily and crizotinib 250mg twice daily. The assumption of the same duration of treatment was based on the claim of non-inferiority in terms of PFS between entrectinib and crizotinib.

- 6.29 The assumed same treatment duration of entrectinib and crizotinib was uncertain because:
- There were a number of transitivity issues between the included studies, making any comparisons between them difficult to interpret;
  - The duration of follow-up differed between the cut-off points in the single arm studies, which may impact both the mean and median duration of therapy. For example, █% of patients remained on treatment at the end of follow-up in the entrectinib PAS (median follow up of 20.6 months), and 60% in the crizotinib study (PROFILE 1001 at the 16 May 2014 cut-off; median follow up of 16.4 months); and
  - The submission compared the median duration of therapy; however, it would be more appropriate to use the mean duration of therapy. Given that there were differing durations of follow-up between the studies, the evaluation considered a restricted mean analysis would be more reasonable.
- 6.30 The PSQR noted that data for the mean duration of treatment were not available for any of the crizotinib studies and therefore it was not possible to present a study-based CMA using the mean duration of treatment for entrectinib and crizotinib.
- 6.31 The submission did not include any additional costs or cost-offsets in the cost-minimisation analysis.
- 6.32 The submission presented a cost-minimisation analysis using the published price of crizotinib based on an in-principle agreement that there is no difference in the effective ex-manufacturer prices of entrectinib and crizotinib. The results of cost-minimisation analysis are summarised below.

**Table 8: Results of the cost-minimisation analysis for entrectinib versus crizotinib**

Drug	Strength (mg)	Pack Quantity	Daily dose (mg)	Total mg per pack	Days of treatment per pack	Max qty packs	AEMP	DPMQ
Crizotinib	250	60	500	15,000	30	1	\$7,128.30 <sup>a</sup>	\$7,280.42
Entrectinib	200	90	600	18,000	30	1	\$7,128.30 <sup>a</sup>	\$7,280.42

Source: Table 3.4, Section 3 of the submission

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

<sup>a</sup> The Sponsor is not privy to the effective ex-manufacturer price of crizotinib. The submission therefore based the cost-minimisation analysis and financial estimates on the published dispensed price of crizotinib.

- 6.33 The PBAC previously considered that the cost per patient of crizotinib in the ROS1-positive setting should be the same as the ALK-positive setting. The price of crizotinib is therefore weighted between the ALK-positive and ROS1-positive patient populations, to account for the different observed treatment duration (paragraph 5.25, Crizotinib, PSD, July 2018 PBAC meeting). The PBAC recommended the cost-minimised ex-manufacturer price of entrectinib should be based on the ex-manufacturer price for crizotinib in the ROS1-positive patient population.

### Drug cost per patient

- 6.34 The drug cost per patient of entrectinib is \$ [REDACTED]. This was based on the published DPMQ of crizotinib (\$7,280.42) and mean duration of entrectinib treatment of [REDACTED] months (estimated by the area under the curve of the extrapolated time to off treatment data from the entrectinib PAS). The submission assumed that the cost per patient with entrectinib and crizotinib is the same.
- 6.35 The average duration of therapy with entrectinib in the financial estimates was based on the area under the curve of the extrapolated time to off treatment (TToT) data from the entrectinib ROS1-positive PAS. As in the cost-minimisation analysis, the submission assumed that the average duration of treatment with crizotinib would be the same as entrectinib. Whether or not the exponential parametric function was the most appropriate to extrapolate TToT remains uncertain, as the submission failed to explore the use of alternative parametric functions. However, given that the submission has assumed the same treatment duration of crizotinib and entrectinib, the actual duration of therapy does not have an impact on the estimated financial impact of listing entrectinib.

**Table 9: Drug cost per patient for entrectinib and crizotinib**

	Entrectinib trial dose and duration	Entrectinib financial estimates	Crizotinib trial dose and duration	Crizotinib financial estimates
Mean dose	600 mg (three 200mg capsules) daily until progression or unacceptable toxicity <sup>g</sup>		Crizotinib 250 mg (one 250 mg capsule) twice daily until progression or unacceptable toxicity	
Mean duration	[REDACTED] months at 31 October 2018 cut off (median follow up 20.6 months; [REDACTED]% still on treatment at cut-off date)	[REDACTED] months <sup>a</sup> ([REDACTED] scripts)	NR <sup>e</sup>	[REDACTED] months <sup>f</sup> ([REDACTED] scripts)
Cost/patient/month <sup>b,c,d</sup>	\$7,387	\$7,387	NR <sup>e</sup>	\$7,387
Cost/patient/course <sup>a,b,d</sup>	\$ [REDACTED]	\$ [REDACTED]	NR <sup>e</sup>	\$ [REDACTED]

Source: Compiled during the evaluation based on information presented in Section 4.2 and Table 2.13, Section 2 of the submission. NR = not reported.

