5.07 LORLATINIB, Tablet 25 mg, 100 mg, Lorviqua®, Pfizer Australia Pty Ltd

1 Purpose of Application

1.1 The submission requested a Section 85 Authority Required listing for lorlatinib for the treatment of patients with metastatic (Stage IV) anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC), who have disease progression following treatment with a prior ALK inhibitor.

1.2 The basis for the submission was a cost-minimisation analysis (CMA) against alectinib 600 mg twice daily (BID). The key components of the submission are summarised in Table 1. While the submission nominated ceritinib as a secondary clinical comparator, it was not included in the CMA.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with ALK-positive metastatic (Stage IV) NSCLC previously treated with one or more ALK-TKIs
Intervention	Lorlatinib 100 mg film-coated tablets orally QD
Comparator	Main: alectinib[a]; Secondary: ceritinib[b]; Potential near market comparator: brigatinib[c]
Outcomes	Objective tumour response rates (ORR); intracranial objective response (IC-ORR); duration of response (DOR); intracranial duration of response (IC-DOR); progression-free survival (PFS); overall survival (OS); patient reported outcomes (PROs); safety
Clinical claim[d]	Alectinib: non-inferior efficacy and safety

QD = once a day
Source: Table 1.1.1, p4 of the submission; ceritinib TGA PI and FDA prescribing information; brigatinib FDA prescribing information.
Abbreviations: ALK = Anaplastic lymphoma kinase; FDA = Food and Drug Administration; TGA = Therapeutic Goods Administration.
Notes:
[a] The dose of alectinib is 600 mg capsules orally BID (total daily dose: 1,200 mg).
[b] The ceritinib PI stated (p1) that the recommended dose of ceritinib is 450 mg taken orally once daily with food at the same time each day. However, the dose of ceritinib was 750 mg in the trial evidence presented in Section 2 of the submission.
[c] The dose of brigatinib according to the US FDA 180 mg orally QD, with a 7-day lead in at 90 mg QD (total daily dose: 90 mg for first 7-days, then 180 mg).
[d] The submission also claimed non-inferior efficacy and safety compared with ceritinib and brigatinib.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing criteria are added in italics and suggested deletions are crossed out with strikethrough.

2.2 The requested listing is presented below.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LORLATINIB				Lorviqua® Pfizer Australia Pty Ltd
25 mg tablet, 90	1	1	$[redacted] (Published)	
100 mg tablet, 30	1	1	$[redacted] (Published)	

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic)
Condition:	~~A~~non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Streamlined
Treatment criteria:	~~Must be treated by a medical practitioner~~
Clinical criteria:	The treatment must be as monotherapy, AND *The patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement,* *AND* The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND Patient must have a WHO performance status of 2 or less, AND ~~The condition must have progressed following treatment with a prior ALK inhibitor *crizotinib and at least one other ALK inhibitor*;~~ OR *The condition must have progressed following treatment with an ALK inhibitor other than crizotinib;OR* Patient must have developed intolerance to a prior ALK inhibitor of a severity necessitating permanent treatment withdrawal.

Population criteria:	~~Patient must have prior evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as ≥ 15% positive cells by fluorescence in situ hybridisation (FISH) testing.~~
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LORLATINIB				Lorviqua® Pfizer Australia Pty Ltd
25 mg tablet, 90	1	1	$[redacted] (Published)	
100 mg tablet, 30	1	1	$[redacted] (Published)	

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic)
Condition:	~~A~~*n*on-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Streamlined
Treatment criteria:	~~Must be treated by a medical practitioner~~
Clinical criteria:	The treatment must be as monotherapy, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND ~~Patient must not have progressive disease.~~ *Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition*.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

2.3 The submission proposed that a special pricing arrangement (SPA) apply to lorlatinib, as the proposed comparators are subject to SPAs.

2.4 The PBS listings for crizotinib, alectinib and ceritinib are line-agnostic (not restricted to a line of therapy), whereas the requested listing for lorlatinib was for patients who have progressed on treatment with an ALK-Tyrosine Kinase Inhibitor (TKI). However, the PBAC noted that the requested PBS restriction for lorlatinib would allow its use as second-line therapy post crizotinib, which is broader than the proposed TGA

indication, based on the single arm phase 1/2 Study B7461001 (study 1001 from herein).

2.5 It was unclear how the criterion that a "Patient must have developed intolerance to a prior ALK inhibitor of a severity necessitating permanent treatment withdrawal" would be met. Lorlatinib is a pharmacological analogue of its nominated main comparator (alectinib); hence, access based on prior intolerance would be expected to be limited. However, the Pre-Sub-Committee-Response (PSCR) argued that lorlatinib should be made available to the minority of patients who may be affected, given the differences in pharmacological action and safety profile to other ALK-TKIs, and the rates of discontinuation due to adverse events seen in trials for those drugs.

2.6 The proposed listing for lorlatinib required prior evidence of ALK gene rearrangement by fluorescence in situ hybridisation (FISH) testing, in order to access PBS-subsidised treatment. Currently, FISH testing for ALK status is funded by the Medicare Benefits Scheme (MBS) under Item 73341, for access to crizotinib, ceritinib or alectinib under the PBS.

2.7 The submission requested grandfathering for an estimated less than 10,000 patients receiving compassionate supply at the time of submission.

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

3 Background

Registration status

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA delegate's summary was available. The TGA delegate proposed provisional approval, with an indication for the treatment of patients with ALK-positive advanced NSCLC whose disease has progressed on:

- crizotinib and at least one other ALK inhibitor; or
- alectinib as the first ALK inhibitor therapy; or
- ceritinib as the first ALK inhibitor therapy.

3.2 The TGA delegate's decision to approve this indication has been made on the basis of tumour response rate and duration of response in the single arm phase 1/2 study (Study 1001), and noted that continued approval of this indication is contingent on clinical benefit in a confirmatory study, CROWN (i.e. Study B7461006), where results are expected in [redacted], and to be assessed by the TGA in [redacted]. An additional prospective single arm study of patients who have progressed after treatment with alectinib or ceritinib was requested by the European Medicines Agency (EMA), where results are expected in June 2024.

3.3 The confirmatory trial, the Phase III CROWN of lorlatinib compared with crizotinib is being conducted in the first-line setting, which is not consistent with the requested

listing (second-line and subsequent-line settings) being sought in this submission. The Economics Sub-Committee (ESC) considered that the applicability of the CROWN Phase III results was not really a confirmatory trial (being used in the first-line, rather than the second-line setting) and was further limited by the fact that alectinib has become the current guideline recommended standard of care in the first-line setting. Nonetheless, the ESC considered that the results would be informative (the TGA delegate noted that the study design will allow indirect comparison of lorlatinib against other ALK-TKIs through cross-trial analyses).

Previous PBAC consideration

3.4 A summary of the evidence submitted for the listing of ALK-TKIs on the PBS is provided in the table below.

Table 2: Summary of evidence submitted for ALK positive NSCLC

	Crizotinib (Nov 2014)	Ceritinib (Nov 2016)	Alectinib (Jul 2017)	Brigatinib (Nov 2019)	Lorlatinib (Nov2019)
Requested PBS restriction	2nd line (after platinum)	2nd line (after TKI i.e. crizotinib)	2nd line (after TKI i.e. crizotinib, ceritinib)	Locally advanced or metastatic ALK positive NSCLC.	2nd line and subsequent line.
TGA approval at time of submission	No restriction on line of therapy.	2nd line	2nd line	2nd line	2nd line (under the TGA provisional pathway)
Evidence presented to PBAC	2nd line (after platinum) (RCT)	2nd line (RCT)	2nd line (single arm)	[redacted]	2nd line and subsequent line (single arm)
PBAC decision	No restriction on line of therapy	No restriction on line of therapy	No restriction on line of therapy	NA	NA

Source: compiled during the evaluation.
Abbreviations: ALK = anaplastic lymphoma kinase; TKI = tyrosine kinase inhibitor; NA = not applicable; NSCLC = non-small cell lung cancer; ITC = indirect treatment comparison; RCT = randomised controlled trials; TGA = Therapeutics Good Administration; PBAC = Pharmaceutical Benefits Advisory Committee.

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

4 Population and disease

4.1 ALK rearrangements are found in approximately 3-5% of cases of advanced NSCLC and are a distinct molecular subtype of lung cancer. Brain metastases are common in patients with ALK-positive metastatic NSCLC. Central nervous system (CNS) metastases are associated with a reduction in quality of life and reduced life expectancy compared with other metastatic sites, and treatments required for CNS disease control (corticosteroids, surgery, and radiation) are associated with considerable morbidity.

4.2 Most patients who are ALK-positive initially respond to ALK inhibitors, but ultimately experience disease progression within one to two years, potentially due to secondary ALK mutations (Gainor et al., 2016). The use of each ALK inhibitor is associated with the development of a distinct spectrum of ALK resistance mutations, most of which

are difficult to treat and are more common after treatment with second-generation ALK inhibitors (Fontana et al., 2015; Gainor et al., 2016).

4.3 Lorlatinib is a selective, brain penetrant, third-generation tyrosine kinase inhibitor that targets ALK and ROS1. Lorlatinib was developed to address mechanisms of resistance following previous treatment with ALK inhibitor. The NCCN clinical practice guidelines (version 4, 2019) and ESMO guidelines (Planchard et al 2019) recommended lorlatinib be used after alectinib, ceritinib or brigatinib as second-line therapy or after crizotinib as first-line and at least one second-generation ALK-TKI as second-line in the clinical management algorithm.

4.4 The submission argued that there is an urgent need for additional targeted treatments with broader mutational coverage and CNS penetration, given the lack of clinical trial evidence for currently available ALK-TKIs following disease progression on a second-generation ALK-TKI. The ESC considered that clinical efficacy of lorlatinib against ALK resistance mutations was not adequately supported by evidence in the submission.

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

5 Comparator

5.1 The submission nominated alectinib as the main comparator, ceritinib as a secondary comparator, and brigatinib as a near market comparator. The nomination of comparators was based on pharmacological class, and lorlatinib was expected to substitute for alectinib and ceritinib under the PBS.

5.2 Alectinib is considered to be the preferred TKI as first-line therapy in clinical guidelines and the PBS statistics suggested alectinib was the therapy used most in both the first-line and post crizotinib settings. Therefore, lorlatinib would most likely be used following progression on either first-line or second-line alectinib given the clinical management algorithm for current practice and the intended use of lorlatinib.

5.3 The PSCR argued that current clinician preference is for patients who have progressed on alectinib to seek compassionate access to lorlatinib. The PSCR also reiterated that there is a lack of clinical trial evidence for use of chemotherapy in this specific population and treatment setting (ALK-positive NSCLC patients previously treated with an ALK-TKI).

