Corrections have been made to this item. Details of the corrigendum are contained in Section 6.

An addendum to these PSDs, based on PBAC advice from the December 2021 intracycle meeting, has been included at the end of the document (Section 7).

4.01 Lumacaftor and ivacaftor, Tablet containing lumacaftor 100 mg with ivacaftor 125 mg, Orkambi®, Vertex Pharmaceuticals (Australia) Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission provided data to address the requirements of the Managed Access Program (MAP) for the supply of lumacaftor/ivacaftor and tezacaftor/ivacaftor for the treatment of cystic fibrosis (CF) patients homozygous for the F508 deletion.

2 Background

Previous PBAC consideration

2.1 Lumacaftor/ivacaftor was first recommended for listing on the PBS at the July 2018 PBAC meeting for the treatment of patients with CF aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Lumacaftor/ivacaftor was subsequently recommended for patients aged 6 to 11 years at an out-of-session meeting and in patients aged 2 to 5 years at the July 2019 meeting.

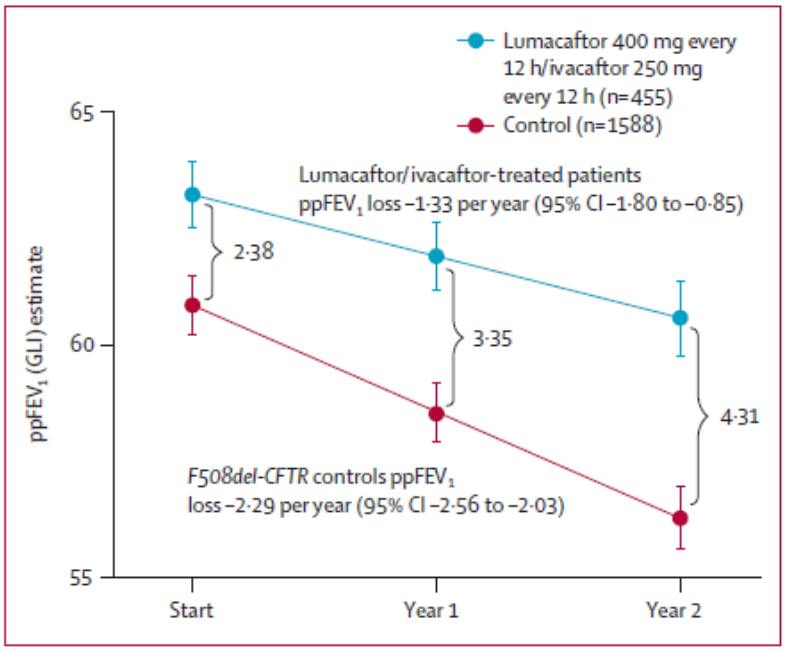
2.2 Tezacaftor/ivacaftor was first recommended at the March 2019 PBAC meeting for the treatment of patients with CF who are aged 12 years and older and homozygous for the F508del mutation in the CFTR gene, and those who carry one copy of the F508del mutation and a residual function mutation. Tezacaftor/ivacaftor was subsequently recommended for patients with CF who have at one least RF mutation on the CFTR gene at the November 2019 PBAC meeting.

2.3 When recommending lumacaftor/ivacaftor and tezacaftor/ivacaftor for listing, the PBAC advised that the Minister implement measures to mitigate uncertainties associated with their cost-effectiveness and overall costs to the PBS. Those measures included a MAP that 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 (paragraphs 6.73-6.79, lumacaftor/ivacaftor public summary document (PSD), July 2018 PBAC meeting).

2.4 In July 2018 the PBAC expressed the view that while there was evidence that lumacaftor/ivacaftor slows the rate of decline in percent predicted forced expiratory volume in one second ($ppFEV_1$) and reduces pulmonary exacerbations up to 96 weeks for some patients, the sustainability of these benefits in the longer term remained uncertain (paragraph 7.8, lumacaftor/ivacaftor PSD, July 2018 PBAC meeting). It was recommended that pursuant to the MAP the sponsor be required to provide data to satisfy the PBAC that the rate of decline in $ppFEV_1$ and reduction in pulmonary exacerbations are sustained over a longer period of time of up to 4 years.

2.5 The decline in lung function of patients treated with lumacaftor/ivacaftor compared with patients receiving BSC only (as measured by the relative rate of decline (rROD) in $ppFEV_1$) was a key input used in the sponsor's July 2018 economic model. The assumption in the model was of a $ppFEV_1$ rROD of 42%, which was informed by a post-hoc analysis where patients receiving lumacaftor/ivacaftor from PROGRESS (an extension study) were matched to eligible control patients from the United States Cystic Fibrosis Foundation Patient Registry (CFFPR) (Figure 1) (Konstan 2017). The PBAC recalled the Konstan 2017 study excluded the initial increase in $ppFEV_1$ in the first 3 weeks of treatment with lumacaftor/ivacaftor from the rate of decline calculation.

Figure 1: Estimated annual rate of $ppFEV_1$, decline with lumacaftor/ivacaftor compared with a matched control group



Source: Konstan 2017 Figure 3 p10.

2.6 In its considerations in July 2018 the PBAC raised a number of concerns regarding the data used for this analysis, including the use of historical US patients for the control cohort (who tend to have worse clinical outcomes compared to ex-US patients). The

US patients were compared with patients in a clinical trial extension study (PROGRESS) which included patients from other countries and trial patients might have been expected to have benefited from optimisation of other aspects of care (paragraph 6.25, lumacaftor/ivacaftor PSD, July 2018 PBAC meeting,). The Pre-Sub-Committee Response (PSCR) disagreed with the assertion that US CF patients have a worse treatment outcome than in other countries, and stated that this has been disproved statistically in recent publications (Schluter et al, 2021; Goss et al, 2014).

3 Summary of the MAP requirements

3.1 A summary of the obligations as stipulated in the MAP and how the submission claimed to address the obligations is provided in Table 1.

Table 1: Obligations as stated in the MAP and the documentation as provided in the Submission

MAP	Submission
The Company's analysis of the rate of decline in lung function in the Report and the application of the point estimate value for rate of decline in lung function in the Company's economic model for Lumacaftor with Ivacaftor 6+ to assess any change in cost effectiveness	Pooled ppFEV$_1$ rROD = 55.7% (from 42%) ICER = $[redacted][1]/QALY in CF patients over 2 years of age (from $[redacted][2]/QALY)
If the Company's analysis of the point estimate value for rate of decline in lung function shows that the assumptions about the rate of decline in lung function in the Company's economic model for Lumacaftor with Ivacaftor 6+ are exceeded during treatment, the degree to which those assumptions are exceeded	As above.
Study VX15-809-110 The Company must finalise and submit to the Commonwealth and the PBAC the full clinical study reports for the interim and final analyses of VX15-809-110	The submission provided the final Clinical Study Report for Study VX15-809-110 dated 24 August 2020.
Data Collection The company must prepare and submit the Data Collection Report to the PBAC that at a minimum shows: • The differences in the rates of decline in lung function (ppFEV$_1$) and pulmonary exacerbations (proxy for the use of the use of pulmonary exacerbations may be the use of IV antibiotics) observed over the 96 week trial period which support the PBAC Recommendation for lumacaftor/ivacaftor 6+ are sustained over a longer time period of up to 4 years; or • The differences in the rates of decline in lung function (ppFEV$_1$) and pulmonary exacerbations (proxy for the use of pulmonary exacerbations may be the use of IV antibiotics) observed over a period of up to 4 years were between those submitted to the PBAC to support the initial recommendation and those of a matched cohort of untreated patients. • Any other information the Company considers relevant.	The submission provided data from 11 studies that reported a rate of decline (ROD) in ppFEV$_1$, where a relative ROD (rROD) with best supportive care (BSC) could be calculated.

MAP	Submission
The Data Collection Report must also include the interim report prepared by the Company of the ongoing post market observations study of the long-term efficacy and safety of lumacaftor with ivacaftor 6+ when initiated in patients aged from 6 to 11 years of age, which the Company is required to conduct as a condition of the TGA approval (The Interim Report).	An interim report of Study 129 (VX18-809-129) was provided in the submission.
As part of the preparation of the Data Collection Report the Company must work with prescribers to ensure patients are registered in the Australian Cystic Fibrosis Database Registry.	The submission did not provide evidence to address this. The PSCR stated the Sponsor did not believe it necessary to outline the measures in place to address this requirement within the submission, given that both the PBS restriction and PBS written authority form stipulate that patients must be enrolled in the ACFDR to obtain PBS-subsidised access. The PSCR reported that demographic data are available for 100% of enrolled patients and at least some clinical measures (i.e. $ppFEV_1$ values used in the rate of decline analysis) are available for 96-97% of enrolled patients.

Source: Table 1.2.1 of the Commentary.
Abbreviations: ACFDR=Australian Cystic Fibrosis Disease Registry; BSC=best supportive care; LUM/IVA=lumacaftor/ivacaftor; PBS=Pharmaceutical Benefits Scheme; PEx=pulmonary exacerbations; ppFEV1=percent predicted forced expiratory volume in one second; rROD = relative rate of decline; sd=standard deviation; TGA=Therapeutic Goods Administration
The redacted values correspond to the following ranges:
[1] *$115,000 to < $135,000/QALY gained*
[2] *$155,000 to < $255,000/QALY gained*

3.2 The MAP stipulated that if the $ppFEV_1$ rROD is at or above 42%, the Subsidisation Caps for Years 3, 4 and 5 defined as Option 1 will apply. However, if the $ppFEV_1$ rROD is less than 42%, then the Subsidisation Caps for Years 3, 4, and 5 will be calculated using the following formula:

Subsidisation Cap = [(SSC – MSC) x ROD / 42%] + MSC Where: SSC: Subsidisation Cap annotated 'Option 1' for relevant year MSC: Minimum Subsidisation Cap annotated under 'Option 2' for the relevant year ROD: point estimate for rate of decline	
Option 1: Year 3: $[redacted][1] Year 4: $[redacted][1] Year 5: $[redacted][2]	*Option 2:* Year 3: $[redacted][3] Year 4: $[redacted][4] Year 5: $[redacted][4]

The redacted values correspond to the following ranges:
[1] *$90 million to < $100 million*
[2] *$100 million to < $200 million*
[3] *$50 million to < $60 million*
[4] *$20 million to < $30 million*

4 Consideration of the evidence

Sponsor hearing

4.1 The sponsor requested a hearing for this item. The sponsor stated the longest possible duration of data collection, taking into account product availability, data lags and the impact of COVID-19 on data collection, is approximately 4.3 years in the US and 17 months in Australia. The sponsor reiterated information provided in the PSCR and pre-PBAC response (discussed in relevant sections below).

