

**6.04 LORLATINIB,  
Tablet 25 mg,  
Tablet 100 mg,  
Lorviqua<sup>®</sup>,  
Pfizer Australia Pty Ltd.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested General Schedule, Authority Required (Telephone/Electronic) listing of lorlatinib for the treatment of patients with Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) with evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus alectinib. The key components of the clinical issues addressed by the submission are summarised below.

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

<b>Component</b>	<b>Description</b>
Population	Patients with locally advanced (stage IIIB) or metastatic (Stage IV) anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have not previously been treated with an ALK tyrosine kinase inhibitor (TKI).
Intervention	Lorlatinib 100 mg and 25 mg film-coated tablets. Recommended dosage: 100 mg orally once daily.
Comparator	Main: Alectinib; Supplementary: Brigatinib
Outcomes	Objective tumour response rates (ORR); intracranial objective response rate, time to progression, and time to response (IC-ORR, IC-TTP, IC-TTR); duration of response (DOR); intracranial duration of response (IC-DOR); progression-free survival (PFS); overall survival (OS); patient reported outcomes (PROs); safety.
Clinical claim	The overall clinical claim was that lorlatinib is non-inferior to the main comparator, alectinib, in terms of efficacy and safety.

Source: Table 1.1.1 of the submission.

**2 Background**

**Registration status**

- 2.1 TGA status at time of PBAC consideration: the submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration the Clinical Evaluation Report (Round 1) was available and the Delegate’s Overview was expected Q3 2021. The sponsor’s pre-PBAC response noted brigatinib was recommended by the PBAC for a line agnostic listing, despite no TGA application for the first line indication underway at the time of PBAC consideration.
- 2.2 Lorlatinib has provisional TGA approval for the treatment of patients with ALK positive advanced NSCLC whose disease has progressed on:

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- Crizotinib and at least one other ALK inhibitor; or
- Alectinib as the first ALK inhibitor therapy; or
- Ceritinib as the first ALK inhibitor therapy.

2.3 A TGA application was lodged on the 23 December 2020 to convert the current provisional registration for second-line treatment of ALK positive advanced NSCLC to full registration for the first line treatment of patients with ALK positive advanced NSCLC. The TGA application is being evaluated under Project Orbis, in collaboration with the United States Food and Drug Administration and other participating regulatory agencies, including Health Canada, and United Kingdom’s Medicines and Healthcare products Regulatory Agency.

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

**Previous PBAC consideration**

2.4 Lorlatinib was listed on the PBS on 1 August 2020 for the treatment of patients with ALK positive metastatic (Stage IV) NSCLC following treatment with an ALK tyrosine kinase inhibitor (TKI) other than crizotinib.

**3 Requested listing**

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
LORLATINIB Tablets 100 mg	1	30	3	\$7,289.46 (published) \$ [REDACTED] (effective)	Lorviqua®, Pfizer Australia Pty Ltd
LORLATINIB Tablets 25 mg	1	90	3	\$7,289.46 (published) \$ [REDACTED] (effective)	

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic)
<b>Condition:</b>	Non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be as monotherapy, AND

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	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.
<b>Population criteria:</b>	Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing
<b>Administrative Advice:</b>	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.

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic)
<b>Condition:</b>	Non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	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.
<b>Administrative Advice:</b>	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.

- 3.1 The submission proposed a special pricing arrangement (SPA). The proposed published and effective dispensed price for maximum quantity (DPMQ) for the requested restriction is the same as that for the current listing of lorlatinib in the refractory setting.
- 3.2 The submission requested a line agnostic PBS listing for lorlatinib consistent with current listings for other ALK TKIs such as alectinib, brigatinib, and ceritinib. The proposed listing allows lorlatinib to be used as either a first- or later-line therapy in advanced ALK positive NSCLC.

## **4 Population and disease**

- 4.1 NSCLC accounts for around 80%-90% of all lung cancers with 3-5% of these cases being associated with ALK gene rearrangements. About 70% of NSCLC patients have advanced (Stage IIIB/IV) disease at diagnosis. Patients with ALK-positive NSCLC

typically present with more metastatic sites than those with other disease subtypes. Central nervous system (CNS) involvement in ALK-positive NSCLC is common, with 20%-40% of patients having brain metastases at diagnosis (NCI, 2019).

- 4.2 Lorlatinib is a third generation, selective adenosine triphosphate (ATP)-competitive, brain-penetrant small-molecule inhibitor of ALK and ROS1 TKI.

## **5 Comparator**

- 5.1 The submission nominated alectinib as the main comparator and brigatinib as a supplementary comparator. The main argument provided in support of this nomination was that alectinib is the treatment that is most likely to be substituted for the proposed extension to the lorlatinib PBS listing. Brigatinib, is expected to be substituted to a much lesser extent over time given its limited share of prescribing for this population.
- 5.2 The nominated comparators were reasonable. The proposed line agnostic listing of lorlatinib will allow its use in the first line setting which will displace alectinib/brigatinib to subsequent treatment lines. The treatment sequence in current Australian clinical practice is essentially first line alectinib (to a smaller extent brigatinib) followed by lorlatinib upon progression. The ESC noted the clinical benefit of using a second-generation ALK TKI (i.e., alectinib or brigatinib) after a third-generation ALK TKI (i.e., lorlatinib) was uncertain but acknowledged it reflected clinical guidelines and was likely to happen in clinical practice.
- 5.3 Under Section 101(3B) of the National Health Act (1953) where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. Alternative therapies to lorlatinib include alectinib, brigatinib and ceritinib.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comments noted the importance of targeted therapies and indicated patients value additional treatment options even if

there is no clinical difference between treatments. One organisation provided results of a patient survey that indicated the adverse events of most to least concern were hypertriglyceridemia, weight gain, fatigue, vision disorders, oedema, anaemia and cognitive effects.

- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the lorlatinib submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the CROWN trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for lorlatinib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>, based on a comparison with crizotinib.

### **Clinical studies**

- 6.4 The submission was based on an indirect treatment comparison (ITC) between lorlatinib and alectinib, using crizotinib as a common reference. This was informed by two trials in locally advanced or metastatic ALK positive NSCLC patients in the first line setting: One Phase III randomised controlled trial (RCT) of lorlatinib 100 mg daily versus crizotinib 250 mg twice daily (CROWN; N=296) and one Phase III RCT of alectinib 600 mg twice daily versus crizotinib 250 mg twice daily (ALEX; N=303).
- 6.5 The submission also presented an ITC between lorlatinib and brigatinib, using crizotinib as a common reference. This was informed by two trials in locally advanced or metastatic ALK positive NSCLC patients in the first line setting: lorlatinib versus crizotinib first line CROWN RCT (N=296) and one Phase III RCT of brigatinib versus crizotinib in the first line setting (ALTA-1L; N=275) comparing brigatinib 180 mg once daily or crizotinib 250 mg twice daily. The PBAC previously recommended brigatinib on a cost-minimisation basis compared to alectinib (paragraph 7.1, brigatinib Public Summary Document (PSD), November 2019 PBAC meeting). The submission described lorlatinib as non-inferior to brigatinib in terms of both effectiveness and safety. The claim of non-inferiority was reasonable in terms of PFS but OS data remain insufficiently mature to substantiate any non-inferiority claim. No formal indirect comparisons between lorlatinib and brigatinib were presented to support a non-inferiority claim for safety. The results of indirect comparison between lorlatinib and brigatinib are not presented herein. .
- 6.6 Details of the studies presented in the submission are provided in the table below.

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<sup>1</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

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Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Lorlatinib</b>		
CROWN (Study B7461006)	A Phase 3, Randomized, Open Label Study of Lorlatinib (PF-06463922) Monotherapy Versus Crizotinib Monotherapy in the First Line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer Protocol: A phase 3, randomised, open label study of lorlatinib (PF-06463922) monotherapy versus crizotinib monotherapy in the first-line treatment of patients with advanced ALK-positive non-small cell lung cancer. B7461006. Final Protocol Amendment 4.  Shaw AT, et al. 2020. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer.	October 2019  <i>NEJM</i> 2020; 383:2018-2029
<b>Main comparator alectinib</b>		
ALEX (NCT02075840)	A Study Comparing Alectinib With Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Participants. <a href="https://clinicaltrials.gov/show/NCT02075840">https://clinicaltrials.gov/show/NCT02075840</a>  Peters, S, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer.  Camidge, D, et al. Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the global phase III ALEX study.  Mok, T. et al. Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study.  Perol, M. et al. Patient-reported outcomes from the randomised phase III ALEX study of alectinib vs crizotinib in patients with ALK-positive non-small-cell lung cancer.	March 2014.  <i>New England Journal of Medicine</i> 2017; 377(9): 829-838.  <i>Journal of Thoracic Oncology</i> 2019;14 (7): 1233-1243.  <i>Annals of oncology</i> 2020; 31(8): 1056-64  <i>Lung Cancer</i> 2019; 138: 79–87
<b>Supplementary comparator brigatinib</b>		
ALTA-1L (NCT02737501)	ALTA-1L Study: A Phase 3 Study of Brigatinib Versus Crizotinib in Anaplastic Lymphoma Kinase Positive (ALK+) Advanced Non-small Cell Lung Cancer (NSCLC) Participants (ALTA-1L): <a href="https://clinicaltrials.gov/ct2/show/NCT02737501">https://clinicaltrials.gov/ct2/show/NCT02737501</a>  Camidge, D. et al. Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: second Interim Analysis of the Phase III ALTA-1L Trial.  Camidge, R. et al. Brigatinib versus Crizotinib in ALK positive non-small-cell lung cancer.	December 2020  <i>Journal of Clinical Oncology</i> 38:3592-3603.  <i>New England Journal of Medicine</i> 2018; 379: 2027-39

Source: Table 2.2.1of the submission

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

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Lorlatinib vs. crizotinib</b>					
CROWN	296	R, OL 20 mths*	Low	Locally advanced or metastatic ALK-positive NSCLC	OS, PFS, QoL and AEs
<b>Alectinib vs. crizotinib</b>					
ALEX	303	R, OL 48.2 mths**	Low	Locally advanced or metastatic ALK-positive NSCLC	OS, PFS, QoL and AEs

Source: Sections 2.3-2.4 of the submission.

R = randomised; OL = open label; mths = months; OS = overall survival; PFS = progression-free survival; QoL = quality of life; AE = adverse events.