5.4 The ESC noted that alectinib has become established as the standard of care among both TKI naïve and crizotinib refractory patients and the rapid uptake of alectinib since its PBS listing, and decline of ceritinib in the same period. The ESC recalled that alectinib was recommended on a cost-minimisation basis compared with ceritinib 750 mg and noted that the ceritinib dosing has been subsequently revised to 450 mg, based on pharmacokinetic data. Accordingly, the use of ceritinib at a dose of 450 mg is less costly than alectinib.

5.5 The ESC considered that lorlatinib would replace chemotherapy or displace it to a later line of treatment given the proposed listing includes second or later-line access of treatment. However, the ESC considered that use of chemotherapy in this setting would be relatively low, given poor survival outcomes at this late stage of disease.

5.6 The ESC agreed that brigatinib would likely be an appropriate near market comparator for lorlatinib.

5.7 The PBAC recalled that ceritinib was listed on a cost-minimisation basis against platinum chemotherapy followed by pemetrexed maintenance therapy (ceritinib Public Summary Document (PSD), Nov 2016) and alectinib on a cost-minimisation basis against ceritinib (alectinib PSD, July 2017).

5.8 The PBAC considered the possibility of ceritinib as a comparator and acknowledged the change in recommended dose of ceritinib to 450 mg daily (noting that the efficacy data for ceritinib are at the 750 mg dose). The Secretariat further examined the utilisation and the average daily dose for ceritinib based on PBS administrative claims data. The market share summary for the most recent 12 months at the time of analysis (1 October 2018 to 30 September 2019) showed the number of scripts of ceritinib comprising 3.3% (n=104) of the total scripts for ALK inhibitors (n=3163) in NSCLC. Since its first listing on the PBS, the median daily dose of ceritinib has been 750 mg (mean daily dose of 786.2 mg).

5.9 The PBAC also considered chemotherapy as a potential comparator, and noted the view put forward by the ESC that use of chemotherapy in this setting would be low.

5.10 The PBAC reviewed the settings where lorlatinib is likely to be used, i.e. following treatment with an ALK inhibitor other than crizotinib (typically alectinib); and following treatment with crizotinib and another ALK inhibitor (again typically alectinib). In both settings, potential comparators would include available ALK inhibitors that had not yet been used (such as ceritinib) and also regimens involving chemotherapy. That is, the PBAC considered that lorlatinib would generally not be used instead of alectinib, but after it. The PBAC also noted distinct limitations in clinical data about ALK inhibitors post-alectinib. On balance, the PBAC took a pragmatic view that the cost-effectiveness of lorlatinib could be informed by a comparison with alectinib.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician emphasised that lorlatinib addresses an unmet clinical need in the treatment of ALK-positive NSCLC, offering high brain permeability in targeting CNS metastases and activity against secondary ALK mutations, where almost all patients relapse due to drug resistance. In response to a

question from the Committee about the sequencing of ALK inhibitors, the clinician highlighted that recent evidence supports the paradigm of treatment with ALK-TKIs until patients become refractory to ALK targeted treatment as patients with TKI resistance may still respond to other TKI therapy. Further, the clinician noted that a lower incidence of serious adverse events was observed with lorlatinib use in practice, with a manageable toxicity profile including hypercholesterolaemia, hypertriglyceridemia and oedema; the clinician reported no concern with cognitive adverse effects.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (118) and organisations (4) via the Consumer Comments facility on the PBS website. The comments highlighted the need for additional treatment options post alectinib to be on the PBS, and described a range of benefits of treatment with lorlatinib including improved quality of life, acceptable safety profile, delaying the initiation of chemotherapy and a longer overall survival.

6.3 The PBAC noted the advice received from Lung Foundation Australia, Rare Cancers Australia, and Centre for Community-Driven Research supported the PBS listing of lorlatinib that would likely provide clinically meaningful PFS and quality of life for patients with ALK-positive NSCLC.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the lorlatinib submission, categorising it as one of the therapies of "high priority for PBS listing" based on the pivotal evidence from Study 1001 (Solomon et al[1]). The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale[2] (ESMO-MCBS) for lorlatinib, which was limited to 3[vii3] (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).

Clinical trials

6.5 The submission was based on a naïve comparison of ten studies:

- Lorlatinib: one single arm study (Study 1001, subgroups: EXP-2 to EXP-5, N=198);
- Alectinib: two single arm studies (NP28761, N=87 and NP28673, N=138) and one single arm from an RCT compared with chemotherapy (ALUR, alectinib arm, N=72);

[1] Solomon BJ, Besse B, Bauer TM, et al: Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 19:1654-1667, 2018

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

[3] [vii]Form 3 used (orphan drug where PFS/ORR are outcomes in trial)

- Ceritinib: three single arm studies (ASCEND-1, N=163, ASCEND-2, N=140 and ASCEND-9, N=20) and one single arm from an RCT compared with chemotherapy (ASCEND-5, ceritinib arm, N=115); and
- Brigatinib: two single arm studies (Gettinger 2016, subgroup, N=79; ALTA, N=222).

6.6 All studies enrolled patients with locally advanced (Stage IIIB) or metastatic (Stage IV) ALK-positive NSCLC previously treated with an ALK-TKI.

6.7 The pivotal studies for alectinib reviewed by the PBAC were NP28761 and NP28673 (alectinib PSD, July 2017). At the time of PBAC review in July 2017, results for the Phase III RCT, ALUR were unpublished, and only available via a media statement released by the sponsor (paragraph 6.6, alectinib PSD, July 2017). Data for ALUR were not considered in the PBAC's deliberations, as the data were not independently evaluated (paragraph 7.8, alectinib PSD, July 2017). The pivotal study for ceritinib was a Phase III RCT, ASCEND-5. Single arm trials of ceritinib, ASCEND-1 and ASCEND-2 were reviewed as part of the evaluation for alectinib (paragraph 6.8, alectinib PSD, July 2017). The PBAC has not reviewed ASCEND-9 as this study was not available at the time of PBAC consideration for alectinib (Hida 2018).

6.8 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Lorlatinib studies		
Study 1001	Phase 1/2 Study of PF-06463922 (an ALK/ROS-1 Tyrosine Kinase Inhibitor) in Patients with Advanced Non-Small Cell Lung Cancer Harbouring Specific Molecular Alterations. Protocol number: B7461001. Interim Clinical Study Report, data cut-off: 15 March 2017. Efficacy Update Report, data cut-off: 02 February 2018. 120-day Safety Update Report.	22 November 2017 18 July 2018 08 March 2018
	Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study.	*Lancet Oncology* 2018; 19(12): 1654–1667.
	Shaw A, Felip E, Bauer T, et al. Lorlatinib in ALK- or ROS1-rearranged non-small cell lung cancer: an international, multicenter, open-label phase 1 trial.	*Lancet Oncology* 2017; 18(12): 1590–1599.
	Bauer T., Shaw A., Johnson M et al. Brain Penetration of Lorlatinib and Cumulative Incidence Rates for CNS and Non-CNS Progression from a Phase 1/2 Study.	*Journal of Thoracic Oncology* 2018; Conference: IASLC 19th World Conference on Lung Cancer; 13(10 Supplement): S382–S383.
	Shaw A.T., Solomon B.J., Besse B et al. ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer.	*Journal of Clinical Oncology* 2019; 37(16): 1370–1379.
Alectinib studies		
NP28761	Shaw A, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small cell lung cancer: A single-group, multicentre, phase 2 trial.	*Lancet Oncology* 2016; 17(2): 234–42.
	Ou S-H., Socinski M.A., Gadgeel S. et al. Patient-reported outcomes in a phase II, North American study of alectinib in patients with ALK-positive, crizotinib resistant, non-small cell lung cancer.	*ESMO Open* 2018; 3(5): doi: 10.1136/esmoopen-2018-000364
	Gadgeel S.M., Gandhi L, Riely G.J. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study.	*Lancet Oncology* 2014; 15(10): 1119–28.
	Camidge D.R.; Gadgeel S.; Ou S.-H. et al. Updated efficacy and safety data from the phase 2 NP28761 study of alectinib in ALK-positive non-small-cell lung cancer.	*Journal of Thoracic Oncology* 2017; Conference: 17th World Conference of the International Association for the Study of Lung Cancer; 12(1 Supplement): S378.
NP28673	Ou S, Ahn J, Govindan R, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small cell lung cancer: A phase II global study.	*Journal of Clinical Oncology* 2016; 34(7): 661–68.
	Barlesi et al. Updated efficacy and safety from the global phase II NP28673 study of alectinib in patients (pts) with previously treated ALK+ non-small-cell lung cancer (NSCLC).	*Annals of Oncology* 2016; 27 (Supplement 6): vi416–vi454.
NP28761/NP28673 Pooled study data	Gadgeel SM, Shaw AT, Govindan R, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer.	*Journal of Clinical Oncology* 2016; 34(34): 4079–4085.
	Yang J, Ou S-H, MD, De Petris L, et al. Pooled Systemic Efficacy and Safety Data from the Pivotal Phase II Studies	*Journal of Thoracic Oncology* 2017; 12(10): 1552–1560.