4.2 The sponsor provided additional information in response to a question from the PBAC regarding the magnitude of the initial improvement in $ppFEV_1$ (i.e., in the first month of treatment) observed with the use of CFTR modulators in the real world setting. The response stated it was problematic to determine the exact magnitude of the acute $ppFEV_1$ change in the first month of treatment using registry data, as measurements are typically not entered into registries regularly or frequently enough to do so (generally, measurements are taken quarterly in the real-world setting). In contrast, the publications of Konstan 2017 and Flume 2021 used data from patients who commenced CFTR modulator treatment within the pivotal clinical trials and then follow their extended use beyond those trials. As such, in these studies where the parent trial data is available, it is possible to identify the magnitude and timing of the initial improvement more precisely. The response stated the real-world experience reported in the published literature from prospective cohort studies or retrospective chart reviews shows $ppFEV_1$ increases at 1 month reinforced those seen in the pivotal clinical trials. The PBAC noted the information provided supported an initial increase in $ppFEV_1$ with subsequent stabilisation or small further increases to 12 months (Tong 2020, Ejiofer 2020, Burgel 2020).

4.3 The sponsor's response also provided additional analyses of the PASS 108 study which estimated the rate of decline in $ppFEV_1$ with lumacaftor/ivacaftor over a later time window in order to exclude the initial improvement in $ppFEV_1$ (patients commenced treatment in 2015 with data from 2016 onwards used in the analysis). The results are discussed in paragraph 4.19.

Consumer comments

4.4 The PBAC noted and welcomed the input from individuals (5) via the Consumer Comments facility on the PBS website. The comments reported the high impact CF has on quality of life and the importance of additional treatment options.

Clinical studies

4.5 The submission presented studies in two separate Data Collection Reports:

- Studies that inform rROD: included 11 studies reporting the ROD in $ppFEV_1$ in patients treated with lumacaftor/ivacaftor or tezacaftor/ivacaftor (see Table 2). These studies were used to inform an updated estimate of the $ppFEV_1$ rROD; and

- Studies with lumacaftor/ivacaftor initiated in patients aged from 6 to 11 years: included three studies reporting the use of lumacaftor/ivacaftor in patients aged from 6 to 11 years (see Table 2). The MAP requested an interim report of the ongoing post marketing study of the long-term efficacy and safety of lumacaftor with ivacaftor when initiated in patients aged from 6 to 11 years of age. This interim report is referred to as Study 129, which utilised data from the Australian Cystic Fibrosis Disease Registry (ACFDR).

4.6 The submission did not include the matched analysis comparing patients from PROGRESS and the US CFFPR (Konstan 2017), which was the study previously used to inform the estimate of ppFEV$_1$ rROD as considered by the PBAC. Konstan 2017 has been re-presented herein.

4.7 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Studies that inform ppFEV$_1$ rROD		
Konstan 2017	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.
PASS 108	An Observational Study to Evaluate the Utilisation Patterns and Long-term Effects of Lumacaftor and Ivacaftor Combination Therapy in Patients With Cystic Fibrosis	Internal Study Report., Interim Study Report 3 *19 November 2019.*
	Bower JK, Tian S, Zahigian R, Sewall A, Wu R, Elbert A. Disease progression in F508del homozygous (F/F) persons with cystic fibrosis treated with lumacaftor/ivacaftor (LUM/IVA): interim results of a long-term safety study using data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR).	J Cyst Fibros 2020; 19S2(suppl):S21
	Knox C, Volkova N, Han Z, Wu R, Wang LT, Elbert A, Tian S. Real-world outcomes among patients with cystic fibrosis treated with lumacaftor/ivacaftor (LUM/IVA) in 2017: an interim analysis of data from the US CF Foundation Patient Registry (CFFPR).	J Cystic Fibrosis 2019; 18 (Supp 1):S22-S23.
Flume 2021	Flume P, Fischer Biner R, Downey DG, et al. Long-term safety and efficacy of tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study.	Lancet Respir Med 2021. Published Online, February 10, 2021. https://doi.org/10.1016/ S2213-2600(20)30510-5
Tong 2020	Tong K, Barker D, France M et al. Lumacaftor/ivacaftor reduces exacerbations in adults homozygous for Phe508del mutation with severe lung disease. Tong K, Dorahy D, France M et al. A multicentre, observational cohort study to determine the efficacy and safety of lumacaftor/ivacaftor in patients with severe lung disease and cystic fibrosis Wark PA, Tong K, Dorahy D et al. A multicentre, observational casecontrol study to determine the effect of lumacaftor/ivacaftor in patients with severe lung disease and cystic fibrosis.	Journal of Cystic Fibrosis. 2020;19(3):415-20. European Respiratory Journal. 2019;54(Supplement 63). Pediatric Pulmonology. 2019;54(Supplement 2):432
ACFDR (≥ 12y)	Final ACFDR ppFEV$_1$ ROD report	Internal Study Report 1 February 2021
Bourgani 2019	Bourgani E, Stagaki E, Gioka M, et al. Two years' experience of lumacaftor/ivacaftor treatment at an adult cystic fibrosis centre in Athens, Greece.	Journal of Cystic Fibrosis. 2019;18(Suppl1):S132.
Mermis 2019	Mermis J, Polineni D, He J. "real world" impact of CFTR modulators (lumacaftor/ivacaftor and tezacaftor/ ivacaftor) on long-term patient outcomes.	Pediatric Pulmonology. 2019;54(Suppl2):350-1.
Muilwijk 2020	Muilwijk D, Zomer DD, Gulmans VAM, et al. Real-world trends in long-term clinical outcomes of lumacaftor/ivacaftor.	Journal of Cystic Fibrosis. 2020;19(Suppl2):S70-S1.
French CF Network		
Collet 2018	Collet C, Bui S, Mittaine M, et al. Lumacaftor/ivacaftor in real life for Phe508del homozygous, adolescents with severe and normal lung function.	Journal of Cystic Fibrosis. 2018;17(Suppl3):S66.
Burgel 2020	Burgel P-R, Munck A, Durieu I, et al. Real-Life Safety and Effectiveness of Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis. Burgel PR, Hubert D, Munck A, et al. Real-life initiation of lumacaftor/ivacaftor in adolescents and adults homozygous for the F508del CFTR mutation: a French nationwide study.	American Journal of Respiratory and Critical Care Medicine. 2020;201(2):188-97. Journal of Cystic Fibrosis. 2019;18(Suppl1):S132.

Trial ID	Protocol title/ Publication title	Publication citation
Ejiofor 2020	Ejiofor LCK, Mathiesen IHM, Jensen-Fangel S, et al. Patients with cystic fibrosis and advanced lung disease benefit from lumacaftor/ivacaftor treatment.	Pediatric Pulmonology. 2020;55(12):3364-70.
King 2021	King SJ, Keating D, Williams E et al. Lumacaftor/ivacaftor-associated health stabilisation in adults with severe cystic fibrosis.	ERJ Open Res 2021; 7 [https://doi.org/ 10.1183/23120541.00203-2020].
Loukou 2020	Loukou I, Moustaki M, Plyta M, Douros K. Longitudinal changes in lung function following initiation of lumacaftor/ivacaftor combination.	Journal of Cystic Fibrosis. 2020;19(4):534-9.
Studies where lumacaftor/ivacaftor were initiated from ages 6 to 11 years		
Study 110 (VX15-809-110)	A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	Internal Study Report 24 August 2020
	Chilvers MA, Davies JC, Carlos M, Tian S, Zifei H, Cornell A. Long-term safety and efficacy of lumacaftor–ivacaftor therapy in children aged 6–11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study.	Lancet Resp Med 2021 S2213-2600(20)30517-8
Study 129	An Observational Study to Evaluate the Real-world Clinical Outcomes of Orkambi in Australian Patients With Cystic Fibrosis Aged 6 Through 11 Years at Therapy Initiation	Internal Study Report v1.0 dated 18 February 2021
PASS 108	An Observational Study to Evaluate the Utilisation Patterns and Long-term Effects of Lumacaftor and Ivacaftor Combination Therapy in Patients With Cystic Fibrosis	Internal Study Report., Interim Study Report 3 *19 November 2019.*
	Bower JK, Tian S, Zahigian R, Sewall A, Wu R, Elbert A. Disease progression in F508del homozygous (F/F) persons with cystic fibrosis treated with lumacaftor/ivacaftor (LUM/IVA): interim results of a long-term safety study using data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR).	J Cyst Fibros 2020; 19S2(suppl):S21

Source: Table 14 p26 of the submission.

4.8 Eleven studies were used to estimate the pooled $ppFEV_1$ rROD in the submission: PASS 108, Flume 2021, Bourgani 2019, Mermis 2019, Muilwijk 2020, an analysis from the Australian CF Disease Registry (referred to as ACFDR ≥ 12 y), Collet 2018, Ejiofor 2020, King 2021, Loukou 2020 and Tong 2020. Of these studies:

- Five studies (PASS 108, Flume 2021, Bourgani 2019, Mermis 2019, Muilwijk 2020) were used to inform the base case pooled analysis of the rROD in $ppFEV_1$ presented in the submission. These were studies where patients had received a mean duration of treatment of approximately 2 years (mean range: 1.7 to 2.9 years). Three of these studies were published as abstracts only (Bourgani 2019, Mermis 2019, Muilwijk 2020).
- Three studies (ACFDR ≥ 12 y; King 2021; Tong 2020) included patients treated with lumacaftor/ivacaftor in Australia. However, these studies were not used in the base case pooled analysis presented in the submission as treatment follow-up was reported after only one year of use.
- Six studies (ACFDR ≥ 12 y, Collet 2018, Ejiofor 2020, King 2021, Loukou 2020, Tong 2020) were included in a sensitivity analysis of the pooled rROD in $ppFEV_1$. The

duration of treatment in these studies was one year. The results initially considered by the PBAC reflected data up to 96 weeks of treatment; results after only 1 year would not appear to further the evidence base. The PSCR disagreed with the evaluation that these studies do not add to the evidence base as a basic tenant of the scientific method is reproducibility. The PSCR stated the additional 6 studies with one year of follow-up demonstrate reproducibility with the original Konstan 2017 study which contained matched data over 96 weeks. The ESC noted the requirement of the MAP was to provide data to show that rates of decline are "sustained over a longer period of time of up to 4 years", rather than reproduce the results from Konstan 2017.

