An addendum has been included at the end of these minutes.

5.13 VANZACAFTOR WITH TEZACAFTOR AND WITH DEUTIVACAFTOR

Tablet containing 4 mg vanzacaftor with 20 mg tezacaftor and with 50 mg deutivacaftor

Tablet containing 10 mg vanzacaftor with 50 mg tezacaftor and with 125 mg deutivacaftor

Alyftrek®

VERTEX PHARMACEUTICALS PTY LTD

1 Purpose of submission

1.1 This Category 2 submission requested a Section 100, Highly Specialised Drugs listing of vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one mutation in the cystic fibrosis transmembrane regulator (CFTR) gene that is responsive to VNZ/TEZ/D-IVA potentiation based on clinical and/or *in vitro* assay data.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). The key components of the clinical claim addressed in the submission are presented in Table 1.

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

Component	Description
Population	People with CF aged 6 years and older with at least one mutation in the CFTR gene that is responsive to VNZ/TEZ/D-IVA based on *in vitro* assay or clinical data
Intervention	VNZ/TEZ/D-IVA
Comparator	• ELX/TEZ/IVA plus BSC in people with at least one ELX/TEZ/IVA and VNZ/TEZ/D-IVA-responsive CFTR mutation • BSC in people with at least one VNZ/TEZ/D-IVA-responsive CFTR mutation that is not responsive to ELX/TEZ/IVA
Outcomes	• Absolute change from baseline in $ppFEV_1$ • Absolute change from baseline in SwCl • Proportion achieving SwCl threshold levels • Measures of pulmonary exacerbations • Measures of nutritional status (weight, weight z-score, BMI, BMI z-score) • Absolute change from baseline in CFQ-R score
Clinical claim	For people with CF aged 6 years and older: • VNZ/TEZ/D-IVA plus BSC is non-inferior on lung function as measured by $ppFEV_1$ and superior in improving CFTR function, as measured by change in SwCl levels, compared with ELX/TEZ/IVA plus BSC in people with at least one CFTR mutation responsive to both ELX/TEZ/IVA and VNZ/TEZ/D-IVA; • VNZ/TEZ/D-IVA plus BSC is superior in terms of overall efficacy compared with BSC alone in people with at least one VNZ/TEZ/D-IVA-responsive CFTR mutation that is not responsive to ELX/TEZ/IVA; • VNZ/TEZ/D-IVA plus BSC is comparable in terms of safety compared with ELX/TEZ/IVA plus BSC or BSC alone in people with at least one CFTR mutation responsive to ELX/TEZ/IVA and/or VNZ/TEZ/D-IVA.

Source: Table 1.2 p29 of the submission.
BMI = body mass index; BSC = best supportive care; CFQ-R = Cystic Fibrosis Questionnaire – Revised Respiratory Domain; CFTR = cystic fibrosis transmembrane regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; SwCl = sweat chloride; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: not registered. VNZ/TEZ/D-IVA was submitted for registration on the Australian Register of Therapeutic Goods (ARTG) on 28 June 2024 for: "…. the treatment of CF in people aged 6 years and older who have at least one F508del mutation or another responsive mutation in the CFTR gene". Orphan Drug Designation was granted by the Therapeutic Goods Administration (TGA) on 28 May 2024. The TGA Clinical Evaluation Report (CER) was available at the time of evaluation. The Clinical Evaluator had no objection to the proposed therapeutic indication.

2.2 VNZ/TEZ/D-IVA was approved by the United States Food and Drug Administration (FDA) in December 2024 for the treatment of CF in patients aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the CFTR gene. On 25 April 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion,

recommending the granting of a marketing authorisation for the treatment of CF in people aged 6 years and older who have at least one non-class I mutation in the CFTR gene.[1]

2.3 On 7 March 2025 the Medicines and Healthcare products Regulatory Agency (MHRA) approved VNZ/TEZ/D-IVA to treat CF in people aged six years and older who have specific mutations in the CFTR gene that have been shown in trials to respond to the therapy.[2]

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg film-coated tablets	Public Published: $21,375.00 Effective: $[redacted] Private Published: $21,423.67 Effective: $[redacted]	1	84	5	Alyftrek®, Vertex Pharmaceuticals
Vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg film-coated tablets	Public Published: $21,375.00 Effective: $[redacted] Private Published: $21,423.67 Effective: $[redacted]	1	56	5	Alyftrek®, Vertex Pharmaceuticals

Private prices were calculated by the evaluation using a $40.00 administration, handling and infrastructure fee and $8.67 preparation fee.
Source: Table 1.12 of the submission
Qty = quantity; Rpts = repeats.

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)
Category / Program: Section 100 – Highly Specialised Drugs Program [Public and Private Hospitals]
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required – non-immediate/delayed assessment by Services Australia
Condition: Cystic fibrosis
Indication: Cystic fibrosis
Treatment Phase: Initial treatment
Administration advice: No increase in the maximum quantity or number of units may be authorised.
Administration advice: No increase in the maximum number of repeats may be authorised
Administration advice:

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/alyftrek
[2] https://www.gov.uk/government/news/triple-combination-medicine-deutivacaftortezacaftorvanzacaftor-approved-for-cystic-fibrosis

Special Pricing Arrangements apply.
Administrative Advice: For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor and vanzacaftor/tezacaftor/deutivacaftor.
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Treatment criteria:
Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
AND
Treatment criteria:
Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
AND
Clinical criteria:
Patient must have at least one mutation in the CFTR gene that is responsive to vanzacaftor/tezacaftor/deutivacaftor potentiation based on clinical and/or in vitro assay data
AND
Clinical criteria:
The treatment must be given concomitantly with standard therapy for this condition
AND
Clinical Criteria:
Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug
Population criteria:
Patient must be at least 6 years of age
Prescribing instructions: For the purposes of this restriction, the list of mutations considered to be responsive to vanzacaftor/tezacaftor/deutivacaftor is defined in the TGA approved Product Information
Prescribing instructions: This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.
Prescribing instructions: The authority application must be in writing and must include: (1) a completed authority prescription; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and

(3) details of the pathology report substantiating the specific mutation considered to be responsive to vanzacaftor/tezacaftor/deutivacaftor as listed in the TGA approved PI - quote each of the: (i) the specific mutation listed in the TGA approved PI (ii) name of the pathology report provider, (iii) date of pathology report, (iv) unique identifying number/code that links the pathology result to the individual patient; and (4) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.

Treatment Phase: Continuing treatment
Treatment criteria:
Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
AND
Treatment criteria:
Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be given concomitantly with standard therapy for this condition.
AND
Population criteria:
Patient must be at least 6 years of age
Prescribing instructions: This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.
The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed Cystic Fibrosis Authority Application Supporting Information Form; and (3) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.

3.1 The submission proposed an initial and continuing restriction for patients aged 6 years or older. The submission stated there were <500 patients (grandfathered patients) currently enrolled in VNZ/TEZ/D-IVA clinical trials in Australia, but a restriction for grandfathered patients was not provided in the submission.