Trial ID	Protocol title/ Publication title	Publication citation
	(NP28673 and NP28761) of Alectinib in ALK-positive Non-Small Cell Lung Cancer.	
	Gadgeel SM, Shaw AT, Barlesi F et al. Cumulative incidence rates for CNS and non-CNS progression in two phase II studies of alectinib in ALK-positive NSCLC.	*British Journal of Cancer* 2018; 118(1): 38–42.
	Ou S.-H., Gandhi L., Shaw A.; et al. Updated pooled analysis of CNS endpoints in two phase II studies of alectinib in ALK+ NSCLC.	*Journal of Thoracic Oncology* 2017; Conference: 17th World Conference of the International Association for the Study of Lung Cancer; 12(1 Supplement): S377.
	Ou S.-H.I., Gandhi L., Gadgeel S.M. et al. Pooled overall survival and safety data from the pivotal phase II studies (NP28673 and NP28761) of alectinib in ALK-positive nonsmall cell lung cancer (NSCLC).	*Journal of Clinical Oncology* 2018; Conference: 2018 Annual Meeting of the American Society of Clinical Oncology; 36(15 Supplement): 9072.
ALUR	Novello S, Mazières, J et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer: results from the phase III ALUR study.	*Annals of Oncology* 2018; 29(6): 1409–1416.
	Mazieres J., Novello S., De Castro J. et al. Patient-reported outcomes and safety from the phase III ALUR study of alectinib vs chemotherapy in pre-treated ALK+ NSCLC.	*Journal of Thoracic Oncology* 2017; Conference: 18th World Conference on Lung Cancer of the International Association for the Study of Lung Cancer; 12(11 Supplement 2): S1897.
Ceritinib studies		
ASCEND-1	Kim DW, Mehr R, Tan, D, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial.	*Lancet Oncology* 2016; 17(4): 452–63.
	Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer.	*The New England Journal of Medicine* 2014; 370(13): 1189–1197.
	Shaw A., Kim D., Solomon B.; et al. Ceritinib in anaplastic lymphoma kinase (ALK)+NSCLC patients pretreated with only crizotinib: ASCEND-1 subgroup analysis.	*Journal of Thoracic Oncology* 2017; Conference: 18th World Conference on Lung Cancer of the International Association for the Study of Lung Cancer; 12(11 Supplement 2): S1896–7.
ASCEND-2	Crino L, Ahn MJ, De Marinis F, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non–small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2.	*Journal of Clinical Oncology* 2016; 34(24): 2866-73.
ASCEND-5	Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial.	*Lancet Oncology* 2017; 18(7): 874-86.
	Mok T.S.K., Scagliotti G., Kim T.M. et al. Patient-reported outcomes (PROs) in ASCEND-5: A randomized, phase 3 study of ceritinib vs chemotherapy (CT) in patients (pts) with advanced anaplastic lymphoma kinase rearranged (ALK+) NSCLC previously treated with CT and crizotinib (CRZ).	*Annals of Oncology* 2016; Conference: ESMO Asia Congress 2016; 27(Supplement 9): ix142-ix143.
ASCEND-9	Hida T, Seto T, Horinouchi H, et al. Phase II study of ceritinib in alectinib-pretreated patients with anaplastic lymphoma	*Cancer Science* 2018; 109(9): 2863–2872.

Trial ID	Protocol title/ Publication title	Publication citation
	kinase-rearranged metastatic non-small-cell lung cancer in Japan: ASCEND-9.	
Brigatinib studies		
ALTA	Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive-non-small-cell lung cancer: A randomized, multicentre Phase II trial.	*Journal of Clinical Oncology* 2017; 35(22): 3490–2498.
	Ahn M., Camidge D.R., Tiseo M. et al. Brigatinib in crizotinib-refractory ALK+ NSCLC: Updated efficacy and safety results from ALTA, a randomized phase 2 trial.	*Journal of Thoracic Oncology* 2017; Conference: 18th World Conference on Lung Cancer of the International Association for the Study of Lung Cancer; 12(11 Supplement 2): S1755–S1756.
	Camidge D.R., Ahn M., Reckamp K. et al. Hypertension with brigatinib: Experience in ALTA, a randomized phase 2 trial in crizotinib-refractory ALK+NSCLC.	*Journal of Thoracic Oncology* 2017; Conference: 18th World Conference on Lung Cancer of the International Association for the Study of Lung Cancer; 12(11 Supplement 2): S1893.
	Langer CJ, Huang H, Huang J, et al. Patient-reported outcomes and quality of life in ALTA: the randomized phase 2 study of brigatinib (BRG) in advanced ALK+ non-small cell lung cancer (NSCLC).	*Journal of Clinical Oncology* 2017, 35(15)
	Ou S.-H.I., Tiseo M., Camidge R.; et al. Intracranial efficacy of brigatinib (BRG) in patients (Pts) With crizotinib (CRZ)-refractory anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) and baseline CNS metastases.	*Annals of Oncology* 2017; Conference: 42nd ESMO Congress; 28(Supplement 5): v480-v481.
Gettinger 2016	Gettinger SN, Bazhenova LA, Langer CJ, et al. Activity and safety of brigatinb in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial.	*Lancet Oncology* 2016; 17(12): 1683–96.
	Bazhevona et al. Brigatinib (BRG) in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC): Long-term efficacy and safety results from a phase 1/2 trial.	*Annals of Oncology* 2017; Conference: 42nd ESMO Congress; 28(Supplement 5): v479-v480.
Analyses of ALTA and Gettinger 2016	Bazhenova L., Hodgson J.G., Langer C.J. et al. Activity of brigatinib (BRG) in crizotinib (CRZ)-resistant ALK+ NSCLC patients (pts) according to ALK plasma mutation status.	*Journal of Clinical Oncology* 2017; Conference: 2017 Annual Meeting of the American Society of Clinical Oncology; 35(15 Supplement): 9065
Pooled: ALTA and Gettinger 2016	Gettinger S., Kim D.-W., Tiseo M. et al. Brigatinib activity in patients with ALK+ NSCLC and intracranial cns metastases in two clinical trials.	*Journal of Thoracic Oncology* 2017; Conference: 17th World Conference of the International Association for the Study of Lung Cancer; 12(1 Supplement 1): S273-S274.

Source: Table 2.2.1 pp54-57 of the submission.

6.9 The key features of the studies are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Lorlatinib					
Study 1001	276 (Phase II)	Multicentre, single-arm, open label (Phase I: Multicentre, single-arm, open label, multi-dose, dose-escalation, safety, PK, PD exploration study) Median duration of treatment (data cut-off: 15-Mar-17): EXP-2, 8.0 months EXP-3, 7.6 months EXP-4: 7.7 months EXP-5, 8.7 months Note: study is ongoing (duration of 3 years), expected study completion date: August 2020	High	Phase II: • EXP-1: Treatment naïve (N=30). • EXP-2: PD after crizotinib (N=27). • EXP-3: PD after crizotinib or other TKI and prior chemotherapy (1 or 2 lines) (N=60). • EXP-4: PD after 2 lines of ALK inhibitor therapy/prior chemotherapy (any no. of lines) (N=65). • EXP-5: Failed 3 lines of ALK inhibitor therapy/prior chemotherapy (any no. of lines) (N=46). • EXP-6: ROS 1-positive, treatment naïve/prior chemotherapy (any no. of lines) (N=47). Subgroups presented: EXP-2, EXP-3, EXP-4 and EXP-5	ORR, IC-ORR OS PFS
Alectinib					
NP28761	87	Multicentre, single-arm, open label Median 17.0 months	High	PD on crizotinib with or without chemotherapy.	ORR, IC-ORR OS PFS
NP28673	138	Multicentre, single-arm, open label Median 21.3 months	High	PD on crizotinib with or without chemotherapy.	ORR, IC-ORR OS PFS
ALUR	107	Multicentre, randomised, active-controlled, Phase III open label study. Median safety follow-up of 6.5 months (alectinib)	Low	PD after crizotinib and chemotherapy. Single arm of RCT presented for alectinib (N=72)	ORR, IC-ORR OS PFS
Ceritinib					
ASCEND-1	163	Multicentre, single-arm, open label Median 11.1 months	High	PD after crizotinib[a] (Subgroup, N=163).	ORR, IC-ORR OS PFS
ASCEND-2	140	Multicentre, single-arm, open label Median 11.3 months	High	PD on crizotinib and chemotherapy.	ORR, IC-ORR OS PFS
ASCEND-9	20	Multicentre, single-arm, open label study in Japan.	High	PD after alectinib (and/or crizotinib) with or without chemotherapy.	ORR, IC-ORR OS PFS
ASCEND-5	231	Multicentre, randomised, active-controlled, open label study Median follow-up was 16.6 months (ceritinib arm).	Low	PD after crizotinib and chemotherapy (one or two lines). Single arm presented for ceritinib (N=115).	ORR, IC-ORR OS PFS

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Brigatinib					
ALTA	222	Multicentre, open label, randomised to one of two brigatinib doses Median follow up 7.8 months (Arm A)/ 8.3 months (Arm B).	Low	PD after crizotinib; prior chemotherapy.	ORR, IC-ORR OS PFS

Gettinger 2016	137	Multicentre, single-arm, open label, multi-dose, dose-escalation study.	High	Crizotinib naïve; PD after crizotinib; and prior chemotherapy.
				Subgroups presented for:
				• ALK-positive NSCLC (N=79)
				• Dose regimen:
				  • 90 mg→180 mg QD (N=25)
				  • 90 mg QD (N=13)
					ORR, IC-ORR
					OS PFS

Abbreviations: ALK = anaplastic lymphoma kinase; IC-ORR = intracranial objective response rate; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS=overall survival; PD = progressive disease; PFS=progression-free survival;
Source: compiled during the evaluation.
Notes: In all studies, response outcomes were assessed by both the investigator and an independent review committee.
[a] ASCEND-1 permitted enrolment of patients who were ALK-TKI naïve, but the submission and evaluation only reviewed characteristics and results for patients with ALK-TKI treatment experience.

6.10 The overall risk of bias for the open-label, single arm non-randomised studies was high; whereas the risk of bias was low in the RCTs. There is a high probability of selection bias (no allocation concealment), performance bias (no blinding of participants or personnel) and detection bias (no blinding of outcome assessment), the magnitude and direction of which cannot be determined. Given the results presented in the submission were based on a naïve comparison of single arms from the included studies, it was not possible to use the event rate in a common reference arm to assess and adjust for any imbalances in both observed and unobserved confounding factors that may exist. In addition, it was not clear how blinding of the independent review committee (IRC) was maintained or drug-relatedness to efficacy outcomes or adverse events (AEs) was assessed given these were single-arm studies.

6.11 There were issues identified in the evaluation with regards to the design of these studies that have major effects on the transitivity of the trials included in the naïve comparison. The comparison of the studies was impacted by the following limitations: differences in baseline patient demographic characteristics (e.g. ethnicity, distribution of ECOG PS, smoking history, CNS or brain metastases); the type of prior treatments received; the extent of use of study drug beyond progression (which particularly impacted on comparisons of overall survival, OS); anti-neoplastic therapies received after discontinuation of study drug; and differences in study recruitment period (the lorlatinib study was conducted more recently than the other studies and thus its patients are more likely to benefit from advances in treatment options and supportive care, which may have biased the analysis in favour of lorlatinib).

6.12 The submission stated (p116) that non-inferiority was interpreted based on the 95% confidence intervals (CIs) of the naïve comparison outcomes and supported by a matching-adjusted indirect comparison (MAIC) analysis. Non-inferiority was also

inferred based on the naïve comparison of the point estimates of the results for each outcome from each study. Reliance on the 95% CI to inform non-inferiority can bias results towards concluding no difference between treatments. As a single-arm study, Study 1001 was not designed to conclude non-inferiority.