4.9 The key features of the studies and the assessment of bias (based on the ROBINS-I tool for assessing risk of bias in non-randomised studies) as undertaken during the evaluation are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias[a]	Patient population
Studies that inform rROD				
Konstan 2017[b]	T:455 C:1,588 N=2,043	Propensity-score-matched cohort study Tx follow up: 120 weeks	moderate to serious	Aged ≥ 12 years with CF homozygous for the F508del mutation Treatment: Patients from PROGRESS Comparator: Patients from US CFFPR.
PASS 108[c]	T:1,881 C:2,686 N=4,567	Prospective, parallel cohort study utilising data collected from existing national CF registries (Data only pertains to US CFFPR in submission) Mean tx duration: 3.0 yrs (3.8 years provided in PSCR).	moderate to serious	Aged ≥ 12 years with CF[c] Treatment: Homozygous for the F508del mutation Comparator: Heterozygous for the F508del with a Class I/II mutation on the second allele;
Flume 2021[b]	T: 407 C:1,383 N=1,790	Propensity-score-matched cohort study Tx follow up: 120 wks;	moderate to serious	Aged ≥ 12 years with CF homozygous for the F508del mutation. Treatment: Patients from EXTEND (tezacaftor/ivacaftor) Comparator: Patients from US CFFPR
Tong 2020	T: 72 C: 33 N=105	Matched parallel cohort study; analysis of patients through a compassionate use program in Australia. Tx duration: at least 1 year	moderate to critical	Aged ≥ 12 years ppFEV$_1$ < 40% Treatment: Homozygous for the F508del Comparator: Class I or II mutations
ACFDR (≥ 12y)	126	Paired historic control cohort study, analysis of data from the Australian CF disease Registry (ACFDR) (mean tx duration: 1.2 yrs)	moderate to critical	Aged ≥ 12 years with CF homozygous for the F508del mutation. ppFEV$_1$: 40% - 90%
Bourgani 2019 (abstract only)	46	Paired historic control cohort study, single centre, OL study in Greece. Mean Tx duration: 1.9 yrs	moderate to critical	Assumed age group: adults Homozygous for the F508del
Mermis 2019 (abstract only)	85	Paired historic control cohort study, single centre, OL study in the US. Mean Tx duration: 1.98 yrs	moderate to critical	Aged ≥ 18 years Assumed homozygous for the F508del. Included patients treated with LUMA/IVA or TEZA/IVA

Trial	N	Design/ duration	Risk of bias[a]	Patient population
Muilwijk 2020 (abstract only)	70	Paired historic control cohort study, single centre, OL study in the Netherlands; Dutch CF Registry. Mean Tx duration: 2.4 yrs	moderate to critical	Assumed age group: adults Homozygous for the F508del
Collet 2018 (abstract only) / Burgel 2020	Collet: 30 Burgel: 845.	Prospective cohort study with paired historic control, OL study in France; French CF Reference Network Mean Tx duration: 1.0 yrs	moderate to critical	Homozygous for the F508del Collet: children/adolescents Burgel: paediatric and adults
Ejiofor 2020	21	Paired historic control cohort study, Analysis of patients through a compassionate use program in Denmark. Median Tx duration: 1.3 yrs	moderate to critical	Homozygous for the F508del Adults: ppFEV$_1$ < 30 or Children: ppFEV$_1$ < 40 or or Two of the following criteria • Adults ppFEV$_1$ < 40 / children ppFEV$_1$ < 60; • ppFEV$_1$ slope < −2.5%, last year • Chronic difficult-to-treat pulmonary infection; • Low BMI
King 2021	24	Paired historic control cohort study, analysis of patients through a compassionate use program in Australia. Tx duration: 1 year	moderate to critical	Aged ≥ 18 years Homozygous for the F508del ppFEV$_1$ < 40%
Loukou 2020	40[d]	Paired historic control cohort study; single centre in Greece. Tx duration: 1 year	moderate to critical	Age: 12 to 23 years Homozygous for the F508del
Studies where lumacaftor/ivacaftor were initiated from ages 6 to 11 years				
Study 110	239	OL, MC, 2-part study 96 weeks (Tx follow up: 120 wks) Mean Tx duration: 1.8 yrs[e]	moderate to critical	Aged 6 to 11 years with CF homozygous for the F508del mutation.
Study 129	179	OL, MC, analysis of data from the ACFDR. Mean Tx duration: 0.8 yrs	moderate to critical	Aged 6 to 11 years. Australian patients with CF homozygous for the F508del mutation;
Pooled-analysis		Assessed ppFEV$_1$ rROD		
Base case	2,489[f]	Included studies: PASS 108 (≥ 12 y), Flume 2021, Bourgani 2019, Mermis 2019, Muiljilk 2020		
Sensitivity	2,802[f]	Included studies: ACFDR (≥ 12 y), PASS 108 (≥ 12 y), Flume 2021, Bourgani 2019, Mermis 2019, Muilwijk 2020, Collet 2018, Ejiofor 2020, King 2021, Loukou 2020, Tong 2020		

Source: Constructed using Table 2.4.1, Table 2.4.5, Table 2.4.8 and Table 2.4.10 of the Commentary; Attachment 7 Pooled ppFEV1 rROD Feb 2021.

a Risk of bias assessed using the ROBINS-I tool. Ratings of bias from lowest to highest risk of bias is low, moderate, serious, critical.

b Reported N in Konstan 2017 and Flume 2021 comparing treatment with lumacaftor/ivacaftor or tezacaftor/ivacaftor vs. no CFTR modulator use include the number of patients as reported in the post-hoc analyses as presented in the evaluation

c PASS 108: the number of patients as reported in the 2018 Disease Progression Cohorts aged 12 years and over; the number of patient in the Disease Progression Cohorts aged 6 years and older were: Treatment group, N=2,287; Comparator group, N=3,527. PASS 108 also included patients aged from 2 years and older.

d Loukou 2020: N=52, the base of N=40 were used in the submission.

e Mean duration of treatment reported in Study 110 in this table only included the mean time in Study 110. The mean exposure in the parent studies was reported as 159.8 days; ~0.44 years.

f Pooled analysis: N reported in the table is as per N used in the pooled analysis and only included the number of patients in the treatment groups and not the comparator groups

ACFDR=Australian Cystic Fibrosis Disease Registry; BMI=body mass index; CF = cystic fibrosis; LUMA/IVA=lumacaftor/ivacaftor; MC = multi-centre; NR=not reported; OL = open label; wks=weeks; y=years; ppFEV1= percent predicted forced expiratory volume in 1 second; rROD=relative rate of decline compared with best supportive care; tx=treatment; US=United States;

4.10 The evaluation reported the risk of bias overall for Konstan 2017, PASS 108, and Flume 2021 is moderate to serious; all other studies had a moderate to critical risk of bias. The ESC noted some studies were only available in abstract form and minimal detail regarding methodology was available.

4.11 Most studies did not include patients that discontinued treatment with lumacaftor/ivacaftor or tezacaftor/ivacaftor in the analyses. Excluding patients that discontinue treatment biases the analyses in favour of the intervention. The PSCR did not agree with this statement. The PSCR stated the research question of relevance was 'What is the relative reduction in the $ppFEV_1$ rate of decline in FF homozygous CF patients continuing to be treated with lumacaftor/ivacaftor, relative to best supportive care'. The PSCR stated this is because in the economic model, a value of 42% for rROD is only applied to those remaining on treatment with those discontinuing treatment reverting immediately to BSC ROD (which is likely a conservative assumption). The PBAC noted the sponsor's pre-subcommittee response, but considered patients who continue treatment may have a different baseline disease trajectory to those who discontinue, and if the baseline disease trajectory is better in those who continue treatment versus those who discontinue, the benefit of treatment will be overestimated.

4.12 There are substantial differences across the studies, including differences in the study designs, baseline characteristics of the patient populations, differences in the use of CFTR modulator therapy and sampling of patients for inclusion in the analyses. The ESC noted the methodological diversity across the study designs and considered quantitatively synthesising evidence of the $ppFEV_1$ rROD by pooling the studies as done in the submission was not appropriate.

4.13 The analysis presented for Flume 2021 used a similar methodology to that used in the Konstan 2017 analysis. The PBAC noted that, as in the Konstan study, the Flume study excluded the increase in $ppFEV_1$ in the first 3 weeks of treatment with CFTR modulator from the rate of decline calculation. Propensity score matching was used to compare treatment and historical control groups in Flume 2021 and Konstan 2017. Previously, the ESC raised concerns with respect to the propensity score matching applied between the PROGRESS study and the US CFFPR cohorts in the Konstan study. The methodology used was a single point-in-time rebalancing at baseline, which did not adjust for the imbalance of any post-baseline differences in variables that were not due to the treatment, or differences in data collection between the patients in PROGRESS and the CFFPR cohort, which may have confounded the outcomes (paragraph 6.22, lumacaftor/ivacaftor PSD, July 2018 PBAC meeting). Propensity score matching conducted for Flume 2021 using the same method is subject to the same issues as identified by the PBAC in respect to Konstan 2017.

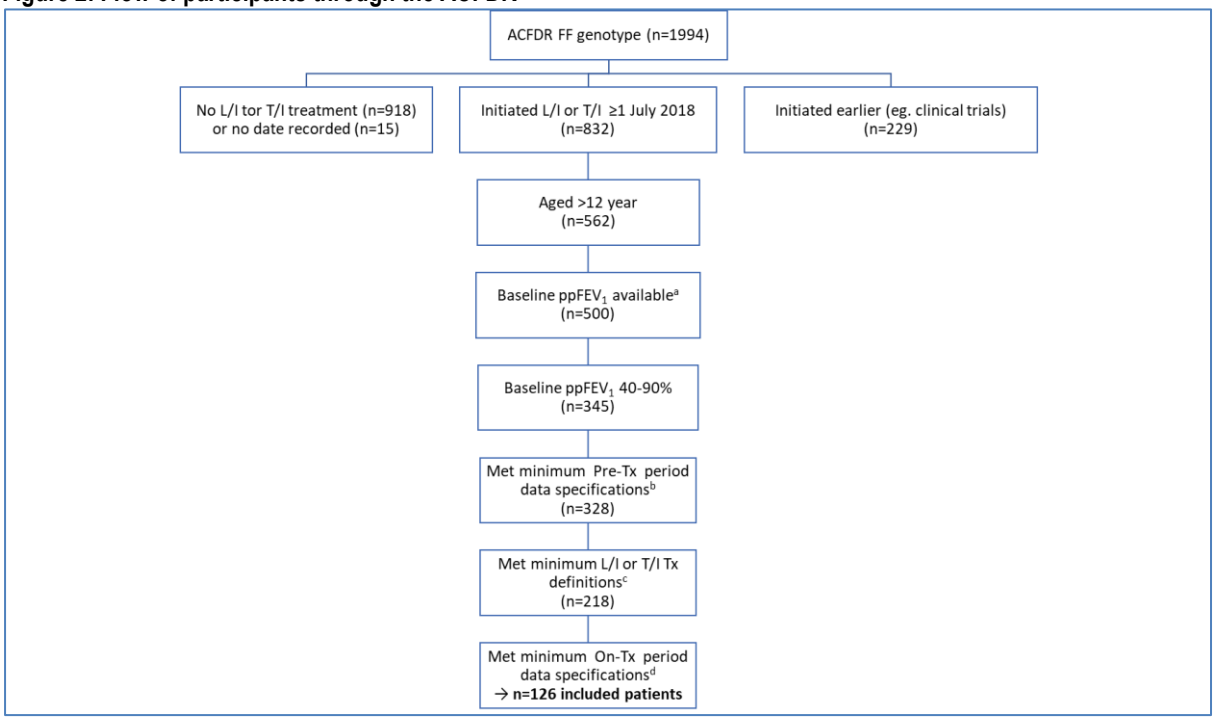
4.14 The ESC noted PASS 108 was an unmatched parallel cohort study comparing patients with CF who were homozygous for the F508del mutation and treated with lumacaftor/ivacaftor to patients with CF who were heterozygous for the F508del mutation with a Class I or Class II mutation on the second allele and not treated with a CFTR modulator. The ESC noted the comparative analysis for PASS 108 used only US patients which may mitigate some of the previous concerns regarding the Konstan 2017 analysis which compared US patients to non-US patients (paragraph 2.6). The PBAC noted the PASS 108 study assumed that treated homozygous and untreated heterozygous F508del are exchangeable. The PBAC further noted that a high proportion of patients switched from lumacaftor/ivacaftor to another CFTR modulator (1,823 patients out of 5,508, 33%; PASS 108 Clinical Study Report, Fig 4) and overall only 42% (2,287 patients) of the original year 1 lumacaftor/ivacaftor cohort were included in the ROD analysis. In comparison, 88% of the original year 1 cohort for the control group were included in the ROD analysis. The PBAC noted there are likely to be differences across the cohort of lumacaftor/ivacaftor treated patients included in the analysis (continuers, 42% of patients) versus the cohort of lumacaftor/ivacaftor treated patients excluded from the analysis (discontinuers, 58% of patients), and it is not possible to identify a control cohort equivalent to the lumacaftor/ivacaftor continuers. If the baseline disease trajectory is better in continuers versus discontinuers, the benefit of lumacaftor/ivacaftor treatment will have been overestimated. Overall, the PBAC considered the results of PASS 108 were likely to be biased in favour of treatment with lumacaftor/ivacaftor**.**