<sup>a</sup> Area under the curve of the extrapolated time to off treatment (TToT) data from the entrectinib ROS1-positive primary analysis set.

<sup>b</sup> Published dispensed price. The submission stated that this cost-minimisation was presented on an in-principle agreement that there is no difference in the effective ex-manufacturer price of entrectinib and the effective ex-manufacturer price of crizotinib.

<sup>c</sup> Assuming one month is equal to  $(365.25/12) = 30.44$  days

<sup>d</sup> Assuming an average dose of 600 mg daily (three 200mg capsules), consistent with the draft Product Information.

<sup>e</sup> Mean duration of crizotinib in the included crizotinib studies was not reported in the study publications. The median duration of treatment ranged from 15 months to 22.4 months, although between 22% and 35% remained on treatment at the end of follow up.

<sup>f</sup> Assuming that crizotinib has the same treatment duration as entrectinib.

<sup>g</sup> Some patients in the entrectinib primary analysis set did not receive the dosing regimen outlined in the draft TGA Product information (600 mg once daily), with only [REDACTED]% of patients in the entrectinib primary analysis set receiving the proposed dose.

### Estimated PBS usage & financial implications

- 6.36 This submission was not considered by DUSC.
- 6.37 The submission used an epidemiological approach to estimate the number of patients who would be eligible for entrectinib. The PBAC considered this approach was

appropriate given that crizotinib only became available on the PBS in January 2019 and its usage data in the proposed population were not yet mature.

6.38 The key inputs for financial estimates are summarised below.

**Table 10: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Lung cancer incidence	AIHW (2019) incidence for 2015 and Cancer Australia (2019) for 2018, extrapolated using a linear function.	This figure appeared slightly higher than that estimated by the AIHW for 2020 and 2021, although this had limited impact on the overall estimated patient population.
Proportion of patients with NSCLC	86.6%, based on Mitchell (2013).	This appeared reasonable.
Proportion of patients diagnosed with Stage IIIB and Stage IV disease	65.5% based on Mitchell (2013)	This data source was reasonable, and consistent with previous PBAC decision making (Table 2, PD-L1 Stakeholder Meeting Outcome Statement, February 2019)
Proportion of patients diagnosed at stage IIIA disease	11.8% based on Mitchell (2013).	
Proportion of Stage IIIA disease that progresses to Stage IIIB or Stage IV over one year	60% based on Table 17, Pembrolizumab PSD, November 2018 PBAC meeting	
Proportion of patients with non-squamous or NOS disease	74.2% based on Paragraph 6.63, Nivolumab PSD, November 2016 PBAC meeting	
Proportion of patients with PS of 0-2	80.1% based on Mitchell (2013).	This proportion was based on all NSCLC patients, not just those with non-squamous disease (23.2% of NSCLC patients in Mitchell et al 2013 had squamous histology).
Proportion of patients ROS1-positive	1.6%, based on Paragraph 6.1, Crizotinib PSD, July 2018 PBAC Meeting.	This is a proportion of all patients with NSCLC, not patients with non-squamous NSCLC with a performance status of 0-2.
Market share	█%, █% and █% in Years 1-3 of listing, increasing to █% in years 4-6.	It is unclear whether entrectinib will capture █% of the TKI market in this patient population. However, this will not impact on the cost to the PBS if the duration of therapy is equivalent.

Source: Compiled during the evaluation based on information presented in Section 4.2 of the submission.

AIHW = Australian Institute of Health and Welfare; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand-1; PS= performance status; PSD = public summary document

6.39 Although some of the parameters used to derive the estimated patient population are uncertain, there is no impact on the financial estimates given that the submission has assumed a one-to-one substitution of crizotinib for entrectinib, and a cost-minimised price between these two therapies.

6.40 The estimated use and financial implications of an entrectinib PBS listing are summarised below (based on the published price of crizotinib).

**Table 11: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed <sup>a</sup>	█	█	█	█	█	█
<b>Estimated financial implications of entrectinib</b>						
Cost to PBS/RPBS less copayments	\$█	\$█	\$█	\$█	\$█	\$█
<b>Estimated financial implications for crizotinib</b>						
Cost to PBS/RPBS less copayments	\$█	\$█	\$█	\$█	\$█	\$█
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$0	\$0	\$0	\$0	\$0	\$0

Source: Table 4.8 and Table 4.15, Section 4 of the submission

<sup>a</sup> Assuming █ scripts per patient as estimated by the submission. The submission assumed the full █-month treatment course would be dispensed in the first year of listing. This was incorrect.