3.2 The requested published price is higher than the ELX/TEZ/IVA published price. The submission requested the published price of ELX/TEZ/IVA as of 1 January 2025 (i.e. the price prior to flow on price reductions) be used for the published price of VNZ/TEZ/D-IVA.

3.3 The Secretariat noted that flow-on changes will be required for the following administrative advice that lists the current PBS listed CFTR therapies to include VNZ/TEZ/D-IVA: 'For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor and vanzacaftor/tezacaftor/ deutivacaftor.'

3.4 The Secretariat noted inclusion of the following wording in the relevant Prescribing Instruction may be appropriate, consistent with the ELX/TEZ/IVA listing, depending on the final approved Product Information: "Mutations that are not listed in the TGA approved PI but considered to be responsive to vanzacaftor/tezacaftor/ deutivacaftor can be accepted with a confirmation that these patients do not harbour two Class I mutations".

4 Population and disease

4.1 CF is a rare, genetic, systemic disease caused by a mutation in the CFTR gene that encodes epithelial chloride transport, the CFTR protein. CF is associated with progressive loss of lung function, pancreatic insufficiency, malnutrition, low body mass index (BMI), frequent pulmonary exacerbations, and premature death.

4.2 Patients with CF inherit two mutated copies of the CFTR gene, one from each parent. The most common mutation in Australia is F508del which is present in at least one allele in approximately 90% of CF patients. Genotyping of the second allele characterises the patient's mutation. Approximately 50% of CF patients are homozygous for the F508del mutation (F/F) in Australia. Other mutations can be characterised as F/Gating (F/G), F/minimal function (F/MF), F/residual function (F/RF), F/other or non-F508del. The Australian Cystic Fibrosis Data Registry (ACFDR) Annual Report 2023 estimated that ~9% have a non-F508del mutation and for ~1% the mutation is not known.[3]

4.3 The PBAC has seen numerous applications for the listing of CFTR modulators for use in the treatment of patients with CF. This submission is specific to the use of VNZ/TEZ/D-IVA in patients with CF aged 6 years and older with a mutation that is responsive to VNZ/TEZ/D-IVA.

4.4 The submission stated that VNZ/TEZ/D-IVA is a new treatment option for the small number of patients with mutations that are not responsive to ELX/TEZ/IVA but are responsive to VNZ/TEZ/D-IVA. According to bespoke ACFDR data provided in the submission, in 2023 the rarity of the non-F508del, non-ELX/TEZ/IVA responsive CFTR mutations, represents approximately ~9 people with CF in Australia. Additionally, VNZ/TEZ/D-IVA is a treatment alternative for patients who have discontinued treatment with ELX/TEZ/IVA for a variety of reasons. The ACFDR Report 2023 estimated that as of 31 December 2023, there were 189 patients who discontinued ELX/TEZ/IVA.

5 Comparator

5.1 The submission nominated two comparators:

- ELX/TEZ/IVA plus BSC for patients with CF and a mutation that is responsive to both ELX/TEZ/IVA and VNZ/TEZ/D-IVA. ELX/TEZ/IVA received a positive recommendation by the PBAC for the treatment of patients who have at least one mutation in the CFTR gene that is responsive to ELX/TEZ/IVA (paragraph 7.1, elexacaftor/tezacaftor/ivacaftor minutes, March 2025 PBAC meeting) and was PBS listed on 1 July 2025.

[3] ACFDR Annual Report 2023

- BSC for patients with CF and a mutation that is responsive to VNZ/TEZ/D-IVA only. This was appropriate as patients with CF who have one of the 31 mutations that is responsive to VNZ/TEZ/D-IVA only are currently not eligible for any PBS-listed CFTR modulator. BSC includes daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents, anti-inflammatories, bronchodilators, and daily physiotherapy.

5.2 Some patients in the requested population are eligible for IVA, lumacaftor/ivacaftor (LUM/IVA) and/or tezacaftor/ivacaftor (TEZ/IVA) in addition to ELX/TEZ/IVA. The ACFDR estimated that as of 31 December 2023, there were 142 patients using IVA, 308 patients using LUM/IVA, and 613 patients using TEZ/IVA.[4] It is unclear if these patients are eligible for ELX/TEZ/IVA and if so, if they would switch to VNZ/TEZ/D-IVA given they did not switch to ELX/TEZ/IVA. The pre-subcommittee response (PSCR) stated that it is likely the remaining patients on IVA and TEZ/IVA will switch to ELX/TEZ/IVA once the March 2025 recommendation is implemented, prior to the availability of VNZ/TEZ/D-IVA. The PSCR noted that in patients eligible for more than one CFTR modulator, ELX/TEZ/IVA is accepted as the superior treatment option over IVA, LUM/IVA and TEZ/IVA, as evidenced by its high uptake rates once PBS listed and is therefore appropriately nominated as the single comparator for VNZ/TEZ/D-IVA.

5.3 The currently available CFTR modulators that are PBS listed for patients aged 6 years and older, are summarised in Table 2. The ESC noted TEZ/IVA, LUM/IVA and IVA are available for some populations, but considered that, on balance, ELX/TEZ/IVA was the appropriate comparator in the ELX/TEZ/IVA responsive population.

Table 2: Currently available CFTR modulators that are PBS listed for patients over 6 years of age

	F508del (~90% population)				Non-F508del (<10% population)*		
	F/F	F/other			ELX/TEZ/IVA responsive	TEZ/IVA responsive	IVA responsive
		IVA responsive	Not-IVA responsive	TEZ/IVA responsive			
6 to 12 years	LUM/IVA ELX/TEZ/IVA	IVA ELX/TEZ/IVA	ELX/TEZ/IVA	ELX/TEZ/IVA	ELX/TEZ/IVA	ELX/TEZ/IVA	IVA ELX/TEZ/IVA
12+ years	LUM/IVA TEZ/IVA ELX/TEZ/IVA	ELX/TEZ/IVA IVA	ELX/TEZ/IVA	TEZ/IVA ELX/TEZ/IVA	ELX/TEZ/IVA	TEZ/IVA ELX/TEZ/IVA	IVA ELX/TEZ/IVA

Source: prepared by the evaluation for the Commentary using pbs.gov.au
* ELX/TEZ/IVA for non-F508del mutations that are responsive to ELX/TEZ/IVA was PBS listed on 1 July 2025
CFTR = cystic fibrosis transmembrane regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = homozygous for the F508del mutation; F/other = heterozygous for the F508del mutation; IVA = ivacaftor; LUM/IVA = lumacaftor/ivacaftor; mths = months; PBS = Pharmaceutical Benefits Scheme; TEZ/IVA = tezacaftor/ivacaftor.