4.15 The submission presented an analysis that was commissioned from the ACFDR of patients with CF homozygous for the F508del mutation, aged more than 12 years old initiating lumacaftor/ivacaftor or tezacaftor/ivacaftor between the 1 July 2018 and the 29 February 2020, and a $ppFEV_1$ between 40% and 90%. The submission reasoned that the data requested from the ACFDR were specific to patients aged ≥12 years to align with Konstan 2017. The ACFDR had 1,994 patients homozygous for the F508del mutation and 832 initiated treatment after the index date (Figure 2). However, data for only 126 patients (12%) are included in the analysis presented by the submission. The criterion excluding patients based on baseline $ppFEV_1$ that was not between 40% to 90% resulted in the exclusion of 155 people aged ≥12 years (from 500 to 345 patients), which is high given that the data from the ACFDR included by the submission were only from 126 patients. Access to CFTR modulators on the PBS is not limited by $ppFEV_1$. The ESC considered it would have been informative for the analysis of the data from the ACFDR to more closely reflect the use of CFTR modulators in Australian clinical practice (i.e., patients ≥ 2 years, no restriction on $ppFEV_1$), rather than aligning to Konstan 2017 (i.e., restricting to patients aged ≥ 12 year, baseline $ppFEV_1$ 40% to 90%). The pre-PBAC response provided some additional analyses without patients excluded on the basis of $ppFEV_1$ (see paragraph 4.24).

4.16 For the ACFDR analysis, the submission stated a weighted average annual change (slope) was calculated for each period for each patient and then the mean slope for

each period was calculated for the total cohort (n=126). The ESC considered a more appropriate, and more contemporary, method of statistical analysis would use regression techniques that also adjust for the starting $ppFEV_1$ (i.e., a random-intercept, random-slope model). However, the method of statistical analysis was secondary to the ESC concerns about exclusions based on age (<12 years) and $ppFEV_1$ (<40%, >90%). Also, the short follow-up time (1.7 years) meant that the results of the study were not helpful to reduce uncertainty around the input into the economic model (i.e., rROD=42%, sustained over the time horizon of the model).

Figure 2: Flow of participants through the ACFDR



ACFDR=Australian Cystic Fibrosis Disease Registry FF= heterozygous for the F508del mutation; L/I=lumacaftor ivacaftor; T/I=tezacaftor ivacaftor; $ppFEV_1$= percent predicted forced expiratory volume in 1 second; Tx= treatment

Source: correspondence provided by sponsor, 1 April 2021. Information regarding footnotes in figure not provided.

Comparative effectiveness

4.17 A summary of the results of the change in $ppFEV_1$ in Konstan 2017, PASS 108, Flume 2021 and Tong 2020, the studies with parallel control arms, is provided in Table 4. The mean $ppFEV_1$ rROD based on the annualised changed in $ppFEV_1$ ranged from 42% to >100%. The Tong 2020 study is difficult to interpret because the sample size is small and only patients with $ppFEV_1$ <40% were included.

Table 4: Change in ppFEV$_1$ in the Konstan 2017, PASS 108, Flume 2021 and Tong 2020 studies

	Konstan 2017		PASS 108				Flume 2021		Tong 2020	
	LUM/IVA	Control	LUM/IVA	Control	LUM/IVA	Control	TEZ/IVA	Control	LUM/IVA	Control
	≥ 12y	≥ 12y	≥ 6y	≥ 6y	≥ 12y [b]	≥ 12y [b]	≥ 12y	≥ 12y	≥ 12y	≥ 12y
	N=455	N=1,588	N=2,287	N=3,527	N=1,881	N=2,686	N=407	N=407$_w$/ 1,383[a]	N=72	N=33
Duration of follow up (years)	2.3		2.9		3.0		2.3		Approx. 1	
ppFEV$_1$										
N	455	1,588	2,072	3,153	1,776	2,540	407	1,383	72	33
Baseline/ prior to tx, mean (sd)	59.8 (13.8)	61.8 (16.3)	81.4 (19.8)	78.4 (21.5)	79.1 (18.1)	74.7 (19.4)	59.0 (14.5)	59.4 (9.3)	37.4 (11.3)	34.3 (8.5)
ppFEV$_1$: Absolute change										
N	NR	NR	2,046	3,114	1,754	2,508	NR	NR	NR	NR
Mean (sd) [95% CI]	NR	NR	-3.73 (10.1) [-4.2, -3.3]	-6.85 (11.3) [-7.2, -6.5]	-3.73 (9.9) [NR]	-7.46 (11.2) [NR]	NR	NR	NR	NR
ppFEV$_1$ slope	%/year	%/year	%/year	%/year	%/year	%/year	%/year	%/year	%/month	%/month
Annualised change ppFEV$_1$, mean (sd) (95% CI)	-1.33 (-1.80, -0.85)	-2.29 (-2.56, -2.03)	-0.93 [c]	-1.71 [c]	-0.93 [c]	-1.87 [c]	-0.80 (-1.31, -0.30)	-2.08 (-2.34, -1.82)	0.107 (−0.074, 0.288)	−0.379 (−0.646, 0.105)
ppFEV$_1$ rROD	41.9%		45.6%[d]		50.3%[e]		61.5%		>100%	

Source: Table 2.5.1 of the Commentary.

a Flume 2021: Demographics presented in Flume 2021 for the controls represents the weighted sample size of the historical control group using the inverse of the number of controls in each matched set to account for one-to-many matching used in the analysis. These are only relative values and not absolute values. This is reported in the column heading as N=407$_w$/ 1,383.

b The PASS 108 CSR reported results in two age groups: ages ≥ 12 and <18; and age≥18. Results for patients ≥ 12 years for PASS 108 were calculated by the submission using a weighted average of the number of patients in the two age groups; Footnote of Table for PASS 108 states that Demographic data for patients aged ≥12 years were not reported in US CFFR IA3 tables. These were obtained by ad hoc data request, Obj3_Table 1.0 and 1.1, dated 25/09/2020, Data on File. Some data could not be verified during the evaluation.

c Submission calculation (annualised change from 2014 to 2018: LUMA/IVA, -3.73 / 4 (years) = -0.93; Control, -7.46 / 4 (years) = -1.87. During the evaluation similar calculations were applied to the subgroup of patients aged ≥ 6 years: LUMA/IVA, -3.73 / 4 years = -0.93, Control, -6.85 / 4 years = -1.71.

d Calculated during evaluation:(-1.71--0.93)/-1.71)

e Reported in submission as 50.1%; corrected during evaluation to 50.3% (calculation: [-1.87/-0.93]/-1.87))

Abbreviations: CI=confidence interval; N=number; p=probability; LUMA/IVA=lumacaftor/ivacaftor; ppFEV$_1$=percent predicted forced expiratory volume in one second; sd=standard deviation; rROD=relative rate of decline; TEZA/IVA=tezacaftor/ivacaftor

4.18 The PSCR provided data from additional follow up of the PASS 108 study (Table 5 and 6). Patients aged ≥6 years experienced a rROD ppFEV$_1$ of 45.8% on lumacaftor/ ivacaftor (based on mean 3.7 years treatment) and patients aged ≥12 years experienced a rROD ppFEV$_1$ of 47.3% on lumacaftor/ivacaftor (based on mean 3.8 years treatment).

Table 5: **PASS 108 Disease Progression Cohorts through Q3 2019: Patient characteristics & exposure duration**

	Comparator (≥6-year-old) N=3,137	LUM/IVA (≥6-year-old) N=1,498	Comparator (≥12-year-old) N=2,327	LUM/IVA (≥12-year-old) N=1,198
Age in 2019, mean (sd)	23.2 (10.8)	22.3 (9.5)	27.1 (9.9)	25.0 (8.9)
Gender, male n (%)	1,655 (52.8)	952 (63.6)	1,253 (53.8)	787 (65.7)
LUM/IVA exposure group: <1 year ≥1-<2 years ≥2-<3 years ≥3-<4 years ≥4 years	N/A	 0 0 273 (18.2) 722 (48.2) 503 (33.6)	N/A	 0 0 45 (3.8) 654 (54.6) 499 (41.7)
Median exposure, years Mean exposure, years (sd) Range exposure, years		3.8 3.7 (0.5) 2.5 – 4.7		3.9 3.8 (0.4) 2.6 – 4.7

Source: Table 3, PSCR
Abbreviations: LUMA/IVA=lumacaftor/ivacaftor; sd=standard deviation;

Table 6: PASS 108 Disease Progression Cohorts through Q3 2019: Change in ppFEV$_1$ from baseline

	Comparator (≥6-year-old) N=3,137	LUM/IVA (≥6-year-old) N=1,498	Comparator (≥12-year-old) N=2,327	LUM/IVA (≥12-year-old) N=1,198
Pre-study baseline (2014), ppFEV$_1$, %: n Mean (sd)	 2,791 80.24 (20.80)	 1,336 83.42 (19.27)	 2,202 76.47 (20.59)	 1,128 81.16 (19.43)
Change from baseline to Q3 2019, ppFEV$_1$, %: n Mean (sd)	 2,746 -7.21 (12.62)	 1,319 -3.91 (10.47)	 2,167 -7.73 (12.80)	 1,114 -4.07 (10.23)
Annualised change (2014 to Q3 2019), ppFEV$_1$, %/year[a]	-1.52	-0.82	-1.63	-0.86
% reduction in ppFEV$_1$ ROD (2014 to Q3 2019)	45.8%		47.3%	

Source: Table 4, PSCR. [a] Change from baseline divided by 4.75 years to reflect data through to Q3
Abbreviations: LUMA/IVA=lumacaftor/ivacaftor; ppFEV$_1$=percent predicted forced expiratory volume in one second; sd=standard deviation; ROD=rate of decline;

4.19 In response to a question from the PBAC (see paragraph 4.2), the sponsor provided additional analyses of the PASS 108 study which estimated the annual change in ppFEV$_1$ with lumacaftor/ivacaftor over a later time window in order to exclude the initial improvement in ppFEV$_1$ (data from 2016 to Q3 2019 used in the analysis; all patients commenced treatment in 2015). The sponsor concluded that the annual change in ppFEV$_1$ is remarkably constant over time. The PBAC noted, as expected, the annual change increases when the initial treatment period is excluded (from -0.86 [Table 6] to -0.99 per year for the cohort aged ≥12 years; from -0.82 [Table 6] to -0.91 per year for the cohort aged ≥6 years). The sponsor reported the rROD as 47.0% for the cohort aged ≥12 years and 51.3% and for the cohort ≥6 years. The PBAC noted the rROD was potentially overestimated as it was based on an annual change of -1.87 for the control group rather than the rates reported using the data from the Q3 2019 cohort (-1.63 and -1.52, Table 6).