6.13 The submission presented a post-hoc analysis – a MAIC of lorlatinib compared to alectinib, ceritinib and brigatinib based on studies presented in the naïve comparison. The key outcomes presented in the MAIC analyses were PFS and OS. In general, a MAIC can account for between trial imbalances in observed covariates, however, a MAIC cannot adjust for differences in treatment administration, co-treatments or treatment switching. Although the use of individual patient data (IPD) within a MAIC — as applied for lorlatinib in the submission — can remove or reduce observed cross-trial differences, unobserved differences may result in residual confounding. The submission used an unanchored method to conduct the MAIC whereby the absence of a common comparator arm is an important limitation, as validation of matching or the use of relative effect measures is not possible. In commenting on the use of MAICs, the NICE Decision Support Unit (DSU) noted (p14) that little is known about the reliability or the general properties of MAIC methods (relative to indirect treatment comparisons via a common reference), particularly in the context of NICE technology appraisal.

6.14 Patients treated with lorlatinib in Study 1001 were assigned statistical weights that adjust for over or under-representation, relative to that observed in each comparative evidence source. The submission claimed that there was "a good distribution of weights across the studies" (p187). The manner in which the weights in the MAIC were estimated or applied could not be verified. The means are reported in the submission and the MAIC report; variances for each baseline characteristic were not reported. Visual inspection of the histograms provided shows the distribution of the weights was skewed; with some weights as high as a factor of three.

6.15 The MAIC presented in the submission assumed (p179) that the distribution of the treatment effect modifiers did not differ between the studies. This is an implausibly strong assumption, which assumed that all prognostic variables and effect modifiers are accounted for and correctly specified. There is a possibility of residual bias due to unobserved prognostic variables and effect modifiers. The accuracy of the resulting estimates is unknown as there is no analysis of the potential magnitude of residual bias, and no indication of the degree of error in unanchored MAIC estimations. As noted by the NICE DSU, the inclusion of single-arm studies in such an analysis is thus subject to the additional assumptions and biases incurred by these study designs.

6.16 The MAIC relied on a subset of patients from Study 1001 (EXP-2, n=27; EXP-3 n=32). The submission stated (p183) that these subgroups from EXP-2 and EXP-3A were most similar to patients included in the majority of the comparator studies in terms of line of therapy. While this may be reasonable with respect to prior ALK-TKI exposure in Study 1001, it may not be reasonable with respect to prior exposure to chemotherapy.

Moreover, reliance on these subgroups greatly diminishes the sample size from which inferences of comparative effect are being drawn within the submission. Study 1001 was based on 276 patients, while results for lorlatinib in the MAIC rely on data from only 59 patients. The marked reduction of the sample size (effectively by 80%) reduced the stability of the results as inferences are heavily dependent on a smaller number of individuals.

6.17 The PSCR argued that the overall population of the study which formed the basis of the MAIC for lorlatinib (N=198) was robust in the context of this rare cancer. However, the ESC considered that it was difficult to draw meaningful conclusions in terms of PFS and OS from the MAIC analysis because the MAIC relied on a substantially small subset (N=59) of patients and the assumptions made were not justifiable. The ESC considered that the MAIC could not overcome the transitivity issues in the trials included in the naïve comparison and the inherent uncertainty of a naïve comparison, which utilised single arm studies with no connective evidence. Thus, it added very little to the primary analyses.

6.18 Moreover, the ESC noted that the submission did not provide the details of the MAIC for evaluation. Thus, it was not possible to evaluate the data included in the MAIC or the calculations applied. Upon request, a sample of the code used for the MAIC was provided by the sponsor during the evaluation. However, the ESC noted that it remained insufficient to permit adequate verification of the MAIC.

Comparative effectiveness

6.19 A summary of the effectiveness (objective response rate (ORR) and intra-cranial ORR (IC-ORR)) for lorlatinib, alectinib, ceritinib and brigatinib in patients with disease progression following treatment with a prior ALK inhibitor is provided in Table 5 and Table 6. From these results, the ESC considered that the point estimates of ORR and IC-ORR were comparable for lorlatinib, alectinib and brigatinib, but slightly lower for ceritinib – noting the naïve nature of the comparison. However, the CIs overlapped across the studies.

6.20 The primary outcome of Study 1001 was ORR by IRC. The discordance rate between IRC and investigator assessment for ORR for the pooled cohort EXP2:EXP5 was 17.8% and 25.9% for IC-ORR. Differences in response based on assessment method are observed in most of the response categories, which compromise the robustness of the data and were larger in the assessment of CNS metastases for lorlatinib treated patients (EMA report p105).

Table 5: Results of objective response rate across the single-arm studies

Regimen	Population	N	Response assessor	ORR n/N (%) (95% CI (%))	CR n/N (%)	PR n/N (%)	DOR, median months (95%CI)
Lorlatinib							
Study 1001 (02 Feb 18)	EXP-2: EXP-5	198	IRC	[redacted]/198 ([redacted]) ([redacted], [redacted])	[redacted]/198 ([redacted])	[redacted]/198 ([redacted])	([redacted], [redacted])
Alectinib							
NP28761 (27 Apr 15)	RE population	67	IRC	35/67 (52.2) (40, 65)	*0*	*35/67 (52.2)*	*13.5 (6.7, NE)*
NP28673 (*01-Feb-16*)	*ITT*	*138*	IRC	*70/138 (50.8) (41.6, 60.0)*	*NR*	*NR*	*14.1 (10.9, NE)*
NP28761/ NP28673	RE population (pooled)	189	IRC	97/189 (51.3) (44.0, 58.6)	*0*	*97/189 (51.3)*	14.9 (11.1, 20.4)
ALUR (26-Jan-17)	ITT (alectinib)	72	IRC	27/72 (37.5) (26, 50)	*0*	27/72 (37.5)	9.3 (6.9, NE)
Ceritinib							
ASCEND-1 (14-Apr-14)	FAS	163	*IRC*	*75/163 (46.0) (38.2, 54.0)*	*3/163 (1.8)*	*72/163 (44.2)*	*8.8 (6.8, 13.1)*
ASCEND-2 (26 Feb 14)	FAS	140	IRC	50/140 (35.7) (27.8, 44.2)	*0*	*50/140 (35.7)*	*9.7 (5.6, 12.9)*
ASCEND-5 (26 Jan 16)	FAS (ceritinib)	*115*	*IRC*	*45/115 (39.1) (30.2, 48.7)*	*NR*	*NR*	6.9 (5.4, 8.9)
ASCEND-9 (31 Jul 17)	FAS	20	Investigator	5/20 (25.0) (8.7, 49.1)	*1/20 (5.0)*	*4/20 (20.0)*	6.3 (3.5, 9.2)
Brigatinib							
ALTA: 90-180 mg (21 Feb 17)	ITT	*110*	*IRC*	*60/110 (55) (45, 64)*	*NR*	*NR*	*14.8 (12.6, NR)*
Gettinger 2016	FAS	71[a]	IRC	45/71 (63) (51, 75)	*NR*	*NR*	14.5 (9.0, 26.1)
(21 Feb 17)	FAS, 90→180 mg QD	25	IRC	19/25 (76) (55, 91)	*NR*	*NR*	14.9 (7.9, 33.3)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; FAS = full analysis set; IRC = independent review committee; NE = not evaluable; NR = not reported; ORR = objective response rate; PP = per protocol; PR = partial response; RE = response evaluable.

Note: Figures in italics were extracted during evaluation.

[a] NSCLC cohort (Phase I/II): (N=79), but analysis dropped 8 patients that were crizotinib naïve.

Source: Study 1001, Table 2.5.1 pp117-118, Table 2.5.3 p123, Table 2.5.7 p131, Figure 2.5.4, Figure 2.5.5, Figure 2.5.6 pp132-133 of the submission; Appendix C, Table 8 p14 and Table 10 p17 of the submission; NP28761, Shaw 2016 p238; NP28673, Barlesi 2016 (abstract), Yang 2017 p1553; Ou 2016 supplement Table S3 p16; ASCEND-1, Kim 2016 Table 2 p455, appendix table 5; ASCEND-9, Hida 2018 Table 2 p2867; ALTA, Ahn 2017, abstract.

Table 6: Results of IRC assessed IC-ORR across the studies in patients with CNS lesions at baseline

Regimen	Population	N[a]	IC-ORR n/N[b] (%) (95% CI (%))	IC-DOR median (95%CI)
Lorlatinib				
Study 1001 (02 Feb 18)	EXP-2: EXP-5	198	[redacted]	[redacted]
Alectinib				
NP28761	*CNS-lesions measurable*[c]	87	12/16 (75.0) (47.6, 92.7)	11.1 (5.8, NE)
	CNS lesions[d]	67	21/52 (40.4) (27, 55)	*11.1 (10.8, NE)*
NP28673	*CNS-lesions measurable*[c]	138	20/35 (57) (39.4, 73.7)	11.1 (7.1, NE)
	CNS lesions[d]	138	36/84 (42.9) (32.1, 54.1)	*10.3 (7.6, 11.2)*
NP28761/ NP28673	*CNS-lesions measurable*[c]	189	32/50 (64.0) (49.2, 77.1)	10.8 (7.6, 14.1)
	CNS lesions[d]	189	58/136 (42.6) (34.2, 51.4)	11.1 (10.3, NE)
ALUR	ITT, *CNS-lesions measurable*[c] (alectinib arm)	72	13/24 (54.2) (33, 74)	NR
	ITT (alectinib arm)	72	18/50 (36.0) (23, 51)	NR
Ceritinib				
ASCEND-1	CNS-lesions measurable[c], post-hoc analysis	163	10/28 (35.7) (19, 56)	11.1 (2.8, NE)
ASCEND-2	Active target lesions at baseline	140	*13/33 (39.4) (22.9, 57.9)*	*NR*
ASCEND-5	Active target lesions at baseline (ceritinib arm)	115	6/17 (35.3) (14.2, 61.7)	6.9 (2.7, 8.3)
ASCEND-9	*CNS lesions*[d]	*20*	*3/12 (25.0) (95 CI - NR)*	*11.6 (range: 4.8-23.0)*
Brigatinib				
ALTA	CNS-lesions measurable[c] 90 mg QD	112	13/26 (50.0) (95% CI – NR)	NE
	CNS-lesions measurable[c], 180 mg QD	110	12/18 (66.7) (95% CI – NR)	NR
Gettinger 2016	CNS-lesions measurable[c]	71	8/15 (53) (27, 79)	*NR*[e]
	CNS lesions non-measurable		*11/31 (35) (19, 55)*	

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; FAS = full analysis set; IC-ORR = intracranial objective response rate; IRC = independent review committee; NE = not evaluable; NR = not reported; ORR = objective response rate; PP = per protocol; PR = partial response; RE = response evaluable.

Note: Figures in italics were extracted during evaluation.

[a] N in this column denoted the total number of patients.

