7.10 LUMACAFTOR WITH IVACAFTOR
Tablet containing lumacaftor 200 mg with ivacaftor 125 mg, Orkambi®, Vertex Pharmaceuticals (Australia) Pty Ltd

1 Purpose of Application

1.1 A resubmission to request a Section 100, Highly Specialised Drug Program, Authority Required listing for lumacaftor 200 mg with ivacaftor 125 mg fixed dose combination (lumacaftor/ivacaftor) for treatment of patients with cystic fibrosis (CF) aged ≥12 years who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This was the fourth submission for this indication. The first submission was considered by the PBAC in March 2016, a minor resubmission was considered in November 2016 and a major resubmission was considered in July 2017.

2 Requested listing

2.1 The submission requested the following listing:

Requested restriction

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
lumacaftor 200 mg/ ivacaftor 125 mg tablets	Pack containing 112 tablets	5	$18,750 (published)	Orkambi™ Vertex Pharmaceuticals (Australia) Pty Ltd

Condition:	Cystic Fibrosis (CF)
PBS Indication:	Treatment of cystic fibrosis in patients aged ≥ 12 years who are homozygous for the *F508del* mutation in the CFTR gene.
Treatment phase:	N/A
Restriction: Section 100 (HSD)	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined

Treatment criteria:	Patients must be assessed through a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit, AND Patient must be homozygous for the F508del mutation in the CFTR gene AND The treatment must be given concomitantly with standard therapy for this condition
Clinical criteria:	Treatment of cystic fibrosis in patients aged years ≥ 12 years who are homozygous for the F508del mutation in the CFTR gene.
Population criteria:	Patients must be aged ≥ 12 years.
Foreword:	N/A
Definitions:	N/A
Prescriber Instructions:	The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and (3) a signed patient acknowledgement; or an acknowledgement signed by a parent or authorized guardian; if applicable; and (4) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the *F508del* mutation on the CFTR gene.
Administrative Advice:	N/A
Cautions:	N/A

Abbreviations: CF=cystic fibrosis; CFTR cystic fibrosis transmembrane conductance regulator; HSD=highly specialised drugs
Source: Table 1.4.2, p 58 of the submission

Suggested wording for the restriction

2.2 See Section 8 for PBAC recommended wording for the restriction.

2.3 The recommended dose is two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours. The treatment is ongoing for the lifetime of the patient. Dose reductions are recommended in the TGA approved product information (PI) for patients with moderate or severe hepatic impairment.

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

3 Background

3.1 TGA status at the time of PBAC consideration: Lumacaftor/ivacaftor was registered by the TGA for "the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene" on 8 March 2016.

3.2 This was the fourth PBAC submission requesting listing for lumacaftor/ivacaftor for the treatment of patients with cystic fibrosis (CF) aged ≥12 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane

conductance regulator (CFTR) gene. A summary of the price, key clinical data and clinical claim presented in each submission is provided in Table 1.

Table 1: Summary of price, key clinical data and clinical claim in current and previous submissions requesting listing of lumacaftor/ivacaftor

Submission	PBAC meeting	Price, key clinical data and clinical claim
1	March 2016	**Price:** $[redacted] per patient per year **Key Clinical data:** TRAFFIC & TRANSPORT 24 week Randomised Controlled Trials (RCTs) PROGRESS 96 week open label extension trial – 24 week interim results. **Claim:** Lumacaftor/ivacaftor improves key CF treatment outcomes which are associated with prolongation of life expectancy – FEV_1, BMI and rate of pulmonary exacerbations – and provides a durable benefit in this otherwise relentlessly progressive, fatal disease. Further, lumacaftor/ivacaftor on top of BSC has an equivalent safety profile to BSC (Vertex submission to March 2016 PBAC, pp. 117). No decline in FEV_1 for Orkambi treated patients over time. The PBAC did not accept this claim.
2	November 2016	**Price:** $[redacted] per patient per year** **Key Clinical data:** TRAFFIC & TRANSPORT 24 week RCTs PROGRESS 96 week open label extension trial – 24 week interim results. **Claim:** Evidence from two large, high quality, Phase 3, placebo-controlled randomised trials indicates that lumacaftor/ivacaftor improves key CF treatment outcomes that are associated with prolongation of life – a benefit that is over-and-above that currently provided by BSC (Vertex sub to Nov 16 PBAC, pp 4). No decline in FEV_1 for Orkambi treated patients over time. The PBAC did not accept this claim.
3	**July 2017**	**Price:** $[redacted] per patient per year** **Key Clinical data:** TRAFFIC & TRANSPORT 24 week RCTs PROGRESS 96 week open label extension trial – 96 week results, part reported. **Claim:** New longer-term efficacy data from PROGRESS demonstrates sustained improvements in key CF treatment outcomes that are associated with prolongation of life. Despite the progressive nature of cystic fibrosis, mean ppFEV1 remained above the pre-treatment baseline after up to 120 weeks of cumulative exposure to lumacaftor/ivacaftor. In addition, there were sustained benefits of combined lumacaftor/ivacaftor therapy on pulmonary exacerbation rates and patient-reported respiratory symptoms, and continued improvement in nutritional status. These data show that lumacaftor/ivacaftor combination therapy provides multisystem benefits that continue to dampen the expected disease trajectory

Submission	PBAC meeting	Price, key clinical data and clinical claim
		over the longer term, and suggests that lumacaftor/ivacaftor is a disease modifying therapy in cystic fibrosis (Vertex submission to July 2017 PBAC meeting pp 140). No decline in FEV_1 for Orkambi treated patients over time. The PBAC did not accept this claim.
4	**July 2018**	**Price:** $[redacted] per patient per year**‡ **Key Clinical data:** TRAFFIC & TRANSPORT 24 week RCTs PROGRESS 96 week open label extension trial – FINAL STUDY RESULTS provided 12 June 2018 (report dated 25 October 2016) **Claim:** Decrease in rate of decline in FEV_1 for Orkambi treated patients 42%‡ of untreated patients.

** Price achieved though proposed financial caps if proposed usage levels met.
‡ Price offer reduced to $[redacted] per patient per year from $[redacted] per patient per year in prePBAC response. Claim regarding rate of decline in FEV1 revised in pre-PBAC response from [redacted]% to 42%.

3.3 A major submission for lumacaftor/ivacaftor was rejected at the March 2016 PBAC meeting on the basis of an unacceptably high and uncertain incremental cost effectiveness ratio at the requested price, and uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements in lung function and survival (paragraph 7.1, March 2016 Public Summary Document (PSD)).

3.4 A minor resubmission was also rejected by the PBAC at its November 2016 meeting noting that the issues it previously identified in its consideration of the March 2016 submission had not been addressed. The PBAC further noted the continued uncertainty regarding long-term benefits of treatment on lung function and overall survival (paragraph 7.1, November 2016 PSD).

3.5 At the July 2017 meeting, lumacaftor with ivacaftor was not recommended by the PBAC on the basis of uncertainty around the longer term impact of lumacaftor/ivacaftor on lung function and survival beyond 2 years of treatment and unacceptable cost effectiveness at the requested price.

3.6 The PBAC noted that updated evidence from the PROGRESS extension study as reported in the Lancet (Konstan, et al. (2017)[1]). demonstrated that the modest 2.81 percentage point improvement in ppFEV1 in lumacaftor/ivacaftor treated patients versus placebo at 24 weeks observed in TRAFFIC/TRANSPORT was not maintained after an additional 96 weeks of treatment. The PBAC considered the claim that lumacaftor/ivacaftor slows the rate of decline in ppFEV1 beyond 24 weeks,

[1] Konstan, M. W., McKone, E. F., Moss, R. B., et al. (2017). Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): A phase 3, extension study. The Lancet Respiratory Medicine 2017. 5 (2): 107-18.

compared with patients treated with BSC, was not adequately supported by the evidence presented in the resubmission.

3.7 However, the PBAC noted that on the basis of the direct randomised trials presented by the resubmission, a patient treated with lumacaftor/ivacaftor could expect to have one fewer pulmonary exacerbation over 2.5 years, and one fewer hospitalisation due to a pulmonary exacerbation over 3 years. The PBAC therefore considered that the claim of superior comparative effectiveness was reasonable.

3.8 The PBAC noted that the economic model included in the resubmission was based on the assumption that lung function was maintained for patients treated with lumacaftor/ivacaftor for the reminder of their life, and this was inconsistent with the longer-term clinical evidence. Accordingly, the PBAC defined a scenario which it considered more informative for decision making, by changing inputs to the resubmission's economic model to better reflect the available clinical data. This scenario resulted in an unacceptably high incremental cost effectiveness ratio (ICER) of significantly more than $200,000 per quality adjusted life year (QALY) gained.

3.9 At the July 2017 meeting and on the request of the Minister (delegate) under section 101(3) of the Act, the PBAC considered the price or range of prices at which it considered treatment with lumacaftor/ivacaftor would be acceptably cost-effective for the purposes of the Act. The PBAC advised that the maximum ICER it would consider to be acceptably cost effective, noting the precedent of ivacaftor, would be around $105,000 -$200,000 per QALY gained. Based on its revised scenario, the PBAC advised that the maximum DPMQ that it would consider to be acceptably cost-effective would be around $[redacted] (or around $[redacted] per patient per year, assuming 11 packs per patient per year) which would result in an ICER of $105,000/QALY - $200,000/QALY.

3.10 A copy of the minutes from the July 2017 meeting is provided in Appendix 1.

4 Population and disease

4.1 Cystic fibrosis is an autosomal recessive disease caused by mutations in the CFTR gene. Cystic fibrosis is a progressive multi-organ disease that primarily affects the pulmonary and digestive systems.

4.2 As per the three previous submissions, this submission proposed that lumacaftor/ivacaftor be administered in addition to current best supportive care in patients aged 12 years and older who are homozygous for the F508 deletion mutation CFTR gene.

4.3 A separate submission to the July 2018 meeting of the PBAC has requested lumacaftor/ivacaftor be PBS subsidised for use, in addition to current best supportive care, in patients aged 6 - 11 years inclusive, who are homozygous for the F508 deletion mutation CFTR gene.

5 Comparator

5.1 As per the three previous submissions, best supportive care (BSC) was nominated as the comparator. The PBAC previously accepted that this is the appropriate comparator (paragraph 7.4, March 2016 PSD).

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a combined hearing for both lumacaftor with ivacaftor submissions (patients aged 6 – 11 years [item 5.08] and patients aged 12 years and older – [item 7.10]). The presentation focussed predominantly on treatment outcomes in younger patients (aged 6 - 11 years); however, the clinician noted the benefits of treatment with lumacaftor/ivacaftor in both age groups. The clinician stressed the importance of early treatment in CF to prevent or delay lung damage and reduce the rate of decline in lung function; and highlighted a recent study by Graber *et al* (2018)[2] to demonstrate that treatment with Orkambi in patients aged 12 years and older results in improvement in CFTR function. The Graber *et al* (2018) study, which measured CFTR biomarkers over a treatment period of 24 weeks, concluded that the results "*indicate that lumacaftor–ivacaftor combination therapy improves CFTR activity in Phe508del homozygous patients with CF to levels comparable to the lower range of values seen in patients harbouring CFTR residual function mutations (p.1439)*".

6.2 In response to a question from the PBAC regarding differences observed in patient response in the PROGRESS trial (response analysis of absolute change from baseline in $ppFEV_1$ – see paragraphs 6.11 and 6.12), the clinician expressed the view that looking at responders, particularly in relation to absolute changes in FEV_1 is not meaningful for comparison and does not show the effect of lumacaftor/ivacaftor on CFTR function.

Consumer comments

6.3 The PBAC noted and welcomed the input from individuals (3980), health care professionals (45) and organisations (5) via the Consumer Comments facility on the PBS website for both lumacaftor with ivacaftor submissions combined (patients aged 6 – 11 years [item 5.08] and patients aged 12 years and older – [item 7.10]). The comments described a range of benefits of treatment with lumacaftor/ivacaftor, including improvement in lung function, reduction in chest infections and exacerbations, weight gain, fewer hospital visits, fewer medications to be consumed on a daily basis, slowing disease progression, and improvement in quality of life. The

[2] Graeber, S.Y., *et al* (2018). Effects of Lumacaftor–Ivacaftor Therapy on Cystic Fibrosis Transmembrane Conductance Regulator Function in Phe508del Homozygous Patients with Cystic Fibrosis**.** *American journal of respiratory and critical care medicine,* Volume 197, Number 11, pp 1433 – 1442.

comments noted that the very high cost of the drug on the private market puts it out of the financial reach of Australian patients and a number of comments expressed frustration that lumacaftor/ivacaftor has not yet been recommended for listing, despite a number of submissions being made to the PBAC.

6.4 The PBAC noted the advice received from the Cystic Fibrosis Centre Directors (representing interests from the Cystic Fibrosis Specialist Interest Group of the Thoracic Society of Australia and New Zealand, and Cystic Fibrosis Australia) and Cystic Fibrosis SA. The PBAC specifically noted the advice that the use of lumacaftor/ivacaftor may halt or slow decline in lung function; reduce hospital stays, IV treatments and hospitalisation costs; and improve nutritional status and quality of life. The advice received from the Cystic Fibrosis Centre Directors also noted that in the experience of Australian CF physicians who have used this drug in trials and on the compassionate Special Access Scheme, patients have experienced a reduction in acute respiratory exacerbations. The advice states that "acute respiratory exacerbations in CF result in worsening of lung function, permanent loss of lung function and decreased survival" and that "any therapy that reduces the rate of acute exacerbations is likely therefore to have a very beneficial effect on the clinical course of patients with CF." The PBAC noted that although this advice was supportive of the evidence provided in the submission, the authors were not able to provide data from Australian patients to substantiate these observations ahead of PBAC consideration.

Clinical trials

6.5 No new clinical trials were presented in the resubmission.

6.6 However, at the request of the Department, further results from the PROGRESS study (VX12-809-105) were provided by the sponsor on 12 June 2018 in the form of the PROGRESS study final study report, Version 1.0, dated 25 October 2016. Previously the PBAC had only been provided with Konstan, et al. (2017).

Trial ID	**Protocol title/ Publication title** PROGRESS study final study report, Version 1.0, dated 25 October 2016.	**Publication citation**
Direct randomised trials		
Traffic	Clinical study report VX12-809-103 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	8 September 2014
Transport	Clinical study report VX12-809-104 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation.	2 September 2014
	Wainwright CE, Elborn JS, Ramsey B, Marigowda G et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR.	New England Journal of Medicine 2015; 373:220-23
Rollover extension study		
Progress	Clinical study report VX12-809-105 A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation	25 October 2016
	Elborn, J., Ramsey, B. and Boyle, M. B. Lumacaftor in combination with ivacaftor in patients with cystic fibrosis who were homozygous for the F508del-CFTR mutation.	The 38th annual European Cystic Fibrosis Conference, Brussels, Belgium, 10-12 June 2015
	Konstan, M. W., McKone, E. F., Moss, R. B., et al. (2017). Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): A phase 3, extension study.	The Lancet Respiratory Medicine 2017. 5 (2): 107-18.
	Konstan, M., McKone, E., Moss, R., et al. Evidence of reduction in annual rate of FEV_1 decline and sustained benefits with lumacaftor and ivacaftor (LUM/IVA) in patients (PTS) with CF homozygous for f508del-cftr.	Pediatric Pulmonology 2016. 51: 260.

Comparative effectiveness

6.7 The primary outcome at 24 weeks in the TRAFFIC and TRANSPORT trials was an absolute increase in ppFEV1 of 2.8 percentage points (95% CI: 1.80, 3.82). The PBAC previously considered that it was uncertain whether the observed improvement in ppFEV1 represented a clinically significant difference noting that it was considerably smaller than the improvement of 10.58 percentage points (95% CI: 8.57, 12.59) demonstrated for ivacaftor monotherapy for patients with cystic fibrosis with a G551D or other class III gating mutation in the CFTR gene on at least one allele (paragraph 7.6, March 2016 PSD). In addition, the incremental improvements (compared with placebo) demonstrated in patients' weight and quality of life as measured using the revised Cystic Fibrosis Questionnaire (CFQ-R) for ivacaftor monotherapy in this different patient population were considered more compelling than for lumacaftor/ivacaftor.

6.8 The Pre-Sub-Committee Response (PSCR) for the July 2017 submission argued it was not appropriate to directly compare the magnitude of $ppFEV_1$ improvement observed with lumacaftor/ivacaftor with that observed with ivacaftor monotherapy because of differences in disease aetiology between the two treatment populations. Whilst acknowledging these differences in the genetic basis of the disease, the June 2017 ESC nevertheless noted that the magnitude of the change in $ppFEV_1$ was less than that for ivacaftor monotherapy in Class III gating mutations and that the clinical significance of the 2.81 percentage point improvement remained uncertain.

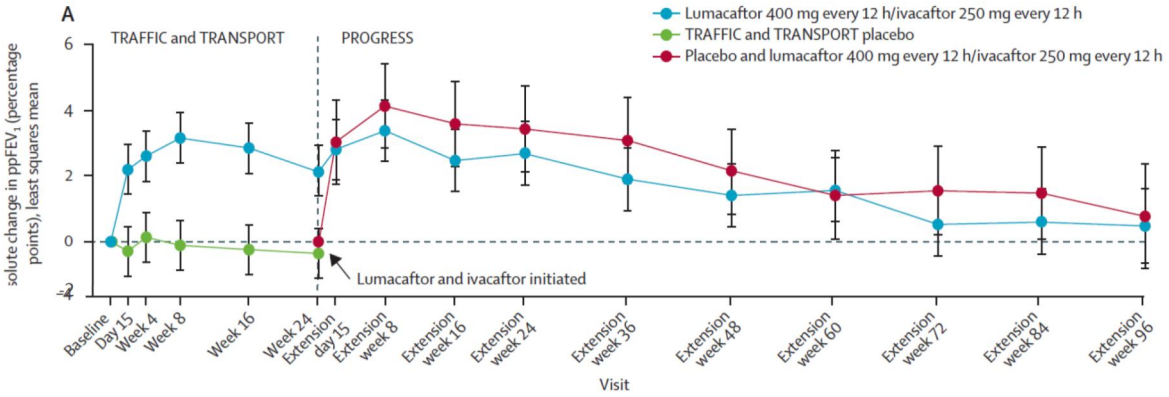
6.9 The clinical evidence provided to the July 2017 PBAC from the PROGRESS extension study indicated that there was a decline in $ppFEV_1$ for lumacaftor/ivacaftor treated patients over time with the modest 2.81 percentage point improvement observed in TRAFFIC and TRANSPORT not being maintained at weeks 72 or 96 of the extension study. Using the pre-specified analysis methods, the ESC noted that the change in $ppFEV_1$ from baseline in lumacaftor/ivacaftor treated patients was no longer statistically significant at extension weeks 72 or 96 (i.e. up to 120 continuous weeks of treatment). Patients who had been treated with placebo and transitioned to lumacaftor/ivacaftor treatment demonstrated a change of 1.5 percentage points in $ppFEV_1$ after 72 weeks of treatment, although the difference with baseline was no longer statistically significant at 96 weeks. These data are illustrated in Table 2 and Figure 1.

Table 2: Absolute changes from baseline in ppFEV$_1$ in TRAFFIC or TRANSPORT and PROGRESS

	TRAFFIC or TRANSPORT least squares mean, (95% CI), p value†		PROGRESS least squares mean, (95% CI), p value†	
	Placebo (n=371)	**Lumacaftor/ivacaftor (n=369)**	**Placebo transitioned to lumacaftor/ivacaftor (n=176)**	**Continued lumacaftor/ivacaftor (n=369*)**
Week 24	–0·4 (–1·2 to 0·4), p=0·3494	2·2 (1·3 to 3·0), p<0·0001	..	..
Extension week 72	..	..	1·5 (0.2, 2·9), p=0·0254	0·5 (–0·4 to 1·5), p=0·2806
Extension week 96	..	..	0·8 (–0·8, 2·3), p=0·3495	0·5 (–0·7 to 1·6), p=0·4231

Source: Table B.7-2, page 128 July 2017 resubmission.
Abbreviations: ppFEV$_1$ = percent predicted FEV$_1$, CI = confidence interval.
†For the placebo and lumacaftor/ivacaftor groups, baseline from TRAFFIC or TRANSPORT was used; for the placebo transitioned to lumacaftor/ivacaftor group, baseline from PROGRESS was used. All p values (including for TRAFFIC or TRANSPORT data) are within treatment.
* This number is as presented in the submission. 369 patients in TRAFFIC and TRANSPORT had received at least one dose of lumacaftor/ivacaftor 400mg/250mg twice daily and therefore are included in safety analyses. 341 of these patients enrolled in PROGRESS study, and 340 received at least one dose.

Figure 1: Absolute change in ppFEV$_1$ in TRAFFIC, TRANSPORT and PROGRESS, least square mean



Source: Konstan et al, 2017

6.10 The PSCR to the July 2017 PBAC meeting argued that the main objective of CF treatment is to minimise the rate of deterioration over time and that it is not meaningful to simply compare the ppFEV1 at week 96 of PROGRESS for lumacaftor/ivacaftor treated patients with their own baseline ppFEV1 given that, had those patients received BSC, they would have deteriorated to a greater extent over this time period. However, the ESC noted that the updated data from PROGRESS and the argument in the PSCR contradicted the assumption in the July 2017 economic model that patients treated with lumacaftor/ivacaftor do not experience a decline in ppFEV1 over time.