4.20 The pre-PBAC response provided longer-term follow-up for patients completing the PROGRESS study (in 2015) by identifying these patients in the US CFFPR. A total of 256 patients receiving lumacaftor/ivacaftor in 2016 provided consent for additional data collection, of whom 202 continued to receive lumacaftor/ivacaftor over the following three years (through 2018). The ROD in $ppFEV_1$ was estimated to be 0.95% per year, which was noted to be lower than the ROD of 2.29% per year reported in the Konstan for the control group. The PBAC noted this was from an enriched population of continuers and one of the reasons patients may discontinue treatment is because they were not doing well on lumacaftor/ivacaftor.

4.21 The estimated $ppFEV_1$ rROD across the remaining studies was 56% to >100% (Table 7). The PBAC noted the initial increase in $ppFEV_1$ in treated patients across the studies appeared small, ranging from 0.2% to 3.8% in the first year of treatment, compared to the 2.8% (2 to 11 years of age)/ 3.0% (≥ 12 years of age) increase in the first 24 weeks previously considered by the PBAC.

Table 7: Change in $ppFEV_1$ in the remaining studies

	Bourgani 2019	Mermis 2019[d]	Muilwijk 2020	Collet 2018	Ejiofor 2020	King 2021	Loukou 2020
	LUMA/IVA	L/I & T/I	LUMA/IVA	LUMA/IVA	LUMA/IVA	LUMA/IVA	LUMA/ IVA
	N=46	N=85	N=70	N=30	N=21	N=24	N=40
$ppFEV_1$							
Baseline[a], mean	61.0	64.9	60.2[b]	85.1	38.7 (median)	34.7	
Change, mean	Yr 1: +0.2% Yr 2: +4.3%	NR	Yr 3: +1.7%	Yr 1: +3.5%	6 mo: +5.8% Yr 1: +3.8%	Yr 1: +1.45%	Yr 1: +1.2%
$ppFEV_1$ slope	Mean %/year	Mean L/year[d]	Mean %/year	NR %/year	Median %/year	Mean %/year	Mean %/year
Pre-CFTR modulator	-4.2	-0.068	-1.80	-2.2	-2.6	-2.10	-0.99
Post-CFTR modulator	+1.2	-0.030	-0.80	+4.6	+2.1	+1.45	+3.38
$ppFEV_1$ rROD[e]	>100%	55.9%	55.6%	>100%	>100%	>100%	>100%

Source: Table 10 p21, Table 11 p21, Table15 p27, Table 16 p28, Table 19 p30, Table 20 p31, Table 21 p31, Table 24 p33, Table 25 p33, Table 26 p34, Table 27 p35, Table 31 p38, Table 32 p38, Table 33 p39, Table 34 p39, Table 35 p40, Table 36 p40 of the submission; Attachment 7 Pooled ppFEV1 rROD;

a Reported baseline assumed to be immediately before prior to treatment unless otherwise stated.

b Muilwijk 2020; reported as the baseline for the control i.e., mean ppFEV1 at beginning of five-year pre-initiation period. Prior to treatment mean baseline ppFEV1 was 50.0 (2.3).

d Mermis 2019: Absolute FEV1 (litres/min) reported rather than ppFEV1.

e It is not mathematically correct to calculate % reduction if slopes differ in direction. Reported as >100%.

Abbreviations: CFTR= Cystic fibrosis transmembrane conductance regulator; CI=confidence interval; IQR= Interquartile range; LUMA/IVA=lumacaftor/ivacaftor; N=number; p=probability; $ppFEV_1$=percent predicted forced expiratory volume in one second; rROD=relative rate of decline; sd=standard deviation.

4.22 The PBAC noted for the studies which compared patients prior to and after treatment, the benefit from treatment is likely to be overestimated due to 'regression to the

mean', i.e., reductions in $ppFEV_1$ may have influenced the decision to commence treatment and thus the decline in $ppFEV_1$ prior to treatment is likely to be larger than on average.

4.23 The rate of pulmonary exacerbations and use of intravenous antibiotics among patients receiving treatment with lumacaftor/ivacaftor was consistently lower across all studies reporting these outcomes.

4.24 In the analysis of patients from the ACFDR aged 12 years and over (N=126) provided in the submission, the weighted average annual change in $ppFEV_1$ in the year prior to treatment with a CFTR modulator was -1.91, and after approximately 15 months of treatment was +2.39. The estimated mean $ppFEV_1$ rROD after approximately 15 months of treatment was >100%. Results are representative of 12% of patients registered on the ACFDR who have received treatment with a CFTR modulator, with a $ppFEV_1$ between 40% and 90%. The pre-PBAC response stated most patients (281/562, 56.7%) were ineligible for inclusion as they did not meet the criteria defined a priori essential to perform the rROD analyses (i.e., ≥10 months since initiation measurement, baseline $ppFEV_1$ measure available, ≥3 $ppFEV_1$ measures in either period). The pre-PBAC response provided an additional analysis of the ACFDR data that did not restrict patients based on baseline $ppFEV_1$ (Table 8). The PBAC noted the annual change in $ppFEV_1$ per year in the first 15 months of treatment was +1.31%.

Table 8: ACFDR analysis provided in submission and updated analysis provided in pre-PBAC response

	Analysis provided in submission ($ppFEV_1$ 40-90), n=126	**Revised analyses provided in pre-PBAC response (any $ppFEV_1$), n=179**
Male, n (%)	54 (63)	113 (63)
Age, years (mean, SD)	25.9 (9.0)	24.8 (8.8)
$ppFEV_1$, % (mean, SD)	69.1 (13.6)	75.0 (20.2)
Duration CFTR modulator use from initiation, months (mean, SD)	20.2 (2.0)	20.2 (1.9)
Duration of on-CFTR modulator analyses[a], months (mean, SD)	14.6 (3.3)	14.6 (3.3)
pre-CFTR modulator weighted average annual change in $ppFEV_1$	-1.91%/year	-1.10%/year
on-CFTR modulator weighted average annual change in $ppFEV_1$	+2.39%/year	+1.31%/year
ppFEV1 rROD	**>100%[b]**	**>100%[b]**

CFTR=Cystic fibrosis transmembrane conductance regulator; ppFEV1 =percent predicted forced expiratory volume in one second rROD =relative rate of decline; S=standard deviation

[a] To patient's last ppFEV1 measure used in analyses (truncated by COVID).

[b] It is not mathematically correct to calculate % reduction if slopes differ in direction

Pooled analysis

4.25 The submission's pooled point estimate of the relative rate of decline in lung function (rROD $ppFEV_1$) for lumacaftor/ivacaftor compared to BSC was 55.7% based on five studies (PASS 108, Flume 2021, Bourgani 2019, Mermis 2019, Muilwijk 2020) that included patients that had been treated for more than two years. As discussed in paragraph 4.12, the ESC did not consider pooling of the data appropriate.

Studies where lumacaftor/ivacaftor were initiated from ages 6 to 11 years

4.26 For patients aged 6-11 years initiating treatment with lumacaftor/ivacaftor; the absolute change in ppFEV$_1$ from baseline to 12 months was not significant in Study 129 (-0.9%; 95%CI -2.1, 0.3), or in patients who transitioned from placebo to lumacaftor/ivacaftor treatment in Study 110 (0.0; 95%CI -2.7, 2.7); whereas a small change was observed in patients who received lumacaftor/ivacaftor in the parent study and in Study 110 (i.e., from the baseline of the parent study to week 96 of Study 110; approximately 120 weeks) (+3.1%; 95%CI, 1.0, 5.1). The PSCR stated the results from Study 129 are interim results as the duration of local follow-up is currently limited given the later access to lumacaftor/ivacaftor in Australia relative to the US. The PSCR stated Study 129 was designed to meet TGA requirements with reporting only after 5 years (an interim report was not requested by the TGA).

4.27 In Study 110, of the patients who transitioned from placebo to lumacaftor/ivacaftor, 31 (32.3%) had experienced at least one pulmonary exacerbation event; of the patients that received lumacaftor/ivacaftor in the Study 109 and in Study 110, 51 (49.5%) had experienced at least one pulmonary exacerbation. Few of the pulmonary exacerbation events in Study 110 required hospitalisation or antibiotic treatment. In Study 129, a pulmonary exacerbation event was defined as any episode requiring home IV or hospitalisation with respiratory symptoms; the number of pulmonary exacerbation events per patient per year was 0.4 (standard deviation, 0.9).

Comparative harms

4.28 Safety outcomes were presented for Study 110 and PASS 108 pertaining to children who initiate lumacaftor/ivacaftor between the ages of 6 to 11 years (see Table 9).

Table 9: Summary of key adverse events in Study 110

	Overall N=239
Any AEs, n (%)	236 (98.7)
Mild	48 (20.5)
Moderate	148 (61.9)
Severe	39 (16.3)
AEs leading to treatment discontinuation	9 (3.8)
Serious AEs	72 (30.1)
Infective PEx of CF	49 (20.5)
Pulmonary function test decreased	4 (1.7)
Constipation	4 (1.7)
AEs leading to death	0
AEs With an Incidence of At Least 10% of patients	
Cough	155 (64.9)
Infective PEx of CF	118 (49.4)
Pyrexia	72 (30.1)
Nasal congestion	55 (23.0)
Headache	55 (23.0)
Oropharyngeal pain	50 (20.9)

Source: pp49 p60, Table 50 p63 of the submission; Table 12-2 p107, Table 12-3 p109, Table 12-7 p 122 Attachment 4 Study 110 CSR,
Abbreviations: AE=adverse event; CF=cystic fibrosis; PEx=pulmonary exacerbations

4.29 A summary of the safety outcomes for lumacaftor/ivacaftor compared with patients in the comparator arm in PASS 108 is presented in Table 9. These data do not suggest any new or unexpected harms associated with longer-term treatment. The PSCR noted the highly patient-relevant treatment benefits clearly demonstrated by these data i.e., a 56% reduction in deaths.

4.30 The PBAC noted the age-adjusted odds ratio for the reduction in pulmonary exacerbations in the PASS 108 study was 0.70 which suggested a smaller treatment effect than that previously applied in the economic model that informed the recommendation to list lumacaftor/ivacaftor for CF patients over 12 years (RR 0.44, 56% reduction in risk).