[4] ACFDR Annual Report 2023

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals who have taken the medicine (2), individuals who would like to take this medicine (25) and other interested individuals (110) and organisations (3) via the Consumer Comments facility on the PBS website. Comments from individuals who have taken VNZ/TEZ/D-IVA noted improvements in lung function tests, sodium chloride markers, weight, energy, sleep and mental health. Individuals who would like to take the medicine described the high impact of CF and noted VNZ/TEZ/D-IVA can help preserve lung function, reduce hospitalisations and reduce the treatment load. Comments noted VNZ/TEZ/D-IVA has shown promising health outcomes for cystic fibrosis sufferers around the world and offered hope beyond what ELX/TEZ/IVA can deliver. Many comments noted that the once daily dosage of VNZ/TEZ/D-IVA will reduce the medication burden for patients with CF and may improve compliance. In particular, comments noted the benefits of once daily dosing in terms of needing to take VNZ/TEZ/D-IVA and ELX/TEZ/IVA with a high fat meal. Comments noted the high financial cost of VNZ/TEZ/D-IVA, if not listed on the PBS.

6.3 Input supporting the listing of VNZ/TEZ/D-IVA was received from Cystic Fibrosis Australia, Cystic Fibrosis Queensland and CF Together. Cystic Fibrosis Australia and Cystic Fibrosis Queensland noted the importance of timely and equitable access to VNZ/TEZ/D-IVA, particularly for patients that may have experienced intolerance or limited outcomes with other therapies. CF Together provided a number of narratives from patients who have experienced side effects while taking ELX/TEZ/IVA, patients who benefitted from ELX/TEZ/IVA but are still unwell and need an alternative treatment and those who would benefit from a once daily treatment option.

Clinical studies

6.4 The submission was based on:

- Two head-to-head studies comparing VNZ/TEZ/D-IVA to ELX/TEZ/IVA in patients aged 12 years and older (Study 102 and Study 103);
- One single arm, 2-part study of VNZ/TEZ/D-IVA in patients aged 6 to 11 years (Study 105). Part 1 (Cohort A1) consisted of 17 patients and a treatment period of 4 weeks. Part 2 (Cohort B1) consisted of 78 patients and a treatment period of 24 weeks. The evaluation focused on Cohort B1;and
- One randomised, 2-part, 4-week study (Study 101) which was presented as additional evidence of safety and efficacy. Part 1 investigated 3 varying doses of VNZ (5 mg, 10 mg, or 20 mg) + TEZ/D-IVA versus placebo in patients with the F/MF mutation. The treatment period was 4 weeks followed by an 18-day washout period. Part 2 investigated VNZ 20 mg and TEZ/D-IVA vs TEZ/IVA in patients with F/F mutation. All patients received TEZ/IVA

for a 4-week run-in period followed by 4-week treatment period and 4-week washout period. The evaluation focused on Part 1, Group 3 (VNZ 20 mg + TEZ/D-IVA) and Part 2.

Non-clinical studies

6.5 The submission presented two non-clinical studies to provide evidence of *in vitro* responsiveness of mutations to VNZ/TEZ/D-IVA. Study U015 presented *in vitro* pharmacological profiling of CFTR mutations in Fischer Rat Thyroid (FRT) cells using VNZ/TEZ/D-IVA. This study provided evidence for 128 mutations that were found to be responsive to VNZ/TEZ/D-IVA. Study U020 was a laboratory study reporting the effect of VNZ/TEZ/D-IVA on chloride transport in human bronchial epithelial (HBE) cells isolated from CF donors heterozygous and homozygous for the N1303K-CFTR mutation.

6.6 Details of the studies presented in the submission are provided in Table 3.

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Clinical studies		
Study 102 VX20-121-102 NCT05033080	A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for F508del and a Minimal Function Mutation (F/MF). Version 3.0 (19 August 2021)	Study 102 Clinical Study Protocol.
	A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for F508del and a Minimal Function Mutation (F/MF). Version 1.0 (05 April 2024)	Study 102 Clinical Study Report.
	Keating C, et al. Vanzacaftor–tezacaftor–deutivacaftor versus elexacaftor–tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials.	Lancet Respir Med 2025: https://doi.org/10.1016/2213-2600(24)00411-9
	Yonker L.M., et al. Vanzacaftor-tezacaftor-deutivacaftor versus elexacaftor-tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials	The Lancet Respiratory Medicine 2025 Vol. 13 Issue 3 Pages 256 https://dx.doi.org/10.1016/S2213-2600%2824%2900411-9
Study 103 VX20-121-103 NCT05076149	A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No F508del Mutation. Version 3.0 (19 August 2021)	Study 103 Clinical Study Protocol.
	A Phase 3, Randomized, Double-blind, Controlled Study	Study 103 Clinical Study Report.

Trial ID	Protocol title/ Publication title	Publication citation
	Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No F508del Mutation. Version 1.0 (05 April 2024)	
Study 105 VX21-121-105 NCT05422222	A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-121/Tezacaftor/Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 Years of Age. Version 4.5US (18 April 2024) A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Vanzacaftor/Tezacaftor/Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 Years of Age: Final analysis for subjects 6 through 11 years of age (Cohorts A1 and B1). Version 1.0 (03 April 2024) Hoppe JE, et al. Vanzacaftor–tezacaftor–deutivacaftor for children aged 6–11 years with cystic fibrosis (RIDGELINE Trial VX21-121-105): an analysis from a single-arm, phase 3 trial.	Study 105 Clinical Study Protocol. Study 105 Interim Clinical Study Report. Lancet Respir Med 2025; https://doi.org/10.1016/S2213-2600(24)00407-7
Study 121-101 VX18-121-101 NCT03912233	A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis. Version 1.0 (29 October 2020) Uluer AZ, et al. Safety and efficacy of vanzacaftor–tezacaftor–deutivacaftor in adults with cystic fibrosis: randomised, double-blind, controlled, phase 2 trials.	Study 121-101 Clinical Study Report. Lancet Respir Med 2023;11:550-62
Non-clinical studies		
Study U015	*In vitro* Pharmacological Profiling of CFTR Mutations in FRT Cells Using Vanzacaftor (VNZ; VX-121), Tezacaftor (TEZ; VX-661), and Deutivacaftor (D-IVA; VX-561): Effects on CFTR Processing and Trafficking and Cl- Transport. 18 January 2024.	Study U015 Nonclinical Study Report.
Study U020	Effect of Vanzacaftor (VNZ; VX-121) in combination with Tezacaftor (TEZ; VX-661) and Deuterated Ivacaftor (D-IVA; VX-561) on Cl- transport in bronchial epithelial cells isolated from CF donors heterozygous and homozygous for the N1303K-CFTR mutation. 17 November 2023.	Study U020 Nonclinical Study Report.

Source: Table 2.2 p57 of the submission.
CFTR = cystic fibrosis transmembrane regulator; Cl = chloride; D-IVA = deutivacaftor; F/G = heterozygous for F508del and a gating mutation; F/MF = heterozygous for F508del and a minimal function mutation; F/RF = heterozygous for F508del and a residual function mutation; FRT = Fischer Rat Thyroid; TEZ = tezacaftor; VNZ = vanzacaftor.