*The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 patients, and the estimated number of scripts dispensed was less than 10,000 scripts.*

- 6.41 The submission stated that all eligible patients are expected to be treated with crizotinib and there would be no increase in the market due to the PBS listing of entrectinib. The ESC agreed with the submission that no market growth for ROS1 inhibitors was expected with the addition of entrectinib on the PBS. However, the ESC noted that there may be a small increase in patient numbers if patients who were intolerant of crizotinib were treated with, and were tolerant of, entrectinib.
- 6.42 The submission estimated that less than 10,000 patients on the access program would be eligible for grandfathering under the proposed PBS restriction. The submission has appropriately treated these patients as current prevalent patients, eligible for crizotinib in the analysis.
- 6.43 The submission estimated that there would be no additional cost to the PBS from the listing of entrectinib since the cost of entrectinib will be fully offset by the substituted cost of crizotinib. The PBAC considered that uncertainty around the assumption of the same duration of treatment for entrectinib and crizotinib is unlikely to have a significant impact on the estimated financial implications of listing entrectinib given the small patient population.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required listing of entrectinib as monotherapy for the treatment of patients with locally advanced (Stage IIIB) or metastatic (Stage IV) c-ros proto-oncogene 1 (ROS1)-positive non-squamous or not otherwise specified (NOS) non-small cell lung cancer (NSCLC). The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of entrectinib would be acceptable if it were cost-minimised against crizotinib.

- 7.2 The PBAC considered there was a clinical need for alternative treatment options for patients with ROS1-positive NSCLC, particularly for patients who are unsuitable or intolerant to crizotinib.
- 7.3 The PBAC considered it would be appropriate to restrict entrectinib to ROS1 inhibitor naïve patients and patients who have developed intolerance to a ROS1-inhibitor given the evidence indicating a lack of response in patients who received previous treatment with a ROS1 inhibitor (see paragraph 3.3). The PBAC noted there would also need to be flow-on restriction changes to the current listing for crizotinib to restrict use to patients who have not received treatment with a ROS1 inhibitor or patients who have experienced intolerance to previous treatment with a ROS1 inhibitor.
- 7.4 The PBAC considered crizotinib to be the appropriate comparator as nominated in the submission.
- 7.5 The PBAC noted the submission was based on a naïve indirect comparison of pooled data (primary analysis set, PAS) for the subgroup of ROS1-positive NSCLC patients (N=53) from three single arm entrectinib studies (ALKA, STARTRK-1 and STARTRK-2) and four single arm crizotinib studies: PROFILE 1001 (N=53); Wu 2018 (N=127); EUCROSS (N=34); and METROS (N=26). The PBAC noted it was difficult to interpret evidence given the nature of a naïve indirect comparison and considerable heterogeneity across the single arm studies of entrectinib and crizotinib (see paragraph 6.14). However, on balance, the PBAC considered it would be reasonable to conclude that entrectinib is non-inferior to crizotinib in terms of efficacy noting the PFS and 12 month OS rates were comparable across the entrectinib PAS and crizotinib studies. The PBAC noted that while median OS had not been reached for the entrectinib PAS, the available data indicated that the trajectory of the OS KM curve for entrectinib PAS would be similar to that for the crizotinib studies. The PBAC considered the available evidence should be interpreted in the context of the rarity of the patient population, and acknowledged that further data to inform a comparison between entrectinib and crizotinib was unlikely to be forthcoming.
- 7.6 The PBAC noted that CNS metastases are associated with poor prognosis in ROS1-positive NSCLC and that CNS penetration with crizotinib is generally poor. The PBAC noted that while the data presented indicated that entrectinib is clinically active in the CNS, there was insufficient evidence to determine whether clinically meaningful improvements in outcomes for patients with CNS metastases would result from treatment with entrectinib noting the number of patients with CNS metastases at baseline in the entrectinib PAS was small.
- 7.7 The PBAC noted that entrectinib was associated with a numerically higher number of serious adverse events compared with crizotinib. However, the PBAC noted that drawing definitive conclusions regarding the comparative safety of entrectinib and crizotinib was difficult given the difference in treatment durations, heterogeneity across the study populations, issues around the attribution of causality of adverse events (see paragraph 6.21) and the different safety profiles of the two drugs. Overall,