Table 10: Safety outcomes: PASS 108, safety cohorts, 2018

Outcome[a]	LUMA/IVA safety cohort, 2018 (all ages) N=4,628		Comparator safety cohort, 2018 (all ages) N=5,666		RR (95%CI), unadjusted	OR (95%CI), Age-adjusted[b]
	n	Risk (%)	n	Risk (%)		
Deaths	30	0.7	84	1.5	0.44 (0.29, 0.66)	0.61 (0.40, 0.94)
Organ transplantations	25	0.5	84	1.5	0.36 (0.23, 0.57)	0.47 (0.30, 0.74)
Hospitalisations (any reason)	1561	33.7	2484	43.8	0.77 (0.73, 0.81)	0.68 (0.63, 0.74)
Pulmonary exacerbation	1470	31.8	2368	41.8	0.76 (0.72, 0.80)	0.70 (0.65, 0.77)
Complications	3,894	84.1	4,925	86.9	0.97 (0.95, 0.98)	1.04 (0.93, 1.17)

Source: Table 51 p63 of the submission; Table 7 p28 Attachment 1a PASS 108 CSR;
a The at-risk population was based on patients with non-missing information
b Adjusted for age in years (continuous) on January 1, 2018
Abbreviations: CI = confidence interval; n = number of participants reporting data; LUMA/IVA=lumacaftor/ivacaftor; N = total participants in group; OR = odds ratio; RR = relative risk

Clinical claim

4.31 The submission claimed that all available evidence supported the $ppFEV_1$ rROD exceeding 42% over time for patients treated with lumacaftor/ivacaftor compared to BSC.

4.32 The evaluation considered the therapeutic conclusion presented in the submission may not be adequately supported by the evidence for the following reasons:

- The individual studies included in the submission were subject to moderate to critical biases.
- Evidence from most of the studies was less informative than the analysis presented in Konstan 2017 included in the original PBAC submission. The mean duration of follow up for Konstan 2017 and Flume 2021 was approximately 2.3 years, for PASS 108 was 3.8 years, for Muilwijk 2020 was 2.4 years and the follow up for the other studies was less than 2 years.

4.33 The evaluation considered the ACFDR analysis provided in the submission was from a limited population of patients aged 12 years and older with a baseline $ppFEV_1$ between 40% to 90%, which was only approximately 12% of patients that have received lumacaftor/ivacaftor or tezacaftor/ivacaftor in Australia. The analysis from the ACFDR was not considered reflective of the totality of the use of lumacaftor/ivacaftor on the PBS as recorded by the ACFDR.

4.34 The submission claimed that the longer-term data from Study 110, Study 129 and PASS 108 provided evidence that the efficacy and safety of treatment with lumacaftor/ivacaftor is maintained into the longer-term for up to 4 years for patients with CF aged from 6 to 11 years. The evaluation considered this claim may not be supported by the evidence presented for the following reasons:

- Study 110 and Study 129 were non-comparative, and subject to considerable bias; the effectiveness and safety estimates are subject to considerable uncertainty.

- Analyses from Study 129 were based on data collected from the ACFDR for a select and potentially non-representative sample of all treated patients. Results presented were based on 179 patients, with one year of follow-up; as such, these data may be premature and no longer-term follow-up is available.

4.35 Overall, the PBAC considered the data presented did not adequately support the claim that $ppFEV_1$ rROD exceeded 42% over time for patients treated with lumacaftor/ivacaftor compared to BSC.

Economic analysis

4.36 The economic evaluation presented was a cost-utility analysis (CUA). The structure of the model was the same as in the previous (re)submissions (March 2016, November 2016, July 2017, July 2018, July 2019), which presented a CUA of lumacaftor/ivacaftor compared with BSC.

4.37 Based on the pooled estimate of $ppFEV_1$ rROD from five studies (paragraph 4.19), the submission revised the estimate informing the $ppFEV_1$ rROD from 42% to 55.7%. The resulting ICER as presented in the submission decreased from $155,000 to < $255,000/QALY gained to $115,000 to < $135,000/QALY gained based on the revised estimate. The PBAC noted the economic model required an estimate of the rROD from week 24 onwards. The PBAC noted the initial increase in $ppFEV_1$ was not excluded when estimating the rROD for four of the five studies included in the pooled estimate and thus considered the rROD was overestimated and the ICER was underestimated.

Financial Management – Risk Sharing Arrangements

4.38 The submission concluded that in light of its estimate of the rROD at 55.7%, it was appropriate that Option 1 of the MAP be enacted. The PBAC considered that data to reliably inform the rROD beyond 24 weeks was not provided by the submission and hence there was not a basis on which to enact Option 1 of the MAP.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC advised the data provided by the sponsor did not meet the requirements of the MAP, and that the long-term benefits of lumacaftor/ivacaftor, in terms of the relative rate of decline in $ppFEV_1$ and the rate of pulmonary exacerbations, remained uncertain. The PBAC considered additional analyses would be required to meet the requirements of the MAP.

5.2 The PBAC recalled the economic model that informed the recommendation to list lumacaftor/ivacaftor for CF patients over 6 years of age assumed an average change in $ppFEV_1$ of +3.0% in the first 24 weeks of treatment followed by a relative rate of decline (rROD) of 42% compared to best supportive care (based on Konstan 2017) for the duration of the model. The PBAC noted the rROD calculation was based on a rate

of decline of 1.33% per year for treated patients and 2.29% per year for BSC patients. The PBAC noted that the assumption of the rate of decline in $ppFEV_1$ with treatment (1.33%/year) being less than for best supportive care (2.29%/year) resulted in progressively larger absolute (i.e., arithmetic) differences in $ppFEV_1$ for the two treatment groups over the model duration (see Figure 1 for the impact over 2 years). The model also assumed a 56% reduction in annual rate of pulmonary exacerbations requiring IV antibiotics or inpatient stays over the modelled time horizon (paragraph 6.57, lumacaftor/ivacaftor PSD, July 2018 PBAC meeting).

5.3 The PBAC noted Flume 2021 was the only additional study which appropriately excluded the first 3 weeks of treatment with CFTR modulator treatment to ensure the initial increase in $ppFEV_1$ was not included in the rate of decline calculation (i.e. the slope of the line as presented in Figure 1 for Konstan 2017). The PBAC noted Konstan 2017 and Flume 2021 compared patients previously enrolled and treated in clinical trials versus untreated external controls. Despite propensity matching, the PBAC considered these studies are at risk of residual confounding due to differences between those selected and willing for trial participation versus those who are not, as well as potential differences in care among study participants vs non-participants.

5.4 The PBAC noted for the remaining studies which did not exclude the initial increase in $ppFEV_1$, the rate of decline with treatment was underestimated and hence the rROD was overestimated. Based on the original model assumptions (3% increase in $ppFEV_1$ with lumacaftor/ivacaftor followed by annual decline in $ppFEV_1$ of 1.33%), the $ppFEV_1$ will not decline to the baseline (prior to treatment) value until after more than 2 years of treatment (initial increase 3%, end year 1 vs baseline: 1.67% increase [3.0-1.33], end year 2 vs baseline: 0.34% increase [1.67-1.33]). Thus for studies with a follow-up of less than 2 years, there should be an overall improvement in $ppFEV_1$ with treatment versus baseline, and the rROD should be >100%.

5.5 The PBAC noted that a total of 11 studies were included in the submission of which only three (Flume 2021, Muilwijk 2020 and PASS 108) provided data over more than 2 years of follow-up. The PBAC further noted that 5 studies were either available in abstract form only or provided limited information regarding study methodology. The PBAC considered the risk of confounding was exacerbated in all studies by only including patients who remained on treatment for the follow-up period (i.e. continuers), as it is not possible to identify the patients equivalent to the 'continuers' in the control group. The PBAC noted if continuers have a better baseline disease trajectory than patients who discontinue treatment, any benefit of treatment will be over-estimated. The PBAC considered all studies were subject to significant limitations.

5.6 The PBAC noted that only the PASS 108 study provided data over a longer follow-up period than Konstan 2017 and hence potentially informed the medium term effect of lumacaftor/ivacaftor. The PBAC noted the limitations of the PASS 108 study included the assumption that treated homozygous and untreated heterozygous F508del patients are exchangeable and the high proportion of patients excluded from the

lumacaftor/ivacaftor cohort, including one-third of patients who switched treatment to another CFTR modulator, mainly tezacaftor/ivacaftor (paragraph 4.14). The PBAC noted that if the baseline disease trajectory is better in the included versus excluded patients, the benefit of lumacaftor/ivacaftor treatment will have been overestimated, and overall considered the results did not reduce uncertainty in the long-term rROD in the economic model.

5.7 The PBAC noted that, based on the PASS 108 study, the change from baseline in $ppFEV_1$ was -3.9% for patients over 6 years of age treated with lumacaftor/ivacaftor compared to -7.2% for patients who were not treated over 4.75 years. The PBAC noted based on the economic model that a 7-8% difference in $ppFEV_1$ would be expected across the treatment groups at 4.75 years. However, the observed difference in the PASS 108 study was 3.3% (7.2%-3.9%). The PBAC noted the data from PASS 108 were inconsistent with an initial increase in $ppFEV_1$ of 3.0% as well as a reduction in the rate of decline beyond the initial increase of <42%. The PBAC noted if the initial increase in $ppFEV_1$ was 3% over 24 weeks as assumed in the economic model, the rROD after 24 weeks of therapy would be substantially less than the 45.8% reported in the submission.

5.8 The PBAC noted the reduction in pulmonary exacerbations observed in the PASS 108 study (adjusted odds ratio of 0.70) was less than the reduction assumed in the original economic model that informed the cost effectiveness of lumacaftor/ivacaftor (relative risk of 0.44).

5.9 The PBAC noted the economic model provided with the submission assumed a relative rate of decline of $ppFEV_1$ of 55.7% after the initial 24 weeks of treatment based on a pooled estimate from 5 studies. The PBAC noted four of the five studies included the initial increase in $ppFEV_1$ in the slope estimation for the rate of decline calculation which is inconsistent with the structure of the economic model (which modelled the initial increase separately) and likely to overestimate the relative rate of decline.

5.10 The PBAC considered the analysis of the ACFDR data provided weak evidence of an initial increase in $ppFEV_1$ but not a sustained reduction in rate of decline over time. The PBAC noted the annual change in $ppFEV_1$ per year in the first 15 months of treatment was +1.31%.

5.11 The PBAC acknowledged that, as anticipated (paragraph 6.78, lumacaftor/ivacaftor PSD, July 2018 PBAC meeting), providing data with longer follow up may be limited by the availability of new CFTR modulators. However, the PBAC considered it may have been appropriate to explore using longer term data from the US CFFPR for patients treated continuously with lumacaftor/ivacaftor and tezacaftor/ivacaftor through consecutive periods of treatment, especially given that tezacaftor/ivacaftor was recommended on a cost-minimisation basis versus lumacaftor/ivacaftor.