\*The ALEX trial has previously been considered by the PBAC (brigatinib PSD, November 2019 PBAC Meeting)

\*\*CROWN - the median durations of follow-up for OS were 20 months in the lorlatinib arm and 19.8 months in the crizotinib arm.

\*\*\*ALEX - the median durations of follow-up for OS were 48.2 months in the alectinib arm and 23.3 months in the crizotinib arm.

6.8 Both the CROWN and ALEX trials had progression-free survival (PFS) as the primary outcome with PFS assessed by a blinded independent review committee (IRC) in CROWN and by investigators in ALEX. In ALEX, PFS was also assessed by an IRC as a secondary outcome.

6.9 For the individual studies CROWN and ALEX, the risk of bias was generally low, although, due to the non-blinded nature of the studies, the risk of bias was high for the primary outcome of investigator assessed PFS in ALEX, and high for quality of life (QoL) and adverse events (AEs) in both studies.

6.10 For the indirect comparison between the two studies, the risk of bias was considered high. The cumulative effect of some dissimilarities in baseline characteristics between the two studies, in terms of metastases involving the CNS, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and disease stage, may have favoured lorlatinib over alectinib in the indirect comparison of effectiveness.

6.11 Common reference adjusted indirect comparisons between lorlatinib and alectinib in the submission were based on the standard Bucher frequentist approach<sup>2</sup>. For the outcome of PFS, indirect comparisons were conducted for either the IRC, or investigator-based assessment, which should have mitigated the risk of bias resulting from different assessors and methods of assessment between the two studies. The submission did not provide a non-inferiority margin to assess non-inferiority.

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<sup>2</sup> Bucher, H. C., et al. (1997). The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of clinical epidemiology* 50(6): 683-691.

## Comparative effectiveness

6.12 The results of indirect comparison in terms of PFS and OS are presented below.

**Table 4: Lorlatinib versus alectinib via crizotinib as the common reference arm – PFS**

Study (treatment)	Treatment	Crizotinib	HR
<b>Progression-free survival - independent review assessment</b>			
<b>CROWN<sup>a</sup> (lorlatinib)</b>			
Events, n/N (%)	41/149 (27.5)	86/147 (58.5)	-
Median PFS, months (95%CI)	NE (NE, NE)	9.3 (7.6, 11.1)	<b>0.28 (0.19, 0.41)</b>
<b>ALEX<sup>b</sup> (alectinib)</b>			
Events, n/N (%)	NR	NR	-
Median PFS, months (95%CI)	25.7 (19.9, NE)	10.4 (7.7, 14.6)	<b>0.50 (0.36, 0.70)</b>
<b>CROWN vs. ALEX</b>	Lorlatinib vs. alectinib (indirect)		<b>0.56 (0.34, 0.93)</b>
<b>Progression-free survival - investigator assessment</b>			
<b>Study (treatment)</b>			
<b>CROWN<sup>a</sup> (lorlatinib)</b>			
Events, n/N (%)	40/149 (26.8)	104/147 (70.7)	-
Median PFS, months (95%CI)	NE (NE, NE)	9.1 (7.4, 10.9)	<b>0.21 (0.14, 0.31)</b>
<b>ALEX<sup>b</sup> (alectinib)</b>			
Events, n/N (%)	62/152 (41)	102/151 (68)	-
Median PFS, months (95%CI)	NE (17.7, NE)	11.1 (9.1, 13.1)	<b>0.47 (0.34, 0.65)</b>
<b>CROWN vs. ALEX</b>	Lorlatinib vs. alectinib (indirect)		<b>0.45 (0.27, 0.75)</b>

Source: Tables 2.5.1, 2.5.2, 2.6.4-5 of the submission; Peters 2017

**Statistically significant results bolded.**

<sup>a</sup>Median duration of follow up for PFS: 18.3 months for lorlatinib and 14.8 months for crizotinib. Data cut-off = March 2020

<sup>b</sup>Median duration of follow up for PFS: 18.6 months for alectinib and 17.6 months for crizotinib. Data cut-off = February 2017

NE = Not estimable as median not reached; HR=Hazard ratio; CI=Confidence interval

**Table 5: Lorlatinib versus alectinib via crizotinib as the common reference arm – OS**

Study (treatment)	Treatment	Crizotinib	HR
<b>CROWN<sup>a</sup> (lorlatinib)</b>			
Events, n/N (%)	23/149 (15.4)	28/147 (19.0)	-
Median OS, months (95%CI)	NE (NE, NE)	NE (NE, NE)	0.72 (0.41, 1.25)
<b>ALEX (December 2017 cut-off<sup>b</sup> (alectinib))</b>			
Events, n/N (%)	43/152 (28.3)	48/151 (31.8)	-
Median OS, months (95%CI)	NE (NR)	NE (NR)	0.76 (0.50, 1.15)
<b>ALEX (November 2019 cut-off<sup>c</sup> (alectinib))</b>			
Events, n/N (%)	51/152 (33.6)	62/151 (41.1)	-
Median OS, months (95%CI)	NE (NR)	57.4 (34.6, NE)	<b>0.67 (0.46, 0.98)</b>
<b>CROWN vs. ALEX (December 2017 cut-off)</b>		Lorlatinib vs. alectinib (indirect)	0.95 (0.47, 1.90)
<b>CROWN vs. ALEX (November 2019 cut-off<sup>d</sup>)</b>		Lorlatinib vs. alectinib (indirect)	1.07 (0.55, 2.11)

Source: Tables 2.5.3, 2.6.6-7 of the submission, Camidge (2019), and Mok (2020)

**Statistically significant results bolded.**

<sup>a</sup>Median duration of follow up: 20.0 months for lorlatinib and 19.8 months for crizotinib.