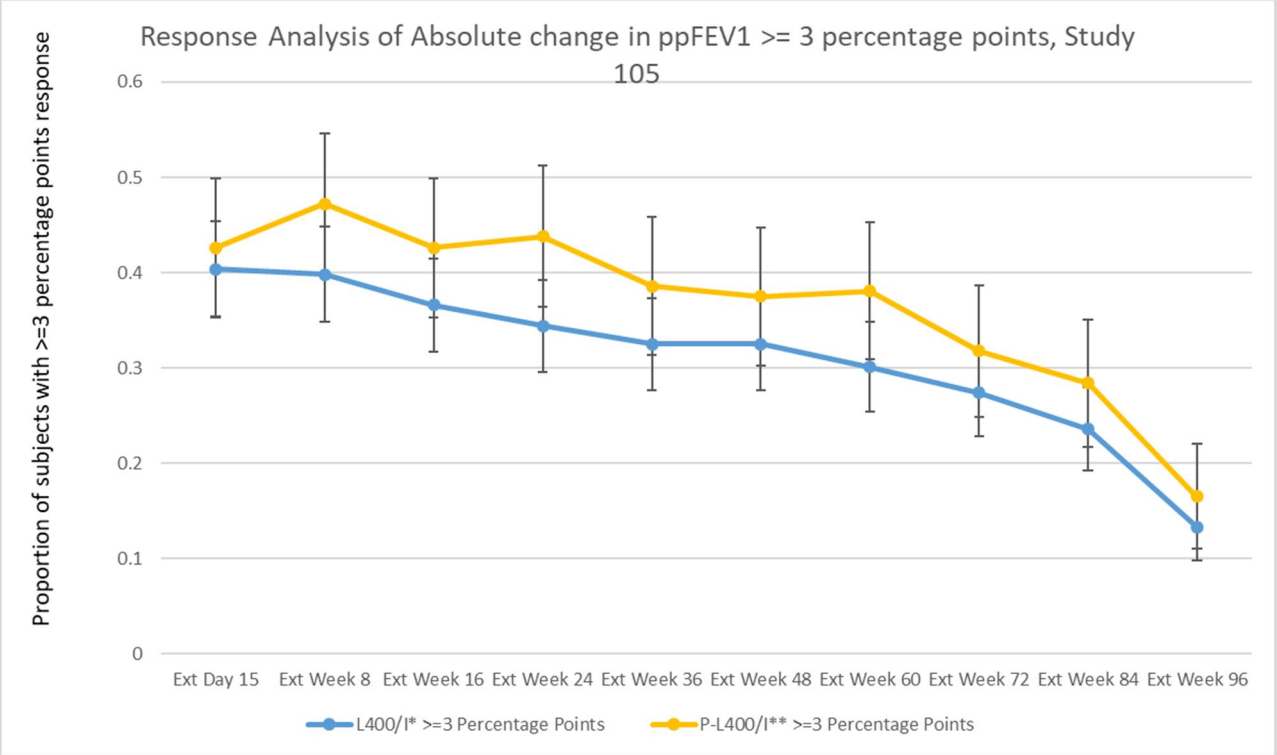
6.11 The June 2017 ESC also noted that the treatment gain of 10.58 percentage points in the clinical trial for ivacaftor for patients with cystic fibrosis with a G551D or other class III gating mutation in the CFTR gene on at least one allele was maintained at up to 144 weeks of treatment (PSD, ivacaftor, March 2014).The final study report for

PROGRESS included results of a response analysis of absolute change from baseline in ppFEV1. Responders were defined as patients with a ≥ 3%, 5% or 10% in $ppFEV_1$ compared to baseline. At Week 72 of Study 105, approximately 30%, 20%, and 10% of subjects were responders, respectively, at the 3, 5, and 10% cut-offs (final study report PROGRESS, version 1.0, 25 October 2016, pp 108).

6.12 The proportion of lumacaftor/ivacaftor patients who achieved an increase in $ppFEV_1$ of at least 3%, 5% or 10% (respectively across the figures over time) is presented in figures 2 - 4. These data indicate that the proportion of patients meeting each of the response criteria declined over time; by 96 weeks, the proportion of patients with a 3% or 5% response was significantly lower (the confidence intervals did not overlap) than at day 15. The proportion of patients with a 10% response was relatively stable over the period, but was also significantly lower at 96 weeks among those continuing lumacaftor/ivacaftor from previous studies. However, it was not lower for those who had switched from placebo to lumacaftor/ivacaftor.

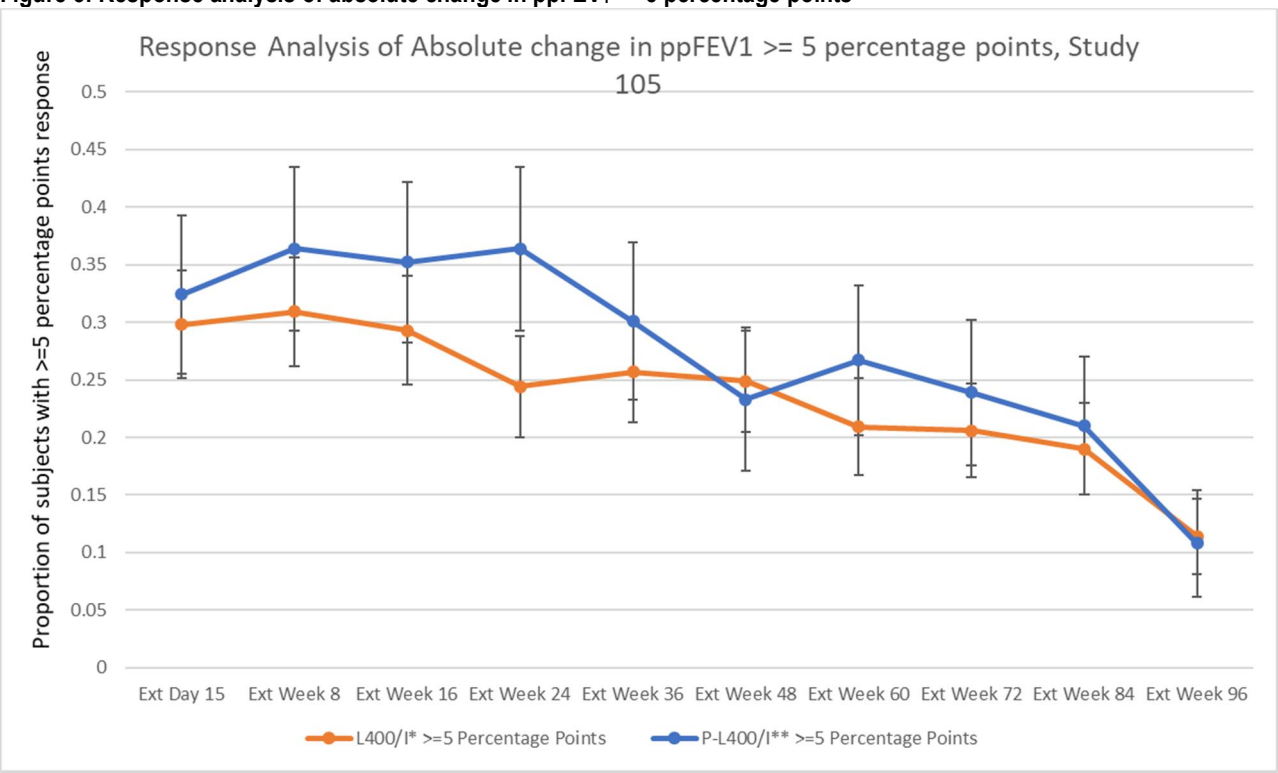
6.13 In the Pre-PBAC Response , the sponsor expressed concern that undue emphasis may be placed on responder analyses. The sponsor noted that patients with CF experience a constant downward trajectory in $ppFEV_1$ over the course of their lifetime and therefore it is unreasonable to benchmark treatment success using percentage improvement in $ppFEV_1$ as a responder metric. The sponsor further stated that the objective of CF treatment is to maintain lung function. The PBAC acknowledged that maintaining or slowing decline in lung function was the main aim of CF treatment. However, the committee noted that the available data suggest considerable heterogeneity in the clinical benefit received by patients and that the uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements in lung function and survival remains.

Figure 2: Response analysis of absolute change in ppFEV$_1$ >= 3 percentage points



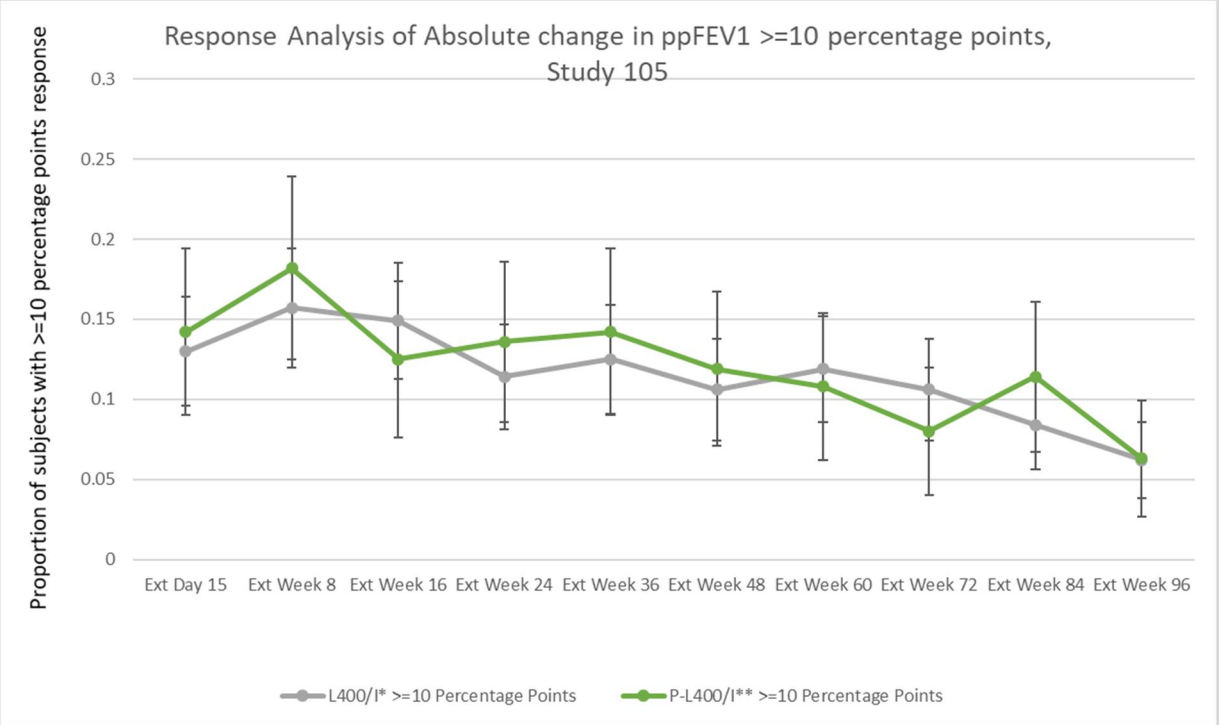
Source: Prepared during the evaluation from data as specified in the Table Annexe (Table 6).
Abbreviations: CI=confidence intervals; Ext=extension; ppFEV=percent predicted forced expiratory volume.

Figure 3: Response analysis of absolute change in ppFEV$_1$ >= 5 percentage points



Source: Prepared during the evaluation from data as specified in the Table Annexe (Table 6).
Abbreviations: CI=confidence intervals; Ext=extension; ppFEV=percent predicted forced expiratory volume.

Figure 4: Response analysis of absolute change in ppFEV$_1$ >= 10 percentage points



Source: Prepared during the evaluation from data as specified in the Table Annexe (Table 6).
Abbreviations: CI=confidence intervals; Ext=extension; ppFEV=percent predicted forced expiratory volume.

6.14 The changes from baseline in pulmonary exacerbation (PE) events in TRAFFIC, TRANSPORT and PROGRESS are shown in Table 3. The annualised rates for lumacaftor/ivacaftor were lower than the rates in the placebo group up to week 24.

Table 3: Changes from baseline in pulmonary exacerbation events in TRAFFIC or TRANSPORT and PROGRESS

	TRAFFIC or TRANSPORT* n (95% CI)		**PROGRESS*** n (95% CI)	
Pulmonary exacerbation events per patient-year	**Placebo (n=371)**	**Lumacaftor/ ivacaftor (n=369)**	**Placebo transitioned to lumacaftor/ ivacaftor (n=176)**	**Continued lumacaftor/ ivacaftor (n=369)**
All events	1.14 (0.97 to 1.34)	0.70 (0.57 to 0.84)	0.69 (0.56 to 0.85)	0.65 (0.56 to 0.75)
Requiring hospital admission	0.45 (0.36 to 0.57)	0.17 (0.12 to 0.25)	0.30 (0.22 to 0.40)	0.24 (0.19 to 0.29)
Requiring intravenous antibiotics	0.58 (0.47 to 0.72)	0.25 (0.19 to 0.33)	0.37 (0.29 to 0.49)	0.32 (0.26 to 0.38)

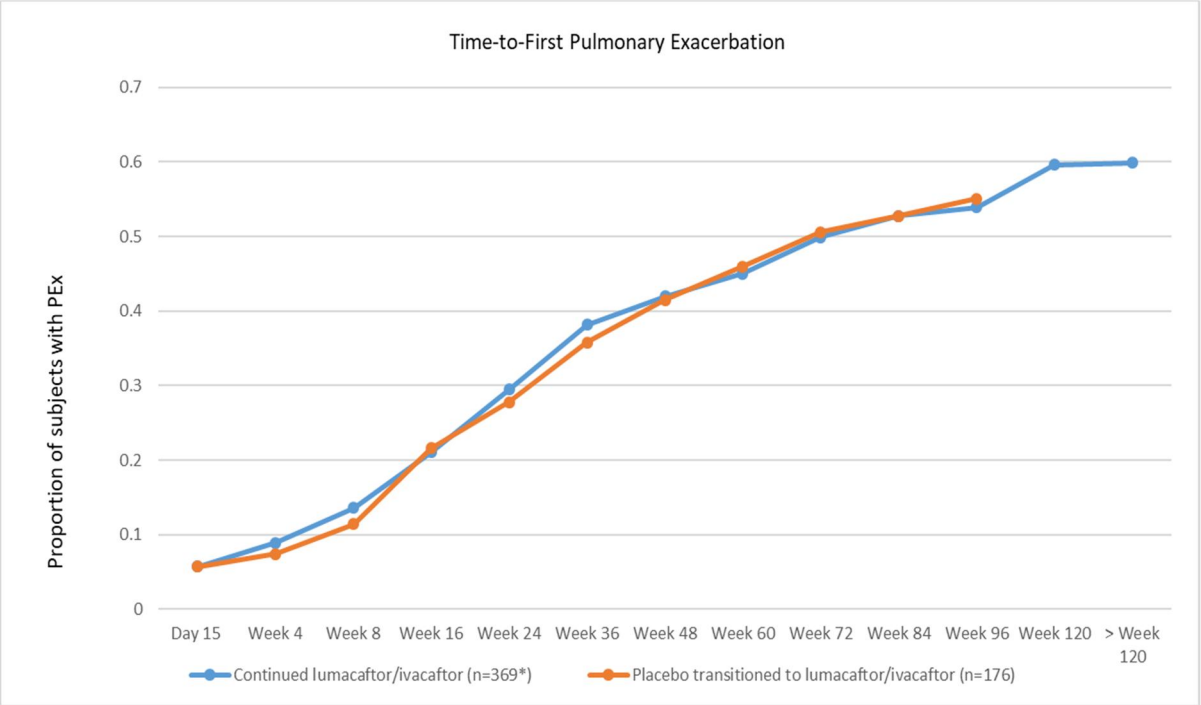
Source: Table B.7-14, page 133 July 2017 resubmission.
Abbreviations: CI = confidence interval.
* The analyses for TRAFFIC or TRANSPORT included events through to week 24. The pulmonary exacerbations analyses for PROGRESS included events throughout the cumulative study period (TRAFFIC or TRANSPORT and PROGRESS), such that the placebo transitioned to lumacaftor/ivacaftor group received up to 96 weeks of active treatment and the lumacaftor/ivacaftor group received up to 120 weeks of active treatment.

6.15 The final study report for the PROGRESS study shows there was an increase in the proportion of patients experiencing a pulmonary exacerbation (Figures 5 and 6). The pre-PBAC Response asserted that Figures 5 and 6 are a "gross misrepresentation of the pulmonary exacerbation (PEx) data over time", stating that the figures, which use time-to-event-data, would be expected to go up over time as they are cumulative probability curves. The sponsor further stated that the use of time-to-

event-data is inappropriate as time-to-first event data does not capture multiple events per patient, which is highly relevant in CF.

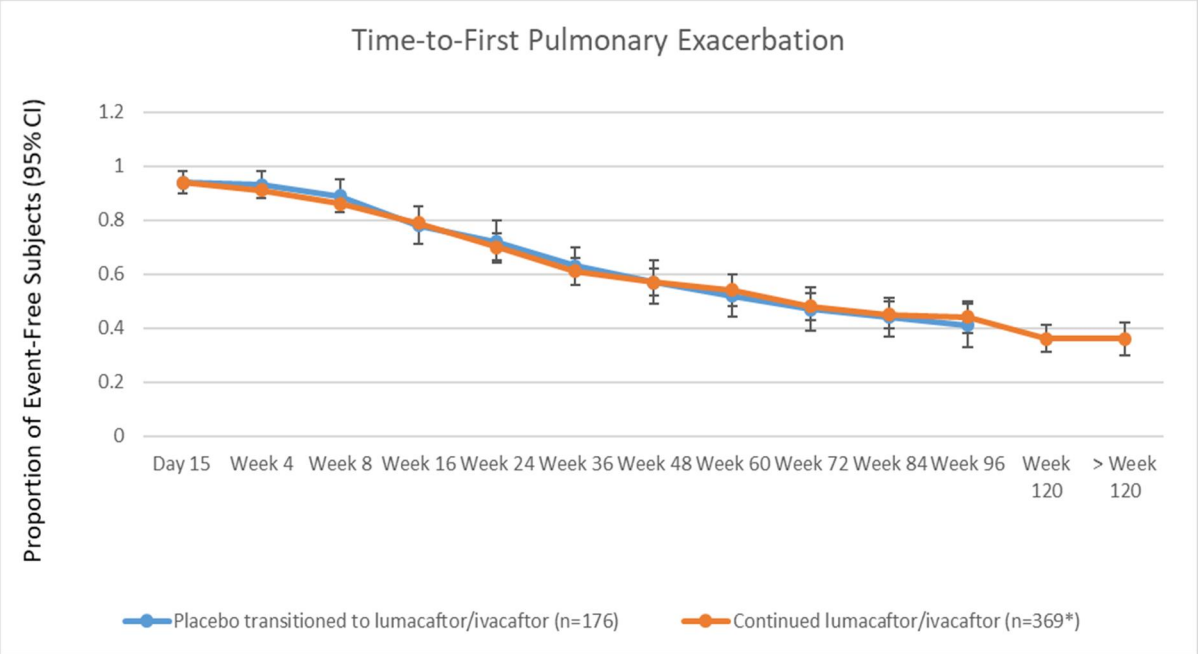
6.16 The PBAC noted the sponsors request that "only the correct presentation and interpretation of the PEx is made available to the PBAC". The PBAC considered that these figures should be retained in the documentation for this consideration as Figures 5 and 6 are informative for clinicians and patients.

Figure 5: Time-to-First Pulmonary Exacerbation Study 105



Source: Prepared during the evaluation from data as specified in the Table Annexe (Table 5).
Abbreviations: Ext=extension; PEx=pulmonary exacerbations.
Note: Information was not available to allow the presentation of confidence intervals for these point estimates.

Figure 6: Time-to-First Pulmonary Exacerbation Study 105



Source: Prepared during the evaluation from data as specified in the Table Annexe.
Abbreviations: CI=confidence intervals; Ext=extension.

6.17 At the request of the Department, in the pre-PBAC Response, the sponsor provided an additional analysis of the pulmonary exacerbation data from the PROGRESS study to determine if there is an increase in the rate of pulmonary exacerbations over time, as this analysis was not included in the final study report for PROGRESS. The sponsor stated that the results, presented in Table 4 below, "clearly indicate that there is no increase in the annualised rate of PEx — in fact at 0.60 events/patient-year after 2 years of treatment this remains approximately half that of placebo patients in TRAFFIC/TRANSPORT (which was 1.14 events/patient-year)." The pre-PBAC Response , also argued that PEx are the primary cause of morbidity in CF and are associated with a permanent decline in lung function. The PBAC acknowledged that a reduction in PEx is an important clinical outcome for CF patients; however, as discussed in paragraph 6.12 in relation to ppFEV$_1$, the PBAC considered that there was still uncertainty around the longer term impact of lumacaftor/ivacaftor on PEx (beyond 96 weeks).

Table 4 Pulmonary exacerbations by study period: Full analysis set

PROGRESS time interval	TRAFFIC/TRANSPORT + PROGRESS time interval	L400, N=369	Placebo, N=371
NA	0 – 24 weeks	0.70 [a]	1.14 [a]
		L400/I, N=340	**P-L400/I, N=176**
0 – 24 weeks	24 – 48 weeks	0.66 [b]	0.70 [b]
24 – 48 weeks	48 – 72 weeks	0.78 [b]	0.81 [b]
48 – 72 weeks	72 – 96 weeks	0.60 [b]	0.77 [b]

a Source: Table B.7-14, page 133 July 2017 resubmission.
b Source: VX15-809-105 Final Ad Hoc, 21June2018 (requested by OHTA). Data not reliable week 72-96 due to small sample size

6.18 The changes from baseline in CFQ-R in TRAFFIC, TRANSPORT and PROGRESS are shown in Table 5. The numerical improvement observed in CFQ-R at 24 weeks for lumacaftor/ivacaftor treated patients was not statistically significantly different to the improvement observed in placebo treated patients. The final study report for the PROGRESS study (Version 1.0 25 October 2016) provides results for CFQ-R at each study visit (Figure 7).

6.19 The final study report for the PROGRESS study states that the minimum clinically important difference (MCID) for the CFQ-R respiratory domain score is considered to be 4 points. At Week 72 of the PROGRESS study, the LS mean absolute change in CFQ-R respiratory domain score was 5.7 points (P <0.0001) for the L400q12h/I group (continued lumacaftor/ivacaftor) and 3.3 points (P = 0.0124) for the P-L400q12h/I group (placebo transitioned to lumacaftor/ivacaftor) in the primary in the primary analysis.The improvement in CFQ-R was below the MCID of 4 points for both groups at 96 weeks.

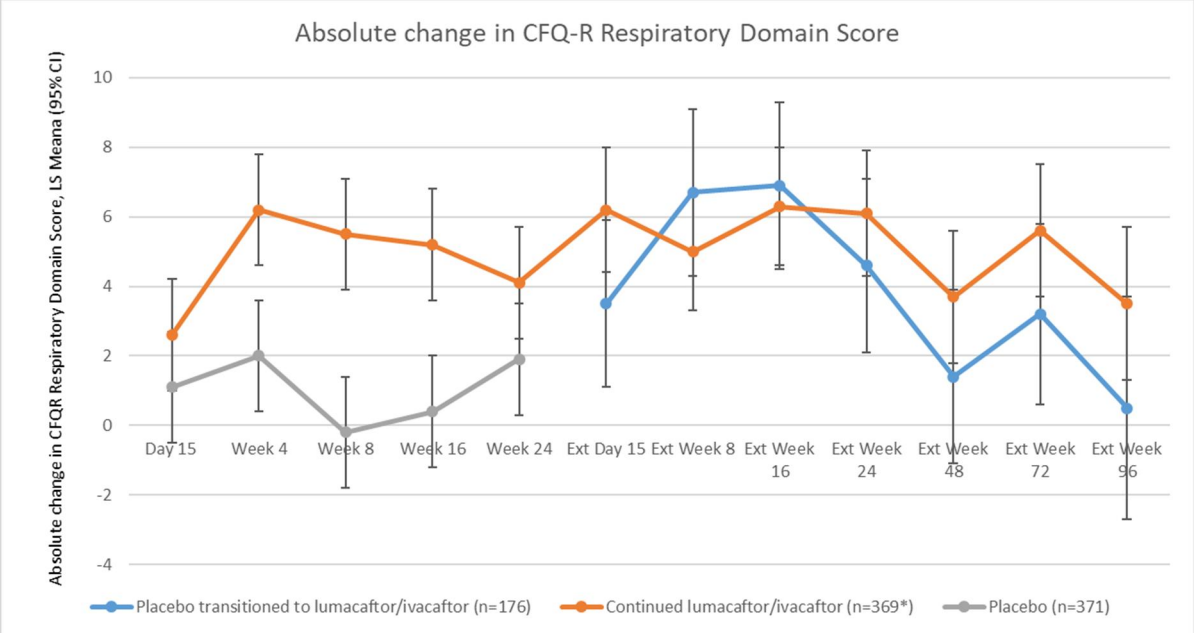
6.20 The absolute change from baseline in body mass index (BMI) continued to increase through to 96 weeks in PROGRESS in patients previously treated with both lumacaftor/ivacaftor and placebo in TRAFFIC/TRANSPORT (see Table 4 and Figure 8).