6.7 The key features of the clinical studies are summarised in Table 4. Study 101 was assessed by the evaluation as having a low risk of bias; however, the study was short in duration (4-week treatment period), with a small sample size in Part 2 (n=29). Study 102 and 103 were assessed as having a low risk of bias. Study 105 was assessed as having a high risk of bias largely due to the single-arm, non-comparative design, absence of blinding, and short duration of treatment (24 weeks) which made it vulnerable to confounders and uncertainty.

6.8 All four studies specified a baseline ppFEV$_1$ value (≥ 40% and ≤ 90% of predicted normal for age, sex, and height in Study 101, 102 and 103, and ≥ 60% in Study 105). In addition, the mean age of patients in Studies 101, 102 and 103 was > 30 years, with the minimum age of 12 years (Study 102 and 103) and 18 years (Study 101). Across studies 101, 102, 103 and 105, the majority of patients had prior treatment with a CFTR modulator, with the majority having received ELX/TEZ/IVA (> 85% in Study 102, > 67% in Study 103, > 79% in Study 105). Patients in Study 101 Part 2 received 4 weeks of TEZ/IVA before being randomised. The median exposure to ELX/TEZ/IVA prior to enrolment in Study 102 and 103 was > 2 years and in Study 105 was > 1 year.

Table 4: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
VNZ/TEZ/D-IVA vs ELX/TEZ/IVA						
Study 102	435	R, DB, 52 wks	Low	Patients with CF aged ≥ 12 years with F/MF mutation	Primary: absolute change from baseline in ppFEV$_1$ through 24 weeks Secondary: Absolute change from baseline through Week 24 in SwCl, proportion of patients with SwCl < 60 mmol/L, proportion of patients with SwCl < 30 mmol/L, number of PEx through Week 52, absolute change from baseline through Week 52 in ppFEV$_1$, SwCl, absolute change from baseline through Week 24 in CFQ-R RD	Not used
Study 103	597	R, DB, 52 wks	Low	Patients with CF aged ≥ 12 years with F/F, F/G, F/RF or another ETI-responsive mutation	Primary: absolute change from baseline in ppFEV$_1$ through 24 weeks Secondary: Absolute change from baseline through Week 24 in SwCl, proportion of patients with SwCl < 60 mmol/L, proportion of patients with SwCl < 30 mmol/L, number of PEx through Week 52, absolute change from baseline through Week 52 in ppFEV$_1$, absolute change from baseline through Week 52 in SwCl, absolute change from baseline through Week 24 in CFQ-R RD	Not used
VNZ/TEZ/D-IVA						
Study 105	Cohort A1 n=17 Cohort B1 n=78	OL, 24 wks	High	Patients with CF aged 6 to 11 years with at least 1 TCR mutation	Primary outcome: Secondary outcome: absolute change from baseline through Week 24 in SwCl; ppFEV$_1$; BMI; BMI-for-age-z-score; weight; weight-for-age; CFQ-R RD, drug acceptability assessment, number of PEx and CF-related hospitalisations through Week 24, proportion of patients with SwCl < 60 mmol/L through Week 24, proportion of patients with SwCl < 30 through Week 24.	Not used
VNZ/TEZ/D-IVA vs TEZ/IVA						
Study 101	Part 1 n=58 Part 2 n=28	R, DB, 4 wks	Low	Patients with CF aged ≥ 18 years with F/MF mutation (Part 1) and F/F mutation (Part 2)	Primary: absolute change from baseline in ppFEV$_1$ through Day 29 Secondary: absolute change from baseline through Day 29 in SwCl, CFQ-R	Not used

Source: pp2-6 Study 101 CSR; pp2-6 Study 102 CSR; pp2-6 Study 103 CSR; pp2-6 Study 105 CSR.

BMI = body mass index; DB = double blind; CF = cystic fibrosis; CFQ-R RD = Cystic Fibrosis Revised Respiratory Domain; ETI = elexacaftor/tezacaftor/ivacaftor; F/F = homozygous for the F508del mutation; F/G = heterozygous for the F508del and a gating mutation; F/MF = heterozygous for the F508del and a minimal function mutation; F/RF = heterozygous for the F508del and residual function mutation; MC = multi-centre; NA = not applicable; OL = open label; OS = overall survival; PEx = pulmonary exacerbations; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; R = randomised; SwCl = sweat chloride; TCR = triple combination responsive; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor; wks = weeks.

Comparative effectiveness

Clinical Studies

6.9 The absolute change from baseline in $ppFEV_1$, in Study 102, 103 and 105 is presented in Table 5.

6.10 With respect to Study 102 and Study 103, the primary endpoint of non-inferiority compared to ELX/TEZ/IVA was met (in that the difference and its confidence interval excluded the submission's nominated minimal clinical important difference of 3 percentage points).

6.11 The treatment effect observed at Week 24 in Study 102 and Study 103 was maintained at Week 52. The least squares (LS) mean change in $ppFEV_1$ from baseline (after the 4-week run in period) through Week 24 or Week 52 was less than 1 percentage point for each respective arm. Given that the majority of patients had used ELX/TEZ/IVA for a median duration > 2 years, and had a median age > 30 years, it is possible that patients had some measure of irreversible lung damage and had achieved a ceiling effect.

6.12 Study 105 (in patients aged 6 to 11 years) had a LS mean change from baseline for $ppFEV_1$ of 0.0 percentage points, which is plausible as the mean baseline $ppFEV_1$ was > 99; this study may therefore provide limited information with respect to efficacy for this endpoint.

Table 5: Absolute change from baseline in $ppFEV_1$ in Study 102, Study 103 and Study 105 (FAS)

	Study 102		Study 103		Study 105 Cohort B1
	ELX/TEZ/IVA n=202	VNZ/TEZ/D-IVA n=196	ELX/TEZ/IVA n=289	VNZ/TEZ/D-IVA n=284	VNZ/TEZ/D-IVA n=78
Baseline $ppFEV_1$, mean (SD)	67.2 (14.6)	67.0 (15.3)	66.4 (14.9)	67.2 (14.6)	99.7 (15.1)
Absolute change through Week 24					
n	193	187	276	268	77
LS mean change (SE)	0.3 (0.3)	0.5 (0.3)	0.0 (0.2)	0.2 (0.3)	0.0 (1.0)
LS mean difference, 95% CI	NA	0.2 (-0.7, 1.1)	NA	0.2 (-0.5, 0.9)	NR
1-sided p value for non-inferiority	NA	**<0.0001**	NA	**<0.0001**	NR
Absolute change through Week 52					
n	196	189	277	271	NR
LS mean change (SE)	0.4 (0.3)	0.5 (0.3)	0.0 (0.2)	0.3 (0.2)	NR
95% CI of LS mean	-0.3, 1.0	-0.1, 1.1	-0.5, 0.5	-0.2, 0.8	NR
LS mean difference, 95% CI	NA	0.1 (-0.8, 1.0)	NA	0.3 (-0.4, 1.0)	NR

Source: Table 2.33 p 96; Table 2.34 p97; Table 2.46 p109; of the submission.
CI = confidence interval; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; FAS = full analysis set; LS = least squares; NA = not applicable; NR = not reported; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; SD = standard deviation; SE = standard error; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.
Bold indicates a significant result.