- the PBAC considered there are likely no substantive differences in safety between entrectinib and crizotinib.
- 7.8 The equi-effective doses proposed in the submission were entrectinib 600 mg daily and crizotinib 250 mg twice daily, based on a claim of non-inferiority in terms of PFS between the two drugs and an assumption that the average duration of treatment with entrectinib would be the same as crizotinib. The PBAC considered it was reasonable to assume that the average duration of treatment would be the same for both drugs given the point estimates for median duration of treatment and PFS were similar between entrectinib and crizotinib. In this regard, the PBAC accepted the equi-effective doses and cost-minimisation approach taken in the submission.
- 7.9 The PBAC noted that whether the listing of entrectinib on the PBS will be cost-neutral to government health budgets is dependent on the assumption of the same average treatment duration for entrectinib and crizotinib. The PBAC considered that while there was some uncertainty around this assumption, any impact on the financial implications of listing entrectinib would likely be minimal given the rarity of the disease. The PBAC considered that there would likely be negligible market growth from the PBS listing of entrectinib.
- 7.10 The PBAC recalled its November 2019 recommendation to increase the number of repeats for alectinib, ceritinib and crizotinib from 1 to 3 in both initial and continuing treatment phases (paragraph 4.1, alectinib and crizotinib PSD, November 2019). The PBAC considered this change should be applied to all tyrosine kinase inhibitors including entrectinib for consistency.
- 7.11 The PBAC recommended that a grandfather listing be in place for a period of 12 months to transition approximately less than 10,000 patients from clinical trials and compassionate access programmes to PBS-subsidised use.
- 7.12 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* entrectinib should not be treated as interchangeable with any other drugs on an individual patient basis.
- 7.13 The PBAC advised that entrectinib is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that the Early Supply Rule should not apply.
- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because entrectinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over crizotinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by *the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.16 The PBAC advised that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
ENTRECTINIB entrectinib 200 mg capsule, 90	NEW	1	90	3	Rozlytrek®	Roche Products Pty Ltd

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – In Writing
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Indication:</b> Stage IIIB (local advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) <b>Treatment Phase:</b> Initial treatment <b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>▪ The treatment must be as monotherapy <b>AND</b></li> <li>▪ The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC <b>AND</b></li> <li>▪ Patient must have a WHO performance status of 2 or less <b>AND</b></li> <li>▪ Patient must have evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing <b>AND</b></li> <li>▪ Patient must not have received prior treatment with a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor for this condition; or</li> <li>▪ Patient must have developed intolerance to a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor necessitating permanent treatment withdrawal.</li> </ul>
<b>Prescribing Instructions:</b> The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.
<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to:  Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
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Public Summary Document – March 2020 PBAC Meeting

<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Indication:</b> Stage IIIB (local advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>▪ The treatment must be as monotherapy</li> <li><b>AND</b></li> <li>▪ Patient must have previously received PBS-subsidised treatment with this drug for this condition</li> <li><b>AND</b></li> <li>▪ Patient must not have developed disease progression while being treated with this drug for this condition</li> </ul>
<b>Administrative Advice:</b> Applications for authorisation under this criterion may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – In Writing Only
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Indication:</b> Stage IIIB (local advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment Phase:</b> Grandfather treatment
<b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>▪ Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [insert listing date]</li> <li><b>AND</b></li> <li>▪ The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC</li> <li><b>AND</b></li> <li>▪ The treatment must be as monotherapy</li> <li><b>AND</b></li> <li>▪ Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with this drug for this condition</li> <li><b>AND</b></li> <li>▪ Patient must not have developed disease progression while being treated with this drug for this condition</li> <li><b>AND</b></li> <li>▪ Patient must have evidence of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing prior to initiating non-PBS subsidised treatment with this drug for this condition</li> </ul>
<b>Prescribing Instructions:</b> The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.  A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.

**Administrative Advice:**

This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](http://www.servicesaustralia.gov.au)

Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at [www.servicesaustralia.gov.au/hpos](http://www.servicesaustralia.gov.au/hpos)  
Or mailed to:

Services Australia  
Complex Drugs  
Reply Paid 9826  
HOBART TAS 7001

**8.2 Flow-on changes to crizotinib in ROS1-NSCLC:**

*Add the following clinical criterion into the initial treatment listing*

**Clinical criteria:**

Patient must not have received prior treatment with a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor for this condition; or

Patient must have developed intolerance to a c-ROS proto-oncogene 1 (ROS1) receptor tyrosine kinase inhibitor necessitating permanent treatment withdrawal.

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **9 Context for Decision**

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

## **10 Sponsor's Comment**

Roche welcomes the PBAC's decision to recommend entrectinib for patients with advanced ROS1-positive NSCLC and are working with the Department of Health towards a PBS listing at the earliest opportunity.