Table 5: Changes from baseline in CFQ-R respiratory domain score and BMI in TRAFFIC, TRANSPORT and PROGRESS

	TRAFFIC or TRANSPORT		PROGRESS	
	Placebo (n=371)	Lumacaftor/ ivacaftor (n=369)	Placebo transitioned to lumacaftor/ ivacaftor (n=176)	Continued lumacaftor/ ivacaftor (n=369)
Absolute change from baseline in CFQ-R respiratory domain score, least squares mean, 95% CI, (points), p value†				
Week 24	1.9 (0.3 to 3.5) p=0.0213	4.1 (2.5 to 5.7) p<0.0001	..	..
Extension week 72	..	..	3.3 (0.7 to 5.9) p=0.0124	5.7 (3.8 to 7.5) p<0.0001
Extension week 96	..	..	0.5 (–2.7 to 3.6) p=0.7665	3.5 (1.3 to 5.8) p=0.0018
Absolute change from baseline in body-mass index, least squares mean, 95% CI, (kg/m^2), p value†				
Week 24	0.13 (0.04 to 0.23) p=0.0066	0.37 (0.28 to 0.47) p<0.0001	..	..
Extension week 72	..	..	0.62 (0.45 to 0.79) p<0.0001	0.69 (0.56 to 0.81) p<0.0001
Extension week 96	..	..	0.76 (0.56 to 0.97) p<0.0001	0.96 (0.81 to 1.11) p<0.0001

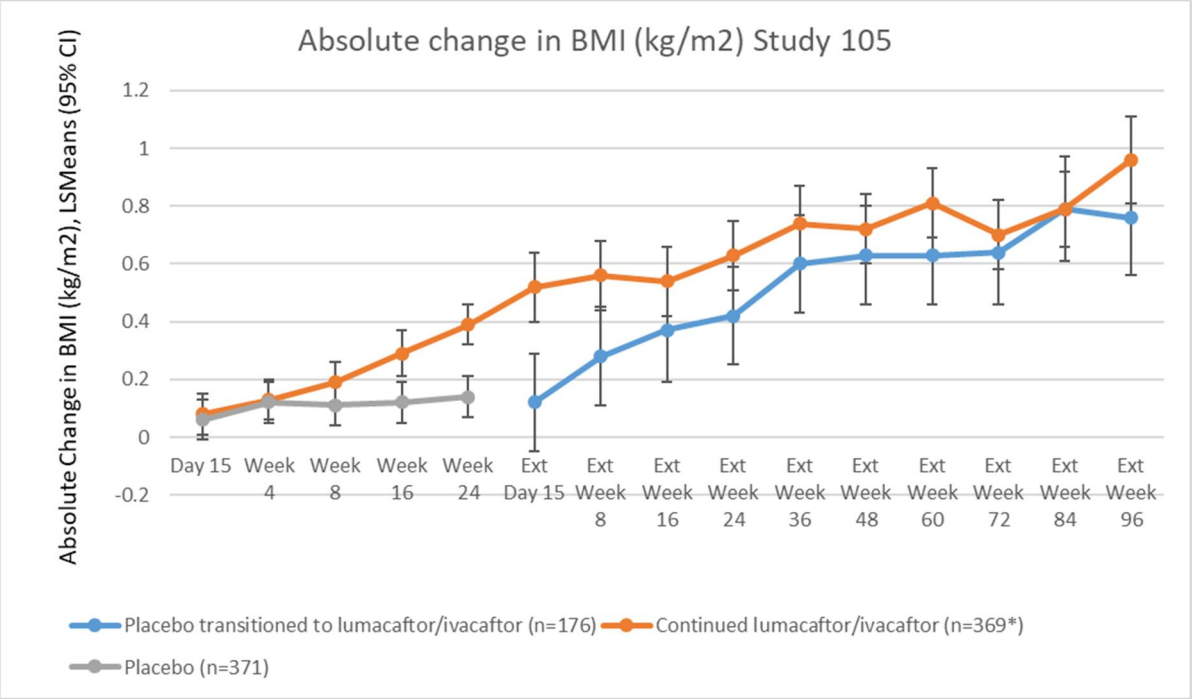
Source: Table B.7-11 and B.7-12, page 129 and 131 July 2017 resubmission.
Abbreviations: CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval.
†For the placebo and lumacaftor/ivacaftor groups, baseline from TRAFFIC or TRANSPORT was used; for the placebo transitioned to lumacaftor/ivacaftor group, baseline from PROGRESS was used. All p values (including for TRAFFIC or TRANSPORT data) are within treatment.
All p values (including for TRAFFIC or TRANSPORT data) are within treatment.

Figure 7: Absolute change in CFQ-R Respiratory Domain Score, Study 105



Source: Prepared during the evaluation from data as specified in the Table Annexe (Table 9).
Abbreviations: CFQ-R=Cystic Fibrosis Questionnaire-Revised; CI=confidence intervals; Ext=extension; LS=least squares.

Figure 8: Absolute change in BMI (kg/m²) Study 105



Source: Prepared during the evaluation from data as specified in the Table Annexe (Table8).
Abbreviations: BMI=body mass index; CI=confidence intervals; Ext=extension; LS=least squares; kg=kilograms.

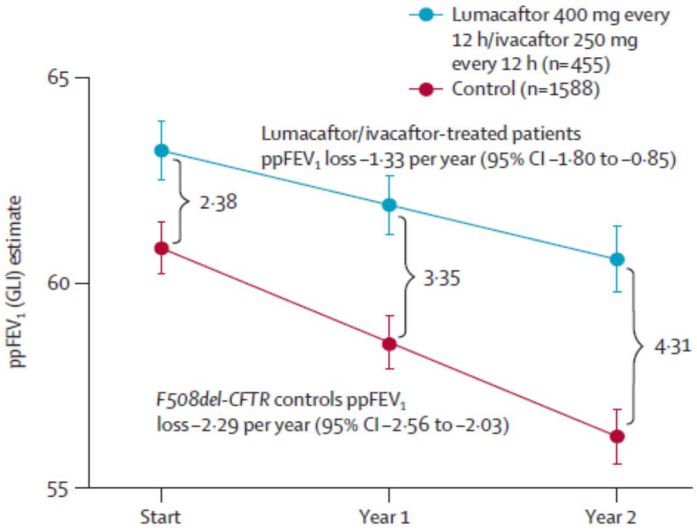
6.21 The July 2017 resubmission claimed that the new longer-term efficacy data from PROGRESS demonstrated sustained improvements in key CF treatment outcomes that are associated with prolongation of life. Despite the progressive nature of CF, mean $ppFEV_1$ remained above the pretreatment baseline after up to 120 weeks of cumulative exposure to lumacaftor/ivacaftor (although this difference was not statistically significant). The resubmission also claimed that the sustained benefits on PE rates and patient-reported respiratory symptoms, together with continued improvement in nutritional status, showed that lumacaftor/ivacaftor provides multisystem benefits that continue to dampen the expected disease trajectory over the longer term, and suggest that lumacaftor/ivacaftor is a disease modifying therapy in CF.

6.22 To place the rate of decline in $ppFEV_1$ observed in the PROGRESS study in context, the July 2017 resubmission presented an analysis that compared the rate of decline with that of a matched control registry. In this analysis, 455 patients treated with lumacaftor/ivacaftor in PROGRESS were matched with 1,588 control patients from the US Cystic Fibrosis Foundation Patient Registry (CFFPR). Matching was performed using a propensity score approach, with matching being based on variables including age, sex, spirometry measures, nutrition and bacteriology. The June 2017 ESC noted the groups appeared to be fairly well matched but that some key variables, including BMI and use of corticosteroids, were excluded from the propensity score model and it was therefore difficult to assess whether these variables were balanced between the treatment arms after matching. The June 2017 ESC also noted the methodology

was a single point-in-time rebalancing at baseline which did not adjust for the imbalance that is reintroduced subsequent to baseline. Accordingly, if there were any post-baseline differences in variables that were not due to the treatment, or if there were differences in data collection between the patients in PROGRESS and the CFFPR cohort, these may have confounded the outcomes.

6.23 The estimated annualised rate of lung function decline in this analysis was -1.33 percentage points (95% CI: -1.80, -0.85) in lumacaftor/ivacaftor-treated patients. This rate was less than the rate in the matched CFFPR controls (-2.29 percentage points, 95% CI: -2.56, -2.03; p<0.001) and represented a 42% decrease in the rate of $ppFEV_1$ decline in lumacaftor/ivacaftor-treated patients compared with the matched controls (or conversely, lumacaftor/ivacaftor treated patients experienced a decline in $ppFEV_1$ that was 58% of the decline in the matched registry controls). The relative rates of decline are depicted in Figure 9 below.

Figure 9: Estimated annual rate of $ppFEV_1$ decline with lumacaftor/ivacaftor treated patients compared with a matched control group.



Source: Figure B.7-9 p134 July 2017 resubmission.
The lines shown are calculated slopes for annualised rates of decline in each group. A significant difference between groups in the rate of lung function decline was observed (p<0.001). Post-baseline data were limited to 2 years; visits occurring at 21 days of treatment initiation baseline or earlier were excluded from the analysis.
Bars show standard error.
Abbreviations: GLI = Global Lungs Initiative; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second.

6.24 A rate of change analysis was also performed for secondary outcomes where data from the PROGRESS study were compared with the CFFPR cohort. These data indicated a positive rate of change in the lumacaftor/ivacaftor group for weight for age and BMI-z score (with the matched cohort declining over time) and a greater rate of change in the treatment group for BMI (kg/m^2) versus the matched cohort.

6.25 The PBAC agreed in July 2017 that patients appeared to be fairly well matched in terms of the variables used for the propensity scoring approach. However, the PBAC considered that the historical control patients from the CFFPR were nevertheless unlikely to be representative of the patients in TRAFFIC/TRANSPORT, and hence PROGRESS, and the comparison of the reduction in the rate of decline in FEV_1 in

PROGRESS versus the CFFPR was likely to be biased in favour of lumacaftor/ivacaftor. More specifically:

- The historical controls were drawn from the CFFPR which included only patients from the US, while the patients in PROGRESS were from the CF clinics across North America, Europe and Australia that participated in TRAFFIC/TRANSPORT. The PBAC noted a recent cohort study (Stephenson et al, 2017[3]) that found a 10 year difference in the median age of survival for CF patients in the US CFFPR (40.6 years) compared to the Canadian Cystic Fibrosis Registry (50.9 years). The study found that this difference persisted after adjustment for risk factors associated with survival, with the exception of private insurance status among US patients, and concluded that the Canadian survival advantage may in part be explained by differential access to transplantation, increased post-transplant survival, and differences in health care systems. The clinician at the sponsor hearing in July 2017 also noted that patients in the US tend to perform worse on average than patients in other countries, such as the UK. Accordingly, the PBAC considered that the higher rate of decline in FEV_1 in the US CFFPR may have been at least partly due to it consisting entirely of historical US patients, compared with PROGRESS which included patients from other countries, and in which patients might be expected to have benefited from optimization of other aspects of care. Further increasing uncertainty about the benefit of lumacaftor/ivacaftor was the closure of US clinical trial sites which presumably resulted in further depletion of the PROGRESS patient population with US patients over time.
- The PBAC considered that due to the requirements of the trial protocols (e.g. inclusion/exclusion criteria, monitoring and support provided), and the specialised centres involved, that the patients enrolled in the trials were likely to have a better prognosis on average than the CFFPR control patients. The PBAC noted that the reduction in FEV_1 over 24 weeks for patients treated with placebo in the TRAFFIC/TRANSPORT trials was 0.4 percentage points and that this was much lower than the reduction observed in the CFFPR control patients over 1 and 2 years (2.29 percentage points). The PBAC considered that this difference suggested that the prognosis of patients in the trials differed substantially from CFFPR controls. Further, the PBAC noted that the reduction in FEV_1 in the placebo arm in a trial for tezacaftor/ivacaftor in a similar patient population as TRAFFIC/TRANSPORT was 0.6 percentage points over 24 weeks (EVOLVE study[4]).

[3] Stephenson AL; Sykes J; Stanojevic S; *et al*. *Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States: A Population-Based Cohort Study*. Annals of Internal Medicine, 2017; 166(8):537-546.

[4] Vertex pharmaceuticals media release, 28 March 2017, Two Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment Met Primary Endpoints with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis

Thus the PBAC considered that it was not valid to compare the 2.29 percentage point reduction in FEV_1 in historical controls from CFFPR with that observed among treated patients in PROGRESS.

6.26 Overall, the PBAC considered that the matched analysis did not adequately support the claim of a reduction in the rate of decline in FEV_1 with lumacaftor/ivacaftor compared with BSC.

6.27 The current resubmission did not provide any new data on the rate of decline of $ppFEV_1$ in untreated patients to better inform this comparison, despite patient level $ppFEV_1$ data being collected through the Australian Cystic Fibrosis Data Registry. The pre-PBAC Response stated again that "long-term data to a total of 120 weeks from the PROGRESS trial confirms that the rate of decline in lung function is lessened by 42% by Orkambi® (p<0.001), that the rate of pulmonary exacerbations continues to be approximately half that experienced by the TRAFFIC/TRANSPORT placebo-treated patients and that BMI continues to increase".

6.28 The Clinical Study Report for PROGRESS presented subgroup analyses in absolute change in $ppFEV_1$ to 96 weeks for a range of patient subgroups, including: age; $ppFEV_1$ severity at screening of the previous study; sex; prior use of inhaled antibiotic, bronchodilator, hypertonic saline or corticosteroids; and *P aeruginosa* status at baseline of the previous study. Overall, the CSR stated that "[t]here were no trends suggestive of meaningful differences between any of the subgroups. For some subgroups, interpretation of outcomes should be treated with caution due to the small number of subjects." (p.133 of CSR Study 105). The results from the subgroup analysis are presented in Table 6.

Table 6: Subgroup analysis with whole trial population results– absolute changes from baseline in $ppFEV_1$. PROGRESS

Population	**Placebo transitioned to lumacaftor/ivacaftor (n=176)**		**Continued lumacaftor/ivacaftor (n=369*)**	
	n LS mean, p value†; Mean (SD)	(LS 95% CI)	n LS mean, p value†; Mean (SD)	(LS 95% CI)
Whole	75, 0.8 p=0.3495; 1.2 (8.9)	(–0·8, 2·3),	147, 0.5, p=0.4231; 1.2 (8.9)	(–0.7,1.6),
	n, Mean (SD) [min,max]	(95% CI)	n, Mean (SD) [min,max]	*(95% CI)*
Age < 18 years	19, 3.0 (11.2) [-22.5, 21.8]	*(-2.4,8.4)*	50, -0.4 (9.9) [-28.5, 22.5]	*(-3.21,2.41)*
Age ≥ 18 years	56, 0.5 (8.0) [-18.6, 30.5]	*(-1.64,2.64)*	97, 2.0 (8.3) [-26.3, 24.5]	***(0.33,3.67)***
Sex Male	36, 1.9 (10.0) [-22.5, 30.5]	*(-1.48,5.28)*	77, 1.3 (8.8) [-28.5, 18.9]	*(-0.7,3.3)*
Sex Female	39, 0.5 (7.9) [-18.6, 21.8]	*(-2.06,3.06)*	70, 1.0 (9.2) [-22.2, 24.5]	*(-1.19,3.19)*
Region: North America	13, -2.2 (8.9) [-22.5, 11.1]	*(-7.58,3.18)*	29, -0.1 (9.4) [-28.5, 245]	*(-3.68,3.48)*
Region: Europe	50, 1.2 (8.1) [-18.6, 21.8]	*(-1.1,3.5)*	96, 2.2 (9.1) [-26.3, 24.4]	***(0.36,4.04)***
Region: Australia	12, 4.7 (11.3) [-7.4, 30.5]	*(-2.48,11.88)*	22, -1.7 (6.8) [-18.6, 11.4]	*(-4.71,1.31)*

Population	Placebo transitioned to lumacaftor/ivacaftor (n=176)		Continued lumacaftor/ivacaftor (n=369*)	
$ppFEV_1$ at screening < 70	58, 0.4 (8.9) [-22.5, 30.5]	*(-1.94,2.74)*	99, 1.7 (9.2) [-26.3, 24.5]	*(-0.13,3.53)*
$ppFEV_1$ at screening ≥ 70	17, 3.8 (8.6) [-7.6, 21.7]	*(-0.62,8.22)*	48, 0.1 (8.4) [-28.5, 19.3]	*(-2.34,2.54)*
$ppFEV_1$ at baseline < 40	4, 3.0 (6.9) [-3.0, 12.9]	*(-7.98,13.98)*	14, 7.0 (8.8) [-7.4, 24.5]	***(1.92,12.08)***
$ppFEV_1$ at baseline ≥ 40	71, 1.1 (9.0) [-22.5, 30.5]	*(-1.03,3.23)*	133, 0.6 (8.8) [-28.5, 24.4]	*(-0.91,2.11)*
Prior use of inhaled antibiotic – yes	48, 0.5 (8.9) [-22.5, 21.8]	*(-2.08,3.08)*	78, 1.0 (9.3) [-28.5, 24.5]	*(-1.1,3.1)*
Prior use of inhaled antibiotic - no	27, 2.4 (9.0) [-9.0, 30.5]	*(-1.16,5.96)*	69, 1.3 (8.6) [-22.2, 22.5]	*(-0.77,3.37)*
Prior use of inhaled bronchodilator – yes^	63, 0.3 (8.7) [-22.5, 30.5]	*(-1.89,2.49)*	130, 0.9 (9.0) [-28.5, 24.5]	*(-0.66,2.46)*
Prior use of inhaled bronchodilator – no^	12, 5.6 (8.9) [-7.6, 21.8]	*(-0.05,11.25)*	17, 3.2 (8.0) [-11.8, 17.1]	*(-0.91,7.31)*
Prior Use of Inhaled Bronchodilator: Short-Acting only	20, -1.5 (7.5) [-18.6. 11.1]	*(-5.01,2.01)*	56, 2.2 (9.4) [-28.5, 24.5]	*(-0.32,4.72)*
Prior Use of Inhaled Bronchodilator: Short-Acting and Long-Acting or Long-Acting only	43, 1.2 (9.2) [-22.5, 30.5]	*(-1.63,4.03)*	74, 0.0 (8.7) [-26.3, 24.4]	*(-2.02,2.02)*
Prior Use of Inhaled Bronchodilator: No Prior Inhaled Bronchodilator Use	12, 5.6 (8.9) [-7.6, 21.8]	*(-0.05,11.25)*	17, 3.2 (8.0) [-11.8, 17.1]	*(-0.91,7.31)*
Prior Use of Inhaled Hypertonic Saline: No	40, 1.0 (8.3) [-18.6, 21.8]	*(-1.65,3.65)*	56, 3.0 (8.2) [-11.0, 24.4]	***(0.8,5.2)***
Prior Use of Inhaled Hypertonic Saline: Yes	35, 1.3 (9.7) [-22.5, 30.5]	*(-2.03,4.63)*	91, 0.0 (9.2) [-28.5, 24.5]	*(-1.92,1.92)*
Prior Use of Inhaled Corticosteroids: No	29, 0.7 (9.0) [-18.6, 21.8]	*(-2.72,4.12)*	63, 2.3 (7.9) [-16.0, 18.9]	***(0.31,4.29)***
Prior Use of Inhaled Corticosteroids: Yes	46, 1.5 (9.0) [-22.5, 30.5]	*(-1.17,4.17)*	84, 0.3 (9.6) [-28.5, 24.5]	*(-1.78,2.38)*
Pseudomonas aeruginosa Status at Baseline: Negative	18, -0.6 (9.1) [-22.5, 19.7]	*(-5.13,3.93)*	37, 2.1 (8.1) [-11.8, 19.3]	*(-0.6,4.8)*
Pseudomonas aeruginosa Status at Baseline: Positive	57, 1.7 (8.9) [-18.6, 30.5]	*(-0.66,4.06)*	110, 0.9 (9.2) [-28.5, 24.5]	*(-0.84,2.64)*

Source: CSR 105 Section 14.2. Table 14.2.1.2.2a, Table 14.2.1.1.1a, Table 14.2.1.1.4a, Table 14.2.1.1.2a, Table 14.2.1.1.3a, Table 14.2.1.1.5a, Table 14.2.1.1.6a, Table 14.2.1.1.7a, Table 14.2.1.1.8a, Table 14.2.1.1.9a, Table 14.2.1.1.10a, Table 14.2.1.1.11a. *The 95% confidence intervals for the subgroup means were calculated during the evaluation.*

Abbreviations: CI = confidence interval, LS = least squares; n = number of participants reporting data; N = total participants in group; ppFEV1 = percent predicted FEV1, SD = standard deviation.

†For the placebo and lumacaftor/ivacaftor groups, baseline from TRAFFIC or TRANSPORT was used; for the placebo transitioned to lumacaftor/ivacaftor group, baseline from PROGRESS was used. All p values (including for TRAFFIC or TRANSPORT data) are within treatment.

***** This number is as presented in the submission. 369 patients in TRAFFIC and TRANSPORT had received at least one dose of lumacaftor/ivacaftor 400mg/250mg twice daily and therefore are included in safety analyses. 341 of these patients enrolled in PROGRESS study, and 340 received at least one dose.

^ On the bronchodilator page, only those coded as bronchodilator were included.