<sup>b</sup>Camidge (2019): Median duration of follow up: 27.8 months for alectinib and 22.8 months for crizotinib

<sup>c</sup>Mok (2020): Median duration of follow-up for OS was 48.2 months with alectinib and 23.3 months with crizotinib

NE = not estimable; NR = not reported; HR=Hazard ratio; CI=Confidence interval

6.13 The indirect comparisons indicated there was a statistically significant PFS benefit associated with lorlatinib compared with alectinib. Caution is required in the interpretation of these results given 1) the indirect nature of the comparisons, 2) noted differences in patient/disease characteristics between the CROWN and ALEX

trial populations (baseline CNS metastases, previous brain radiotherapy and performance status), and 3) the relatively immature lorlatinib data compared to that for alectinib.

- 6.14 The OS data remained immature for both the CROWN and ALEX studies, although the data from CROWN were relatively less mature. For the CROWN interim data cut-off March 2020, median OS duration was not reached with 17.2% of events (51/296) across the lorlatinib and crizotinib arms. For the most updated ALEX data cut-off November 2019, median OS duration not reached with 37.0% of events (113/303) across the alectinib and crizotinib arms.
- 6.15 There was no statistically significant difference in OS benefit observed between lorlatinib and alectinib. This comparison is problematic given 1) the immature OS data from the studies, 2) notable differences in follow-up durations between the studies (March 2020 cut-off for CROWN 20 months, November 2019 data cut-off for ALEX 48.2 months), and 3) the potential for confounding from any differences between the trials in terms of clinical practice, baseline prognostic risk, and the types and durations of treatments used post progression.
- 6.16 The submission also presented indirect comparisons of investigator assessed objective response rate, intracranial objective response rate and the proportion of patients with a duration of response greater than 12 months. The indirect results favoured lorlatinib over alectinib although there is need for caution when interpreting these results given different treatment effects in the common reference arms.

### ***Comparative harms***

- 6.17 The submission presented adjusted indirect comparisons of safety between lorlatinib and alectinib for any adverse event (AE), discontinuations due to AEs, and serious AEs. Relative risks (RRs) and odds ratios (ORs) were presented as comparative treatment effect measures.
- 6.18 Overall, there were no statistically significant differences between lorlatinib and alectinib for study treatment discontinuation and serious AEs, although there was a trend towards an increased risk associated with lorlatinib. More mature data for lorlatinib are required to inform on longer-term comparative safety.
- 6.19 To further explore comparative safety, additional indirect comparisons were conducted during the evaluation for Grade  $\geq 3$  AEs, treatment-related AEs, dose reductions due to AEs, and dose interruptions due to AEs. Results for Grade  $\geq 3$  AEs and treatment-related AEs of any grade are summarised below. The Pre-Sub-Committee Response (PSCR) stated a formal ITC for Grade  $\geq 3$  AEs was not performed for the submission since the CROWN study presented Grade 3-4 AEs combined and Grade 5 AEs separately, while the available reporting of the ALEX study presented Grades 3-5 AEs as a combined endpoint. The PSCR stated that given the potential for double counting of AEs when combining the reported Grade 3-4 and Grade 5 from the CROWN study, the ITC performed by the evaluation may be biased in favour of

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alectinib. The ESC considered it was reasonable to combine Grade 3-4 and Grade 5 AEs as it would be expected that they would be mutually exclusive events.

**Table 6: Lorlatinib versus alectinib via crizotinib as the common reference arm - Patients with Grade ≥ 3 adverse events**

Study (data cut-off)	Comparison	Experimental Treatment n/N (%)	Crizotinib n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)
CROWN <sup>a</sup>	Lorlatinib vs crizotinib	115 / 149 (77.2)	86 / 142 (60.5)	2.20 (1.32, 3.67)	1.27 (1.09, 1.49)
ALEX (February 2017) <sup>b</sup>	Alectinib vs. crizotinib	63 / 152 (41.0)	76 / 151 (50.0)	0.70 (0.44, 1.10)	0.82 (0.64, 1.05)
ALEX (November 2019) <sup>c</sup>	Alectinib vs. crizotinib	79 / 152 (52.0)	85 / 151 (56.3)	0.84 (0.54, 1.32)	0.92 (0.75, 1.14)
CROWN vs. ALEX (February 2017)	<b>Indirect comparison</b> Lorlatinib vs. alectinib			3.15 (1.59, 6.24)	1.55 (1.15, 2.08)
CROWN vs. ALEX (November 2019)	<b>Indirect comparison</b> Lorlatinib vs. alectinib			2.62 (1.33, 5.18)	1.38 (1.06, 1.79)

Source: Table 2.5.19 of the submission, Section 2.5.3 of the submission, and Peters (2017) and Mok (2020) publications for the ALEX 2017 and 2019 data cut-offs, respectively.