[b] N in this column denoted the number of patients with CNS disease.

[c] CNS-lesions measurable: based on patients with measurable CNS disease at baseline;

[d] CNS lesions: Based on patients with measurable and non-measurable CNS lesions i.e. CNS metastases at study entry

[e] Gettinger 2016 reported median duration of intracranial response was 18.9 months (5.5 to not reached; n=19; includes one patient who had a response but no scan after the response) (Table 6 p1693).

Source: Table 2.5.3 p123, Table 2.5.4 p126, Table 2.5.8 p134, Table 2.5.10 p135, Table 2.5.14 p141, Table 2.5.16 p143 of the submission.

6.21 A summary of the effectiveness (overall survival (OS) and progression free survival (PFS)) for lorlatinib, alectinib, ceritinib and brigatinib is provided in Table 7 and Table 8. The OS data for all studies were relatively immature, with only [redacted]%-[redacted]% of patients across the studies having experienced an event (i.e. death). In Study 1001 (lorlatinib), the number of death events across the cohorts ranged from [redacted]% to [redacted]% (data-cut off: 02-Feb-18). Given the small sample sizes, the results from these analyses are highly sensitive to number of events (i.e. deaths) and high rates of censoring ([redacted]%, EXP-2 to EXP-5), which biases the analysis in favour of treatment where data are less mature.

6.22 The median OS was not reached (95% CI: [redacted] months, [redacted]) in Study 1001. A total of [redacted] patients ([redacted]%) were censored for OS, most of whom ([redacted]; [redacted]%) were censored because they were alive at the cut-off date (02-Feb-18). The survival probability, for the total population, at 12 months was [redacted]% (95%CI: [redacted], [redacted]) and at 18 months was [redacted]% (95%CI: [redacted], [redacted]). For context, the ESC noted that the survival probabilities reported were comparable to that previously accepted for a cost-effective listing of crizotinib (68.9%, crizotinib PSD, March 2017).

6.23 The median PFS (IRC assessed) ranged from [redacted] months across the lorlatinib cohorts in Study 1001. At the updated data-cut off for lorlatinib (02-Feb-18), the proportion of patients censored for PFS assessment across the cohorts ranged from [redacted]% to [redacted]% (EXP2 to EXP5, [redacted]%).

Table 7: Median OS across the arms of the studies

Regimen	Population	N	Deaths, n (%)	Median OS, months (95% CI)	Median duration of follow up, months
Lorlatinib					
Study 1001 (02 Feb 18)	EXP-2: EXP-5	198	[redacted] ([redacted])	[redacted] ([redacted], [redacted])	[redacted]
Alectinib					
NP28761	ITT	87	36 (41.4)	22.7 (17.2, NE)	17
NP28673	ITT	*138*	60 (43.5)	26 (21.5, NE)	21.3
NP28761/ NP28673	ITT	225	96 (42.7)	26 (21.4, NE)	NR
ALUR	ITT (alectinib)	72	16 (22.2)	12.6 (9.7, NE)	6.5
Ceritinib					
ASCEND-1	FAS	163	63 (38.7)	16.7 (14.8, NE)	11.1
ASCEND-2	FAS	140	NR	14.9 (13.5, NE)	11.3
ASCEND-5	FAS (ceritinib)	*115*	48 (41.7)	18.1 (13.4, 23.9)	*16.6*
ASCEND-9	FAS	20	*5 (20.0)*	*NR*	*11.6*
Brigatinib					
ALTA	ITT, 90 mg QD	112	*43 (38)*	NR (20.2, NR)	16.8
(21-Feb-17)	ITT, 90→180 mg QD	*110*	*32 (29)*	27.6 (27.6, NR)	18.6
Gettinger 2016	FAS	71	NR	30.1 (21.4, NR)	NR
	FAS, 90 mg QD	13	NR	21.2 (9.9, 47.6)	NR
	FAS, 90→180 mg QD	25	NR	29.5 (21.4, NR)	NR

Abbreviations: CI = confidence interval; FAS = full analysis set; IRC = independent review committee; ITT = intention to treat; NE = not evaluable; NR = not reported; OS = overall survival.

Source: Table 2.5.6 p130, Table 2.5.12 p139, Table 2.5.18 p146 of the submission; Study 1001 CSR Table 14.2.2.6.3.1.1.1 pp814-815 and Table 14.2.2.6.3.2.1.1 pp816-817; ASCEND-9, Hida 2018 p2865 and p2867; ALTA, Ahn 2017, abstract, cut-off date 21-Feb-17; Gettinger 2016, Bazhenova 2017), abstract, cut off date 21-Feb-17.

Notes: Figures in italics were extracted during evaluation; the submission reported results for NP28761 and NP28673 were obtained from the alectinib PSD and not the publications.

Table 8: Median PFS across the arms of the studies

Regimen	Population	N	Response assessor	Patients with event, n (%)	Median PFS, months (95% CI)	Median duration of follow up months
Lorlatinib						
Study 1001 (02 Feb 18)	EXP-2: EXP-5	198	IRC	[redacted]	[redacted]	[redacted]
Alectinib						
NP28761	ITT	87	IRC	58 (66.7)	8.2 (6.3, 12.6)	*17.0*
NP28673	ITT	*138*	IRC	98 (71.0)	*8.9 (5.6, 12.8)*	*21.3*
NP28761/ NP28673	ITT	225	IRC	156 (69.3)	8.3 (7.0, 11.3)	NR
ALUR	ITT (alectinib)	*72*	IRC	*28 (38.9)*	7.1 (6.3, 10.8)	*6.5*
Ceritinib						
ASCEND-1	FAS	163	*IRC*	NR	7.0 (*5.7, 8.7*)	*11.1*
ASCEND-2	FAS	140	IRC	NR	*7.2* (*5.4, 9.0*)	*11.3*
ASCEND-5	FAS (ceritinib)	*115*	*IRC*	83 (72.0)	5.4 (4.1, 6.9)	*16.6*
ASCEND-9	FAS	20	Investigator	18 (90.0)	3.7 (1.9, 5.3)	*11.6*
Brigatinib						
ALTA	ITT, 180 mg QD	*110*	*IRC*	*45 (41)*	*16.7 (11.6, NR)*	*18.6*
(21-Feb-17)	ITT, 180 mg QD	110	*Investigator*	*55 (50)*	15.6 (11.1, 19.4)	
Gettinger 2016	FAS	71	*Investigator*	*NR*	13.2 (*9.2, 16.7*)	*NR*
(21-Feb-17)	FAS, 90→180 mg QD	25	*Investigator*	*NR*	16.3 (9.2, 28.1)	*NR*

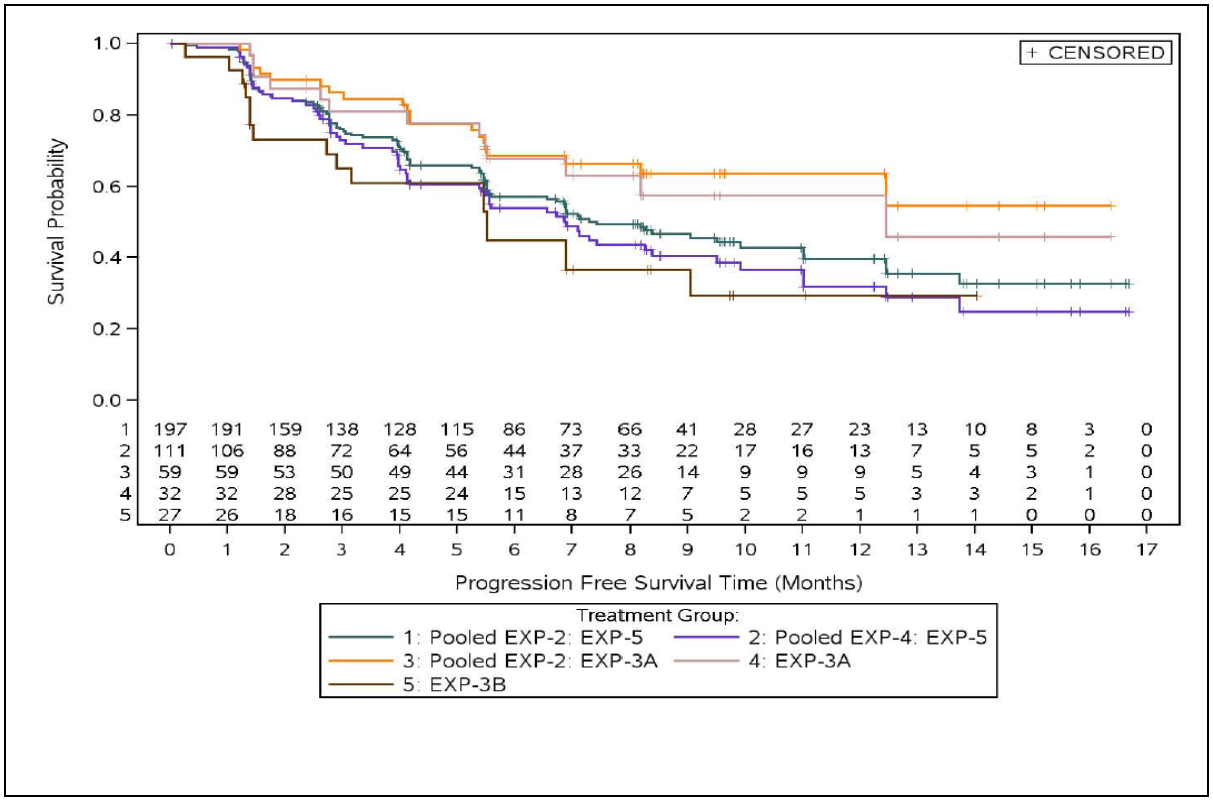
Abbreviations: CI = confidence interval; FAS = full analysis set; IRC = independent review committee; ITT = intention to treat; NE = not evaluable; NR = not reported; OS = overall survival.

Source: Table 2.5.5 pp128-119, Table 2.5.11 p136, Figure 2.5.8 p137 of the submission; Appendix C Table 12 p18 of the submission. ASCEND-1, Kim 2016 Appendix table 5 p7; ASCEND-2, Crino et al 2016, Table 2 p2869 and Figure 1C p2870; ASCEND-5, Shaw 2017 p879; ALTA, Kim 2017, Figure 2 p2494 and data supplement Fig S1 p8; Gettinger 2016, Bazhenova 2017.

Notes: Figures in italics were extracted during evaluation; the submission reported results for NP28761 and NP28673 were obtained from the alectinib PSD and not the publications.