Comparative harms

6.29 A summary of the adverse events for lumacaftor/ivacaftor versus placebo is presented in Table 7 below.

Table 7: Summary of adverse events in TRAFFIC and TRANSPORT

AE Category	TRAFFIC		TRANSPORT		Pooled	
	Lumacaftor/ ivacaftor (N=182)	Placebo (N=184)	Lumacaftor/ ivacaftor (N=187)	Placebo (N=186)	Lumacaftor/ ivacaftor (N=369)	Placebo (N=370)
Total number of AEs	1019	994	1111	1138	2130	2132
Subjects with any AEs, n (%)	174 (95.6)	174 (94.6)	177 (94.7)	181 (97.3)	351 (95.1)	355 (95.9)
Subjects with Grade 3/4 AEs, n (%)	19 (10.4)	25 (13.6)	26 (13.9)	34 (18.3)	NR	NR
Subjects with AEs by relationship: 'Related' or 'possibly related", n (%)	91 (50)	49 (26.6)	100 (53.5)	80 (43)	NR	NR
Subjects with AEs leading to treatment discontinuation, n (%)	6 (3.3)	4 (2.2)	11 (5.9)	2 (1.1)	17 (4.6)	6 (1.6)
Subjects with AEs leading to treatment interruption, n (%)	14 (7.7)	10 (5.4)	8 (4.3)	15 (8.1)	22 (6.0)	25 (6.8)
Subjects with SAEs, n (%)	33 (18.1)	49 (26.6)	31 (16.6)	57 (30.6)	64 (17.3)	106 (28.6)
Subjects with related SAEs, n (%)	8 (4.4)	3 (1.6)	6 (3.2)	5 (2.7)	14 (3.8)	8 (2.2)
Subjects with AEs leading to death, n (%)	0	0	0	0	0	0

Source: Table B.6.4, p112 July 2017 resubmission. Table 12-2, TRAFFIC CSR, p 188; Table 12-2, TRANSPORT CSR, p 201.
Abbreviations: AE = adverse event; n = size of subsample; N = number of subjects; SAE = serious adverse event, NR = not reported.

6.30 In the randomised trials, the most common adverse events experienced by patients who received lumacaftor/ivacaftor were dyspnoea (14.0% versus 7.8% on placebo), diarrhoea (11.0% versus 8.4% on placebo), and nausea (10.2% versus 7.6% on placebo). Serious adverse reactions occurring in at least 0.5% of patients on lumacaftor/ivacaftor and in a greater proportion of lumacaftor/ivacaftor patients than placebo patients were hepatobiliary events.

6.31 The final study report for the PROGRESS open label study (version 1.0, 25 October 2016) records that a total of 1017 (98.8%) subjects had at least one AE during the PROGRESS study period. The most common AEs (≥20% of subjects overall) by preferred term (PT) were infective PEx of CF (65.0%), cough (47.2%), sputum increased (22.1%), and hemoptysis (20.7%), all of which were expected manifestations of CF disease. Outcomes were generally similar across treatment groups; however, as expected with the known safety profile of lumacaftor/ivacaftor, a higher incidence of respiratory events (e.g., respiration abnormal and dyspnea) was observed in the lumacaftor/ivacaftor-naïve groups than in the L600qd/I and L400q12h/I groups. In addition, AEs related to transaminase elevations had a higher incidence in the LUM/IVA-naïve group than in the L600qd/I andL400q12h/I groups.

6.32 Serious adverse events were experienced by 45% of patients in PROGRESS, the most frequently reported being infective PEs of CF (in 33% of patients), haemoptysis (3%), and distal intestinal obstruction syndrome (3%).

6.33 Two deaths occurred in the lumacaftor 400 mg/ivacaftor 250 mg every 12h group during the course of PROGRESS: one patient died from respiratory failure related to infective PE, and one from distal intestinal obstruction syndrome. Neither of the deaths was considered to be related to the study drug.

Benefits and harms

6.34 On the basis of the direct randomised trials presented by the resubmission, treatment with lumacaftor/ivacaftor resulted in approximately a 2.81 percentage point larger increase in absolute ppFEV1 compared with placebo over a median duration of follow-up of 24 weeks.

6.35 On the basis of the direct randomised trials presented by the resubmission, a patient treated with lumacaftor/ivacaftor could expect to have one fewer pulmonary exacerbation over 2.5 years and one fewer hospitalisation due to a pulmonary exacerbation over 3 years.

6.36 Patients treated with lumacaftor/ivacaftor who continued therapy after completion of the original randomised trials continued to show an improvement in their lung function over baseline. However, the extent of that improvement decreased over time and by 96 weeks of treatment this difference was no longer statistically significant compared with before they commenced the trials.

6.37 On the basis of direct evidence from the trials, the overall frequency of adverse events being reported was comparable between lumacaftor/ivacaftor and placebo groups. Dyspnoea (14.0% versus 7.8% on placebo), diarrhoea (11.0% versus 8.4% on placebo), and nausea (10.2% versus 7.6% on placebo) occurred more frequently in the lumacaftor/ivacaftor group. Hepatobiliary serious adverse events had been reported in TRAFFIC and TRANSPORT, and occurred in at least 0.5% of patients on lumacaftor/ivacaftor and in a greater proportion of lumacaftor/ivacaftor patients than placebo patients. Following discontinuation of lumacaftor/ivacaftor, liver function tests returned to baseline or improved substantially in all patients.

6.38 For patients who continued to receive (or commenced) lumacaftor/ivacaftor therapy after the TRAFFIC and TRANSPORT trials ended, the most common adverse events reported were cough (44%), increased sputum (22%), and haemoptysis (20%) and may resolve without discontinuing treatment. A trend of an increase in blood pressure associated with extended lumacaftor/ivacaftor therapy had been identified and routine blood pressure monitoring is recommended. The most frequently reported serious adverse events in this group were infective PEs of cystic fibrosis (in 33% of patients), haemoptysis (3%), and distal intestinal obstruction syndrome (3%).

6.39 The final PROGRESS study report indicates that 14.9% of the Final Analysis Set for this study discontinued study treatment because of an “adverse event” or “subject

refused further dosing" (PROGRESS study report Version 1.0, 25 October 2016, pp 78).

Clinical claim

6.40 The March 2016 submission described lumacaftor/ivacaftor as superior in terms of comparative effectiveness as it improved key CF outcomes that are associated with prolongation of life expectancy. The July 2017 and current resubmission claimed that the longer term data from the PROGRESS study provided further evidence that lumacaftor/ivacaftor is a disease modifying therapy.

6.41 The March 2016 submission claimed the drug is equivalent to BSC in terms of comparative safety, and the current resubmission argued that the longer term safety profile was consistent with the previous data in TRAFFIC and TRANSPORT.

6.42 In March 2016, the PBAC noted the improvement in exacerbations, weight gain, BMI, the hospitalisation rate and antibiotic use associated with treatment with lumacaftor/ivacaftor in the short-term but considered that the impact of lumacaftor/ivacaftor on improvements in long-term lung function and survival was uncertain. In addition, the PBAC considered that the claim of equivalent comparative safety was reasonable in the short-term but noted the long-term safety of lumacaftor/ivacaftor is unknown.

6.43 In the July 2017 resubmission, evidence from the PROGRESS extension study demonstrated that the modest increase in ppFEV1 in lumacaftor/ivacaftor treated patients demonstrated in TRAFFIC and TRANSPORT was not maintained through to 120 weeks.

6.44 The PSCR for the July 2017 submission argued the main objective of treatment with lumacaftor/ivacaftor is to minimise the rate of deterioration over time, noting the matched analysis of the comparative rates of decline of ppFEV1 which represented a 42% decrease in the rate of ppFEV1 decline in lumacaftor/ivacaftor-treated patients compared with a matched cohort. The PSCR further argued that the clinical impact of slowing CF progression over time was reflected to some extent by the maintenance of the absolute reduction in PE events per patient-year for up to 120 weeks of treatment.

6.45 In July 2017, the PBAC considered the claim that lumacaftor/ivacaftor slows the rate of decline in ppFEV1 beyond 24 weeks, compared with patients treated with BSC, was not adequately supported by the resubmission for the reasons outlined in paragraph 6.25. However, the PBAC noted improvements in other clinical measures, including a reduction pulmonary exacerbations and an increase in body mass index, were maintained beyond the 24 week trial period, and therefore considered that the claim of superior comparative effectiveness for these outcomes was reasonable.

6.46 In July 2017, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the updated data from the PROGRESS study provided in the current resubmission. There is evidence of drug-related adverse

events including respiratory adverse events (e.g. haemoptysis, cough), hepatobiliary events and development of hypertension associated with continued therapy. The July 2018 submission does not alter the clinical claim.

6.47 The PBAC considered that the claim that lumacaftor/ivacaftor slows the rate of decline in ppFEV1 and reduces PEx for up to 96 weeks may be reasonable. However, the PBAC remained concerned that the available data suggest considerable heterogeneity in the clinical benefit received by patients and there is no information to demonstrate that the slower rate of decline or reductions in PEx are maintained over a longer period, which is important in the context of a life-long progressive disease.

6.48 The PBAC considered that a Managed Access Program (MAP) would allow patients access to subsidised treatment with lumacaftor with ivacaftor whilst providing the sponsor with the opportunity to demonstrate that the differences in the rates of decline in lung function (ppFEV1) and PEx observed over a 96 week trial period are sustained over a longer time period of at least 4 years in real clinical practice.

6.49 The PBAC noted that Vertex plans to bring forward new treatments for patients who are homozygous for the f508del mutation in the CFTR gene, with tezacaftor and ivacaftor currently undergoing regulatory review in some countries and a triple therapy combination treatment in clinical trials. The PBAC recognized that this might limit the availability of longer term data for lumacaftor with ivacaftor but considered that the MAP could allow the PBAC to be provided with longer term data for patients treated continuously with lumacaftor with ivacaftor, as well as treatment with tezacaftor with ivacaftor or triple therapy, or through consecutive periods of treatment with more than one of these regimens.

6.50 As in its July 2017 consideration, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data for the reasons outlined in paragraph 6.45.

Economic analysis

6.51 The structure of the model was the same as the previous submissions (March 2016 November 2016 and July 2017) which presented a cost-utility analysis compared with BSC.

6.52 In July 2017 the PBAC considered that the claim made at that time that lumacaftor/ivacaftor slows the rate of decline in ppFEV1 beyond 24 weeks, compared with patients treated with BSC, was not adequately supported. The PBAC defined an alternative scenario which it considered informative for decision making. Specifically, the PBAC made the following changes to Base case in the July 2017 resubmission:

- The estimated decline in $ppFEV_1$ in lumacaftor/ivacaftor treated patients was set to 100% of BSC after 24 weeks. The PBAC considered that this assumption was a more realistic interpretation of the available data than the submission's

assumption of no change in $ppFEV_1$ for lumacaftor/ivacaftor patients. Furthermore, the PBAC considered this assumption may still favour lumacaftor/ivacaftor, as lumacaftor/ivacaftor treated patients would therefore always maintain the 2.8 percentage point difference in $ppFEV_1$, compared with BSC patients; the PBAC considered that the difference in $ppFEV_1$ may in fact reduce over the long-term.

- Assuming 75% of hospitalisations are due to PEs
- Removal of the F1 5% statutory price reduction and the assumed [redacted]% generic price reduction, in line with the PBAC Guidelines V5.0 (p82) which states that submissions should value future costs at current prices. The PBAC also noted that as lumacaftor/ivacaftor is likely to be replaced with tezacaftor/ivacaftor and triple therapy with the "next generation correctors" over the next several years, it is unlikely that lumacaftor/ivacaftor will be in use at the time that the submission assumed the price will reduce by [redacted]%.

6.53 The PBAC's scenario resulted in an ICER of around more than $200,000 per QALY gained (presented in Table 8 with July 2017 base case 1 for comparison).

Table 8: Results of scenario analysis conducted by PBAC in July 2017

Scenario	Inc. cost ($)	Inc. effect (LYs)	Inc. effect (QALYs)	ICER ($/QALY gained)
July 2017 resubmission, base case 1	$[redacted]	4.640	4.659	$[redacted]
PBAC scenario for decision making	$[redacted]	1.144	0.720	$[redacted]

Source: Constructed during the preparation of the PBAC minutes.

6.54 At the July 2017 meeting and on the request of the Minister (delegate) under section 101(3) of the Act, the PBAC considered the price or range of prices at which it considered treatment with lumacaftor/ivacaftor would be acceptably cost-effective for the purposes of the Act. The PBAC advised that the maximum ICER it would consider to be acceptably cost effective, noting the precedent of ivacaftor, would be around $105,000/QALY - $200,000/QALY. Based on its revised scenario, the PBAC advised that the maximum DPMQ that it would consider to be acceptably cost-effective would be around $[redacted] (or around $[redacted] per patient per year, assuming 11 packs per patient per year) which would result in an ICER of $105,000 - $200,000/QALY.

6.55 The current resubmission (July 2018) presented a model which incorporated patients 2 years and over, adjustments were made to the economic model for patients aged 12 years and older by using the 'patient filter' functionality provided in the Excel workbook. Accordingly, aspects of the model specification or outputs which were specific to the 2-5 age group are not presented in this overview.

6.56 The model initially provided with the July 2018 submission adjusted the rate of decline in the lumacaftor/ivacaftor treatment group to [redacted]% of that in the BSC group; reinstates the 5% and [redacted]% price reductions; and assumes that all CF hospitalisations are due to PEx, and that there was a reduction of 61% of hospitalisations.

6.57 Table 9 presents a summary of the FEV1, weight for age z-score and pulmonary exacerbation input parameters applied in the base case of the economic model. These inputs are presented by treatment (BSC alone or lumacaftor/ivacaftor) and by patient age group. The summary also presents these input parameters by the modelled time period (i.e. ≤24 weeks (within the period of the pivotal trials) and >24 weeks (extrapolated beyond the pivotal RCT period) or as otherwise specified.

Table 9: Summary of FEV_1, weight for age z-score and pulmonary exacerbation economic model inputs by treatment, patient age and modelled time period

Parameter description	Age group (years)	BSC alone		lumacaftor/ivacaftor	
		Model input ≤ 24 weeks	Model input > 24 weeks	Model input ≤ 24 weeks	Model input > 24 weeks
Change in $ppFEV_1$	2–8	[redacted]%	-[redacted]% (annual change)	+[redacted]% (2–11 years of age)	[redacted]% of the decline seen in BSC at appropriate age
	9–12		-[redacted]% (annual change)		
	13-17		-[redacted]% (annual change)	+[redacted]% (12+ years of age)	
	≥ 18		-[redacted]% (annual change)		
Change in Weight for age z-score	All	-[redacted] (per annum) (≤ first 2 years of model)	[redacted] (> first 2 years of model)	[redacted] (per annum) (≤ first 2 years of model)	[redacted] (> first 2 years of model)
Annual rate of pulmonary exacerbations requiring IV antibiotics or inpatient stay	≥ 2–11 years	[redacted]		[redacted]	
	≥ 12–17 years	[redacted]		[redacted]	
	≥ 18 years	[redacted]		[redacted]	

Abbreviations: BSC, best supportive care; FEV_1, forced expiratory volume in 1 second; IV, intravenous.
Source Table 3.4.12 Orkambi 12+ submission to July 2018 PBAC, pp 47.

6.58 The key components of the economic evaluation are presented in Table 10.

Table 10: Summary of model structure and rationale

Component	Summary
Time horizon	Lifetime in the modelled base case. Patients aged ≥ 12 years: 24 weeks in TRAFFIC/TRANSPORT and PROGRESS (extension to 96 weeks). Patients aged 6-11 years: 24 weeks in Study 109.
Outcomes	Quality-adjusted life years.
Methods used to generate results	Individual patient microsimulation. Liou CPH model used to apply the effect of nine risk factors on the baseline hazard of mortality.
Health states	As a microsimulation, changes are recorded in the underlying risk factors (as above) for each patient. Utility values are applied to health states based on $ppFEV_1$ status of normal (>90%), mild (70-90%), moderate (40-70%) and severe (<40%).
Cycle length	Four weekly cycle for the initial two years, annual thereafter.
Transition probabilities	Modelled survival using Liou CPH model. Treatment effects were based on Study 109 ($ppFEV_1$ for patients aged 6-11 years) and TRAFFIC/TRANSPORT (weight-for-age z-score). Changes in treatment effect and patient characteristics over time from PROGRESS (decline in $ppFEV_1$ post 24 weeks) and change in weight-for-age z-score. Baseline hazard function from Cystic Fibrosis Registry of Ireland 2013.

Abbreviations: CPH = Cox Proportional Hazards; FEV_1 =forced expiratory volume in one second; pp = percent predicted;
Source: Table 3.1.1, p.151 of the submission

6.59 The key drivers of the model are in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Proposed Financial Cap	Annual Cap of $[redacted] applied for lumacaftor/ivacaftor drug cost	High, favours lumacaftor/ivacaftor
Modelled change in $ppFEV_1$ in lumacaftor/ivacaftor patients.	Treatment effect continued beyond 24 week trial period for life time. Updated data from extension trial PROGRESS were not included in the model.	High, favours lumacaftor/ivacaftor
Modelled change in $ppFEV_1$ in BSC patients.	Annual decline in $ppFEV_1$ after the first 24 weeks	High, favours lumacaftor/ivacaftor
Assumption of price reduction at patent expiry.	[redacted]% price reduction at end of patent life	High, favours lumacaftor/ivacaftor
Assumption of reduction in PE-related hospitalisation costs for lumacaftor/ivacaftor.	61% reduction in PE-related hospitalisation costs; estimated by multiplying hospitalisation costs associated with BSC by 0.61.	Moderate, favours lumacaftor/ivacaftor
Extrapolation of survival	Liou et al (2001), extrapolation of effect of intermediate outcomes on survival.	High, favours lumacaftor/ivacaftor

Abbreviations: BSC = best supportive care; PE = pulmonary exacerbation; $ppFEV_1$= per cent predicted forced expiratory volume in one second.
Source: compiled during the evaluation.

6.60 Results from the economic evaluation with a respecified base case (to reflect use only in those 12 and older) are presented in Table 12. These results show that the cost per QALY gained for patients aged 12 years and older was $105,000/QALY - $200,000/QALY. Including the 6-11 year age group reduced the ICER to $105,000 - $200,000/QALY.

Table 12: Results of the economic evaluation

Step and component	Lumacaftor/ivacaftor	Best supportive care	Increment
Patients aged 6 years and older, revised base case with cap			
Costs	$	$469,441	$
QALYs	8.30	6.08	2.21
Incremental cost/extra QALY gained			$
Patients aged 12 years and older, scenario with cap			
Costs	$	$437,044	$
QALYs	6.91	4.94	1.97
Incremental cost/extra QALY gained			$
Patients aged 12 years and older, scenario without cap			
Costs	$	$437,044	$
QALY	6.91	4.94	1.97
Incremental cost/extra QALY gained			$

Abbreviations: QALY=quality adjusted life year.
Note: Base case ICER from the submission of patients aged 2 years and older is $105,000 QALY - $200,000/QALY with incremental cost of $ and incremental QALY of 2.29.
Source: Compiled during the evaluation setting the patient filter to patients aged 6 years and older. Excel spreadsheet "Orkambi 2+ cost effectiveness model March 2018 FINAL', sheet 'Results'.

6.61 The model initially provided with the July 2018 submission incorporated a decline in ppFEV1 in lumacaftor/ivacaftor patients beyond the 24 weeks trial period to life time at a rate of % of BSC decline. This decline was informed by the longer term ppFEV1 data from the extension trial PROGRESS, which showed that patients on lumacaftor/ivacaftor had a decline in FEV that was 58% that of a matched control group in follow up to 96 weeks. This differs from the July 2017 resubmission of lumacaftor/ivacaftor in patients aged 12 years and older as previously it was assumed that there was no decline in ppFEV1 post 24 weeks in the lumacaftor/ivacaftor treated patients. Sensitivity analyses setting the rate of decline to 42% (as per the PROGRESS study) and 100% of BSC (see Table 13) resulted in ICERs of $105,000/QALY - $200,000/QALY and more than $200,000/QALY.

Table 13: Sensitivity analysis with varying rate of FEV1 decline

Submission and Price	Age Cohort	FEV1 rate of decline versus baseline	5% and % price reduction	ICER
July 18 Vertex $	6+	42%	Yes	$
	12+	42%	Yes	$
	6+	100%	Yes	$

Abbreviation: FEV_1=forced expiratory volume in one second;
Source: *Compiled during the evaluation setting the patient filter to patients aged 6 years and older Excel spreadsheet "Orkambi 2+ cost effectiveness model March 2018 FINAL', sheet 'Results'.*

6.62 In the pre-PBAC Response the sponsor offered a reduction in the effective price to $ per patient per year and revised the rate of decline for the on treatment group in the economic model to 42%. These changes resulted in revised ICERs of $105,000/QALY - $200,000/QALY (see Table 14) for the 2+ population, $105,000/QALY - $200,000/QALY for the 6+ population, and $105,000/QALY - $200,000/QALY for the 12+ population.

6.63 The pre-PBAC response estimated that the total gross cost of listing lumacaftor/ivacaftor over the first four years for the entire 2+ population with the

revised price proposal of [redacted] per patient per year and with adjustments for uptake, dose adjustment and compliance to be more than $100 million (compared with the more than $100 million initially estimated in the July 2018 submission).

Table 14: Estimated ICER at effective price of $[redacted] per patient per year and with rate of decline 42% of BSC

Patient cohort (years)	ICER
≥ 2	$[redacted]
≥ 6	$[redacted]
≥ 12	$[redacted]

The redacted table shows ICERs in the range of $105,000/QALY - $200,000/QALY.

6.64 Further sensitivity analyses are presented in the ESC advice for item 5.08 lumacaftor with ivacaftor for 6 – 11 year olds.

Drug cost/patient/year: $[redacted]

6.65 The pre-PBAC response offers a total expenditure cap which it states will deliver a cost per patient of $[redacted] per year vis-à-vis a list price of $18,750 per 28 days treatment (approx $244,000 per year).

6.66 However, the submission bases its calculation of the cost per patient on the average number of patients who initiate treatment in each of the first 4 years of listing. As not all patients will commence treatment on the first day of their first year and some patients will discontinue treatment, this overestimates total usage and underestimates the rebate required to achieve a cost per patient per year of $[redacted].

Table 15: Rebate calculations

Cost per patient	
DPMQ	$18,750
Annual cost	$[redacted]
Dose reduction for liver impairment adjustment 5.73%	$[redacted]
Compliance adjustment 90%	$[redacted]
Rebate need to achieve $[redacted] price	[redacted]%

Source: Compiled by the secretariat

Estimated PBS usage, financial implications & risk share arrangements

6.67 The sponsor's pre-PBAC revised estimates for patients 2+ and older are presented in Table 16 (See also ESC advice item 5.08 July 2018 meeting).