<sup>a</sup>March 2020 interim data cut-off: The median duration of treatment with lorlatinib not been reached and was therefore not estimable and was 9.6 months in the crizotinib treatment arm.

<sup>b</sup>February 2017 data cut-off: The median duration of treatment was 17.9 months with alectinib and 10.7 months with crizotinib.

<sup>c</sup>November 2019 data cut-off: median treatment duration was 28.1 months with alectinib and 10.8 months with crizotinib.

**Table 7: Lorlatinib versus alectinib via crizotinib as the common reference arm - Patients with treatment-related adverse events (any grade)**

Study (data cut-off)	Comparison	Experimental Treatment n/N (%)	Crizotinib n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)
CROWN <sup>a</sup>	Lorlatinib vs crizotinib	144 / 149 (96.6)	133 / 142 (93.7)	1.95 (0.64, 5.96)	1.03 (0.98, 1.09)
ALEX (November 2019) <sup>b</sup>	Alectinib vs. crizotinib	123 / 152 (80.9)	134 / 151 (88.7)	0.54 (0.28, 1.03)	0.91 (0.83, 1.00)
CROWN vs. ALEX (November 2019)	<b>Indirect comparison</b> Lorlatinib vs. alectinib			3.62 (1.00, 13.18)	1.13 (1.02, 1.26)

Source: Table 2.5.19 of the submission, Section 2.5.3 of the submission, and Mok (2020) publication for the ALEX November 2019 data cut-off.

<sup>a</sup>March 2020 interim data cut-off for CROWN: The median duration of treatment with lorlatinib not been reached (not estimable) and was 9.6 months in the crizotinib treatment arm.

<sup>b</sup>November 2019 data cut-off: median treatment duration was 28.1 months with alectinib and 10.8 months with crizotinib. Treatment-related adverse events from ALEX were only reported for the extended November 2019 data cut-off reported in Mok (2020).

6.20 The indirect comparisons indicated an increased risk of Grade ≥ 3 AEs associated with lorlatinib compared with alectinib. The ESC noted the most common Grade 3-5 AEs reported in patients treated with alectinib were laboratory abnormalities (Peters 2017) and the most common Grade 3-4 AEs reported in patients treated with lorlatinib were hypertriglyceridaemia (20%) hypercholesterolaemia (16%), increased weight (17%) and hypertension (10%) (Shaw 2020).

6.21 The ESC noted central nervous system effects have been observed in patients treated with lorlatinib including psychotic effects, changes in cognitive function (including

memory impairment, disturbance in attention and amnesia), mood (including anxiety, depression and affect lability), speech and mental status changes. The ESC acknowledged these events are generally mild and manageable with dose delay and/or reduction but noted they were not AEs generally associated with other ALK TKIs and they were likely to be highly clinically significant in some patients. In the CROWN trial, 2% (n=3/149) of patients had Grade 3 cognitive and 1% (n=2/149) had Grade 3 mood AEs, compared to none in the crizotinib arm, nor any reported in the ALEX trial.

- 6.22 The PSCR noted that the PBAC had previously considered that all ALK TKIs have different safety profiles and accepted that there are likely no substantive differences in safety between them. The ESC considered the additional data provided by the CROWN study for the first line use of lorlatinib indicated there were important differences in the safety profile of lorlatinib compared to the other ALK TKIs.
- 6.23 The indirect comparison indicated there was an increased risk of treatment-related AEs (any grade) associated with lorlatinib compared with alectinib (RR = 1.13 (95% CI: 1.02, 1.26)).
- 6.24 There was a trend towards a higher risk of dose interruptions due to an AE (RR = 1.37 (95% CI: 0.84, 2.24) and dose reductions due to an AE (RR = 1.59 (95% CI: 0.85, 2.98)), associated with lorlatinib compared with alectinib. The pre-PBAC response noted the dose intensities observed in the clinical studies for lorlatinib (94.5%) and alectinib (95.6%) were similar which suggests the trend towards a higher frequency of dose interruptions for lorlatinib is not clinically meaningful.

### ***Clinical claim***

- 6.25 The submission described lorlatinib as non-inferior to alectinib in terms of both effectiveness and safety.
- 6.26 Notwithstanding the limitations of indirect comparisons, and noting the potential for confounding from varying follow up durations across the CROWN and ALEX trials, the ESC considered the clinical claim presented in the submission appeared reasonable in terms of PFS. For OS, the evaluation considered the non-inferiority claim could not be substantiated. The data from CROWN were based on an interim analysis and were immature. Only 17.2% of events (51/296) had occurred across the treatment arms by the March 2020 interim data cut-off. The ESC considered the claim of non-inferiority for OS was uncertain due to the immaturity of the data but acknowledged lorlatinib was unlikely to be inferior to alectinib.
- 6.27 The ESC considered the clinical claim of non-inferiority for safety was not adequately supported by the evidence. Noting the indirect nature of the comparisons and varying follow-up durations across the CROWN and ALEX studies, the results indicated that lorlatinib may be associated with an increased risk of some AEs compared to alectinib. The pre-PBAC response maintained that first-line treatment with lorlatinib is generally tolerable and adverse events may be manageable with dose reduction, temporary discontinuation, and/or standard supportive medical therapy, when needed.