6.24 The Study 1001 CSR and associated publication (Solomon 2018) did not report the Kaplan-Meier plots for OS. The Kaplan-Meier plot for PFS in Study 1001 is provided in Figure 1.

Figure 1: Study 1001, PFS based on ICR (Phase 2) – ITT Population, Pooled and Subgroup populations



Source: Figure 2.5.3 p129 of the submission; Study 1001 CSR Figure 17 p193.
Abbreviations: EXP = expansion; ITT = intention-to-treat.

6.25 The HRQoL results in Study 1001 showed that the majority of patients had either improved (42.7%) or stable (39.6%) global QoL during treatment (including all cycles). The results presented were for all cohorts including patients from EXP-1 (crizotinib naïve) and EXP-6 (ROS1 positive) and therefore included patients that are not relevant to the proposed listing.

Comparative harms

6.26 A summary of the safety outcomes across the single arm studies is presented in Table 9. The submission noted (p205; Appendix C p34) that there were differences in the safety profiles of lorlatinib compared to alectinib, ceritinib and brigatinib, the main differences being:

- Lorlatinib: CNS effects, hyperlipidaemia, and AV block were AEs of special interest noted in the lorlatinib draft PI and not noted for other ALK-TKIs.
- Alectinib: myalgia and creatinine phosphokinase elevation were prominent in the alectinib trials.
- Ceritinib: a boxed warning on the ceritinib PI cautions for the following SAEs: QT interval prolongation; interstitial lung disease/pneumonitis, including fatal cases;

hepatotoxicity, including drug-induced liver injury; and gastrointestinal toxicity. Ceritinib was associated with a higher incidence of Grade 3-4 diarrhoea, nausea and vomiting.

- All the other ALK-TKIs (lorlatinib, alectinib and brigatinib) have precautions pertaining to interstitial lung disease/pneumonitis in their (draft) PIs/FDA prescribing information.
- Brigatinib: pulmonary adverse reactions, hypertension, bradycardia and visual disturbance.

Table 9: Summary of key adverse events in the trials

Patients, n (%)	Lorlatinib	Alectinib				Ceritinib				Brigatinib	
	Study 1001	NP28761	NP28673	Pooled total	ALUR	ASCEND-1	ASCEND-2	ASCEND-5	ASCEND-9	ALTA[a]	
										90 mg	90→180 mg
	N= 295[d]	N=87	N=138	N=253	N=70	N=246[b]	N=140	N=115	N=20	N=109	N=110
Treatment duration (weeks)[c], mean (range)	*59.9 (0.1, 172.7)*	*51.0 (3.0, 124)*	*60.7 (2.4, 129.0)*	*56.9 (0.1, 152.6)*	Median 20.1 (0.4, 62.1)	Median 38.6 (0.4, 105.9)	Median *38.2 (0.4-84.3)*	Median 30.3 *IQR*:13.3, 54.1)	Median *16.1 (1.7, 65.7)*	*64.9 (0.1, 152.3)*	*72.1 (0.3, 170.4)*
Any AEs											
Total	294 (99.7)	87 (100)	137 (99.3)	*250 (98.8)*	54 (77.1)	246 (100)	140 (100.0)	*115 (100)*	*20 (100)*	*109 (100)*	*110 (100)*
Drug related	280 (94.9)	69 (79.3)	104 (75.4)	*197 (77.9)*	NR	238 (97)	135 (96.4)	110 (95.7)	*NR*	*89 (81.7)*	*105 (95.5)*
SAEs											
Total	*98 (33.2)*	15 (17.2)	31 (22.5)	*55 (21.7)*	13 (18.6)	117 (48)	57 (40.7)	49 (42.6)	10 (50.0)	*54 (49.5))*	*62 (56.4)*
Drug related	20 (6.8)	3 (3.4)	10 (7.2)	*15 (5.9)*	NR	29 (12)	24 (17.1)	13 (11)		*8 (7.3)*	*20 (18.2)*
AE leading to disc.	*21 (7.1)*	2 (2.3)	12 (8.7)	*15 (5.9)*	4 (5.7)	26[d] (11)	11 (7.9)	6 (5.2)	3 (15.0)	*4 (3.7)*	*12 (10.9)*
AE leading to:											
Temp. interrupt	132 (44.7)	*31 (36)*	-	-	13 (18.6)	181 (74)	-	-	-	*45 (41.3)*	*68 (61.8)*
Dose reduction	65 (22.0)	14 (16)	14 (10)	-	3 (4.3)	152 (62)	76 (54.3)	*71 (61)*	-	*8 (7.3)*	*32 (29.1)*
Dose reduction or interruption	NR	*37 (42.5)*	*38 (27.5)*	*83 (32.8)*	-	-	-	92 (80.0)	20 (100)	-	-
AE Grade ≥ 3											
Total	*G3/4:184 (62.4) G5: 33 (11.2)*	*36 (41.4)*	*55 (39.9)*	*100 (39.5)*	19 (27.1)	200 (81)	100 (71.4)	*G3: 86 (74.8) G4: 18 (15.7)*	G3/4: 14 (70)	*69 (63.3)*	*78 (70.9)*
Drug related	121 (41.0)	12 (13.8)	16 (11.6)	*33 (13.0)*		125 (51)	64 (45.7)		12 (60)	*26 (23.9)*	*50 (45.5)*
Death due to AE	0	2 (2.3)	5 (3.6)	*7 (2.8)*	0	2 (0.8)	NR	2 (1.7)	*0*	NR	NR

Note: figures in italics were calculated or extracted during evaluation. Abbreviations: AE = adverse event; SAE = serious adverse events; Temp. interrupt = temporary interruption/discontinuation of treatment.
Source: Table 2.5.20 p149, Table 2.5.21 pp151-152, p170, pp173-174, Table 2.5.32 p171, p185, pp175-176, Table 2.8.5 p206 of the submission; lorlatinib EMA Assessment Report, Table 70 p110; Table 71 p111 (URL: https://www.ema.europa.eu/en/documents/assessment-report/lorviqua-epar-public-assessment-report_en.pdf); alectinib EMA Assessment Report, Table 56 p97, Table 57 p98; brigatinib EMA assessment Report, Table 65 p101, Table 67 p102; Kim et al (2016) p459 and Appendix table 11, table 14; Crino et al (2016), Appendix Table A2; Shaw et al (2017) p882; Hida et al (2018) p2867.

[a] ALTA reported as treatment emergent adverse events.

[b] Information only available for combined ALK inhibitor naïve (N=83) and ALK inhibitor pre-treated (N=163) population.

[c] Duration of treatment in Study 1001 were reported in months; duration of treatment across all studies this were recalculated during the evaluation to weeks to allow for comparison across the studies.

[d] Source used for reporting of adverse events for Study 1001 during the evaluation was the lorlatinib EMA Assessment report.

6.27 The ESC noted that lorlatinib generally had a numerically higher number of AE Grade ≥ 3 and SAEs than alectinib, and lower number than ceritinib. It considered that lorlatinib discontinuation rates were generally similar to other ALK-TKIs, and noted that no deaths were attributed to the study drug.

6.28 In prior considerations of ALK-TKIs (alectinib and ceritinib) for use in patients with ALK-positive advanced NSCLC, the ESC considered that there were insufficient data to fully define the safety profile of alectinib, especially in terms of the less common AEs, and clinical data comparing alectinib to other ALK inhibitors were particularly limited. The ESC had considered that alectinib's safety profile would vary with its clinical place in therapy (paragraph 6.37, alectinib PSD, July 2017).

Benefits/harms

6.29 The naïve comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of lorlatinib, alectinib, ceritinib and brigatinib. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.30 The submission described lorlatinib as:

- non-inferior in terms of effectiveness compared with alectinib and non-inferior in terms of safety compared to alectinib.
- non-inferior in terms of effectiveness compared with ceritinib and non-inferior in terms of safety compared to ceritinib.
- non-inferior in terms of effectiveness compared with brigatinib and non-inferior in terms of safety compared to brigatinib.

6.31 During the evaluation the therapeutic conclusions presented in the submission were considered not adequately supported by the evidence presented for the following reasons:

- The key clinical evidence for lorlatinib presented in the submission was from a subgroup of patients from Study 1001 with ALK-positive NSCLC who had received prior treatment with one or more ALK-TKIs. Study 1001 was non-randomised, single arm, and open label. As such, the study is subject to considerable bias; the effectiveness and safety estimates are subject to considerable uncertainty.
- The claim of non-inferior efficacy and safety was based on a naïve comparison of the subgroup of patients from Study 1001, and the single arms of non-comparative studies and RCTs for alectinib and ceritinib. There were significant transitivity issues with the included trials, mainly pertaining to the study design characteristics. The comparison of the studies was restricted by the baseline characteristics reported across the studies, the types of prior treatments received and the extent of use of study drug beyond progression.

- The submission claimed that the results of the MAIC supported the conclusions from the naïve comparison. However, the MAIC relied on an implausible assumption that the distribution of the treatment effect modifiers did not differ between the studies, applied methods for adjustment which differed from those intended by the developers of this method, relied on a sample size that was approximately 20% of that applied to the naïve comparison, and the inclusion of data from single arm studies in a MAIC is subject to the additional assumptions and biases incurred by these study designs.

6.32 The PBAC previously considered in the assessment of alectinib that, notwithstanding these and other inherent limitations of indirect comparisons between single arm studies, on balance, the submission's claim of non-inferior comparative effectiveness against ceritinib, was acceptable. The PBAC had also considered that alectinib and ceritinib had different side effect profiles. The PBAC advised that, although currently available clinical data was insufficient to fully define the safety profile of alectinib, it was reasonable to conclude that it was non-inferior in terms of comparative safety, compared with ceritinib. In making the alectinib recommendation, the PBAC noted the relatively small population of patients with ALK-positive NSCLC and the clinical need for additional targeted therapies with different safety profiles than currently available treatments for this condition (paragraphs 7.5, 7.2 and 6.44, alectinib PSD, July 2017).

6.33 The ESC considered that the available data for lorlatinib did not adequately demonstrate non-inferior efficacy or safety.

6.34 Whilst the ESC agreed that treatments providing broader mutational coverage and CNS penetration comprised a high unmet clinical need, it considered that the submission had not provided adequate evidence to support the hypothesised benefit of lorlatinib in meeting these needs in the treatment of ALK-positive NSCLC. The pre-PBAC response argued that clinical evidence for activity against known ALK resistance mutations was demonstrated in the publication of the primary outcomes from Study 1001, *"using structure-based drug design, this macrocyclic tyrosine kinase inhibitor was developed to penetrate the blood–brain barrier and to retain potency against most known ALK resistance mutations that can develop during treatment with crizotinib and second-generation tyrosine kinase inhibitors, including the ALK Gly1202Arg*" (Solomon et al., 2018).