Table 16: Submission's prePBAC estimated use and financial implications, patients aged 2 years and older

	Source	Year 1	Year 2	Year 3	Year 4	Average/ Total
Treated patients	Section 4 spreadsheet, Cost to Govt PBS, row 5	[redacted]	[redacted]	[redacted]	[redacted]	Average: [redacted]
Proposed Financial Cap	Suggested distribution	$[redacted]	$[redacted]	$[redacted]	$[redacted]	Total: $[redacted]

Source: Table 3 of prePBAC response, item 7.10 July 2018

The redacted table shows that at Year 4, the estimated number of patients was less than 10,000.

6.68 The PBAC considered the submission's estimates for the 12+ group to be too high for the following reasons as documented in the Overview:

- The submission assumed that patients could only discontinue therapy in the first year. This is based on the pooled discontinuation rates from TRAFFIC and TRANSPORT (6.8% applied to patients aged 6 years and older). The final PROGRESS study report indicates that 14.9% of the Final Analysis Set for this study discontinued study treatment because of an "adverse event" or "subject refused further dosing" (PROGRESS study report Version 1.0, 25 October 2016, pp 78).

  Note: The final PROGRESS study report indicates "Other" was the most frequent reason for treatment discontinuation (36.1% of overall subjects), and the vast majority of these discontinuations were because subjects transitioned from study drug to the commercially available supply of drug (PROGRESS study report Version 1.0, 25 October 2016, pp 77). This overview does not propose that the discontinuations resulting from patients moving to commercially available drug be taken account for in adjusting the submission's estimates.

  The assumption made is that discontinuing patients will discontinue treatment throughout the year, so that on average each patient receives the equivalent of half of a year's supply in the year in which they discontinue treatment may be reasonable.

- The submission assumed that patients who become eligible for treatment each year receive a full year of treatment. A more reasonable assumption is that initiating patients will commence treatment throughout the year, so that on average each patient receives the equivalent of half of a year's supply in the year in which they commence treatment.

6.69 The PBAC noted the revised financial impact of listing lumacaftor/ivacaftor taking into account these issues as reported in Table 17.

Table 17: Estimated use and financial implications, patients aged 12 years and older

	Year 1	Year 2	Year 3	Year 4	Year 5
*Number of patients treated**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gross cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
With rebate applied					
With [redacted]% rebate ($[redacted] per patient per year)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

* This number includes and adjustment to all for patients initiating and discontinuing treatment throughout the year (i.e. the patient number is expressed as the number treated for a full year equivalents)

Source: Compiled by the secretariat based on submission section 4 spreadsheet with adjustments to remove patients <12 years, to allow discontinuations in year 2 in line with outcomes of PROGRESS study, and with initiating patients in year 3 onwards receiving the equivalent of half of a year's supply in the year in which they commence treatment

The redacted table shows that at Year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS (with rebate) would be $60 more than $100 million.

6.70 The PBAC considered that patients with ppFEV1 < 40% at baseline should be eligible for PBS-subsidised access to ivacaftor with lumacaftor, irrespective that a ppFEV1 <40% was an exclusion criteria in the pivotal randomised clinical trials TRAFFIC and TRANSPORT. A total of 39 (7.6%) patients with a ppFEV1 < 40% were enrolled in the open label PROGRESS extension L400q12h/I and P-L400q12h/I study groups (PROGRESS study report Version 1.0, 25 October 2016, pp 84).The PBAC noted that the estimates in Table 17 include patients with a ppFEV1 <40%.

6.71 The PBAC noted that the sponsor proposed the effective price per patient be achieved [redacted]

6.72 The PBAC considered this approach to be associated with a significant risk [redacted]

Managed Access Program

6.73 The PBAC considered that a Managed Access Program (MAP) for lumacaftor with ivacaftor would allow patients to access treatment through the PBS whilst providing the sponsor with an extended period to provide further data to satisfy the PBAC that the benefits of treatment are sustained over a longer period.

6.74 Under such an MAP, subsidy could be paid at the sponsor's asking price of $[redacted] per patient per year for a period of two and a half years to allow the sponsor to provide further data to satisfy the PBAC that the differences in the rates of decline in lung function ($ppFEV_1$) and pulmonary exacerbations observed over the 96 week trial period are sustained over a longer time period of at least 4 years in real clinical practice.

6.75 If, by the end of the two and a half year initial period of the MAP, the sponsor's assumptions on rate of decline have not been substantiated or have only been partially substantiated, through a submission to the PBAC and the PBAC affirming the cost-effectiveness of the medicine, the PBAC considered that the price paid for lumacaftor with ivacaftor should reduce to a level consistent with the evidence provided. If that were the case, the minimum price paid in the second half of the MAP would be $[redacted] per patient per year consistent with the assumption that patients treated with lumacaftor/ivacaftor maintain an advantage over untreated patients after 96 weeks, but that treated patients decline at a similar rate to untreated patients.

6.76 The PBAC noted that under this MAP the indicative cost to the Commonwealth of subsidising lumacaftor with ivacaftor for the 12 years and older age group would be more than $100 million over 5 years, with the cost to the Commonwealth increasing to up to more than $100 million over 5 years upon the sponsor satisfying the requirements of the MAP (see Table 20).

Table 20: Indicative cost to Commonwealth of listing ivacaftor with lumacaftor for patients aged 12 years and over

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
MAP conditions not met	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
MAP conditions met	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

6.77 The estimated net cost to the PBS if the conditions of the MAP are met was $60 – more than $100 million in Year 1, increasing to $60 – more than $100 million in Year 5. The cost over the first five years of listing to the PBS was estimated to be more than $100 million. If the conditions of the MAP are not met, the estimated net cost to the PBS was $60 – more than $100 million in Year 1, decreasing to $20 - $60 million in Year 5. The cost over the first five years of listing to the PBS in that scenario was estimated to be more than $100 million.

6.78 The PBAC noted that the sponsor plans to bring forward new treatments for patients who are homozygous for the f508del mutation in the CFTR gene, with tezacaftor with ivacaftor currently undergoing regulatory review and a triple therapy combination treatment in clinical trials. The PBAC recognized that this might limit the availability of longer term data for lumacaftor with ivacaftor but considered that the MAP could allow the PBAC to be provided with longer term data for patients

treated continuously with lumacaftor with ivacaftor, as well as treatment with tezacaftor with ivacaftor or triple therapy, or through consecutive periods of treatment with more than one of these regimens.

6.79 The PBAC considered that it would be appropriate for the Minister to enter into a deed with the sponsor to specify the annual patient cost, overall financial caps and terms of the MAP.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of lumacaftor with ivacaftor on the basis that it should be available only under special arrangements under section 100 (Highly Specialised Drugs Program) and only in the circumstances: for the treatment of patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The PBAC recommended the special arrangements and circumstances described in the tables in section 8 below.

7.2 The PBAC is satisfied that lumacaftor with ivacaftor provides, for some patients, a significant improvement in efficacy over best supportive care.

7.3 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of lumacaftor with ivacaftor would be acceptable if the following measures were implemented to contain risks associated with the cost-effectiveness and overall cost of the drug to the PBS.

- A Managed Access Program as described in paragraphs 6.73 – 6.79 above;
- A Special Pricing Arrangement to give effect to the offered price of $[redacted] per patient per year; and
- Caps on [redacted] in line with the estimates in Table 20 above.

7.4 The PBAC recognised the potential clinical value of lumacaftor/ivacaftor in the treatment of cystic fibrosis in patients aged 12 years or older who are homozygous for the F508del mutation and recognised the strong support for subsidised access to this medicine and acknowledged the many consumer comments and the correspondence from the Cystic Fibrosis Centre Directors and Cystic Fibrosis SA relating to this resubmission

7.5 The PBAC recalled that it did not recommend the listing of lumacaftor with ivacaftor in response to the sponsor's submission at its July 2017 meeting on the basis of unacceptably high cost-effectiveness at the requested price and uncertainty around the longer term impact of lumacaftor with ivacaftor on lung function and survival beyond 2 years of treatment.

7.6 In recommending lumacaftor/ivacaftor at this meeting, the PBAC noted that the sponsor had offered an effective annual price per patient that is [redacted]% lower than the

price offered in July 2017 (current: $[redacted] per patient per year; July 2017: [redacted] per patient per year). The sponsor had also revised a key assumption in its economic model, with the decrease in rate of decline of ppFEV1 in the on-treatment group now assumed to be 42% of untreated patients (previous assumption was of no decline in ppFEV1 for treated patients).

7.7 Although the PBAC remained concerned that (a) the rate of decline assumption was overly optimistic and likely to be biased in favour of lumacaftor/ivacaftor (see paragraphs 6.25 – 6.27 above), and (b) the rate of decline difference might not be sustained in the longer term, the PBAC considered lumacaftor/ivacaftor to be acceptably cost-effective at the new offered price and with the additional measures for managing risk described at 7.3 above.

7.8 The PBAC considered that while there was evidence that lumacaftor with ivacaftor slows the rate of decline in ppFEV1 and reduces pulmonary exacerbations (PEx) up to 96 weeks for some patients; the sustainability of these benefits in the longer term remain uncertain. If a MAP of the type described in these minutes was implemented, and should the sponsor's assumptions on rate of decline not be substantiated or be only partially substantiated through a submission to the PBAC and PBAC affirming the cost-effectiveness of the medicine within two and a half years of PBS listing, the price paid for lumacaftor with ivacaftor would reduce to a level consistent with the evidence provided. For instance, should the PBAC not affirm the cost-effectiveness of the medicine within two and a half years, the price paid in two and a half years from the listing date should reduce to $[redacted] per patient per year, the price that is considered cost-effective under the assumption that patients treated with lumacaftor/ivacaftor maintain an advantage over untreated patients after 96 weeks, but that treated patients decline at a similar rate to untreated patients. The PBAC noted that that price would be the price at which it advised the Minister, in July 2017, lumacaftor and ivacaftor would be cost-effective on the basis of the information then available to it.

7.9 The PBAC did not consider that lumacaftor/ivacaftor should be treated as interchangeable with any other drugs.

7.10 The PBAC advised that lumacaftor/ivacaftor is not suitable for prescribing by nurse practitioners.

7.11 The PBAC recommended that the Early Supply Rule should not apply.

Outcome:
Recommended

8 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LUMACAFTOR + IVACAFTOR				
Lumacaftor 200 mg + ivacaftor 125 mg	112	5	Orkambi®	Vertex Pharmaceuticals (Australia) Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Initial
Restriction:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation; AND Must be treated in a centre with expertise in cystic fibrosis, OR Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.
Clinical criteria:	Patient must be homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; AND The treatment must be given concomitantly with standard therapy for this condition.
Population criteria:	Patient must be 12 years of age or older.
Prescriber Instructions:	The patient must be registered in the Australian Cystic Fibrosis Database Registry. Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug. The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and and (3) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene; and (4) the result of a FEV_1 measurement performed within a month prior to the date of application. Note: FEV_1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV_1 is measured; and (5) evidence that the patient has either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities; and (6) a copy of a current medication history; and (7) height and weight measurements at the time of application; and (8) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.
Administrative Advice:	Special pricing arrangements apply No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.

	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
PBS Indication:	Cystic Fibrosis
Treatment phase:	Continuing
Restriction:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation; AND Must be treated in a centre with expertise in cystic fibrosis, OR Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be given concomitantly with standard therapy for this condition.
Population criteria	Patient must be 12 years of age or older.
Prescriber Instructions	Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug. Patients who have an acute infective exacerbation at the time of assessment for continuing therapy may receive an additional one month's supply in order to enable the assessment to be repeated following resolution of the exacerbation. The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Continuing Application Supporting Information Form; and (3) the result of a FEV1 measurement performed within a month prior to the date of application. Note: FEV1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV1 is measured; and (4) a copy of a current medication history; and (5) height and weight measurements at the time of application; and (6) the number of days of CF-related hospitalisation (including hospital-in-the home) in the

	previous 6 months.
Administrative Advice:	Special pricing arrangements apply No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.

Appendix 1: lumacaftor with ivacaftor, July 2017 PBAC minutes

REJECTIONS

At its meeting between **5** and **7 July 2017**, the PBAC decided not to recommend to the Minister (under section 101(3) of the *National Health Act 1953* ("the Act")) that lumacaftor with ivacaftor be made available as a pharmaceutical benefit under Part VII of the Act.

A note of the PBAC's decision follows.

7.04 LUMACAFTOR AND IVACAFTOR Tablet containing lumacaftor 200 mg with ivacaftor 125 mg, Orkambi®, Vertex Pharmaceuticals (Australia) Pty Ltd

11 Purpose of Application

11.1 Resubmission to request a Section 100 (Highly Specialised Drugs Program) Authority Required listing for lumacaftor 200 mg with ivacaftor 125 mg fixed dose combination (lumacaftor/ivacaftor) for the treatment of patients with cystic fibrosis (CF) aged ≥12 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

11.2 The first submission for lumacaftor/ivacaftor was considered by the PBAC in March 2016, and a minor resubmission was considered in November 2016.

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

Component	Description
Population	CF patients aged ≥12 years who are homozygous for the F508del mutation in the CFTR gene
Intervention	Lumacaftor 400 mg/ivacaftor 250 mg twice daily
Comparator	Best supportive care
Outcomes	$ppFEV_1$; pulmonary exacerbations (including those requiring hospitalisation and/or IV antibiotics); changes in BMI and quality of life (using the CFQ-R).
Clinical claim	In CF patients aged ≥12 years who are homozygous for the F508del mutation, lumacaftor/ivacaftor is more effective than best supportive care in improving the outcomes above and is of similar safety.

Source: Compiled during the evaluation.
Abbreviations: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; BMI = body mass index; CFQ-R = cystic fibrosis questionnaire – revised.

12 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
LUMACAFTOR + IVACAFTOR lumacaftor 200 mg + ivacaftor 125 mg tablet	112	5	$[redacted]	Orkambi®	VR

Category/Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☒ Medical Practitioners
PBS Indication:	Cystic fibrosis
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	~~Patient must be assessed through a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit,~~ ~~AND~~ ~~Patient must be homozygous for the F508del mutation in the CFTR gene,~~ ~~AND~~ ~~The treatment must be given concomitantly with standard therapy for this condition.~~ *Must be treated by a specialist respiratory physician with expertise in cystic fibrosis, OR* *Must be treated in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation;* *AND* *Must be treated in a centre with expertise in cystic fibrosis, OR* *Must be treated in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.*
Clinical criteria:	~~Treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the *F508del* mutation in the CFTR gene.~~ *Patient must be homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene;* *AND* *Patient must have a sweat chloride value of greater than or equal to 60 mmol/L;* *AND* *Patient must have a FEV_1 of ≥40% of predicted normal for age, sex, and height;* *AND* *Patient must have experienced chronic sinopulmonary disease, OR* *Patient must have experienced gastrointestinal abnormalities, OR* *Patient must have experienced nutritional abnormalities;* *AND* *The treatment must be given concomitantly with standard therapy for this condition.*
Population criteria:	Patient must be 12 years of age or older.
Prescriber Instructions	~~The authority application must be in writing and must include:~~ ~~(1) a completed authority prescription form; and~~ ~~(2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and~~ ~~(3) a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and~~ ~~(4) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene.~~

	Patients receiving PBS-subsidised treatment with this drug must be registered in the Australian Cystic Fibrosis Database Registry. *Treatment must not be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing this drug.* The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Lumacaftor with Ivacaftor Authority Application Supporting Information Form; and (3) a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and (4) a copy of the pathology report detailing the molecular testing for the patient being homozygous for the F508del mutation on the CFTR gene*; and* *(5) the result of a FEV_1 measurement performed within a month prior to the date of application. Note: FEV_1, must be measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time FEV_1 is measured; and* *(6) evidence that the patient has either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities; and* *(7) a copy of a current medication history* *(8) a copy of a sweat chloride result; and* *(9) height and weight measurements at the time of application; and* *(10) a baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the home) in the previous 12 months.*
Administrative Advice	*Special pricing arrangements apply* *No increase in the maximum number of repeats may be authorised.* *No increase in the maximum quantity or number of units may be authorised.* *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

2.2 The recommended dose is two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours. The treatment is ongoing for the lifetime of the patient. Dose reductions are recommended in the TGA approved product information (PI) for patients with moderate or severe hepatic impairment.

2.3 No special pricing arrangements were proposed in relation to the DPMQ. However, the resubmission proposed to cap the gross cost to the PBS in the first five years of listing, by way of a reduction on the total projected expenditure. The resubmission also proposed a [redacted]

2.4 The ESC noted that the TRAFFIC and TRANSPORT trials required patients to have a $ppFEV_1$ of ≥40% and ≤90% adjusted for age, gender and height. The PBAC had previously determined that the efficacy and safety of lumacaftor/ivacaftor in patients with ppFEV1 <40% and >90% had not been evaluated and is unknown (paragraph 2.2, March 2016 Public Summary Document (PSD)). The Secretariat has suggested including a clinical criterion that "Patient must have a FEV1 of ≥40% of predicted normal for age, sex, and height" in the above requested listing.

2.5 The requested basis for listing is cost-effectiveness compared with the nominated comparator (best supportive care).

13 Background

3.1 TGA status at the time of PBAC consideration: Lumacaftor/ivacaftor was registered by the TGA for "the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene" on 8 March 2016.

3.2 A major submission for lumacaftor/ivacaftor was rejected at the March 2016 PBAC meeting on the basis of an unacceptably high and uncertain incremental cost-effectiveness ratio at the requested price, and uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements in lung function and survival (paragraph 7.1, March 2016 PSD). A minor resubmission was also rejected by the PBAC at its November 2016 meeting noting that the issues it previously identified in its consideration of the March 2016 submission had not been addressed. The PBAC further noted the continued uncertainty regarding long-term benefits of treatment on lung function and overall survival (paragraph 7.1, November 2016 PSD).

3.3 A summary of the key differences between the March 2016 major submission, the November 2016 minor resubmission and the current resubmission is provided in Table 2.

Table 2: Summary of the previous and current (re)submissions

Component	March 2016 major submission and November 2016 minor resubmission	July 2017 major resubmission
Requested PBS listing	Treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.	As per March 2016, with changes suggested by the Secretariat during the evaluation of the March 2016 submission. November 2016 suggested changes were not incorporated.
Requested price	S100 HSD public hospital DPMQ: $[redacted]	As per March 2016
Main comparator	Best supportive care **PBAC comment:** Best supportive care was the appropriate comparator (7.4 of March 2016 PSD)	As per March 2016
Clinical evidence	Two head-to-head trials comparing lumacaftor/ivacaftor to placebo at 24 weeks; TRAFFIC (n=374) and TRANSPORT (n=376). Supportive evidence for further 24 weeks from one extension study (PROGRESS, n=516).	As per March 2016 with the addition of extension study PROGRESS to week 96.
Key effectiveness data	Absolute increase in $ppFEV_1$ of 2.8% (measured as the average of weeks 16 and 24). Reduction in the annualised rate of pulmonary exacerbations, including those that required hospitalisation and/or IV antibiotics. **PBAC comment:** "…it was uncertain whether this observed improvement in $ppFEV_1$ [2.81%] represented a clinically significant difference, noting that this was considerably smaller than the improvement of 10.58% (95% CI: 8.57, 12.59) demonstrated for ivacaftor monotherapy." (paragraph 7.6 of March 2016 PSD)	The increase in $ppFEV_1$ observed in TRAFFIC and TRANSPORT at week 24 in lumacaftor/ivacaftor treated patients was not maintained at week 72 or 96. While $ppFEV_1$ did remain above the original pre-treatment baseline at these time points, this difference was not statistically significant.
Clinical claim	Superior in terms of comparative effectiveness and equivalent in terms of comparative safety over best supportive care. **PBAC comment**: "The extrapolation of short-term results to longer term efficacy was uncertain" and "long-term safety of lumacaftor/ivacaftor is unknown" (paragraph 7.7 and 7.10 of March 2016 PSD)	The resubmission claimed that longer-term data from the PROGRESS study provided further evidence that lumacaftor/ivacaftor is a disease modifying therapy, and the longer-term safety profile was consistent with the previous data in TRAFFIC and TRANSPORT.
Economic evaluation	Cost-utility model with cost/QALY of: • March 2016: $[redacted] more than $200,000. • November 2016: [redacted] more than $200,000 (revised to include a financial cap and reduce time to patent expiry and time to [redacted] price reduction). **PBAC comment**: "Unacceptably high and uncertain ICER at the requested price and uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements on lung function and overall survival (paragraph 7.1 of March 2016 PSD) There was "continuing uncertainty regarding long-	Cost-utility model with cost/QALY of: • Base Case 1: $105,000 - $200,000. • Base Case 2: $105,000 - $200,000.

Component	March 2016 major submission and November 2016 minor resubmission	July 2017 major resubmission
	term benefits of treatment" and the ICER was likely under-estimated. (paragraph 7.1 and 7.3 of November 2016 PSD)	
Number of patients	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5
Estimated net cost to PBS	More than $100 million in Year 1 increasing to more than $100 million in Year 5 for a total of more than $100 million over the first 5 years of listing. (March 2016). **PBAC comment**: "noted the significant opportunity cost of listing lumacaftor/ivacaftor, particularly in the context of the uncertainty of the long-term improvements in lung function" (paragraph 7.16 of March 2016 PSD) Cap on the first five years gross PBS cost (without co-payments deducted) to $[redacted] (November 2016).	Proposal to cap the gross cost to the PBS (without co-payment deducted) to more than $100 million in each of the first 5 years of listing.
Risk sharing arrangement and pay-for-performance	The sponsor was open to discussing the details of the requested listing and the final pricing arrangement. (March 2016). Proposal to cap the gross cost to the PBS (without co-payments deducted) as above and the sponsor indicated a willingness to discuss [redacted] (November 2016)	Proposal to cap the gross cost to the PBS (without co-payments deducted) as above. In addition, a proposal was presented to [redacted]

Source: Resubmission table, page (i) to (iii) of July 2017 resubmission and compiled during the evaluation.
Abbreviations: ICER, incremental cost effectiveness ratio; ACFDR, Australian Cystic Fibrosis Disease Registry; PSD, Public Summary Document.

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

14 Population and disease

4.1 CF is an autosomal recessive disease caused by mutations in the CFTR gene. CF is a progressive multi-organ disease that primarily affects the pulmonary and digestive systems.

4.2 As per the March 2016 and November 2016 submissions, the major resubmission proposed that lumacaftor 400 mg/ivacaftor 250 mg twice daily be administered in addition to current best supportive care in patients aged 12 years and older who are homozygous for the F508 deletion mutation in the CFTR gene. The ESC noted that over 90% of the Australian cystic fibrosis patient population have at least one F508del mutation, and around 50% are homozygous for the mutation, in the CFTR

gene[5].