5.12 The PBAC considered the assumption that treatment with lumacaftor/ivacaftor or tezacaftor/ivacaftor provided a relative rate of decline in $ppFEV_1$ of 42% compared to

BSC was sustained in the long term has not been adequately substantiated, based on the data provided by the sponsor to date.

5.13 The PBAC advised that in accordance with the MAP the sponsor should provide evidence and data that there is a sustained reduction in the rate of decline in $ppFEV_1$ for up to four years (excluding any initial improvement in $ppFEV_1$). The PBAC considered that, at a minimum, the following information pertaining to the PASS 108 study should be provided in the resubmission:

- The ROD and rROD for the Year 3 Orkambi Disease Progression Cohort (n=2,287) and the Comparator Disease Progression Cohort (n=3,527) for the time periods (i) 0 to 6 months; (ii) 6 months to 2 years and (iii) 2 years to the maximum follow up available. The PBAC acknowledged the sponsor's statement that it was problematic to determine the exact magnitude of the acute $ppFEV_1$ change in the first month of treatment using registry data (paragraph 4.2); however, this analysis will provide an indication of the interval-specific time trends in $ppFEV_1$.
- Results for ROD and rROD should be presented for patients who started on lumacaftor/ivacaftor and then switched to tezacaftor/ivacaftor and to any alternative CFTR modulators. For completeness, a similar analysis should be provided for patients who discontinued lumacaftor/ivacaftor but did not switch to other CFTR modulators.
- A comparison of baseline characteristics for patients in the Year 1 Orkambi Disease Progression Cohort (n=5,508) who are excluded from the Year 3 Orkambi Disease Progression Cohort because they (i) switched to alternative CFTR modulators or (ii) were lost to follow up or discontinued lumacaftor/ivacaftor for reasons other than switching.
- Any updated PASS 108 analyses. The PBAC noted interim analysis 4 and the final report were planned for 2020 and 2021, respectively. The PBAC noted elexacaftor/ivacaftor/tezacaftor became available in the US in October 2019 but considered it unlikely all patients would immediately switch treatment and data with further follow up for lumacaftor/ivacaftor should be available. The analyses above should also be provided using the updated data.

5.14 The PBAC advised a resubmission should be provided for consideration at the December 2021 PBAC meeting, and that this would require the submission to be lodged by 15 September.

5.15 The PBAC noted that the evidence provided did not meet the requirements of the MAP and did not enable it to advise the Minister as to the point estimate for the rate of decline in lung function. The PBAC considered that the data provided did not justify the application of the subsidisation caps identified as Option 1 in the MAP.

Outcome:

Advice provided

6 Corrigendum

The following changes were made to this document:

Change made	Date of revision	Corrigendum table published in PSD?*
Para 4.3 and para 4.19 - Amended "2014" to "2015"	25 October 2021	No

*The initial PSD will contain all ratified corrections that were identified during the Public Summary Document (PSD) process. Therefore, a corrigendum table will be published in the PSD on the PBS website if corrections are made after the initial PSD is published.

Addendum to the July 2021 PBAC PSD:

4.01 Lumacaftor and ivacaftor, Tablet containing lumacaftor 100 mg with ivacaftor 125 mg, Orkambi®, Vertex Pharmaceuticals (Australia) Pty Ltd

7 Background

7.1 As per paragraph 5.13 (above), at the July 2021 meeting the PBAC requested further analyses from the US CFFPR to clarify whether the rROD in $ppFEV_1$ was at least 42% compared to BSC for a period of up to four years. The PBAC requested interval specific analyses: (i) 0 to 6 months; (ii) 6 months to 2 years and (iii) 2 years to the maximum follow up available. The reason for requesting the time interval 0 to 6 months was that the economic model assumed an absolute increase in $ppFEV_1$ of 3.0% (for children aged 2-11 years) or 2.8% (for children aged ≥12 years) in the first 24 weeks and then assumed a rROD of 42% after 24 weeks. The PBAC also requested analyses which did not exclude patients who switched to alternative CFTR modulators.

7.2 The PBAC request from the July 2021 meeting for clarifying analyses and how the resubmission addressed them are summarised in Table 11, below.

Table 11: PBAC request for clarifying analyses and how these were addressed in the resubmission

Issues identified by the PBAC at the July 2021 PBAC meeting	PBAC request for clarifying analyses (July 2021)	How the resubmission addressed the issue (November 2021 resubmission)
rROD may attenuate over time.	Provide interval-specific analyses for 6 months to 2 years, 2 years and beyond. Provide interim analysis 4 (IA4) from PASS 108.	The resubmission provided interval-specific analyses for 12 months to 2 years and 2+ years, with a maximum of about 5 years' follow-up (and allowing for censoring). The submission provided IA4 from PASS 108, which had 5 years' follow-up[1].
The complete-case analyses (as pre-specified in PASS 108) may be biased due to exclusion of patients who had a sub-optimal response or who had treatment limiting toxicities.	Provide analyses for patients who started on LUM/IVA and then switched to any alternative CFTR modulators, and for patients who discontinued LUM/IVA but did not switch to other CFTR modulators.	The new analyses included patients treated with LUM/IVA (irrespective of whether they transitioned to TEZ/IVA) and allowed for censoring. (However, 11% of patients in the LUM/IVA group appeared to be lost to follow-up in that they were censored because there was no record of continuing use of LUM/IVA or TEZ/IVA in the US CFFPR.)

The economic model assumed an absolute increase in ppFEV1 of +3.0% (2-11 years) /+2.8% (12+ years) in the first 24 weeks (and assumed rROD versus BSC of 42% after 24 weeks).	Provide an estimate of the change in $ppFEV_1$ for the time interval 0 to 6 months (i.e., about 24 weeks)	In order to exclude the acute improvement that occurs soon after commencement of LUM/IVA the resubmission provided analyses in which the rate of decline for LUM/IVA patients was calculated starting from their 'Post-Index measure', where the post-Index measurement was defined as the first available $ppFEV_1$ measure occurring at least 22 days after the Index date. The resubmission provided rROD for the time period 0 to 12 months, which showed a small decline in $ppFEV_1$ in the LUM/IVA cohort. However, this analysis did not address the assumption of the absolute increase in $ppFEV_1$ of +2.8%/+3.0% in the first 24 weeks as per the original LUM/IVA economic model.

1. The submission advised that any further longitudinal surveillance of LUM/IVA and TEZ/IVA in the US is now significantly impacted due to the uptake of ELX/TEZ/IVA (commercial availability since Oct 2019) i.e., the majority of eligible F508del/F508del patients ≥6 years of age being treated with a CFTR-modulator in the US are now receiving ELX/TEZ/IVA rather than LUM/IVA and TEZ/IVA.

7.3 The analyses included in the resubmission are listed below (also see Table 11, above):

- Planned fourth annual interim analysis (IA4) from PASS 108, US CFFPR
    - Follow-up for five years (2014 to 2019, complete-case analysis: $ppFEV_1$ measurements in 2014 and 2019)
- Modified overall and interval-specific analyses allowing for censoring, US CFFPR
    - Allowing for censoring, with possible follow-up to nearly five years
    - Exclusion of the acute increase in $ppFEV_1$ by excluding measurements within the initial 21 days
    - Provision of interval specific rRODs: 0 to 12 months, 12 months to 2 years, 2+ years
    - A comparison of baseline patient characteristics for included and excluded patients in the LUM/IVA cohort for IA3
- Updated analyses from the Australian CF Data Registry.

8 Summary of November 2021 resubmission

8.1 A comparison of the design of the planned IA4 and the modified analyses allowing for censoring (both from US CFFPR) is presented in Table 12.

Table 12: Comparison of IA4 and modified analyses allowing for censoring, US CFFPR

	IA4 (complete case analysis)	**Modified analyses (allowing for censoring[1])**
Age	6+ years	6+ years
Sample size F/F (LUM/IVA) F/MF (control)	 843[3] 1,692	 5,268 4,920
Length of follow-up	mean=3.9 years maximum=5 years	Mean=38.26 months follow-up 4+ years LUM/IVA: 1125/5268 21.4% Control: 1555/4920 31.6%
Baseline year	2014	2014 to 2017[2]
Final follow-up year	2019	2019
$ppFEV_1$ measurements	The best available $ppFEV_1$ measurement from four quarters from the baseline year (2014) and the follow-up year (2019)	Patients included in the analysis were required to have 3+ post-index visit $ppFEV_1$ measurements in 3 different quarters to 30-Sep-2019
Exclusion of $ppFEV_1$ measurements within 21 days of starting LUM/IVA	no	yes

1. Censor events were defined as follows:
   - Indication of death, transplantation, or pregnancy between their Index date and either the 30 September 2019 or another censor event date (whichever is earlier), inclusive. This event date = first date of this event (note: for pregnancy, event date = 1.1 of pregnancy event year).
   - Indication of any interventional trial involvement between 1 June 2018 and either the 30 September 2019 or another censor event date (whichever is earlier), inclusive. This event date = 1.1 of trial event year.
   - Indication of ELX/TEZ/IVA use between their Index date and either the 30 September 2019 or another censor event date (whichever is earlier), inclusive. This event date = first date of this event.
   - [for LUM/IVA group only] Indication of having had two consecutive encounters without either LUM/IVA or TEZ/IVA treatment at any time between their Index date and either the 30 September or another censor event date (whichever is earlier), inclusive. This event date = first date indicating treatment cessation.
2. For the LUM/IVA cohort, individual baseline dates were after 1 July 2014 (allowable through to Sept 2017). For the control cohort, to account for any possible temporal effect, the baseline period was randomly allocated from within a distribution of 2015 to 2017 quarters to align with the distribution of the LUM/IVA-treated group's baseline period.
3. The initial cohort sizes were: LUM/IVA: 5508, control: 3990. When the pre-specified exclusions were applied the cohort sizes were LUM/IVA: 969, control: 1989. The exclusions were: death, transplant, loss to follow-up, commenced other CFTR modulator, no record of continuing LUM/IVA (LUM/IVA group only) and mutation change (control group only). The final cohort sizes in the above table are those with non-missing $ppFEV_1$ values.