6.13 The absolute change from baseline through Week 24 for other secondary endpoints for Study 102, Study 103 and Study 105 is presented in

6.14 Table 6. At baseline all patients in all 3 studies were below the threshold for diagnosing CF i.e., SwCl < 60 mmol/L. At the end of the 24-week treatment period, treatment with VNZ/TEZ/D-IVA resulted in improvements in SwCl compared to ELX/TEZ/IVA as measured by the LS mean difference in Study 102 and 103. This treatment effect was maintained at Week 52. Patients in Study 105 also experienced a numerical decrease in SwCl.

6.15 In Study 102 and 103, the proportion of patients with SwCl < 60 mmol/L and < 30 mmol/L increased over time, with the exception of the ELX/TEZ/IVA arm in Study 102 in which the proportion of patients who were < 60 mmol/L and < 30 mmol/L decreased through Week 24 and Week 52. The odds ratios at each time point for both the < 60 mmol/L and the < 30 mmol/L category favoured the VNZ/TEZ/D-IVA arm and demonstrated superiority of VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA. Similarly, in Study 105, the proportion of patients with SwCl < 60 mmol/L and < 30 mmol/L increased over time. By Week 24, 95% of patients were below the threshold for diagnosing CF and more than 50% had a SwCl level that was normal.

Table 6: Summary of SwCl results in Study 102, Study 103 and Study 105 (FAS)

	Study 102		Study 103		Study 105 Cohort B1
	ELX/TEZ/IVA n=202	**VNZ/TEZ/D-IVA n=196**	**ELX/TEZ/IVA n=289**	**VNZ/TEZ/D-IVA n=284**	**VNZ/TEZ/D-IVA n=78**
Baseline SwCl (mmol/L)	54.3 (18.2)	53.6 (17.0)	42.1 (17.9)	43.4 (18.5)	40.4 (20.9)
Absolute change through Week 24					
n	194	185	276	270	77
LS mean change (SE)	0.9 (0.8)	-7.5 (0.08)	-2.3 (0.7)	-5.1 (0.7)	-8.6 (1.2)
LS mean difference, 95% CI	NA	-8.4 (-10.5, -6.3)	NA	-2.8 (-4.7, -0.9)	NR
2-sided P value for non-inferiority	NA	**<0.0001**	NA	**0.0034**	NR
Absolute change through Week 52					
n	195	188	277	271	
LS mean change (SE)	0.5 (0.7)	-7.5 (0.7)	-2.2 (0.6)	-5.0 (0.6)	NR
LS mean difference, 95% CI	NA	-8.0 (-9.9, -6.1) **p<0.0001**	NA	-2.8 (-4.6, -1.0) **p=0.0024**	NR
Baseline SwCl <60 mmol/L					
n, proportion	124 (0.62)	131 (0.68)	234 (0.83)	230 (0.82)	65 (0.84)
SwCl <60 mmol/L through Week 24[a]					
n, proportion	116 (0.59)	153 (0.81)	251 (0.89)	246 (0.90)	74 (0.95)
Odds Ratio[b] 95% CI	**NA**	**4.28 (2.57, 7.11) p <0.0001**	NA	1.10 (0.65, 1.87)	NR
SwCl <60 mmol/L through Week 52[c]					
n, proportion	115 (0.58)	151 (0.78)	250 (0.88)	247 (0.90)	NR
Odds Ratio[b]	NA	3.59 (2.39, 5.38) **p <0.0001**	NA	1.20 (0.78, 1.84)	NR
Baseline SwCl <30 mmol/L					
n, proportion	19 (0.10)	17 (0.09)	80 (0.28)	72 (0.26)	30 (0.39)
SwCl <30 mmol/L through Week 24[a]					
n, proportion	13 (0.07)	37 (0.20)	95 (0.34)	105 (0.38)	41 (0.53)
Odds Ratio[b] 95% CI	NA	**7.19 (3.54, 14.59) <0.0001**	NA	**2.06 (1.33, 3.18) p=0.0012**	NR
SwCl <30 mmol/L through Week 52[c]					
n, proportion	14 (0.07)	37 (0.19)	92 (0.32)	103 (0.37)	NR
Odds Ratio[b] 95% CI	NA	5.77 (3.33, 9.99) **<0.0001**	NA	**1.98 (1.36, 2.88) p=0.0003**	NR

Source: Table 2.35 p100; Table 2.36 p102; Table 2.37 p102; Table 2.38 p 103; Table 2.39 p103; Table 2.45 p108 of the submission; Table 14.2.2.3; Table 14.2.3.1 p430; Table 14.2.3.2 p431; Table 14.2.4.1 p434-435; Table 14.2.5.2 p439; Table 14.2.6.1 pp442-443; Table 14.2.6.2. p443; Study 102 CSR; Table 14.2.4.1 pp508-509; Table 14.2.2.3; 14.2.5.1 pp512-513; Table 14.2.6.1 pp516-517; Table 14.2.7.2.2b1 pp352-353 Study 103 CSR.
CI = confidence interval; CSR = clinical study report; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; FAS = full analysis set; GGE = generalized estimating equations; LS = least squares; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SwCl = sweat chloride; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.
Bold indicates a significant result.
[a] Average of weeks 16 and 24
[b] Estimated by GEE model; odds ratio > 1 favours VNZ/TEZ/D-IVA
[c] Average of weeks 16, 24, 36 and 52

6.16 The absolute change from baseline in CFQ-R RD score through Week 24 (Study 102, 103 and 105) and through Week 52 (Study 102 and 103) is shown in Table 7.

Table 7: Absolute change from baseline in CFQ-R RD score through Week 24 and 52, Study 102 and 103 (FAS) and through Week 24, Study 105 (FAS)

	Study 102		Study 103		Study 105[a]
	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	VNZ/TEZ/D-IVA N=78
Baseline CFQ-R RD, mean (SD)	82.9 (15.7)	85.8 (14.7)	85.6 (13.2)	85.7 (13.2)	84.8 (16.1)
Absolute change through Week 24					
LS mean change (SE)	-1.7 (1.0)	0.5 (1.1)	-1.2 (0.8)	-1.2 (0.8)	3.9 (1.2)
95% CI of LS mean	-3.8, 0.3	-1.5, 2.6	-2.7, 0.4	-2.8, 0.3	-1.5, 6.3
LS mean difference, 95% CI	NA	2.3 (-0.6, 5.2)	NA	-0.1 (-2.3, 2.1)	NR
Absolute change through Week 52					
LS mean change (SE)	-1.6 (1.0)	0.8 (1.0)	-1.0 (0.7)	-0.4 (0.7)	NR
95% CI of LS mean	-3.5, 0.3	-1.1, 2.7	-2.5, 0.4	-1.8, 1.1	NR
LS mean difference, 95% CI	NA	2.4 (-0.3, 5.1)	NA	0.7 (-1.4, 2.7)	NR

Source: Table 2.41 p105; Table 2.48 p110 of the submission.