4.3 The evaluation noted that lumacaftor/ivacaftor was approved for use in patients aged 6-11 years of age by the US Food and Drug Administration (FDA) on 28 September 2016 and asked the sponsor to advise of current plans for seeking to extend Australian marketing approval for lumacaftor/ivacaftor to this age group. The PSCR and pre-PBAC response did not address this request for information. [redacted]

4.4 The evaluation also noted that on 27 March 2017, the sponsor announced[6] results from two Phase 3 studies of a tezacaftor/ivacaftor combination treatment that showed statistically significant improvements in lung function (ppFEV1) in patients aged 12 and older who were homozygous for the F508del mutation. The sponsor also announced plans to submit a New Drug Application to the FDA and a Marketing Authorization Application to the European Medicines Agency in the third quarter of 2017 for the combination therapy. The evaluation noted that if lumacaftor/ivacaftor was PBS listed for the requested indication it would likely be used as a comparator for tezacaftor/ivacaftor in a future submission to the PBAC. The evaluation asked the sponsor to advise of current plans for seeking Australian marketing approval for tezacaftor/ivacaftor. The PSCR and pre-PBAC response did not address this request for information. [redacted] In addition, the PBAC was also aware that phase 1 and 2 clinical trials are currently ongoing for triple therapy regimens of tezacaftor/ivacaftor plus a "next generation corrector" in various CF populations, including patients homozygous for F508del[7].

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

15 Comparator

5.1 Best supportive care (BSC) was nominated as the comparator. The PBAC previously accepted that this is the appropriate comparator (paragraph 7.4, March 2016 PSD).

16 Consideration of the evidence

[5] Cystic fibrosis in Australia 2014, 17th annual report, Australian cystic fibrosis data registry, p13.
[6] Vertex pharmaceuticals media release, 28 March 2017, Two Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment Met Primary Endpoints with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis.
[7] Clinicaltrials.gov identifiers: NCT02951182, NCT02951195 and NCT03029455.

Sponsor hearing

6.2 The sponsor requested a hearing for this item. The clinician discussed what outcomes are informative for deciding which treatments are useful for CF and noted that very few treatments modify the course of the disease. The clinician noted that the pattern of response in terms of FEV_1 for lumacaftor/ivacaftor is similar but less than that demonstrated with ivacaftor for the class III gating patient population who typically have milder disease than the homozygous F508del population of interest for lumacaftor/ivacaftor. The clinician stressed the importance of reducing the rate of decline in lung function. Further, the clinician claimed that a change in FEV_1 was not a good predictor of the longer-term decline in lung function, or long-term health outcomes, which some evidence suggests may be influenced by metabolic affects. Specifically, the clinician was of the opinion that the short-term change in FEV_1 demonstrated in trials is independent of the long-term rate of decline. In response to a question from the PBAC regarding the utility of the propensity matched analysis of lumacaftor/ivacaftor treated patients in the PROGRESS extension study against a historical cohort drawn from the US CF registry (see paragraph 6.19), the clinician noted that patients in the US tend to perform worse on average than patients in other countries such as the UK. The PBAC considered that the hearing was informative as it provided a clinical perspective on the outcomes of interest in the treatment of CF.

Consumer comments

6.3 The PBAC noted and welcomed the input from individuals (214) and one organisation via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with lumacaftor/ivacaftor, including improvement in lung function, reduction in chest infections and exacerbations, weight gain, fewer hospital visits, fewer medications to be consumed on a daily basis, slowing disease progression, improvement in quality of life and enabling greater participation in society (including less time off work and school for illness). The comments noted that the very high cost of the drug on the private market puts it out of the financial reach of Australian patients. The comments also noted that lumacaftor/ivacaftor is a treatment which targets the underlying genetic defect which causes CF, rather than treating the symptoms of the disease.

6.4 The PBAC noted the advice received from Cystic Fibrosis Australia (CFA) that CFA considers lumacaftor/ivacaftor to be an essential medicine that treats the underlying cause of the disease. CFA stated that treatment with lumacaftor/ivacaftor slows decline in lung function, reduces hospitalisations, exacerbations and antibiotic use, and increases BMI. The CFA further noted the anxiety and depression experienced by patients with CF. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.5 The resubmission was based on the same two head-to-head trials as the March 2016

major submission, TRAFFIC (n=374) and TRANSPORT (n=376), comparing lumacaftor 400 mg/ivacaftor 250 mg twice daily to placebo. Of the patients in these trials, 516 patients received the same dose of lumacaftor/ivacaftor in an extension study, PROGRESS. While data at 24 weeks in this study had been presented in the original submission, the current resubmission presented further data at 72 weeks and 96 weeks of the extension phase (i.e. up to 120 weeks of treatment for those in the lumacaftor/ivacaftor treatment group in TRAFFIC/TRANSPORT).

6.6 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Traffic	Clinical study report VX12-809-103 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	8 September 2014
Transport	Clinical study report VX12-809-104 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation.	2 September 2014
	Wainwright CE, Elborn JS, Ramsey B, Marigowda G et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR.	New England Journal of Medicine 2015; 373:220-23
Rollover extension study		
Progress	Clinical study report VX12-809-105 A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation Interim analysis 2 (IA2) at Week 24	18 May 2015
	Elborn, J., Ramsey, B. and Boyle, M. B. Lumacaftor in combination with ivacaftor in patients with cystic fibrosis who were homozygous for the F508del-CFTR mutation.	The 38th annual European Cystic Fibrosis Conference, Brussels, Belgium, 10-12 June 2015
	Konstan, M. W., McKone, E. F., Moss, R. B., et al. (2017). Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): A phase 3, extension study.	The Lancet Respiratory Medicine 2017. 5 (2): 107-18.
	Konstan, M., McKone, E., Moss, R., et al. Evidence of reduction in annual rate of FEV_1 decline and sustained benefits with lumacaftor and ivacaftor (LUM/IVA) in patients (PTS) with CF homozygous for f508del-cftr.	Pediatric Pulmonology 2016. 51: 260.

Source: Table B.2-3, page 64-65 of resubmission.

6.7 The key features of the direct randomised trials and the extension study are summarised in Table 4.

Table 4: Key features of the included evidence, lumacaftor/ivacaftor vs. placebo

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
TRAFFIC	374[a]	R, DB, MC 24 weeks	Low	Aged 12 or older Homozygous for the F508del mutation	Absolute change in $ppFEV_1$, BMI, CFQ-R, PEs, EQ-5D-3L	Absolute change in $ppFEV_1$, weight for age z-score, PEs
TRANSPORT	376[b]	R, DB, MC 24 weeks	Low	Aged 12 or older Homozygous for the F508del mutation	Absolute change in $ppFEV_1$, BMI, CFQ-R, PEs, EQ-5D-3L	Absolute change in $ppFEV_1$, weight for age z-score, PEs
PROGRESS	516[c]	Extension study for further 72/96 weeks with all patients receiving lumacaftor 400mg/ ivacaftor 250mg twice daily.	High	Aged 12 or older Homozygous for the F508del mutation rolling over from TRAFFIC and TRANSPORT	Safety of long-term treatment, absolute change in $ppFEV_1$, BMI, CFQ-R, PEs	Not used.

Source: compiled during the evaluation

DB=double blind; MC=multi-centre; R=randomised; CFQ-R=cystic fibrosis questionnaire - revised; BMI=body mass index; PE = pulmonary exacerbation

[a] n=374 in the 2 arms of the trial included in the analysis. The trial had a third arm (600 mg lumacaftor qd, 250 mg ivacaftor q12h) with n=185

[b] n=376 in the 2 arms of the trial included in the analysis. The trial had a third arm (600 mg lumacaftor qd, 250 mg ivacaftor q12h) with n=187

[c] n = 516 in the group included in the analysis, of whom 176 transitioned from placebo. The study had a second arm (600 mg lumacaftor qd, 250 mg ivacaftor q12h) with n=514

6.8 A large proportion of patients in PROGRESS discontinued treatment prior to completion; 82% completed extension week 72, and 42% completed extension week 96. Reasons for discontinuation included adverse events (7%, n=38), refusal of further dosing (9%, n=46), terminated treatment by sponsor (4%, n=19) and "other" (33%, n=170). The latter largely occurred between week 72 and week 96 and the resubmission stated this was largely due to commercial drug availability in the US and subsequent closure of clinical trial sites. Accordingly, the main efficacy analyses in the resubmission were done for visits up to extension week 72, with sensitivity analyses done for visits up to extension week 96. The evaluation noted that this high attrition rate suggested an increased risk of bias in this study in respect of outcome reporting, the direction of which is unknown. It is unclear if patients who discontinued between weeks 72 and 96 performed "better" or "worse" on lumacaftor/ivacaftor than those who remained. However, the ESC noted that over 16% patients chose to discontinue treatment before week 96 due to adverse events or refusal of further dosing.

Comparative effectiveness

6.9 The primary outcome at 24 weeks in the TRAFFIC and TRANSPORT trials was an absolute increase in $ppFEV_1$ of 2.8 percentage points (95% CI: 1.80, 3.82). The PBAC previously considered that it was uncertain whether the observed improvement in $ppFEV_1$ represented a clinically significant difference noting that it was considerably smaller than the improvement of 10.58 percentage points (95% CI: 8.57, 12.59) demonstrated for ivacaftor monotherapy for patients with cystic fibrosis with a G551D or other class III gating mutation in the CFTR gene on at least one allele (paragraph 7.6, March 2016 PSD). In addition, the incremental improvements (compared with placebo) demonstrated in patients' weight and quality of life as

measured using the revised Cystic Fibrosis Questionnaire (CFQ-R) for ivacaftor monotherapy in this different patient population were considered more compelling than for lumacaftor/ivacaftor.

6.10 The PSCR argued it was not appropriate to directly compare the magnitude of $ppFEV_1$ improvement observed with lumacaftor/ivacaftor with that observed with ivacaftor monotherapy because of differences in disease aetiology between the two treatment populations. Whilst acknowledging these differences in the genetic basis of the disease, the ESC nevertheless noted that the magnitude of the change in $ppFEV_1$ was less than that for ivacaftor monotherapy in Class III gating mutations and that the clinical significance of the 2.81 percentage point improvement remained uncertain.

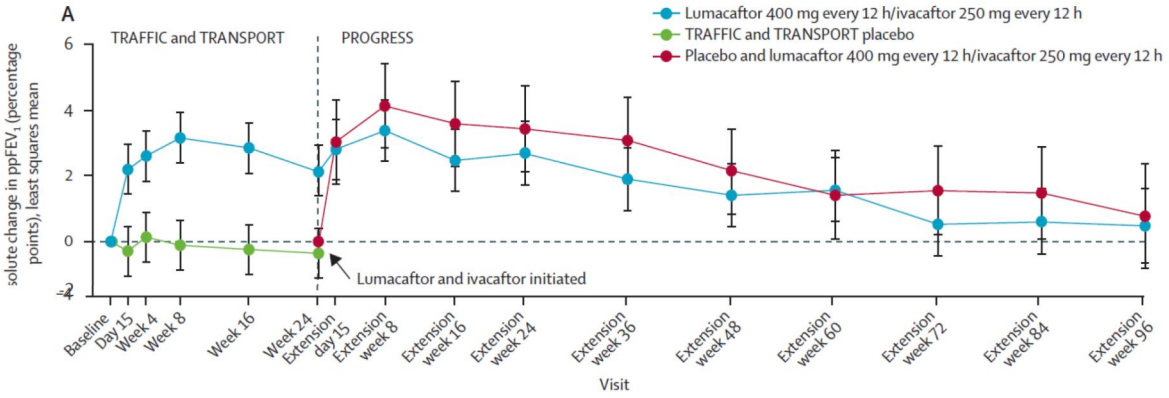
6.11 The clinical evidence from the PROGRESS extension study indicated that there was a decline in $ppFEV_1$ for lumacaftor/ivacaftor treated patients over time with the modest 2.81 percentage point improvement observed in TRAFFIC and TRANSPORT not being maintained at weeks 72 or 96 of the extension study. Using the pre-specified analysis methods, the ESC noted that the change in $ppFEV_1$ from baseline in lumacaftor/ivacaftor treated patients was no longer statistically significant at extension weeks 72 or 96 (i.e. up to 120 continuous weeks of treatment). Patients who had been treated with placebo and transitioned to lumacaftor/ivacaftor treatment demonstrated a change of 1.5 percentage points in $ppFEV_1$ after 72 weeks of treatment, although the difference with baseline was no longer statistically significant at 96 weeks. These data are illustrated in Table 5 and Figure 1.

Table 5: Absolute changes from baseline in ppFEV1 in TRAFFIC or TRANSPORT and PROGRESS

	TRAFFIC or TRANSPORT least squares mean, (95% CI), p value†		PROGRESS least squares mean, (95% CI), p value†	
	Placebo (n=371)	Lumacaftor/ivacaftor (n=369)	Placebo transitioned to lumacaftor/ivacaftor (n=176)	Continued lumacaftor/ivacaftor (n=369*)
Week 24	–0·4 (–1·2 to 0·4), p=0·3494	2·2 (1·3 to 3·0), p<0·0001	..	..
Extension week 72	..	..	1·5 (0.2, 2·9), p=0·0254	0·5 (–0·4 to 1·5), p=0·2806
Extension week 96	..	..	0·8 (–0·8, 2·3), p=0·3495	0·5 (–0·7 to 1·6), p=0·4231

Source: Table B.7-2, page 128 July 2017 resubmission.
Abbreviations: $ppFEV_1$ = percent predicted FEV_1, CI = confidence interval.
†For the placebo and lumacaftor/ivacaftor groups, baseline from TRAFFIC or TRANSPORT was used; for the placebo transitioned to lumacaftor/ivacaftor group, baseline from PROGRESS was used. All p values (including for TRAFFIC or TRANSPORT data) are within treatment.
* This number is as presented in the submission. 369 patients in TRAFFIC and TRANSPORT had received at least one dose of lumacaftor/ivacaftor 400mg/250mg twice daily and therefore are included in safety analyses. 341 of these patients enrolled in PROGRESS study, and 340 received at least one dose.

Figure 1: Absolute change in ppFEV1 in TRAFFIC, TRANSPORT and PROGRESS, least square mean



Source: Konstan et al, 2017

6.12 The PSCR argued that the main objective of CF treatment is to minimise the rate of deterioration over time and that it is not meaningful to simply compare the $ppFEV_1$ at week 96 of PROGRESS for lumacaftor/ivacaftor treated patients with their own baseline $ppFEV_1$ given that, had those patients received BSC, they would have deteriorated to a greater extent over this time period. However, the ESC noted that the updated data from PROGRESS and the argument in the PSCR contradicted the assumption in the economic model that patients treated with lumacaftor/ivacaftor do not experience a decline in $ppFEV_1$ over time.

6.13 The ESC also noted that the treatment gain of 10.58 percentage points in the clinical trial for ivacaftor for patients with cystic fibrosis with a G551D or other class III gating mutation in the CFTR gene on at least one allele was maintained at up to 144 weeks of treatment (PSD, ivacaftor, March 2014).

6.14 The changes from baseline in pulmonary exacerbation (PE) events in TRAFFIC, TRANSPORT and PROGRESS are shown in Table 6. The annualised rates for lumacaftor/ivacaftor were lower than the rates in the placebo group up to week 24.

Table 6: Changes from baseline in pulmonary exacerbation events in TRAFFIC or TRANSPORT and PROGRESS

	TRAFFIC or TRANSPORT* n (95% CI)		PROGRESS* n (95% CI)	
Pulmonary exacerbation events per patient-year	**Placebo (n=371)**	**Lumacaftor/ ivacaftor (n=369)**	**Placebo transitioned to lumacaftor/ ivacaftor (n=176)**	**Continued lumacaftor/ ivacaftor (n=369[I])**
All events	1.14 (0.97 to 1.34)	0.70 (0.57 to 0.84)	0.69 (0.56 to 0.85)	0.65 (0.56 to 0.75)
Requiring hospital admission	0.45 (0.36 to 0.57)	0.17 (0.12 to 0.25)	0.30 (0.22 to 0.40)	0.24 (0.19 to 0.29)
Requiring intravenous antibiotics	0.58 (0.47 to 0.72)	0.25 (0.19 to 0.33)	0.37 (0.29 to 0.49)	0.32 (0.26 to 0.38)

Source: Table B.7-14, page 133 July 2017 resubmission.
Abbreviations: CI = confidence interval.
* The analyses for TRAFFIC or TRANSPORT included events through to week 24. The pulmonary exacerbations analyses for PROGRESS included events throughout the cumulative study period (TRAFFIC or TRANSPORT and PROGRESS), such that the placebo transitioned to lumacaftor/ivacaftor group received up to 96 weeks of active treatment and the lumacaftor/ivacaftor group received up to 120 weeks of active treatment.

6.15 The PSCR noted that the absolute PE event rate per patient-year for patients treated with lumacaftor/ivacaftor in TRAFFIC/TRANSPORT remained similar in PROGRESS; that is, the rate of PEs is approximately halved by lumacaftor/ivacaftor relative to placebo and this is maintained in patients who are treated for up to 120 weeks. The ESC further noted that the PE event rate in the patients treated with placebo in TRAFFIC/TRANSPORT fell after transition to lumacaftor/ivacaftor treatment in PROGRESS. The ESC noted that it was unclear whether this decrease in PE events may have occurred independently of changes in $ppFEV_1$.

6.16 The changes from baseline in CFQ-R in TRAFFIC, TRANSPORT and PROGRESS are shown in Table 7. The numerical improvement observed in CFQ-R at 24 weeks for lumacaftor/ivacaftor treated patients was not statistically significantly different to the improvement observed in placebo treated patients. Furthermore, the ESC noted that while the improvement for the mean respiratory domain score seen at 24 weeks in the lumacaftor/ivacaftor treated group appeared to be maintained at weeks 72 and 96 of PROGRESS, the difference from baseline in the patients who transitioned from placebo to lumacaftor/ivacaftor was not statistically significant at weeks 72 and 96.

6.17 The ESC noted an improvement in the mean CFQ-R respiratory domain score compared with baseline at 72 weeks in PROGRESS for the group of patients who transitioned from placebo to lumacaftor/ivacaftor. However, this improvement was not seen at 96 weeks, despite the improvements in PEs seen in this transition group.

6.18 The absolute change from baseline in body mass index (BMI) continued to increase through to 96 weeks in PROGRESS in patients previously treated with both lumacaftor/ivacaftor and placebo in TRAFFIC/TRANSPORT (see Table 7).

Table 7: Changes from baseline in CFQ-R respiratory domain score and BMI in TRAFFIC, TRANSPORT and PROGRESS

	TRAFFIC or TRANSPORT		PROGRESS	
	Placebo (n=371)	**Lumacaftor/ ivacaftor (n=369)**	**Placebo transitioned to lumacaftor/ ivacaftor (n=176)**	**Continued lumacaftor/ ivacaftor (n=369)**
Absolute change from baseline in CFQ-R respiratory domain score, least squares mean, 95% CI, (points), p value†				
Week 24	1.9 (0.3 to 3.5) p=0.0213	4.1 (2.5 to 5.7) p<0.0001	..	..
Extension week 72	..	..	3.3 (0.7 to 5.9) p=0.0124	5.7 (3.8 to 7.5) p<0.0001
Extension week 96	..	..	0.5 (–2.7 to 3.6) p=0.7665	3.5 (1.3 to 5.8) p=0.0018
Absolute change from baseline in body-mass index, least squares mean, 95% CI, (kg/m^2), p value†				
Week 24	0.13 (0.04 to 0.23) p=0.0066	0.37 (0.28 to 0.47) p<0.0001	..	..
Extension week 72	..	..	0.62 (0.45 to 0.79) p<0.0001	0.69 (0.56 to 0.81) p<0.0001
Extension week 96	..	..	0.76 (0.56 to 0.97) p<0.0001	0.96 (0.81 to 1.11) p<0.0001

Source: Table B.7-11 and B.7-12, page 129 and 131 July 2017 resubmission.
Abbreviations: CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval.
†For the placebo and lumacaftor/ivacaftor groups, baseline from TRAFFIC or TRANSPORT was used; for the placebo transitioned to lumacaftor/ivacaftor group, baseline from PROGRESS was used. All p values (including for TRAFFIC or TRANSPORT data) are within treatment.
All p values (including for TRAFFIC or TRANSPORT data) are within treatment.

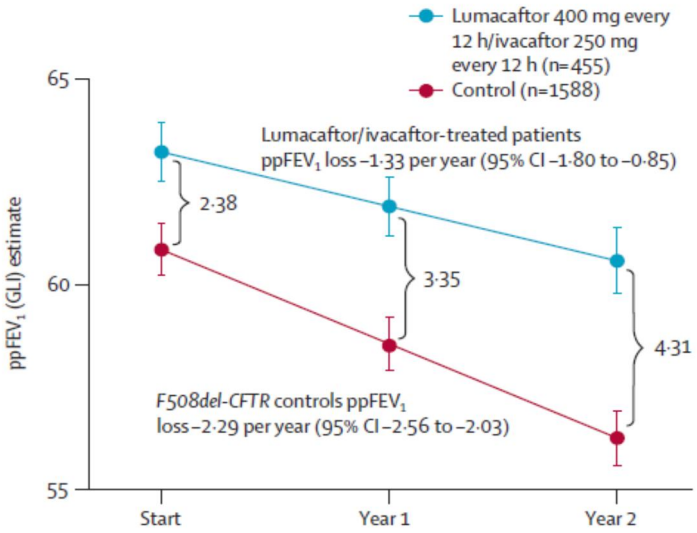
6.19 The resubmission claimed that the new longer-term efficacy data from PROGRESS demonstrated sustained improvements in key CF treatment outcomes that are associated with prolongation of life. Despite the progressive nature of CF, mean $ppFEV_1$ remained above the pretreatment baseline after up to 120 weeks of cumulative exposure to lumacaftor/ivacaftor (although this difference was not statistically significant). The resubmission also claimed that the sustained benefits on PE rates and patient-reported respiratory symptoms, together with continued improvement in nutritional status, showed that lumacaftor/ivacaftor provides multisystem benefits that continue to dampen the expected disease trajectory over the longer term, and suggest that lumacaftor/ivacaftor is a disease modifying therapy in CF.

6.20 To place the rate of decline in $ppFEV_1$ observed in the PROGRESS study in context, the resubmission presented an analysis that compared the rate of decline with that of a matched control registry. In this analysis, 455 patients treated with lumacaftor/ivacaftor in PROGRESS were matched with 1,588 control patients from the US Cystic Fibrosis Foundation Patient Registry (CFFPR). Matching was performed using a propensity score approach, with matching being based on variables including age, sex, spirometry measures, nutrition and bacteriology. The ESC noted the groups appeared to be fairly well matched but that some key variables, including BMI and use of corticosteroids, were excluded from the propensity score model and it was

therefore difficult to assess whether these variables were balanced between the treatment arms after matching. The ESC also noted the methodology was a single point-in-time rebalancing at baseline which did not adjust for the imbalance that is reintroduced subsequent to baseline. Accordingly, if there were any post-baseline differences in variables that were not due to the treatment, or if there were differences in data collection between the patients in PROGRESS and the CFFPR cohort, these may have confounded the outcomes.