6.35 The PBAC considered that the cost-effectiveness of lorlatinib could be informed by a comparison against alectinib. On balance the PBAC considered it likely that effectiveness of lorlatinib would be similar to that of alectinib.

6.36 The PBAC noted that lorlatinib was associated with a numerically higher number of Grade ≥ 3 adverse events (AE) and serious AEs, but similar rates of discontinuations compared to alectinib and a lower number of serious AEs than ceritinib and brigatinib with a longer duration of treatment. The PBAC noted that all ALK-TKIs have different

safety profiles, making the comparisons difficult, however accepted that there is no substantive differences in safety.

Economic analysis

6.37 The equi-effective doses proposed in the submission were lorlatinib 100 mg QD and alectinib 600 mg BID. These are the daily doses recommended in the respective PIs for the two drugs, and the doses used in the lorlatinib and alectinib studies. The submission did not estimate the equi-effective doses of lorlatinib compared with ceritinib and did not present a CMA against this comparator. The PSCR argued that it was not possible to determine the equi-effective doses of lorlatinib and ceritinib given that the ceritinib TGA approved dose appears to have been adjusted based on pharmacokinetic (PK) data, rather than outcomes data. The PK study on which the dose adjustments were based had a patient population that was only partly applicable to the requested PBS population (a mix of treatment naïve (29%), post chemotherapy (22%) and post crizotinib (48%) patients), with limited efficacy outcomes reported.

6.38 In claiming that the equi-effective doses are the recommended daily doses of each drug (lorlatinib and alectinib), the submission implicitly assumed that the mean duration of treatment and the mean relative dose intensity in clinical practice would be the same for both drugs. Limited data are available to enable a robust comparison of the treatment duration of lorlatinib with alectinib.

6.39 Of relevance to the current consideration for lorlatinib, during the PBAC's previous assessment of alectinib, the ESC and PBAC considered the following issues with respect to the assumption relating to duration of treatment:

- The ESC advised that alectinib should be cost-minimised to ceritinib on the basis of the total drug cost that achieved the same overall survival outcomes (paragraph 7.9, alectinib PSD, July 2017).
- The PBAC considered that a study-based CMA, allowing for the difference in PFS/treatment duration and relative dose intensity observed in the alectinib and ceritinib studies, introduced uncertainty, as (i) such an approach would be confounded by the differences in the duration of follow-up for each of the studies; (ii) both ceritinib and alectinib studies allowed patients to continue treatment beyond disease progression and; (iii) the impact of the data for treatment duration and PFS used as a proxy for treatment duration being censored (paragraph 7.9, alectinib PSD, July 2017). On balance, the PBAC advised that, in order to reduce the financial risk to the Commonwealth, the differential duration of therapy be taken into account in calculating the cost-minimisation approach (paragraph 7.10, alectinib PSD, July 2017)
- The PBAC further advised that the effective price for alectinib be no higher than the effective price for ceritinib, on the basis of cost per day of treatment, with alectinib 600 mg (4 x 150 mg capsules) twice daily and ceritinib 750 mg (5 x 150 mg capsules)

daily considered to be the equi-effective doses, also taking into account the different durations of therapy (paragraph 7.11, alectinib PSD, July 2017).

6.40 The submission proposed a published ex-manufacturer price for lorlatinib of $[redacted] per pack of lorlatinib for both strengths. The submission calculated the cost per day based on the dispensed price per maximum quantity (DPMQ) and not the approved ex-manufacturer price (AEMP). This was recalculated during the evaluation. The PSCR argued that there was no requirement for a CMA to be conducted using AEMP rather than DPMQ. The Department noted that pricing agreements are made by Government under the National Health Act 1953 at the ex-manufacturer level. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. The results based on published prices are presented in Table 10.

Table 10: Results of the cost-minimisation analysis

Name, restriction, manner of administration, form	Max Qty (units)	Days of treatment per pack	DPMQ (published)	AEMP (published)	Treatment Cost (daily)		Dosage regimen assumption
					DPMQ[a]	AEMP[b]	
Alectinib 150 mg capsule	224	28	$6,805.20	$6,653.08	$243.04	*$237.61*	*600 mg BID*
Lorlatinib 100 mg tablet	30	30	$[redacted]	$[redacted]	$[redacted]	*$[redacted][c]*	*100 mg QD*
Lorlatinib 25 mg tablet	90	30	$[redacted]	$[redacted]	$[redacted]	*$[redacted]*	*75 mg QD[d]*
Lorlatinib 25 mg tablet	*90*	*45*	*$[redacted]*	*$[redacted]*	[redacted]	*$[redacted]*	*50 mg QD[d]*
Ceritinib 150 mg capsule	*150*	*50*	*$7,280.42*	*$7,128.30*	*NR*	*$142.57*	*450 mg QD*
Ceritinib 150 mg capsule	*150*	*30*	*$7,280.42*	*$7,128.30*	*NR*	*$237.61*	*750 mg QD*

Source: Att4_Section 3_lorlatinib.xlsx and Table 3.4.1 p212 of the submission.
Abbreviations: AEMP = Approved ex-manufacturer price; BID = Twice Daily; DPMQ = Dispensed price for maximum quantity; NR = not reported; QD = once daily; Qty = Quantity.
Notes: Figures in italics were extracted during evaluation.
[a] DPMQ divided by days of treatment per pack.
[b] AEMP divided by days of treatment per pack.
[c] Price difference between lorlatinib and alectinib for daily cost of treatment is [redacted] cents. Over 30 days the difference in cost is $[redacted].
[d] Assumed dose reduction due to AE.

6.41 Based on the proposed published AEMP, the estimated cost per day of lorlatinib 100 mg QD is $[redacted] higher than the cost per day of alectinib 600 mg BID and ceritinib at 750 mg QD, with the difference in price over 30 days of supply being $[redacted]. The cost per day of the ceritinib dose of 450 mg QD is considerably lower than lorlatinib 100 mg QD, where the daily difference in price was $[redacted] per day, and over 30 days was $[redacted]. The ESC noted that a similar difference is observed between the cost per day for alectinib 600 mg and ceritinib 450 mg.

6.42 The cost-minimisation analysis has not included costs of AEs and treatment monitoring as per draft PI for lorlatinib, and PI for alectinib and ceritinib. The

evaluation had stated that it was possible that the analysis is biased in favour of lorlatinib as additional costs may be incurred due to the AE of hyperlipidaemia (approximately 80% of patients treated with lorlatinib in Study 1001 received treatment for hyperlipidaemia), which would include prescription, monitoring and treatment costs, and due to the AE of AV block where ECG monitoring is recommended. The PSCR argued that no additional costs or cost offsets were considered with respect to safety as they were likely to be balanced between treatments, in line with the claim of non-inferior safety. The ESC agreed, noting that the cost of managing hyperlipidaemia would likely be minimal due to poor prognosis of late stage NSCLC.

Drug cost/patient/course:

6.43 The cost/patient/course for a patient treated with lorlatinib was estimated to be $[redacted]. This was calculated using the proposed published DPMQ of $[redacted] for 30 days' supply, and assuming an estimated average treatment duration of 8 months (the median PFS used as a proxy for treatment duration) based on the cost-minimisation analysis in the submission. Applying the mean duration of treatment of [redacted] months in Study 1001, which included treatment beyond progression, the cost/patient/course was estimated to be $[redacted]. These estimates assume a relative dose intensity of 100%.

6.44 A summary of the drug cost per patient of lorlatinib based on published prices is provided in Table 11.

Table 11: Drug cost per patient for lorlatinib and alectinib

	Lorlatinib			Alectinib		
	Trial dose and duration	**CMA**	**Financial estimates**	**Trial dose and duration**	**CMA**	**Financial estimates**
Equi-effective dose (as per submission)	100 mg QD	100 mg QD[b]	100 mg QD	600 mg BID	600 mg BID	600 mg BID
Duration of treatment						
Mean	[redacted] months	8 months[a]	8.13 months[b]	NP28671/ NP28673: 56.9 weeks	8 months[a]	8.13 months[b]
Median	[redacted] months	NA	NA	(ALUR: 20.1 wks)	NA	NA
Cost/patient/ month	$7,291.29[c]			$7,291.29[c]		
Cost/patient/ course[d]	*$[redacted]*	*$[redacted]*	*$[redacted]*	*$96,482*	*$58,330*	*$59,278*

Abbreviations: BID = twice a day; CMA = cost-minimisation analysis; mg = milligram; NA = not applicable; NR = not reported; QD = daily;
Source: Table 2.4.2 p86, p170, pp173-174, pp175-176, Table 3.4.1 p213 of the submission; Section 4 workbook, spreadsheet t 3a.
Notes: Assuming one month equals 30 days or 4.3 weeks; Number in italics indicate values calculated during evaluation.
[a] Duration of treatment is based on PFS, which is assumed to be the same for both drugs.
[b] Assuming 8.13 scripts are dispensed per patient per year and no wastage.
[c] DPMQ of lorlatinib is $[redacted]; DPMQ of alectinib is $6,805.20, cost per patient per month (30 days): ($6,805.20/28)*30 = $7,291.29.
[d] cost/patient/month x duration of treatment.

Estimated PBS usage & financial implications

6.45 This submission was not considered by DUSC. The submission used a combined epidemiological and market share approach to estimate the extent of use and financial impact of listing lorlatinib 100 mg on the PBS. A summary of the estimated use and financial implications for listing lorlatinib on the PBS is presented in Table 12. These estimates are based on published prices. The results based on effective prices are presented in Table 13.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of lorlatinib						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for alectinib and ceritinib						
Alectinib scripts displaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ceritinib scripts displaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of scripts displaced[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS[d]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4.2.8 pp28-229, Table 4.3.2 pp231-232, Table 4.4.1 p233, Table 4.6.1 p236, Table 4.6.2 pp236-237 of the submission.
Abbreviations: PBS = Pharmaceutical Benefit Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Notes:
[a] Assuming 8.13 scripts are dispensed per patient per year as estimated by the submission.
[b] Includes [redacted] grandfathered patients.
[c] Assuming 8.7 scripts per course of alectinib treatment, and 4.9 scripts per course of ceritinib treatment.
[d] Submission base case assumed substitution of alectinib was [redacted]% and ceritinib was [redacted]%.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS/RPBS would be less than $10 million.