- 6.28 The PBAC considered the claim that lorlatinib was non-inferior to alectinib in terms of PFS was reasonable. The PBAC noted other outcomes (i.e., objective response rate, intracranial objective response rate) also supported the non-inferiority claim. The PBAC considered the claim of non-inferior OS was uncertain due to the immaturity of the clinical data. However, the PBAC considered that, overall, the claim of non-inferior comparative effectiveness was reasonable.
- 6.29 The PBAC considered that the claim of non-inferior comparative safety was uncertain given the different AE profile of lorlatinib. However, the PBAC considered the safety profile of lorlatinib was manageable with dose interruptions, dose reduction and standard medical management.

### **Economic analysis**

- 6.30 The submission presented a cost-minimisation analysis (CMA) comparing lorlatinib with alectinib based on the assumption of non-inferiority in terms of effectiveness and safety. The key components and assumptions of the cost-minimisation analysis are summarised below.

**Table 8: Summary of key components and assumptions of the cost-minimisation analysis**

<b>Component</b>	<b>Summary</b>
Therapeutic claim: effectiveness	Based on evidence presented, effectiveness is assumed to be non-inferior to alectinib
Therapeutic claim: safety	Based on evidence presented, safety is assumed to be non-inferior to alectinib
Evidence base	Indirect comparison of randomised trials for the outcomes: OS and PFS
Equi-effective doses	Lorlatinib 100 mg daily is equivalent to alectinib 600 mg twice daily
Direct medicine costs	Equivalent costs of lorlatinib and alectinib per patient per day
Other costs or cost offsets	There are no additional costs or cost offsets

Source: Table 3-1 of the submission

OS = overall survival; PFS = progression free survival

- 6.31 The equi-effective doses were estimated as lorlatinib 100 mg daily and alectinib 600 mg twice daily, assuming the same mean duration of treatment for the two drugs. The equi-effective doses for lorlatinib and alectinib proposed in the submission represent the daily doses used in the CROWN and ALEX studies, respectively, and are the doses recommended in the corresponding Product Information for the two medicines. There is uncertainty regarding the submission's assumption that the treatment duration of lorlatinib will be the same as that for alectinib. Potential differences in PFS durations and toxicity/tolerability profiles between the two medicines may differentially affect their respective mean treatment durations.
- 6.32 The submission did not consider any additional cost or cost offsets in the CMA. The evaluation considered the indirect comparison results indicated the safety profile of lorlatinib could be worse than that of alectinib, and hence the omission of costs associated with the management of AEs may favour lorlatinib.
- 6.33 The results of the CMA are presented below.

Table 9: Results of the CMA at effective prices

Name, manner of administration, form	Max quantity (units)	Days of treatment/pack	DPMQ	AEMP	Treatment Cost (daily) based on AEMP <sup>a</sup>
Alectinib Capsule 150 mg	224	28	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Lorlatinib 100 mg tablet	30	30	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Lorlatinib 25 mg tablet	90	30	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 3.4.1 of the submission

AEMP = Approved Ex-Manufacturer Price; DPMQ = Dispensed Price for Maximum Quantity.

<sup>a</sup>Treatment costs per day were calculated using the AEMP divided by days of treatment per pack. The AEMP rather than the DPMQ was used as pricing agreements are made by Government under the National Health Act 1953 at the ex-manufacturer level; pharmacy and wholesaler mark-ups were not considered as they do not relate to the cost of the medicine.

DPMQ = AEMP + \$54.14 + \$99.28 + \$7.74

6.34 The ESC considered a CMA to be an appropriate approach although noted that the potential additional costs associated with the increased incidence of AEs with lorlatinib compared with alectinib had not been accounted for.

### ***Drug cost/patient/course***

6.35 Applying the submission’s proposed effective DPMQ, the cost/patient for lorlatinib in the first-line setting was \$ [REDACTED] for a 30-day treatment duration, while the cost/patient for alectinib in the first-line setting was \$ [REDACTED] for a 30-day treatment duration (based on a DPMQ of \$ [REDACTED] for 28-days of treatment). The treatment duration of lorlatinib cannot be reliably determined based on available data. For both lorlatinib and alectinib, patients are to be treated until disease progression.

### ***Estimated PBS usage & financial implications***

6.36 This submission was not considered by DUSC. The submission used a market share approach to estimating the extent of use and financial impact of listing lorlatinib on the PBS. The key inputs for the financial estimates are summarised below.

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Table 10: Key inputs for financial estimates