6.21 The estimated annualised rate of lung function decline in this analysis was -1.33 percentage points (95% CI: -1.80, -0.85) in lumacaftor/ivacaftor-treated patients. This rate was less than the rate in the matched CFFPR controls (-2.29 percentage points, 95% CI: -2.56, -2.03; p<0.001) and represented a 42% decrease in the rate of $ppFEV_1$ decline in lumacaftor/ivacaftor-treated patients compared with the matched controls (or conversely, lumacaftor/ivacaftor treated patients experienced a decline in $ppFEV_1$ that was 58% of the decline in the matched registry controls). The relative rates of decline are depicted in Figure 2 below.

Figure 2: Estimated annual rate of ppFEV1 decline with lumacaftor/ivacaftor treated patients compared with a matched control group.



Source: Figure B.7-9 p134 July 2017 resubmission.
The lines shown are calculated slopes for annualised rates of decline in each group. A significant difference between groups in the rate of lung function decline was observed (p<0.001). Post-baseline data were limited to 2 years; visits occurring at 21 days of treatment initiation baseline or earlier were excluded from the analysis.
Bars show standard error.
Abbreviations: GLI = Global Lungs Initiative; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second.

6.22 A rate of change analysis was also performed for secondary outcomes where data from the PROGRESS study were compared with the CFFPR cohort. These data indicated a positive rate of change in the lumacaftor/ivacaftor group for weight for age and BMI-z score (with the matched cohort declining over time) and a greater rate of change in the treatment group for BMI (kg/m^2) versus the matched cohort.

6.23 The PBAC agreed with the ESC that patients appeared to be fairly well matched in terms of the variables used for the propensity scoring approach. However, the PBAC

considered that the historical control patients from the CFFPR were nevertheless unlikely to be representative of the patients in TRAFFIC/TRANSPORT, and hence PROGRESS, and the comparison of the reduction in the rate of decline in FEV_1 in PROGRESS versus the CFFPR was likely to be biased in favour of lumacaftor/ivacaftor. More specifically:

- The historical controls were drawn from the CFFPR which included only patients from the US, while the patients in PROGRESS were from the CF clinics across North America, Europe and Australia that participated in TRAFFIC/TRANSPORT. The PBAC noted a recent cohort study (Stephenson et al, 2017[8]) that found a 10 year difference in the median age of survival for CF patients in the US CFFPR (40.6 years) compared to the Canadian Cystic Fibrosis Registry (50.9 years). The study found that this difference persisted after adjustment for risk factors associated with survival, with the exception of private insurance status among US patients, and concluded that the Canadian survival advantage may in part be explained by differential access to transplantation, increased post-transplant survival, and differences in health care systems. The clinician at the sponsor hearing also noted that patients in the US tend to perform worse on average than patients in other countries, such as the UK (see paragraph 6.1). Accordingly, the PBAC considered that the higher rate of decline in FEV_1 in the US CFFPR may have been at least partly due to it consisting entirely of historical US patients, compared with PROGRESS which included patients from other countries, and in which patients might be expected to have benefited from optimization of other aspects of care. Further increasing uncertainty about the benefit of lumacaftor/ivacaftor was the closure of US clinical trial sites (see paragraph 6.7) which presumably resulted in further depletion of the PROGRESS patient population with US patients over time.
- The PBAC considered that due to the requirements of the trial protocols (e.g. inclusion/exclusion criteria, monitoring and support provided), and the specialised centres involved, that the patients enrolled in the trials were likely to have a better prognosis on average than the CFFPR control patients. The PBAC noted that the reduction in FEV_1 over 24 weeks for patients treated with placebo in the TRAFFIC/TRANSPORT trials was 0.4 percentage points and that this was much lower than the reduction observed in the CFFPR control patients over 1 and 2 years (2.29 percentage points). The PBAC considered that this difference suggested that the prognosis of patients in the trials differed substantially from CFFPR controls. Further, the PBAC noted that the reduction in FEV_1 in the placebo arm in a trial for tezacaftor/ivacaftor in a similar patient population as TRAFFIC/TRANSPORT was 0.6 percentage points over 24 weeks (EVOLVE study[9]).

[8] Stephenson AL; Sykes J; Stanojevic S; *et al*. *Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States: A Population-Based Cohort Study*. Annals of Internal Medicine, 2017;166(8):537-546.

[9] Vertex pharmaceuticals media release, 28 March 2017, Two Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment Met Primary Endpoints with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis.

Thus the PBAC considered that it was not valid to compare the 2.29 percentage point reduction in FEV_1 in historical controls from CFFPR with that observed among treated patients in PROGRESS.

Overall, the PBAC considered that the matched analysis did not adequately support the claim of a reduction in the rate of decline in FEV_1 with lumacaftor/ivacaftor compared with BSC.

Comparative harms

6.24 A summary of the adverse events for lumacaftor/ivacaftor versus placebo is presented in Table 8 below.

Table 8: Summary of adverse events in TRAFFIC and TRANSPORT

AE Category	TRAFFIC		TRANSPORT		Pooled	
	Lumacaftor/ ivacaftor (N=182)	Placebo (N=184)	Lumacaftor/ ivacaftor (N=187)	Placebo (N=186)	Lumacaftor/ ivacaftor (N=369)	Placebo (N=370)
Total number of AEs	1019	994	1111	1138	2130	2132
Subjects with any AEs, n (%)	174 (95.6)	174 (94.6)	177 (94.7)	181 (97.3)	351 (95.1)	355 (95.9)
Subjects with Grade 3/4 AEs, n (%)	19 (10.4)	25 (13.6)	26 (13.9)	34 (18.3)	NR	NR
Subjects with AEs by relationship: 'Related' or 'possibly related", n (%)	91 (50)	49 (26.6)	100 (53.5)	80 (43)	NR	NR
Subjects with AEs leading to treatment discontinuation, n (%)	6 (3.3)	4 (2.2)	11 (5.9)	2 (1.1)	17 (4.6)	6 (1.6)
Subjects with AEs leading to treatment interruption, n (%)	14 (7.7)	10 (5.4)	8 (4.3)	15 (8.1)	22 (6.0)	25 (6.8)
Subjects with SAEs, n (%)	33 (18.1)	49 (26.6)	31 (16.6)	57 (30.6)	64 (17.3)	106 (28.6)
Subjects with related SAEs, n (%)	8 (4.4)	3 (1.6)	6 (3.2)	5 (2.7)	14 (3.8)	8 (2.2)
Subjects with AEs leading to death, n (%)	0	0	0	0	0	0

Source: Table B.6.4, p112 July 2017 resubmission. Table 12-2, TRAFFIC CSR, p 188; Table 12-2, TRANSPORT CSR, p 201.
Abbreviations: AE = adverse event; n = size of subsample; N = number of subjects; SAE = serious adverse event, NR = not reported.

6.25 In the randomised trials, the most common adverse events experienced by patients who received lumacaftor/ivacaftor were dyspnoea (14.0% versus 7.8% on placebo), diarrhoea (11.0% versus 8.4% on placebo), and nausea (10.2% versus 7.6% on placebo). Serious adverse reactions occurring in at least 0.5% of patients on lumacaftor/ivacaftor and in a greater proportion of lumacaftor/ivacaftor patients than placebo patients were hepatobiliary events.

6.26 In PROGRESS, the most common adverse events reported were cough (44%), increased sputum (22%), and haemoptysis (20%). Most of these adverse events (in 71% of patients) were considered mild or moderate in severity. There was an increase in blood pressure associated with extended lumacaftor/ivacaftor therapy.

6.27 Serious adverse events were experienced by 45% of patients in PROGRESS, the most frequently reported being infective PEs of CF (in 33% of patients), haemoptysis (3%), and distal intestinal obstruction syndrome (3%).

6.28 Two deaths occurred in the lumacaftor 400 mg/ivacaftor 250 mg every 12h group during the course of PROGRESS: one patient died from respiratory failure related to infective PE, and one from distal intestinal obstruction syndrome. Neither of the deaths was considered to be related to the study drug.

Benefits and harms

6.29 A summary of the comparative benefits and harms for lumacaftor/ivacaftor versus placebo as evidenced from the TRAFFIC and TRANSPORT trials is presented in Table 9 below.

Table 9: Summary of comparative benefits and harms for lumacaftor/ivacaftor and placebo

Benefits							
ppFEV$_1$: absolute change from baseline							
	Lumacaftor/ivacaftor			**Placebo**			**LS mean difference lumacaftor/ivacaftor vs. placebo (95% CI)**
	N	**Mean Δ baseline ppFEV$_1$**	**SE**	**n**	**Mean Δ baseline ppFEV$_1$**	**SE**	
Traffic	182	2.16	0.530	184	-0.44	0.524	2.60 (1.18, 4.40)
Transport	187	2.85	0.540	187	-0.15	0.539	3.00 (1.56, 4.44)
Pooled	369	2.49	0.379	371	-0.32	0.376	2.81 (1.80, 3.82)

Harms						
	Lumacaftor /ivacaftor	**Placebo**	**RR (95% CI)**	**Event rate/100 patients per 24 weeks**		**RD**
				Lumacaftor /ivacaftor	**Placebo**	
Subjects with any adverse event						
Pooled	351/369	355/370	0.99 (0.96,1.02)	95.1	95.9	0.00
Subjects with any serious adverse event						
Pooled	64/369	106/370	0.61 (0.46, 0.80)	17.3	28.6	-0.11
Subjects with any treatment related serious event						
Pooled	14/369	8/370	1.75 (0.75, 4.13)	3.8	2.2	0.02

Source: Compiled during the evaluation/Table B.6.1, p102, Table B.6.4, p112 of the submission and calculated during the evaluation
Abbreviations: SE = standard error; mg= milligrams; LS = least squares; ppFEV$_1$ = per cent predicted FEV$_1$; CI = confidence interval; RD = risk difference; RR = relative risk.

6.30 On the basis of the direct randomised trials presented by the resubmission, treatment with lumacaftor/ivacaftor resulted in approximately a 2.81 percentage point larger increase in absolute ppFEV$_1$ compared with placebo over a median duration of follow-up of 24 weeks.

6.31 On the basis of the direct randomised trials presented by the resubmission, a patient treated with lumacaftor/ivacaftor could expect to have one fewer pulmonary exacerbation over 2.5 years and one fewer hospitalisation due to a pulmonary exacerbation over 3 years.

6.32 Patients treated with lumacaftor/ivacaftor who continued therapy after completion of the original randomised trials continued to show an improvement in their lung function over baseline. However, the extent of that improvement decreased over time and by 96 weeks of treatment this difference was no longer statistically significant compared with before they commenced the trials.

6.33 On the basis of direct evidence from the trials, the overall frequency of adverse events being reported was comparable between lumacaftor/ivacaftor and placebo groups. Dyspnoea (14.0% versus 7.8% on placebo), diarrhoea (11.0% versus 8.4% on placebo), and nausea (10.2% versus 7.6% on placebo) occurred more frequently in the lumacaftor/ivacaftor group. Hepatobiliary serious adverse events had been reported in TRAFFIC and TRANSPORT, and occurred in at least 0.5% of patients on lumacaftor/ivacaftor and in a greater proportion of lumacaftor/ivacaftor patients than placebo patients. Following discontinuation of lumacaftor/ivacaftor, liver function tests returned to baseline or improved substantially in all patients.

6.34 For patients who continued to receive (or commenced) lumacaftor/ivacaftor therapy after the TRAFFIC and TRANSPORT trials ended, the most common adverse events reported were cough (44%), increased sputum (22%), and haemoptysis (20%) and may resolve without discontinuing treatment. A trend of an increase in blood pressure associated with extended lumacaftor/ivacaftor therapy had been identified and routine blood pressure monitoring is recommended. The most frequently reported serious adverse events in this group were infective PEs of cystic fibrosis (in 33% of patients), haemoptysis (3%), and distal intestinal obstruction syndrome (3%).

Clinical claim

6.35 The March 2016 submission described lumacaftor/ivacaftor as superior in terms of comparative effectiveness as it improved key CF outcomes that are associated with prolongation of life expectancy. The current resubmission claimed that the longer-term data from the PROGRESS study provided further evidence that lumacaftor/ivacaftor is a disease modifying therapy.

6.36 The March 2016 submission claimed the drug is equivalent to BSC in terms of comparative safety, and the current resubmission argued that the longer-term safety profile was consistent with the previous data in TRAFFIC and TRANSPORT.

6.37 In March 2016, the PBAC noted the improvement in exacerbations, weight gain, BMI, the hospitalisation rate and antibiotic use associated with treatment with lumacaftor/ivacaftor in the short-term but considered that the impact of lumacaftor/ivacaftor on improvements in long-term lung function and survival was uncertain. In addition, the PBAC considered that the claim of equivalent comparative

safety was reasonable in the short-term but noted the long-term safety of lumacaftor/ivacaftor is unknown.

6.38 Evidence from the PROGRESS extension study demonstrated that the modest increase in $ppFEV_1$ in lumacaftor/ivacaftor treated patients demonstrated in TRAFFIC and TRANSPORT was not maintained through to 120 weeks.

6.39 The PSCR argued the main objective of treatment with lumacaftor/ivacaftor is to minimise the rate of deterioration over time, noting the matched analysis of the comparative rates of decline of $ppFEV_1$ which represented a 42% decrease in the rate of $ppFEV_1$ decline in lumacaftor/ivacaftor-treated patients compared with a matched cohort. The PSCR further argued that the clinical impact of slowing CF progression over time was reflected to some extent by the maintenance of the absolute reduction in PE events per patient-year for up to 120 weeks of treatment.

6.40 The PBAC considered the claim that lumacaftor/ivacaftor slows the rate of decline in $ppFEV_1$ beyond 24 weeks, compared with patients treated with BSC, was not adequately supported by the resubmission for the reasons outlined in paragraph 6.22. However, the PBAC noted improvements in other clinical measures, including a reduction pulmonary exacerbations and an increase in body mass index, were maintained beyond the 24 week trial period, and therefore considered that the claim of superior comparative effectiveness for these outcomes was reasonable.

6.41 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the updated data from the PROGRESS study provided in the current resubmission. There is evidence of drug-related adverse events including respiratory adverse events (e.g. haemoptysis, cough), hepatobiliary events and development of hypertension associated with continued therapy. In this regard, the PBAC noted that 16% of patients chose to discontinue use due to adverse events or patient refusal of further dosing.

Economic analysis

6.42 The structure of the model was the same as the previous submissions (March 2016 and November 2016) which presented a cost-utility analysis compared with BSC. A summary of the model structure is presented in Table 10. The resubmission presented two base cases referred to as Base case 1 and Base case 2.

Table 10: Summary of model structure and rationale

Component	Summary
Time horizon	Life time horizon the modelled Base case 1 versus 24 weeks in the trial. A further 96 weeks was presented as supportive evidence, but not used in the model.
Outcomes	QALYs
Methods used to generate results	Microsimulation Cox-proportional hazards survival model (Liou et al, 2001) used to apply the effect of nine risk factors on the baseline hazard of mortality. In lumacaftor/ivacaftor patients $ppFEV_1$, weight-for-age z-score and number of pulmonary exacerbations are based on trial results.
Health states	As a microsimulation, changes are recorded in the underlying risk factors (as above) for each patient. Utility values are applied to health states based on $ppFEV_1$ status of normal (>90%), mild (70-90%), moderate (40-70%) and severe (<40%).
Utilities	Clinician Survey
Cycle length	4 weeks for the initial two years, annual thereafter.

Source: Table D.3.1 of the Commentary.
Abbreviations: $ppFEV_1$ = percent predicted forced expiratory volume in one second; QALY = quality-adjusted life-years.

6.43 Base case 1 included four revisions to the March 2016 model to result in an ICER of $105,000/QALY – $200,000/QALY:

- The assumed date of PBS listing of lumacaftor/ivacaftor changed from 1 July 2016 to 1 February 2018 which reduced the time listed on the PBS until loss of exclusivity from [redacted] years to [redacted] years. The model applied a [redacted]% reduction in the price of lumacaftor/ivacaftor at the end of the patent period ([redacted]). This assumption is contrary to the PBAC Guidelines V5.0 (p82) which state that submissions should value future costs at current prices.
- An F1 statutory 5% price cut was applied to the price of lumacaftor/ivacaftor after the first 5 years of listing. As with the [redacted]% price reduction, the additional 5% price cut is also contrary to the PBAC Guidelines V5.0, but the effect on the ICER of this was relatively smaller than the impact of the assumed price change at patent expiry[10].
- General BSC disease management costs in the lumacaftor/ivacaftor arm were reduced to capture the effect of a reduction in PE-related hospitalisations. The costs for PEs are not linked to events generated in the model in the lumacaftor/ivacaftor arm. Inpatient costs associated with PEs were estimated by multiplying the hospitalisation costs associated with BSC by 0.61, which is based on the reduction of PE-related hospitalisations after 24 weeks of treatment with lumacaftor/ivacaftor in TRAFFIC and TRANSPORT; this inappropriately assumed that all hospitalisations are due to PEs.
- The resubmission estimated that the gross cost to the PBS of listing lumacaftor/ivacaftor would be substantially more than $100 million per year over

[10] This reduction is also outside the terms of the recent Medicines Australia strategic agreement which sees the last F1 5% reduction occurring in April 2022, although the combination drug lumacaftor/ivacaftor may take a flow on F1 5% price reduction from ivacaftor, when the later takes that reduction on 1 April 2019.

5 years. The model was revised to capture the effect of a "base cap" to the gross cost to the PBS at [redacted] over five years [redacted]. While the DPMQ for lumacaftor/ivacaftor was not changed in the resubmission, this application of this "base cap" [redacted]

6.44 Base case 2 included all the changes made in Base case 1 and also excluded all costs associated with BSC in the lumacaftor/ivacaftor group in the extended survival period, resulting in an ICER of $105,000/QALY – $200,000/QALY. This assumed that the use of lumacaftor/ivacaftor essentially normalises bodily functions (e.g. metabolism) that would otherwise require ongoing BSC; the evaluation noted that there is no evidence to support this assumption. The PBAC considered that Base case 2 was not informative given that the requested restriction proposed that lumacaftor/ivacaftor therapy is given concurrently with supportive therapies.

6.45 The key drivers of the model are shown in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Modelled change in $ppFEV_1$ in lumacaftor/ivacaftor patients.	Treatment effect continued beyond 24 week trial period for life time. Updated data from extension trial PROGRESS were not included in the model.	High, favours lumacaftor/ivacaftor
Modelled change in $ppFEV_1$ in BSC patients.	Annual decline in $ppFEV_1$ after the first 24 weeks	High, favours lumacaftor/ivacaftor
Assumption of price reduction at patent expiry.	[redacted]	High, favours lumacaftor/ivacaftor
Assumption of reduction in PE-related hospitalisation costs for lumacaftor/ivacaftor.	61% reduction in PE-related hospitalisation costs; estimated by multiplying hospitalisation costs associated with BSC by 0.61.	High, favours lumacaftor/ivacaftor
Extrapolation of survival	Liou et al (2001), extrapolation of effect of intermediate outcomes on survival.	High, favours lumacaftor/ivacaftor
Utilities	High values for health states obtained via Clinician Survey. The utility values applied for the 'normal' health state ($ppFEV_1$>90%) surpass Australian population norms.	High, favours lumacaftor/ivacaftor

Source: compiled during the evaluation.
Abbreviations: BSC = best supportive care; PE = pulmonary exacerbation; $ppFEV_1$= per cent predicted forced expiratory volume in one second.

6.46 Results from the stepped economic evaluation showing the changes implemented as part of the resubmission are provided in Table 12.

Table 12: Results of the stepped economic evaluation

Step and component	Lumacaftor/ivacaftor	Best supportive care	Increment
March 2016 submission (base case)			
Costs	$[redacted]	$380,017	$[redacted]
QALYs	9.553	4.894	4.659
Incremental cost/extra QALY gained			$[redacted]
November 2016 resubmission (base case)			
Costs	$[redacted]	$380,017	$[redacted]
QALYs	9.553	4.894	4.659
Incremental cost/extra QALY gained			$[redacted]
July 2017 resubmission			
Step 1: Financial cap (base cap) of $[redacted] applied to the March 2016 submission base case			
Costs	$[redacted]	$380,017	$[redacted]
QALYs	9.553	4.894	4.659
Incremental cost/extra QALY gained			$[redacted]
Step 2: Initiation of PBS reimbursement date changed from 1 July 2016 to 1 February 2018			
Costs	$[redacted]	$380,017	$[redacted]
QALYs	9.553	4.894	4.659
Incremental cost/extra QALY gained			$[redacted]
Step 3: F1 price reduction applied			
Costs	$[redacted]	$380,017	$[redacted]
QALYs	9.553	4.894	4.659
Incremental cost/extra QALY gained			$[redacted]
Step 4: PE-related hospital costs reduced for lumacaftor/ivacaftor (Base case 1)			
Costs	$[redacted]	$380,017	$[redacted]
QALYs	9.553	4.894	4.659
Incremental cost/extra QALY gained			$[redacted]

Source: Table D.5.3 of the Commentary.

Abbreviations: PBS = Pharmaceutical Benefits Scheme; PE = pulmonary exacerbation; $ppFEV_1$ = percent predicted forced expiratory volume in one second; QALY = quality-adjusted life-years.

[a] During the evaluation the ICER of $[redacted] per QALY gained could not be replicated using the model in the current resubmission. The following values derived during the evaluation were; cost of LUMA/IVA $1[redacted], cost increment $[redacted]; ICER $[redacted]/QALY gained.

6.47 In previous considerations of lumacaftor/ivacaftor in March 2016 and November 2016, the PBAC considered the estimated cost per QALY gained for lumacaftor/ivacaftor was likely to be underestimated (paragraphs 7.12-7.14, March 2016 PSD; paragraphs 6.13 and 7.3, November 2016 PSD). The following issues were not addressed in the resubmission:

- The model relied on the assumption that treatment effect is sustained beyond the 24 weeks of the TRAFFIC and TRANSPORT trials. The extrapolation of short-term results in $ppFEV_1$ to mortality was highly uncertain, and the assumption that patients in the treatment group could not decline in $ppFEV_1$ was implausible. Updated results from PROGRESS, which show that there was a decline in $ppFEV_1$ in lumacaftor/ivacaftor treated patients, were not incorporated into the economic

model in this resubmission.