CFQ-R RD = Cystic Fibrosis Questionnaire-revised respiratory domain; CI = confidence interval; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; FAS = full analysis set; LS = least squares; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.

[a] the CFQ-R child version was used in Study 105.

6.17 The absolute change from baseline through Week 4 in $ppFEV_1$, SwCl and CFQ-R RD for Study 101 is presented in Table 8. Treatment with VNZ/TEZ/D-IVA resulted in improved $ppFEV_1$, SwCl and CFQ-R RD compared to placebo (for patients with the F/MF mutation) and compared to TEZ/IVA (for patients with the F/F mutation). At the end of the 29-day treatment period, patients in the VNZ/TEZ/D-IVA arms experienced a reduction in SwCl, with mean SwCl falling below the range for diagnosing CF. The improvement in CFQ-R RD exceeded the submission's nominated minimum clinically important difference of 4.0 points. These results should be interpreted with caution due to the short duration and small sample size. Additionally, the control arm in Part 2 of Study 101 (TEZ/IVA) was not a nominated comparator in the submission.

Table 8: Summary of absolute change from baseline in ppFEV1, SwCl and CFQ-R RD through Day 29 in Study 101 (FAS)

	Part 1 (F/MF)		Part 2 (F/F)	
	Placebo (n=10)	**VNZ (20 mg) /TEZ/D-IVA (n = 20)**	**TEZ/IVA (n=10)**	**VNZ (20 mg) /TEZ/D-IVA (n = 18)**
$ppFEV_1$				
Baseline mean (SD)	51.8 (13.1)	60.1 (13.0)	57.4 (15.1)	60.9 (15.4)
Absolute change from baseline in $ppFEV_1$ through Day 29, LS mean (SD) (95% CI)	1.9 (3.0) (-4.1, 8.0)	9.8 (2.0) (5.7, 13.8)	-0.1 (3.0) (-6.4, 6.1)	15.9 (2.3) (11.3, 20.6)
LS mean treatment difference vs. control *P* value	NA	**7.8 (0.4, 15.2)** **p=0.038**	NA	**16.1 (8.2, 23.9)** **p=0.0003**
SwCl				
Baseline mean (SD)	101.6 (8.6)	98.5 (10.0)	92.2 (10.9)	90.5 (11.7)
Absolute change from baseline in SwCl through Day 29, LS mean (SD) 95% CI	2.3 (4.6) (-7.0, 11.6)	-49.5 (3.2) (-55.9, -43.1)	-2.6 (2.8) (-8.2, 3.1)	-45.5 (2.0) (-49.7, -41.3)
LS mean treatment difference vs. control *P* value	NA	**-45.1** **(-58.1, -32.2)** **<0.0001**	NA	**-42.9** **(-50.0, -35.8)** **<0.0001**
CFQ-R-RD				
Baseline mean (SD)	56.7 (14.8)	58.1 (18.9)	69.4 (12.4)	71.3 (17.1)
Absolute change from baseline in CFQ-R RD through Day 29, LS mean (SD) 95% CI	3.3 (6.7) (-10.1, 16.6)	29.8 (4.4) (21.0, 38.7)	-5.0 (5.8) (-16.9, 7.0)	19.4 (4.3) (10.5, 28.3)
LS mean treatment difference vs. control *P* value	NA	**26.6** **(10.5, 42.7)** **0.0017**	NA	**24.4** **(9.5, 39.3)** **0.0025**

Source: Table 11-4 p69; Table 11-5 p71;Table 11-6 p73; Table 11-7 p75; Table 11-8 p77; Table 11-9 p79 Study 101 CSR.
CFQ-R RD = Cystic Fibrosis Questionnaire-Revised Respiratory Domain; CI = confidence interval; CSR = clinical study report; D-IVA = deutivacaftor; FAS = full analysis set; F/F = homozygous for the F508del mutation; F/MF = heterozygous for the F508del and a minimal function mutation; IVA = ivacaftor; LS = least squares; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; SD = standard deviation; SwCl = sweat chloride; TEZ = tezacaftor; VNZ = vanzacaftor; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.
Bold represents a significant result.

Non-clinical evidence

6.18 The chloride transport response from 2 studies (Study U015 and Study U020) was presented as evidence to support the use of VNZ/TEZ/D-IVA in mutations that are responsive to VNZ/TEZ/D-IVA *in vitro*. The level of chloride transport for each mutant CFTR form was expressed as a percentage of normal CFTR. The submission claimed that > 10% net increase in chloride transport is predictive or reasonably expected to predict clinical benefit. The PBAC have previously seen this claim and the ACM have acknowledged that the predictive potential of the FRT assay is acceptable due to the supportive clinical data and the biological relevance in the case of gating mutations (paragraph 6.31, ivacaftor PSD, November 2023 PBAC Meeting).

6.19 Study U015 tested 161 mutations in the FRT model and identified 135 mutations (of which 7 have clinical data showing responsiveness to VNZ/TEZ/D-IVA in Study 103) to be responsive to VNZ/TEZ-D-IVA:

- The F508del-CFTR mutation was responsive to VNZ/TEZ/D-IVA.
- 29 mutations were responsive to VNZ/TEZ/D-IVA that were previously shown to be responsive to ELX/TEZ/IVA.

- 27 mutations were responsive to VNZ/TEZ/D-IVA that were previously shown to be not responsive to ELX/TEZ/IVA.
- 78 mutations were responsive to VNZ/TEZ/D-IVA that were previously tested in Study U032 for responsiveness to ELX/TEZ/IVA.

6.20 Study U020 demonstrated responsiveness of the N1303K-CFTR mutation to VNZ/TEZ/D-IVA in CF-HBE cells, after finding it unresponsive to VNZ/TEZ/D-IVA in the FRT model.