Data	Value	Source/comment
<b>Market Share Model (primary analysis)</b>		
Market growth with existing listings	Yr 1: 16% Yr 2: 8% Yr 3: 4% Yr 4 +: 1.6%	Assumption based on PBS statistics. Growth in PBS services for ALK inhibitors observed in 2020 (30%) was at least partly attributable to patients being grandfathered onto the PBS following the PBS listings of brigatinib (May 2020) and lorlatinib (August 2020), and assumed to steadily decline to population growth (1.6%) by Year 4.
Additional market growth with requested listing of lorlatinib	Yr 1: █% Yr 2: █% Yr 3: █% Yr 4 +: █%	The submission assumed a small increase in overall market as lorlatinib is expected to optimise treatment outcomes in the first-line setting for some patients with brain metastases at diagnosis. Additional growth is expected to be minimal. An increase in displaced subsequent lines of therapy, from the introduction of lorlatinib as first line therapy, is likely to be limited given the poor prognosis of patients who progress on second line or third line therapy.
Script equivalence	1 script lorlatinib = : 1.07 scripts alectinib/brigatinib <sup>a</sup>	Brigatinib PSD, November 2019 TGA-approved PIs for lorlatinib, alectinib and brigatinib
Utilisation of ALK inhibitors by line of therapy	█% first-line █% subsequent lines	Based on the relative duration of first-line treatment to duration of second line treatment. First line lorlatinib median duration of treatment assumed to be similar to that of alectinib from updated analyses of ALEX (median 28.1 months). Subsequent treatment duration of lorlatinib of 8 months appears to have been based on the median PFS for lorlatinib as second line use in Study 1001
Utilisation of lorlatinib for current PBS listing (% of total ALK inhibitor market)	Year 1: █%, Years 2+: █%	Assumed to peak at █% share of subsequent treatment in Years 2-6 (█% x █% = █%). This is consistent with the estimate used for lorlatinib PBAC submission for use as subsequent therapy (November 2019 PBAC submission for lorlatinib).
Substitution of lorlatinib for alectinib and brigatinib in first-line setting (A)	█% in Yr 1, increasing to █% in Yr 6	Assumption was informed by expert opinion. Use is likely to be displaced, rather than substituted.
Reduction in lorlatinib share of the overall market in subsequent lines of treatment (B)	█% in Yr 1, increasing to █% in Yr 6	The submission assumed a two-year delay in impact of 1L uptake on lorlatinib market share on subsequent treatment, based on the median DoT of 28 months reported for alectinib (Mok, 2020).
Net increase in lorlatinib share of overall market due to expanded listing	Yr 1: █% Yr 2: █% Yr 3: █% Yr 4: █% Yr 5: █% Yr 6: █%	Calculation: Substitution in first-line minus reduction in market share as subsequent treatment (A-B)

Source: Table 4.1.1 of the submission; Excel workbook 'Att5\_Section 4\_Lorlatinib'.

1L = first line; ALK = Anaplastic lymphoma kinase; AIHW = Australian Institute of Health and Welfare; PBS = Pharmaceutical Benefits Scheme; MSAC = Medicare Services Advisory Committee; PBAC = Pharmaceutical Benefits Advisory Committee; DoT = duration of treatment; NSCLC = non-small cell lung cancer; Q4 = fourth quarter; PI = Product Information; PSD = Public Summary Document.

<sup>a</sup> One script of lorlatinib provides 30 days' supply, while one script of alectinib and brigatinib provides 28 days' supply, giving a script equivalence of 1:1.07 (30/28).

<sup>b</sup> The effective dispensed price for maximum quantity (DPMQ) for PBS item 11980M was incorrect in the Excel workbook for Section 4 (\$█). The calculated price to pharmacy did not include the wholesale mark-up. The wholesale mark-up calculated for this item (\$46.27) was also incorrect, as it was based on the AEMP for one pack, rather than the AEMP for the maximum quantity of 4 packs (\$█), for which the wholesale mark-up would be \$54.14. This was corrected during the evaluation.

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- 6.37 The submission assumed the ALK TKI market would grow with the existing ALK TKIs and with the requested expansion of lorlatinib listing. The PBAC previously considered that the market growth due to listing another ALK TKI would be minimal (paragraph 7.12, brigatinib, PSD, November 2019 PBAC Meeting).
- 6.38 The market share of lorlatinib in the first line setting was based on expert opinion. The overall market share of lorlatinib considered the increase in use of lorlatinib in the first-line setting and the reduction in lorlatinib market share in later-line settings. The submission also assumed that lorlatinib will substitute equally for alectinib and brigatinib. The ESC considered the market share of lorlatinib in the first line setting (█% in Year 1 increasing to █% in Year 6) was likely an overestimate given the safety profile of lorlatinib. The pre-PBAC response stated the CNS penetration of lorlatinib will make it the treatment of choice in the 25 to 40% of patients with brain metastases at presentation which supported the market share assumptions. The PBAC agreed with the ESC that █% was likely an overestimate and 35% was a more reasonable assumption.
- 6.39 The estimated use of lorlatinib and financial implications of the requested expansion of PBS listing of lorlatinib are summarised below.

**Table 11: Estimated use and financial implications of the requested expansion of PBS listing of lorlatinib**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use of lorlatinib</b>						
Number of scripts dispensed	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of lorlatinib (effective price)</b>						
Cost to PBS/RPBS less copayments	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
<b>Estimated financial implications for alectinib and brigatinib (effective prices)</b>						
Cost to PBS/RPBS less copayments	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>

Source: Table 4.2.11; Table 4.3.2, Table 4.4.2 of the submission and Excel workbook 'Att5\_Section 4\_Lorlatinib'

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

- 6.40 The submission concluded that the cost impact to the PBS of the expansion of the for lorlatinib listing will be minimal, as it will primarily replace the use of the existing PBS-listed ALK inhibitors for first-line treatment of advanced ALK-positive NSCLC, with the substituted medicines having the same cost per day of treatment as lorlatinib. The substitution of lorlatinib for alectinib and brigatinib resulted in small cost savings to the PBS/RPBS. These savings resulted from the difference in dispensed cost per patient per year (\$█) and the number of patient copayments per year (13.0) for lorlatinib compared to alectinib and brigatinib (cost/patient/year \$█, 12.2 copayments/year).