Committee-in-Confidence information

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of lorlatinib						
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for alectinib and ceritinib						
Alectinib scripts displaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ceritinib scripts displaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of scripts displaced[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 4.2.8 pp28-229, Table 4.3.2 pp231-232, Table 4.4.1 p233, Table 4.6.1 p236, Table 4.6.2 pp236-237 of the submission.
Abbreviations: PBS = Pharmaceutical Benefit Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Notes:
[a] Assuming 8.13 scripts are dispensed per patient per year as estimated by the submission.
[b] Includes [redacted] grandfathered patients
[c] Assuming 8.7 scripts per course of alectinib treatment, and 4.9 scripts per course of ceritinib treatment.
[d] Submission base case assumed substitution of alectinib was [redacted]% and ceritinib was [redacted]%.

End Committee-In-Confidence information

6.46 The submission noted that costs to the PBS/RPBS for lorlatinib were most influenced by the change to the mean duration of treatment of lorlatinib (i.e. proxied by the median PFS), the prevalence of ALK re-arrangement in the NSCLC population, the proportion of patients with disease progression, and the number of patients seeking second-line treatment for NSCLC.

6.47 Concomitant medications associated with toxicity of ALK-TKIs and the different AE profiles were not included in the financial estimates. Approximately 80% of patients treated with lorlatinib in Study 1001 received treatment for hyperlipidaemia. Prescription and treatment costs associated with hyperlipidaemia were not included in the analysis. Including these costs would increase the costs to the PBS/RPBS, but would not materially alter the overall cost-effectiveness.

6.48 The submission assumed that lorlatinib will substitute for alectinib and ceritinib such that their relative (remaining) market share proportions are maintained at [redacted]% and [redacted]% over the six years. The use of ceritinib decreased when alectinib was listed on the PBS in both first and second-line therapies.

6.49 Costs associated with displacement of comparator treatments or chemotherapy to later-line use were not included in the submission. The presence of displacement rather than substitution would have the effect of reducing the claimed cost-offsets. The ESC considered that use of ALK-TKI therapy after disease progression on lorlatinib used in the second-line setting (hence third or subsequent line therapy) would be very limited and also that chemotherapy was more likely to be offered after lorlatinib. However, it considered that utilisation of chemotherapy in this setting would be relatively low, given poor survival outcomes at this late stage of disease.

Quality Use of Medicines

6.50 The submission presented a discussion of quality use of medicine issues. However, the submission did not propose the implementation of any specific initiatives to address Quality Use of Medicines issues associated with the listing of lorlatinib.
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 lorlatinib as monotherapy for the treatment of patients with metastatic (Stage IV) anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have disease progression either following treatment with crizotinib and at least one other ALK tyrosine kinase inhibitor (TKI) or following an ALK-TKI other than crizotinib (second-line and subsequent-line settings). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of lorlatinib would be acceptable if it were cost-minimised against alectinib. In making this recommendation, the PBAC considered that there is a high unmet clinical need for effective treatments with broader mutational coverage and intracranial activity for this patient population.

7.2 The PBAC was satisfied that intracranial activity of lorlatinib provides clinical benefit in patients with CNS metastases, based on the primary outcomes (ORR and IC-ORR) of Study 1001, despite the lack of comparative efficacy data for lorlatinib. However, the PBAC noted that activity against secondary ALK mutations was not supported by specific evidence in the submission. Instead, the use of lorlatinib as second-line therapy was justified by a biological rationale that the different pharmacological profile for lorlatinib would likely offer a clinically meaningful effect against specific mutations that confer treatment resistance to prior ALK therapies.

7.3 The PBAC noted that the submission nominated alectinib as the main comparator. The PBAC was mindful that, in most circumstances, alectinib would be used before lorlatinib in the clinical management algorithm. However, the PBAC took the

pragmatic view that a comparison with alectinib would be acceptable to inform the cost-effectiveness of lorlatinib.

7.4 The PBAC also considered that a potential comparator was chemotherapy including the combination therapy with atezolizumab, bevacizumab and platinum doublet chemotherapy (paclitaxel and carboplatin), which is listed on the PBS for metastatic NSCLC following treatment with an ALK inhibitor. In this setting, lorlatinib would likely substitute for chemotherapy or displace it to a later line. However, the PBAC decided that, on balance, an acceptable approach to assess lorlatinib's cost-effectiveness would be a comparison with alectinib.

7.5 The PBAC noted that the submission presented a naïve comparison of a subgroup (EXP-2 to EXP-5) of patients from the single arm phase 1/2 Study 1001 (n=198) and single arms of non-comparative studies and randomised controlled trials (RCTs) for the proposed comparators (alectinib, ceritinib, and brigatinib). In the absence of a common reference arm, it was not possible to conclude that the lorlatinib results are non-inferior in efficacy or safety. The matching-adjusted indirect comparison (MAIC), employed to support the naïve comparison, had a range of methodological issues and inadequately supported assumptions, and was based on a very small number of patients (n=59). Overall, the unanchored MAIC could not overcome transitivity issues and did not provide useful comparative information, particularly for survival outcomes.

7.6 The PBAC considered that the claim of non-inferior effectiveness compared with the proposed comparators in this specific population and treatment setting was not adequately supported by the evidence in the submission. However, the PBAC considered, on balance, it was reasonable to conclude that the effectiveness of lorlatinib would be similar to that of alectinib.

7.7 The PBAC noted that lorlatinib was associated with a numerically higher number of Grade ≥ 3 adverse events (AE) and serious AEs but similar rates of discontinuations compared with alectinib, and a lower number of such AEs than ceritinib or brigatinib. However, the PBAC considered that all ALK-TKIs have different safety profiles, making such comparisons difficult, and accepted that there are likely no substantive differences in safety across all drugs in the submission.

7.8 The equi-effective doses proposed in the submission were lorlatinib 100 mg QD and alectinib 600 mg BID, based on the assumptions that the mean duration of treatment and the mean relative dose intensity in clinical practice would be the same for both drugs. The cost-minimisation approach taken in the submission was to equate the cost per day of lorlatinib with the cost per day of alectinib, assuming that the treatment duration with lorlatinib was going to be the same as alectinib. The comparison of the point estimates for PFS suggested the treatment durations for lorlatinib and alectinib were likely to be similar thus the PBAC accepted the cost per day approach using the equi-effective dose of lorlatinib 100 mg per day and alectinib 1200 mg per day. The

PBAC advised that the cost per day of lorlatinib should be no more than the cost per day of alectinib.

7.9 The PBAC noted that alectinib was listed on a cost minimisation basis compared with ceritinib, and that the recommended dose for ceritinib had changed from 750 mg to 450 mg based on pharmacokinetic (PK) data. However, based on PBS data the lower dose does not yet appear to be used in clinical practice (paragraph 5.8), and there is a lack of clinical data at the lower dose. As an improvement in efficacy or reduction in toxicity with lorlatinib over ceritinib was not demonstrated for some patients, the PBAC considered that lorlatinib 100 mg daily should also be no more costly than ceritinib 750 mg daily.

7.10 The PBAC considered the cost-offsets due to replacement of alectinib and ceritinib to be overestimated, as lorlatinib would be used after alectinib (paragraph 7.3) and the current use of ceritinib is minimal (paragraph 5.8). At least partly countering this, the PBAC noted the cost-offsets associated with a potential reduction in chemotherapy, including atezolizumab combination therapy, were not included. The PBAC therefore considered that the residual uncertainty around financial impact due to lorlatinib use subsequent to alectinib would need to be managed by a risk share arrangement and expenditure caps as for alectinib. The PBAC also considered it may be appropriate that the two drugs share the current RSA caps, but with an increase to the cap based on the estimated use of lorlatinib in Table 13.

7.11 The PBAC noted that all previous ALK-TKI decisions were line-agnostic but the lorlatinib submission did not request a line-agnostic listing. The PBAC considered that the proposed listing in the second-line and subsequent-line settings was appropriate, as there were no comparative data presented in the submission to support use of lorlatinib as first-line therapy.

7.12 The PBAC noted that the requested PBS restriction for lorlatinib would allow its use as second-line therapy post crizotinib, which is broader than the proposed TGA indication. The PBAC advised that it would be appropriate to amend the requested restriction to specify, “The condition must have progressed following treatment with an ALK TKI other than crizotinib”, in line with the proposed TGA indication (see paragraph 3.1).

7.13 The PBAC considered that the inclusion of a criterion to allow access to lorlatinib due to intolerance to a prior ALK inhibitor was not appropriate.

7.14 The PBAC noted that the requested maximum quantity and repeats was the same as the current listing for alectinib, and advised that all ALK inhibitors should be listed with maximum quantity and repeats that provide for consistent lengths of treatment.

7.15 The PBAC recommended the inclusion of a grandfathering restriction as proposed by the submission. The PBAC noted the pre-PBAC response indicated that approximately

less than 10,000 patients would be receiving treatment through the sponsor's patient access program at the time of the proposed PBS listing.

7.16 The PBAC considered that expansion of MBS Item 73341 to include access to lorlatinib would not be required as patients would have had their ALK status confirmed to access a first-line ALK-TKI on the PBS, and instead advised to include the criterion, "The patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement".

7.17 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* lorlatinib should not be treated as interchangeable with any other drugs on an individual patient basis.

7.18 The PBAC advised that lorlatinib is not suitable for prescribing by nurse practitioners.

7.19 The PBAC recommended that the Early Supply Rule should not apply as it currently does not apply to alectinib.

7.20 The PBAC found that the criteria prescribed by *the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for lorlatinib:

(a) The treatment may not provide a substantial and clinically relevant improvement in efficacy over alternative therapies including chemotherapy and alternative ALK therapies.

(b) The treatment is expected to address a high and urgent unmet clinical need.

(c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LORLATINIB			Lorviqua®	Pfizer Australia Pty Ltd
25 mg tablet, 90	1	1		
100 mg tablet, 30	1	1		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic)
Condition:	non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Streamlined
Clinical criteria:	The treatment must be as monotherapy, AND The patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement, AND The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND Patient must have a WHO performance status of 2 or less, AND The condition must have progressed following treatment with an ALK inhibitor other than crizotinib.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LORLATINIB			Lorviqua®	Pfizer Australia Pty Ltd
25 mg tablet, 90	1	1		
100 mg tablet, 30	1	1		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic)
Condition:	non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Continuing treatment

Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Streamlined
Clinical criteria:	The treatment must be as monotherapy, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LORLATINIB			Lorviqua®	Pfizer Australia Pty Ltd
25 mg tablet, 90	1	1		
100 mg tablet, 30	1	1		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic)
Condition:	non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Grandfathering treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Streamlined
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date], AND The treatment must be as monotherapy, AND The patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement, *AND* The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND

	Patient must have a WHO performance status of 2 or less, AND The condition must have progressed following treatment with an ALK inhibitor other than crizotinib.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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

The sponsor had no comment.