6.21 For 167 mutations, the submission did not present direct in vitro evidence to demonstrate responsiveness to VNZ/TEZ/D-IVA, rather it relied on the following to support its claims:

- Based on the evidence from Study U015 that demonstrated that 107 (i.e., 78+29) mutations that were responsive to ELX/TEZ/IVA were also responsive to VNZ/TEZ/D-IVA, the submission included evidence for 130 mutations that did not have direct in vitro data to show responsiveness to VNZ/TEZ/D-IVA, but did have evidence to show responsiveness to ELX/TEZ/IVA in Study P289. The PBAC have previously seen Study P289 in the November 2023 ivacaftor submission and March 2025 ELX/TEZ/IVA submission. The submission relied on the stepwise responsiveness of CFTR modulators demonstrated in Study P289 (i.e. that all IVA responsive mutations are also responsive to TEZ/IVA, and all TEZ/IVA mutations are also responsive to ELX/TEZ/IVA) to support its claim that all ELX/TEZ/IVA responsive mutations are going to be responsive to VNZ/TEZ/D-IVA.
- Evidence for use in 18 mutations was derived from Study 103 and 105. While there was clinical data to support efficacy for these mutations, the submission did not present evidence of *in vitro* data to support the efficacy of VNZ/TEZ/D-IVA in these mutations.
- Two non-canonical mutations demonstrated clinical response to IVA and TEZ/IVA in Study 108 and were therefore assumed to be responsive to VNZ/TEZ/D-IVA.
- Three splice mutations demonstrated clinical response to ELX/TEZ/IVA in Study 124 and in the French compassionate access study (considered in March 2025) and were therefore assumed to be responsive to VNZ/TEZ/D-IVA.
- Fourteen non-canonical splice mutations were included on the basis of the established mechanism of action of CFTR modulators.

6.22 The PBAC have previously made a positive recommendation for ELX/TEZ/IVA based on extrapolation of evidence for rare mutations, noting that the treatment was likely to provide a clinical benefit in the requested populations; however, the magnitude of the benefit was uncertain (paragraph 7.6, ELX/TEZ/IVA minutes, March 2025 PBAC meeting).

Comparative harms

6.23 A summary of the safety data for Study 102 and 103 is presented in Table 9 and for Study 105 in Table 10. The total number of adverse events (AEs) reported was higher in Study 103 than Study 102. Overall, the safety profiles of both treatment arms were similar in each study. The most common AEs were infective pulmonary exacerbations (PEx) of CF, cough, COVID-19, nasopharyngitis and oropharyngeal pain. With the exception of COVID-19, a commonly

transmitted viral infection that is expected to be observed in this population, the most commonly reported AEs were symptoms of CF or exacerbations of CF disease. There were no deaths reported in any studies.

6.24 The safety results for Study 101 demonstrated that VNZ/TEZ/IVA was well tolerated over the 29-day study period. Patients taking VNZ/TEZ/D-IVA reported more AEs, but only the placebo arm reported severe and/or serious AEs. These findings are limited by the small sample size and short treatment period. The most common AEs in patients receiving VNZ/TEZ/D-IVA were cough, increased sputum and headache, which were mostly consistent with manifestations of CF disease. There were no life-threatening AEs or deaths.

Table 9: Summary of AEs, Study 102 and 103 (Safety set) at 52 weeks

	Study 102				Study 103			
Trial ID	**ELX/TEZ/IVA (N=202) n (%)**	**VNZ/TEZ/D-IVA (N=196) n (%)**	**RD (95% CI)**	**RR (95% CI)**	**ELX/TEZ/IVA (N=289) n (%)**	**VNZ/TEZ/D-IVA (N=284) n (%)**	**RD (95% CI)**	**RR (95% CI)**
Number of AEs	1508	1430	NA	NA	2287	2121	NA	NA
Patients with any AEs	196 (97.0)	185 (94.4)	-0.03 (-0.07, 0.01)	0.97 (0.93, 1.01)	273 (94.5)	274 (96.5)	0.02 (-0.01, 0.05)	1.02 (0.99, 1.06)
Related AEs[a]	78 (38.6)	65 (33.2)	-0.06 (0.66, 1.12)	-0.06 (-0.15, 0.04)	97 (33.6)	103 (36.3)	0.03 (-0.05, 0.11)	1.08 (0.86, 1.35)
AEs by maximum severity								
Mild	66 (32.7)	69 (35.2)	0.03 (-0.07, 0.12)	1.08 (0.82, 1.42)	79 (27.3)	97 (34.2)	0.07 (-0.01, 0.14)	1.25 (0.98, 1.60)
Moderate	108(53.5)	96 (49.0)	-0.05 (-0.14, 0.05)	0.92 (0.76, 1.11)	161 (55.7)	143 (50.4)	-0.05 (-0.14, 0.03)	0.90 (0.77, 1.05)
Severe	22 (10.9)	20 (10.2)	-0.01 (-0.07, 0.05)	0.94 (0.53, 1.66)	32 (11.1)	34 (12.0)	0.01 (-0.04, 0.06)	1.08 (0.69, 1.70)
Life-threatening	0	0	0	0	1 (0.3)	0	0.00 (-0.01, 0.00)	NA
Death	0	0	0	0	0	0	0	0
AEs leading to discontinuation	9 (4.5)	4 (2.0)	-0.02 (-0.06, 0.01)	0.46 (0.14, 1.46)	9 (3.1)	14 (4.9)	0.02 (-0.01, 0.05)	1.58 (0.70, 3.60)
AEs leading to interruption	4 (2.0)	8 (4.1)	0.02 (-0.01, 0.06)	2.06 (0.63, 6.74)	8 (2.8)	12 (4.2)	0.02 (-0.02, 0.05)	1.53 (0.63, 3.68)
AEs Grade 3 or higher	22 (10.9)	20 (10.2)	-0.01 (-0.07, 0.05)	0.94 (0.53, 1.66)	33 (11.4)	34 (12.0)	0.01 (-0.05, 0.06)	1.05 (0.67, 1.64)
Serious AEs	41 (20.3)	28 (14.3)	-0.06 (-0.13, 0.01)	0.70 (0.45, 1.09)	40 (13.8)	40 (14.1)	0.00 (-0.05, 0.06)	1.02 (0.68, 1.53)
Related serious AEs[a]	8 (4.0)	4 (2.0)	-0.02 (-0.05, 0.01)	0.52 (0.16, 1.68)	5 (1.7)	3 (1.1)	-0.01 (-0.03, 0.01)	0.61 (0.15, 2.53)
Deaths	0	0	0	0	0	0	0	0

Source: Table 2.54 pp113-114 of the submission.

AE = adverse event; CI = confidence interval; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; n = number of participants reporting data; N = total participants in group; NA = not applicable; RD = risk difference; RR = relative risk; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.

[a] related AEs include patients with AEs that were considered related or possibly related or missing.

Table 10: Summary of AEs, Study 105 at 24 weeks

	VNZ/TEZ/D-IVA	
	Cohort A1 (N=17) n (%)	Cohort B1 (N=78) n (%)
Number of AEs (total)	28	429
Participants with any AEs	12 (70.6)	75 (96.2)
Related AEs[a]	3 (17.6)	23 (29.5)
AEs by maximum severity		
Mild	9 (52.9)	39 (50.0)
Moderate	3 (17.6)	36 (46.2)
Severe	0	0
Life-threatening	0	0
Death	0	0
AEs leading to discontinuation	0	1 (1.3)
AEs leading to interruption	0	1 (1.3)
AEs Grade 3 or higher	0	0
Serious AEs	0	6 (7.7)
Related serious AEs[a]	0	1 (1.3)
AEs leading to death	0	0

Source: Table 2.55 p114 of the submission.
AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; n = number of participants reporting data; N = total participants in group; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.
[a] related AEs include patients with AEs that were considered related or possibly related or missing.