### **Quality Use of Medicines**

- 6.41 The submission presented a discussion of quality use of medicine issues summarised as follows:
- Provision of educational materials for lorlatinib which will include the Product Information, consumer medicine information, patient management and therapeutic guides, and diagnostic testing information and educational programs for oncologists.
  - Engagement with relevant stakeholders, including the Thoracic Oncology Group Australasia, Rare Cancers Australia, and the Lung Foundation, to ensure appropriate targeting and implementation.
  - Provision of routine Periodic Safety Update Report and use of the Pfizer Pharmacovigilance System for the collection and notification of any adverse reaction occurring around the world.

### **Financial Management – Risk Sharing Arrangements**

- 6.42 The submission stated that, the sponsor anticipates that the proposed listing will be subject to a Risk Sharing Arrangement (RSA). The PBAC noted there is currently an RSA in place for lorlatinib, alectinib and brigatinib.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred making a recommendation for the line-agnostic listing of lorlatinib for the treatment of patients with Stage IIIB (locally advanced) or Stage IV (metastatic) non-squamous or not otherwise specified type non-small cell lung cancer (NSCLC) with evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material as the TGA Delegate's Overview was not available at the time of consideration. However, the PBAC was of a mind to recommend the Authority Required line-agnostic listing of lorlatinib based on, among other matters, its assessment that the cost-effectiveness of lorlatinib would be acceptable if it were cost-minimised against the least costly alternative therapy.
- 7.2 The PBAC recalled brigatinib received a positive recommendation for a line agnostic PBS listing prior to having a TGA Delegate's Overview for the first line indication, however considered that, as lorlatinib was currently available on the PBS in the second line setting and there was not an urgent clinical need to list in the first line setting, a deferral was appropriate in the absence of a TGA Delegate's Overview.
- 7.3 The PBAC considered the nominated main comparator of alectinib was reasonable; however, noted brigatinib and ceritinib were alternative therapies. The PBAC noted no evidence was provided in the submission to support the superiority of lorlatinib

against any of the other alternative therapies; therefore, lorlatinib could not be more costly than the alternative therapies.

- 7.4 For the purpose of the CMA, the PBAC considered the equi-effective doses are: lorlatinib 100 mg once daily, alectinib 600 mg twice daily, brigatinib 180 mg once daily and ceritinib 750 mg once daily. The PBAC noted the equi-effective dose of ceritinib is consistent with previous recommendations for lorlatinib (paragraph 7.9, lorlatinib PSD, November 2019 PBAC meeting) and brigatinib (paragraph 7.11, brigatinib PSD, November 2019 PBAC meeting). The PBAC noted the CMA presented in the submission assumed the treatment durations for lorlatinib and alectinib would be the same. The PBAC considered this was uncertain, however noted there was no alternative reliable estimates of the likely treatment durations, and therefore recommended that, after adjustment for equi-effective doses, lorlatinib should be listed on the PBS at a cost per day that is no higher than the cost per day of the alternative therapies.
- 7.5 The PBAC noted the submission was based on an indirect treatment comparison of lorlatinib (CROWN study) and alectinib (ALEX study, n=303), using crizotinib as a common reference in the first-line setting. The PBAC noted the hazard ratio for the indirect comparison of PFS (based on independent review assessment) was 0.56 (95%CI: 0.34, 0.93) favouring lorlatinib. The PBAC noted the hazard ratio for the indirect comparison of OS was 0.95 (95%CI: 0.47, 1.90) favouring lorlatinib (using the December 2017 cut off for the ALEX study). The PBAC noted there were a number of transitivity issues across the trials, including different follow-up durations and different patient/ disease characteristics between the CROWN and ALEX trial populations that may impact on interpretation of the indirect comparison. However, overall, the PBAC considered the claim that lorlatinib is non-inferior to alectinib was reasonable.
- 7.6 The PBAC noted lorlatinib has a different toxicity profile than alectinib with hyperlipidaemia and adverse central nervous system effects occurring more frequently in patients treated with lorlatinib. Notwithstanding the consumer comments referred to above, the PBAC considered that adverse cognitive effects and visual changes would be the most clinically significant. However, the PBAC considered the safety profile of lorlatinib was manageable with dose interruptions, dose reductions and standard medical management.
- 7.7 The PBAC noted the line agnostic listing of lorlatinib will allow its use in the first line setting which will displace the other ALK TKIs to subsequent treatment lines. The PBAC considered the line-agnostic listing of lorlatinib on a cost minimisation basis with the least costly alternative therapy should result in no increase in net cost to the PBS.
- 7.8 The PBAC considered it would be appropriate for expenditure associated with a line agnostic listing of lorlatinib to be included in the current RSA with no increase in

expenditure caps as the listing would result in a change in treatment sequence rather than an increase in utilisation.

**Outcome:**

Deferred

## **8 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.

## **9 Sponsor's Comment**

Pfizer Australia is committed to working with the PBAC and the Department of Health to make lorlatinib available for the first-line treatment of locally advanced or metastatic ALK-positive non-small cell lung cancer at the earliest opportunity.