8.2 The results from IA4 and the modified analysis are shown in Table 13.

Table 13: ROD and rROD, IA4 and modified analyses[1] allowing for censoring, US CFFPR, 6+ years

	IA4 (complete case analysis)	Modified analyses (allowing for censoring)
Mean baseline $ppFEV_1$ (2014)		
F/F (LUM/IVA)	84.5	75.2
F/MF (control)	82.6	74.9
Mean follow-up $ppFEV_1$ (2019)		
F/F (LUM/IVA)	81.1	72[2]
F/MF (control)	77.1	68[2]
Annualised ROD[3]		
F/F (LUM/IVA)	-	-1.15%/year
F/MF (control)	-	-1.92%/year
Mean change in $ppFEV_1$ over 5 yrs		
F/F (LUM/IVA)	-4.0%	-
F/MF (control)	-6.6%	-
rROD[4]	-39.4%	-40.1%

1. The submission stated that all programming and analyses were conducted by the USCFFPR in accordance with their ethics and governance processes.
2. Estimated by applying the annualised ROD to baseline $ppFEV_1$.
3. For each individual patient, the ROD was the slope derived from a simple linear regression (to provide the line of best fit, expressed as change in $ppFEV_1$ per year). The line was fitted to all their available $ppFEV_1$ measurements throughout their follow-up period, as previously defined (ie., for the LUM/IVA group from their Post-Index $ppFEV_1$; for the Control group from their Baseline $ppFEV_1$). The weighted mean and standard deviation for the total period $ppFEV_1$ ROD for the LUM/IVA-treated group and the Control group was then calculated, by weighting each patient's result by their time from the first to last $ppFEV_1$ measurements included in the analyses, in order to weight by the extent of data they contribute.
4. The submission also provided results with censored patients excluded (any initial $ppFEV_1$ measurements excluded in line with the main analyses): annualised ROD—LUM/IVA vs control: -0.88%/year vs -1.59%/year; rROD: -44.7%.

8.3 For the modified analyses, allowing for censoring, the submission provided interval-specific analyses. The results are difficult to interpret because different groups of patients were included in each sub-interval (see footnotes to Table 14).

Table 14: Annualised ROD and rROD for specified time intervals, modified analyses allowing for censoring, US CFFPR, 6+ years

	N[1]	Annualised ROD	rROD[2]
0 to 12 months	4,589	-0.48%	-75.0%
12 months to 2 years	4,300	-1.04%	-45.8%
2+ years	3,476	-0.77%	-59.9%
Total	5,268	-1.15%	-40.1%

1. To have been included in a specific sub-period ROD analyses, a patient must have had at least 3 $ppFEV_1$ measurements in that period – therefore the n for some sub-periods is lower than others, and the same patients are not necessarily included in all sub-periods, although the patient might not have been censored. For this same reason, analyses of sub-periods shorter than 1 year in duration were not viable.
2. To calculate the rROD, the control group annualised ROD was taken to be the same across all time intervals at -1.92% (see Table 13).

8.4 A comparison of the results from Konstan 2017, which was for patients aged 12 years and older, and the corresponding results (12+ years) from the modified analyses of the US CFFPR allowing for censoring are shown in Table 15.

Table 15: Comparison of ROD and rROD, Konstan 2017 and modified analyses of the US CFFPR allowing for censoring, 12+ years

	Annualised ROD LUM/IVA	Annualised ROD control	rROD
Konstan 2017	-1.33%	-2.29%	-41.9
US CFFPR	-1.29%	-2.19%	-41.1%

8.5 The updated results of Australian registry-based analyses commissioned from Monash University (including various sensitivity analyses) showed an increase in $ppFEV_1$ over approximately 29-30 months of follow-up. Consequently, the rROD was >100%.

9 PBAC advice

9.1 The PBAC noted the additional data and updated analyses included in the resubmission and advised that the updated point estimates for rROD (6+ years) provided (for up to 5 years' of follow-up) were less than 42%. Specifically, for the new analysis that accounted for censoring, the point estimate of the rROD was 40.1%. While the submission asserted that the point estimate of 42% had been validated within acceptable margins of error, the PBAC noted that the updated US CFFPR analysis and the pre-specified US CFFPR (PASS108 IA4) analysis did not substantiate an assumption of a rROD in $ppFEV_1$ for LUM/IVA compared to BSC of at least 42%. Therefore, the PBAC's advice to the Minister was that of the available estimates, and notwithstanding residual concerns about bias in the presented analyses, the most reasonable point estimate value for the rate of decline in lung function for LUM/IVA, for the purposes of the Managed Access Program, is 40%.

9.2 The PBAC noted that the length of follow-up in the updated analyses from the Australian registry was about 29-30 months. This limited the use of the updated Australian analyses in substantiating the assumptions about the rate of decline in lung function in the LUM/IVA economic model for a time period longer than the Konstan 2017 study.

9.3 The PBAC noted results from PASS108 IA4 were provided, including the change in $ppFEV_1$ for patients with measurements in both 2014 and 2019. The baseline measurement was the average of the best available measurements for all quarters for the year before commercial availability of LUM/IVA in the US (2014). Subsequent $ppFEV_1$ measurements were the average of the best available measurements for all quarters for the analysis year. The PBAC noted the 5 year (2019) analysis for the cohort aged ≥6 years included 969 patients treated with LUM/IVA (17.6% of the initial cohort of 5,508 patients aged ≥6 years) and 1,989 control (F/MF) patients (49.8% of the initial cohort of 3,990 patients aged ≥6 years). In the LUM/IVA cohort, 2,711 patients (49.2%) were excluded due to commencing a different CFTR modulator and 1,399 patients (25.4%) were excluded due to no record of continuing LUM/IVA use. In the control cohort 1,398 patients (35.0%) were excluded due to commencing a CFTR modulator.

In the LUM/IVA cohort the decline in $ppFEV_1$ from the pre-study (2014) baseline was 3.99%. The corresponding decline in the control cohort was 6.60%, a difference of 2.61% and a rROD of 39%. The PBAC recalled the limitations of these analyses as outlined in paragraph 5.6 above, including the exchangeability of LUM/IVA and control cohorts and the exclusion of a high proportion of patients from the LUM/IVA cohort.

9.4 The PBAC noted the revised US CFFPR analyses included in the resubmission which excluded the initial improvement in $ppFEV_1$, included patients moving to TEZ/IVA and included patient data up to the time of discontinuation using censoring. The PBAC considered the approach used to exclude the initial improvement in $ppFEV_1$ lacked granularity due to infrequent, irregular and variable FEV_1 measurements in the US CFFPR versus the regular protocol defined measurements in Konstan 2017. The mean follow-up for this analysis was about 3 years (i.e., 36 months to 39 months, depending on the cohort). The PBAC noted this analysis included 5,268 patients in the LUM/IVA cohort and 4,920 patients in the control cohort (cohorts aged ≥6 years). The annualised decline in $ppFEV_1$ was 1.15 for the LUM/IVA cohort and 1.92 for the control cohort with a rROD of 40.1%. The PBAC acknowledged that this estimate was subject to statistical variation and that some of the limitations noted for the IA4 analysis remained, but considered this to be the most reasonable point estimate of the longer-term rROD in $ppFEV_1$ for LUM/IVA versus BSC for the purpose of informing the Managed Access Program.

9.5 The PBAC noted reducing the rROD in the economic model from 42% to 40% increased the incremental cost-effectiveness ratio (ICER) from \$155,000 to < \$255,000/QALY (paragraph 4.37) to \$155,000 to < \$255,000/QALY.

9.6 The PBAC noted that the resubmission did not provide an estimate of the change in $ppFEV_1$ for 0 to 6 months based on the US CFFPR data. This interval (0 to 6 months) is important because the LUM/IVA economic model assumed an initial absolute increase in $ppFEV_1$ of 3.0% (for children aged 2-11 years) or 2.8% (for children aged ≥12 years) in the first 24 weeks of treatment. The resubmission did provided analyses for the time period 0 to 12 months, which showed an overall decline in $ppFEV_1$ in the LUM/IVA cohort of 0.48% (Table 14). The PBAC noted the submission's comments on the variability in the frequency of $ppFEV_1$ measurements in population-based registries (e.g. US CFFPR). The submission stated that this variability means that it is not possible to accurately measure the acute increase in $ppFEV_1$ that occurs within weeks of CFTR modulator initiation using registry data. The submission further stated that analyses of sub-periods shorter than 1 year are not viable due to the requirement for at least 3 $ppFEV_1$ measurements within a period to reliably calculate rROD and the infrequency of these measures for most individual patients in the US CFFPR dataset. The PBAC accepted that the initial increase in $ppFEV_1$ could not be estimated with the available registry data.

9.7 However, the PBAC recalled that the economic model used to establish the accepted ICER for the listing of LUM/IVA on the PBS estimated that after 5 years of treatment the absolute difference in the $ppFEV_1$ would be approximately 7.3% (based on an

increase of 2.8% in the initial 0.5 year and an approximate 1% difference in the rate of decline per year [1.33% for LUM/IVA vs 2.29% for BSC, paragraph 5.2] for 4.5 years i.e. 2.8% + 4.5*(~1%) = ~7.3%). Based on the data from the US CFFPR, the absolute difference in $ppFEV_1$ after 5 years was approximately 4 percentage points for both the complete case analysis (PASS 108 IA4: 81.1% vs 77.1%) and the analysis that allowed censoring (72% vs 68%); see Table 13. These are indicative differences not adjusted for baseline $ppFEV_1$. As another estimate, based on the available analyses, the absolute difference in average $ppFEV_1$ after 5 years of treatment was 2.6 percentage points (-4.0% – (-6.6%), Table 13). The PBAC noted that ICERs depend on the absolute treatment effect, and these absolute differences, although indicative, were substantially less than the absolute difference at 5 years estimated in the previously accepted model (~7%) and therefore the true ICER would be higher than previously estimated. The PBAC noted that modelling a 4.5% absolute difference in $ppFEV_1$ at 5 years (by removing the initial increase) increased the ICER to $155,000 to < $255,000/QALY compared with $155,000 to < $255,000/QALY (for the analysis assuming a rROD of 40%, paragraph 9.5).

9.8 While the requirements of the MAP are a matter for the Department, the PBAC considered that it could and should comment on issues relating to the cost-effectiveness of LUM/IVA, including the absolute difference in $ppFEV_1$ estimated by the model at 5 years, regardless of whether or not it was specified in the MAP. Taking into account the above, the PBAC considered that the true ICER for LUM/IVA is likely to be greater than that estimated and deemed high but acceptable at the time of listing (approximately $155,000 to < $255,000/QALY), and therefore LUM/IVA is not cost-effective. The PBAC further noted that the cost of LUM/IVA was a key driver in the economic model and that reductions in its price to account for potential generic competition, as previously claimed by the sponsor, are highly unlikely to be realised, in part due to future patients being treated with alternative newer therapies. The submission for the PBS listing of ELX/TEZ/IVA (considered at the same meeting) was an example of a next-generation therapy becoming available, with expectations of dominating the market once listed.

Outcome:
Advice provided

10 Context for Decision

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

11 Sponsor's Comment

The purpose of this review was to assess the long-term relative rate of decline in lung function of Orkambi® (lumacaftor/ivacaftor) as per the Managed Access Program (MAP) agreed at the time of PBS listing. We note that the PBAC has made comments beyond that required of the MAP, without adequate data or methodology supporting such conclusions.

Vertex was not given any opportunity to submit appropriate data and analyses to address these additional points and does not accept that it was appropriate for the PBAC to draw these conclusions on the basis of the data available to them. As a minimum, the PBAC ought to have given a clear disclaimer about the limitations of this analysis. As a result, Vertex disagrees with the PBAC's conclusion about the cost effectiveness of Orkambi which it believes is based on a flawed analysis of available data.

The long-term benefit of CFTR modulators is well proven as evidenced by independent and Vertex clinical trial data and the support from more than 30 other countries where patients have ongoing access to them.