- The model was sensitive to the assumption that the price of lumacaftor/ivacaftor would fall by [redacted]% at the end of patent protection.
- At the November 2016 meeting, the PBAC noted that while the proposed "base cap" limits risk in terms of overall cost, this approach did not provide a stable estimate of cost effectiveness. In addition, the model assumed that the effective price would apply for [redacted] prior to the end of the patent protection period (at which point the price was assumed to decrease by [redacted]%). The PBAC considered this assumption was inappropriate as the proposed cap on expenditure would only be guaranteed for the first five years of listing (paragraph 7.3, November 2016 PSD). The PSCR stated that the sponsor is open to discussing [redacted]

6.48 The resubmission maintained its assumption of a difference between treatment groups in its approach to the ongoing decline in $ppFEV_1$, assuming that there was no decline for lumacaftor/ivacaftor treated patients but a decline after 24 weeks in BSC patients. The evaluation considered it likely that the approach to modelling the baseline mortality risk (utilising data from the CF Registry in Ireland) already captured the effect of ongoing CF deterioration due to declining $ppFEV_1$ (among other factors). Thus, modelling an additional decline in $ppFEV_1$ for BSC unduly biased the survival of that group relative to the assumed maintenance of a treatment effect (no decline) for lumacaftor/ivacaftor. This is evident in the resulting estimates of median survival produced by the resubmission: 31.92 years for BSC in the model, compared with 39.9 years for the Irish cohort, and 45.48 years for the lumacaftor/ivacaftor group. The ICER is highly sensitive to this assumption: removing the additional decline in $ppFEV_1$ (i.e. assuming that the decline for both groups is captured by the underlying mortality risk) results in an ICER of more than $200,000/QALY.

6.49 The PSCR argued the suggestion that there would be no difference in decline between the treatment groups is misleading to the PBAC. The PSCR further argued it was clinically plausible that the model would project lower median survival for the BSC arm than the projected median survival of the Irish cohort, considering that the modelled patients are older than those in the registry (median age 19.6 years in the registry versus 25.3 in the modelled population), have lower average ppFEV1 (61%) compared with the Irish cohort (80%) and are F508del homozygous; according to MacKenzie et al (2014), homozygous patients have lower projected median survival than the entire CF population. The ESC noted these points and, referring to their March 2016 advice to the PBAC, noted that the Irish registry data encompasses Irish CF patients' survival from 1980-2004, and expressed doubt as to whether this historical data accurately reflects the current survival in the Australian CF population.

6.50 The ESC considered that the assumption that patients in the treatment group could not decline in $ppFEV_1$ was implausible and inconsistent with the results of PROGRESS. The PSCR acknowledged that a sensitivity analysis which included a

decline in $ppFEV_1$ which was 25% that of BSC may be reasonable and informative. The ESC considered this scenario may still favour lumacaftor/ivacaftor, noting the high risk of bias favouring treatment due to rate of discontinuation between week 72 and 96 in PROGRESS (as discussed in paragraph 6.7).

6.51 As with the previous (re)submissions, Liou et al. (2001) was used to estimate the effect of intermediate outcomes on survival. In its previous consideration of ivacaftor monotherapy, the PBAC stated that the use of the Liou et al. data assumed that the 'effects on survival are causal and additive' and that this 'may not be appropriate' (ivacaftor, July 2013 PSD). The Liou et al (2001) equation was used to modify the baseline risk (derived from the CF Cohort Registry from Ireland) and ongoing risk based on the relative change between cycles of the risk factors incorporated in the Liou et al equation (e.g. age, $ppFEV_1$). However, Liou et al developed their equation to estimate survival (mortality) risks based on absolute levels of these factors and not relative values. Adjusting the modelling approach to first estimate the absolute risk in each cycle according to these factors before expressing it as a relative risk increased the ICER to more than $200,000/QALY.

6.52 In March 2016 and November 2016, the PBAC noted that $ppFEV_1$ drives the frequency of exacerbations in the model, and did not accept the additional contribution of PEs on mortality, independent of effect on $ppFEV_1$. The ESC noted it is probable this resulted in double-counting of the effect of lumacaftor/ivacaftor. The resubmission has addressed this by assuming that lumacaftor/ivacaftor treatment conferred a benefit in terms of reduced PE-related hospitalisations. This was captured in the model by reducing the hospitalisation-specific disease management costs applied in the lumacaftor/ivacaftor arm by 61% (annualised reduction in PE-related hospital events recorded across the TRAFFIC and TRANSPORT trials) which assumed that all hospitalisations (using costs reported by van Gool et al (2013)) are due to PEs. The resubmission asserted that an alteration made to the model (Step 4 in Table 12) reflects the independent effects of lumacaftor/ivacaftor on PE related hospitalisations. The costs for PEs are not linked to events generated in the model in the lumacaftor/ivacaftor arm. The evaluation considered that while applying a reduction to costs for PEs avoided may have been appropriate, it was not appropriate to assume that all hospital costs are due to PEs. Assuming that only 50% of hospitalisations are due to PEs increases the ICER to $105,000/QALY – $200,000/QALY. The PSCR stated that data for placebo-treated patients in TRAFFIC/TRANSPORT indicated that 105 of 143 hospitalisations (74.3%) were due to PEs, and therefore 75% of hospitalisations related to PE would be a more appropriate estimate than 50%.

6.53 The ESC noted the utility weights used in the model were based on a small number of clinicians completing the EQ-5D-5L questionnaire by proxy for different bands of $ppFEV_1$. The ESC noted patients with high levels of lung function had implausibly high utility scores and there was also a wide spread of utility scores across lung functions which favoured lumacaftor/ivacaftor.

6.54 The resubmission presented scenario analyses applying discount rates that varied

between [redacted] on costs and effects, and the resubmission reiterated a request from the November 2016 minor resubmission that the PBAC consider an ICER with a lower discount rate than 5%. In November 2016, the PBAC recalled that ivacaftor was recommended for listing with an ICER that was calculated using a 5% discount rate for costs and outcomes (paragraph 7.4, November 2016 PSD) in line with the PBAC Guidelines V5.0. In its consideration of the current resubmission, the PBAC again noted its preference for a discount rate of 5% per annum for both costs and outcomes.

6.55 The resubmission presented a number of univariate sensitivity analyses. The resulting ICERs ranged from $105,000/QALY – $200,000/QALY when the DPMQ price of lumacaftor/ivacaftor reduced by [redacted]%, to more than $200,000/QALY when the annual rate of decline in $ppFEV_1$ in the lumacaftor/ivacaftor arm was reduced to [redacted]% of the reduction in patients treated with only BSC. The results of additional univariate sensitivity analyses conducted during the evaluation showed that the model was highly sensitive to the assumptions regarding the decline in $ppFEV_1$, the [redacted]% price reduction at patent expiry, inclusion of the financial cap, and the approach to modelling of the risk factors. The results of these analyses for Base case 1 are presented in Table 13.

Table 13: Results of the univariate sensitivity analyses conducted during the evaluation

Analysis description	Inc. cost ($)	Inc. effect (QALYs)	ICER ($/QALY gained)
Base case 1	$[redacted]	4.659	$[redacted]
Impact of assuming 50% of hospitalisations are due to a PE	$[redacted]	4.659	$[redacted]
Application of the Liou et al (2001) equation based on absolute values	$[redacted]	3.524	$[redacted]
Using the utility values from Whiting et al.	$[redacted]	3.835	$[redacted]
Estimates of $ppFEV_1$ decline in BSC arm set to 50% of current	$[redacted]	3.459	$[redacted]
Removal of the impact of the financial cap on the effective price	$[redacted]	4.659	$[redacted]
No price reduction at patent expiry	$[redacted]	4.659	$[redacted]
Estimated decline of $ppFEV_1$ in lumacaftor/ivacaftor after 24 weeks set to 25% of BSC	$[redacted]	3.176	$[redacted]
Estimated decline of $ppFEV_1$ in lumacaftor/ivacaftor after 24 weeks set to 50% of BSC	$[redacted]	2.068	$[redacted]
No additional decline in $ppFEV_1$ decline in BSC or lumacaftor/ivacaftor	$[redacted]	1.092	$[redacted]

Source: Constructed during the evaluation
Note: Application of the Liou et al (2001) equation based on absolute values followed the same approach as in the resubmission, but decomposed the estimate of the "Hazard Ratio Relative to the Previous Cycle" into two steps – an estimate of the absolute mortality risk per cycle, and then an estimate of the relative risk hazard per cycle

6.56 The ICERs presented in the resubmission were replicated to determine the DPMQ required to achieve that ICER in the absence of a financial cap. For the resubmission Base case 1 ICER of $105,000/QALY – $200,000/QALY, the effective DPMQ required was $[redacted] (compared with the requested DPMQ of $[redacted]).

6.57 The ESC recalled the advice provided by the PBAC when ivacaftor was recommended in March 2014 with a base case ICER of $$105,000/QALY – $200,000/QALY, that the cost-effectiveness of ivacaftor would be acceptable if the ICER would be around

$60,000 - $80,000 per QALY gained. At that time, the PBAC considered that, in the absence of a lower price, the cost-effectiveness of ivacaftor would be acceptable if a "pay-for-performance" arrangement, together with the other risk sharing measures, was implemented.

6.58 Given that the PBAC considered that the claim that lumacaftor/ivacaftor slows the rate of decline in ppFEV1 beyond 24 weeks, compared with patients treated with BSC, was not adequately supported by the resubmission (for the reasons outlined in paragraph 6.22), the PBAC defined an alternative scenario which it considered informative for decision making. Specifically, the PBAC made the following changes to Base case 1 in the current resubmission:

- The estimated decline in $ppFEV_1$ in lumacaftor/ivacaftor treated patients was set to 100% of BSC after 24 weeks. The PBAC considered that this assumption was a more realistic interpretation of the available data than the submission's assumption of no change in $ppFEV_1$ for lumacaftor/ivacaftor patients. Furthermore, the PBAC considered this assumption may still favour lumacaftor/ivacaftor, as lumacaftor/ivacaftor treated patients would therefore always maintain the 2.8 percentage point difference in $ppFEV_1$, compared with BSC patients; the PBAC considered that the difference in $ppFEV_1$ may in fact reduce over the long-term.
- Assuming 75% of hospitalisations are due to PEs (see paragraph 6.51)
- Removal of the F1 5% statutory price reduction and the assumed [redacted]% generic price reduction, in line with the PBAC Guidelines V5.0 (p82) which states that submissions should value future costs at current prices. The PBAC also noted that as lumacaftor/ivacaftor is likely to be replaced with tezacaftor/ivacaftor and triple therapy with the "next generation correctors" over the next several years, it is unlikely that lumacaftor/ivacaftor will be in use at the time that the submission assumed the price will reduce by [redacted]%.

6.59 The PBAC's scenario resulted in an unacceptably high ICER of significantly more than $1 million/QALY (presented in Table 14, with Base case 1 for comparison).

Table 14: Results of scenario analysis conducted by PBAC

Scenario	Inc. cost ($)	Inc. effect (LYs)	Inc. effect (QALYs)	ICER ($/QALY gained)
Current resubmission, base case 1	$[redacted]	4.640	4.659	$[redacted]
PBAC scenario for decision making	$[redacted]	1.144	0.720	$[redacted]

Source: Constructed during the preparation of the PBAC minutes.

6.60 On the request of the Minister (delegate) under section 101(3) of the Act, the PBAC considered the price or range of prices at which it considered treatment with lumacaftor/ivacaftor would be acceptably cost-effective for the purposes of the Act. In this regard, the PBAC advised that the maximum ICER it would consider to be acceptably cost effective, noting the precedent of ivacaftor, would be around

$105,000/QALY – $200,000/QALY. The PBAC advised that such an ICER would only be acceptable in conjunction with an agreement between the sponsor of lumacaftor/ivacaftor and the Government to cap the maximum financial expenditure based on the submission's utilisation estimates, with a 100% rebate thereafter. Based on its revised scenario, the PBAC advised that the maximum DPMQ that it would consider to be acceptably cost-effective would be around $[redacted] (or around $[redacted] per patient per year, assuming [redacted] packs per patient per year) which would result in an ICER of $105,000/QALY – $200,000/QALY.

Drug cost/patient/year: $[redacted]

6.61 The cost per pack of lumacaftor/ivacaftor (28 days treatment) is $[redacted]. Based on a 15% dose reduction due to hepatic impairment and to account for adherence, the resubmission assumed [redacted] packs per patient per year at a cost of $[redacted] per patient per year. Treatment is ongoing for the lifetime of the patient. No special pricing arrangements were proposed in relation to the DPMQ; however, the resubmission proposed to cap the gross cost to the PBS in the first 5 years of listing by way of [redacted].

Estimated PBS usage & financial implications

6.62 This resubmission was not considered by DUSC. An epidemiological approach was used, similar to the March 2016 submission.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications to Government PBS of lumacaftor/ivacaftor					
Net cost to PBS/RPBS without financial cap	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS with proposed financial cap	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for MBS					
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for the PBS/RPBS/MBS					
Net cost to PBS/RPBS/MBS with proposed financial cap	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated reduced hospitalisation costs					
Net cost associated with reduced hospitalisations	- $[redacted]	- $[redacted]	- $[redacted]	- $[redacted]	- $[redacted]

[a] Assuming 11 scripts per patient per year as estimated by the submission. This number was derived from an assumed adherence rate of 90% and a weighted adjustment for patients with moderate/severe hepatic impairment.
Source: Table E.2-7, page 204; Table E.2-10, page 205-206; Table E.4-1 and E.4-2, page 208 of resubmission.

6.63 At year 5, the estimated number of patients was [redacted] and the net cost to the PBS would be more than $100 million, or including the impact of the proposed financial cap. The total cost to the PBS over the first five years of listing (including the impact of the proposed financial cap) would be more than $100 million per year. The estimated number of patients treated are broadly similar to those presented in the previous (re)submissions, but have been adjusted slightly upwards as a result of the publication of the ACFDR 2014 report, while the original submission had used the 2013 information.

6.64 The size of the eligible population would be overestimated if subsidised access to the treatment was restricted to those patients with a ppFEV$_1$ of $\geq$40% and $\leq$90% in line with the eligibility criteria in the key trials.

6.65 Even if subsidised access were restricted on the basis of ppFEV$_1$, the ESC considered that the size of the eligible population was likely to have been underestimated. The resubmission assumed that there are [redacted] new patients eligible for treatment each year for the first five years (2018-2022). Data from the 2014 ACFDR indicate that there were 598 patients at the end of 2014 aged 6-11 years with a CF diagnosis. With an estimated 51.5% of this cohort (308) homozygous for F508del and becoming eligible at age 12, the increase of [redacted] patients assumed for each year over 5 years is therefore likely to be an underestimate.

6.66 Drug utilisation each year could be overestimated on the basis that:

- The resubmission assumed that patients could only discontinue therapy in Year 1 of their treatment, based on discontinuation rates from TRAFFIC and TRANSPORT.

The ESC noted that data from PROGRESS show that this is not realistic and that there will be a proportion of patients discontinuing treatment beyond this timeframe.

- The resubmission assumed that patients who become eligible for treatment each year receive a full year of treatment. A more reasonable assumption is that initiating patients will commence throughout the year, so that on average each patient receives the equivalent of half of a year's supply.

6.67 The PBAC noted that if lumacaftor/ivacaftor were listed at the DPMQ that it considered to be acceptably cost-effective (of $[redacted], see paragraph 6.59), the net cost to the PBS based on the estimates of utilisation in the resubmission would be over the first five years of listing would need to be recalculated but may be in the vicinity of $20-30 million in each of the first five years of listing.

Financial Management – Risk Sharing Arrangements

6.68 The resubmission proposed a "base" financial cap that reflects [redacted] in the estimated financial impact to the PBS budget (see Table 15). This equates to capping the gross cost to PBS (including co-payments) of lumacaftor/ivacaftor to more than $100 million in each year of listing over the period of five years[redacted].

6.69 In addition, the resubmission proposed [redacted] and proposed that the financial cap on the gross PBS costs could be further reduced if [redacted] Conversely, the resubmission proposed [redacted] receiving PBS-subsidised lumacaftor/ivacaftor would be [redacted] The resubmission stated that patients who previously received non-PBS subsidised lumacaftor/ivacaftor, such as through a clinical trial or compassionate use, would [redacted] The resubmission claimed this is a "pragmatic" approach that would provide high quality and representative data collection.

Table 16: [redacted]

[redacted]				

Source: Table F.2-2, page 214 of the resubmission.

6.70 The resubmission presented a sensitivity analysis for the cost effectiveness of

lumacaftor/ivacaftor based on [redacted], reducing the financial cap if [redacted] The resubmission suggested [redacted] would potentially improve the cost-effectiveness of lumacaftor/ivacaftor. The ESC considered this was inappropriate since it relied on maintaining the underlying efficacy assumptions in the economic model and only adjusting the costs.

6.71 The [redacted] currently in place for ivacaftor monotherapy is designed to detect the magnitude of the overall clinical benefits of treatment for individual patients. [redacted] The resubmission described this approach as "burdensome" to both clinicians and the Department of Health and "complex" from a data collection, data management, and data analysis perspective.

6.72 The ESC considered that the proposal for lumacaftor/ivacaftor is less robust than [redacted] that apply to ivacaftor monotherapy in that they do not rely on [redacted]. In November 2016, the Committee stated that [redacted] than the current one for ivacaftor monotherapy so as to manage the uncertainty regarding long-term benefits of treatment on lung function and overall survival (7.6 November 2016 PSD). The ESC further considered [redacted] would not account for changes [redacted]

6.73 The PBAC considered that [redacted] arrangement would not be suitable for managing the uncertainty in the long-term outcomes of lumacaftor/ivacaftor as multiple factors could impact on [redacted]. Furthermore, [redacted] However, the PBAC agreed with the sponsor that the current ivacaftor [redacted] is complex and administratively burdensome and that [redacted]. In this regard, the PBAC reiterated that lumacaftor/ivacaftor may be acceptable for recommendation at a DPMQ of $[redacted], in conjunction with an agreement between the sponsor of lumacaftor/ivacaftor and the Government to cap the maximum financial expenditure based on this price and the submission's utilisation estimates, with a 100% rebate thereafter.

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

17 PBAC Outcome

17.1 Lumacaftor with ivacaftor was not recommended by the PBAC for listing on the PBS for the treatment of patients with CF aged 12 years or older who are homozygous for the F508del mutation in the CFTR gene on the basis of unacceptable high cost-effectiveness at the requested price and uncertainty around the longer term impact of lumacaftor/ivacaftor on lung function and survival beyond 2 years of treatment.

17.2 The PBAC recognised the potential clinical value of lumacaftor/ivacaftor in the treatment of cystic fibrosis in patients aged 12 years or older who are homozygous for the F508del mutation. The PBAC acknowledged the many consumer comments and the correspondence from Cystic Fibrosis Australia relating to this resubmission and recognised the strong support for subsidised access to lumacaftor/ivacaftor.

17.3 The PBAC recalled that it previously rejected lumacaftor/ivacaftor at its March 2016 meeting on the basis of unacceptably high and uncertain incremental cost-effectiveness ratio at the requested price, and uncertainty around the impact of lumacaftor/ivacaftor on long-term improvements in lung function and survival. The PBAC subsequently rejected a minor resubmission for lumacaftor/ivacaftor at its November 2016 meeting, noting that the resubmission did not address the issues it identified in March 2016.

17.4 The PBAC noted that updated evidence from the PROGRESS extension study demonstrated that the modest 2.81 percentage point improvement in $ppFEV_1$ in lumacaftor/ivacaftor treated patients versus placebo observed in TRAFFIC/TRANSPORT at 24 weeks was not maintained after an additional 96 weeks of treatment.

17.5 The submission argued that slowing the rate of deterioration over time is the main objective of CF treatment. The PBAC noted that the submission presented a matched analysis of 455 patients treated with lumacaftor/ivacaftor in the PROGRESS extension study and 1,588 historical control patients from the US CFFPR to compare the rate of decline in $ppFEV_1$ for lumacaftor/ivacaftor treated patients to the background deterioration that would have occurred with BSC. The resubmission claimed the results of this matched analysis demonstrated that the annual rate of $ppFEV_1$ decline was nearly halved in lumacaftor/ivacaftor treated patients (with an annualized rate of decline of 1.33 percentage points, compared with 2.29 percentage points for the controls). However, as discussed in paragraph 6.22, the PBAC considered that the historical control patients from the CFFPR were unlikely to be representative of the patients in TRAFFIC/TRANSPORT or of Australian CF patients, and hence PROGRESS, and the comparison of the reduction in the rate of decline in $ppFEV_1$ in PROGRESS versus the CFFPR was likely biased in favour of lumacaftor/ivacaftor. Accordingly, the PBAC considered that the claim that lumacaftor/ivacaftor slows the rate of decline in $ppFEV_1$ beyond 24 weeks, compared with patients treated with BSC, was not adequately supported by the resubmission.

17.6 The PBAC noted that improvements in some clinical measures other than lung

function, including a reduction in pulmonary exacerbations and an increase in body mass index, were maintained beyond the 24 week trial period, and therefore considered that the claim of superior comparative effectiveness was reasonable and there is a clinical place for this medicine at a price commensurate with its clinical benefits.

17.7 The PBAC noted that the economic model included in the resubmission was based on the extreme assumption that lung function was maintained for patients treated with lumacaftor/ivacaftor for the reminder of their life, and this was inconsistent with the longer-term clinical evidence. Accordingly, the PBAC defined a scenario which it considered more informative for decision making, by changing inputs to the resubmission's economic model to better reflect the available clinical data (see paragraph 6.58). This scenario resulted in an unacceptably high ICER of significantly more than $1 million per QALY gained.

17.8 The PBAC noted that the net cost of lumacaftor/ivacaftor to the PBS over the first five years of listing (including the proposed financial cap) was estimated to be more than $100 million each year, with [redacted] patients treated in year 5. However, the PBAC considered that the estimates of utilisation in the resubmission, which assumed an increase of [redacted] patients per year, were underestimated based on the ACFDR data which indicate there are [redacted] patients in the 6-11 years homozygous for the F508del mutation at the end of 2014 who will become eligible for treatment within the estimated timeframe.

17.9 The PBAC noted the extent of the price reduction that would be required for lumacaftor/ivacaftor to be considered to be suitably cost effective to enable a recommendation for listing on the PBS (see paragraph 6.60), if implemented in conjunction with risk sharing arrangements (as outlined in paragraph 6.73). The PBAC advised that it would accept a price offer under these terms from the sponsor for PBAC consideration at any time. The PBAC advised that a resubmission, with revisions to the economic model to reflect the available clinical data, would be required to justify a request for a higher price than that advised by the PBAC, or other alternative arrangement.

17.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

18 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

19 Sponsor's Comment

The sponsor had no comment.