Benefits/harms

6.25 A benefits and harms table is not presented as the submission used a cost-minimisation approach.

Clinical claim

6.26 The evaluation considered the submission's claim of non-inferior efficacy, with respect to change in ppFEV$_1$, and superiority, with respect to improving CFTR function as measured by SwCl, for VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA, was adequately supported by the evidence in Study 102 and 103 for the subset of patients with an F/F (Study 103), F/MF (Study 102), F/G (Study 103), F/RF (Study 103) or a non-F ELX/TEZ/IVA-responsive mutation (Study 103, Study 105). The submission's efficacy claim for other mutations not included in Study 102, 103 or 105 is unknown.

6.27 Lung function (as measured by ppFEV$_1$), as opposed to SwCl, is a predictor of survival in patients with CF. While there was an improvement in SwCl, there was no difference in ppFEV$_1$. This implies that the magnitude of benefit in SwCl did not correspond to a similar magnitude of benefit in lung function over the 52-week study period, acknowledging some 'ceiling effects' may have been observed in lung function tests. The PSCR stated that SwCl concentration is a direct measure of CFTR function that predicts disease severity and clinical outcomes including survival in both CFTR modulator-naïve and -treated people with CF.

6.28 The evaluation considered the submission's claim of comparable safety compared with ELX/TEZ/IVA or BSC alone in patients with at least one CFTR mutation responsive to ELX/TEZ/IVA and/or VNZ/TEZ/D-IVA was well supported by the evidence provided in the

submission. Study 102 and 103 demonstrated a similar AE profile between VNZ/TEZ/D-IVA and ELX/TEZ/D-IVA. Study 105 was limited in its capacity to inform a comparison against ELX/TEZ/D-IVA or BSC, as it is single arm by design, but the AE profile was similar to that in Study 102 and Study 103, noting that the longer-term safety of VNZ/TEZ/D-IVA for patients who start treatment at a younger age, was uncertain.

6.29 The submission's efficacy claim for patients 6 to 11 years of age was not well supported by Study 105 as this was a single arm study. The PBAC have previously noted that the efficacy claim of a CFTR modulator can be extrapolated from an older population to a paediatric population (paragraph 6.22 lumacaftor/ivacaftor PSD, July 2023 PBAC Meeting, paragraph 6.32 elexacaftor/tezacaftor/ivacaftor PSD, March 2024 PBAC Meeting). It is possible that the claim of non-inferiority, in terms of $ppFEV_1$, superiority, in terms of SwCl, and comparability in terms of safety, can reasonably be extrapolated from the 12 years and older age group to the 6 to 11 years age group. The PSCR stated the disease process in CF patients of all age groups stems from a common aetiology of dysfunctional CFTR protein that is targeted by VNZ/TEZ/D-IVA. As VNZ/TEZ/D-IVA targets the dysfunctional CFTR, the outcome of treatment with VNZ/TEZ/D-IVA is expected to be comparable between those aged 6-11 years and those aged ≥12 years in the 52-week controlled studies. The PSCR further noted that persistence of efficacy will be confirmed in the long-term OLE study VX22-121-106 (96-week duration for participants from Study 105 Part B), with publication expected in November 2026. This study, along with additional OLE, registry and prospective studies are being conducted to assess the long-term efficacy and safety of VNZ/TEZ/D-IVA.

6.30 The evaluation considered the submission's claim of superiority of VNZ/TEZ/D-IVA compared to BSC in terms of overall efficacy for mutations that are responsive to VNZ/TEZ/D-IVA but not responsive to ELX/TEZ/IVA was not well supported by the evidence presented in the submission. The submission relied on *in vitro* data from Study U015 to demonstrate Cl transport activity in 31 mutations that were found to be responsive to VNZ/TEZ/D-IVA, but not responsive to ELX/TEZ/IVA, as a proxy for efficacy. The PBAC have previously acknowledged the constraints of conducting clinical trials in patients with rare mutations and concluded, in that case, that the claim of superior comparative effectiveness (for all mutation populations) was uncertain but, overall, was likely to be reasonable (paragraph 6.49-6.50, ivacaftor PSD, November 2023 PBAC Meeting).

6.31 The clinical evidence to support the non-inferiority (in terms of absolute change in $ppFEV_1$), superiority (in terms of absolute change in SwCl) and safety of VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA for some of the rarer mutations has relied on evidence from *in-vitro*, rather than clinical, studies. The TGA CER acknowledged that it is not possible to establish clinical efficacy for all the different individual mutations and therefore believed it valid to extrapolate clinical efficacy from in vitro studies (vanzacaftor/tezacaftor/deutivacaftor Clinical Evaluation Report, February 2025).

6.32 There were 149 mutations included in the submission for which there was no direct clinical and/or *in vitro* data demonstrating Cl transport activity for VNZ/TEZ/D-IVA. The submission claimed it is not possible to establish clinical efficacy through trials for many of these CFTR mutations, as they may be found in as few as 1 or 2 people with CF. In the absence of clinical

and/or direct *in vitro* data, the efficacy and safety of VNZ/TEZ/D-IVA for these 149 mutations was uncertain. The PSCR stated extrapolation of efficacy to people with CF with clinically untested genotypes that have in vitro evidence of effect is consistent with prior PBAC decision-making for CFTR modulators. The PSCR further stated that, as accepted by the TGA clinical evaluator, evidence of responsiveness to ELX/TEZ/IVA can be extrapolated to responsiveness to VNZ/TEZ/D-IVA, as all mutations responsive to ELX/TEZ/IVA are also responsive to VNZ/TEZ/D-IVA.

6.33 Noting the limitations of the data, particularly for patients with rare mutations, the ESC considered that, overall:

- The claim that VNZ/TEZ/D-IVA is non-inferior to ELX/TEZ/IVA in terms of lung function and superior in terms of SwCl for patients with ELX/TEX/IVA responsive mutations was adequately supported by the evidence presented for patients ≥ 12 years of age. The claim was not well supported for patients aged 6- to 11-year-olds; however, the ESC noted extrapolation from older age groups has been previously accepted by the PBAC.
- The claim that VNZ/TEZ/IVA is superior in terms of efficacy compared to BSC alone in patients with at least one VNZ/TEZ/D-IVA responsive mutation that is not responsive to ELX/TEZ/IVA was adequately supported, albeit based on in vitro data.
- The claim that VNZ/TEZ/IVA has comparable safety to ELX/TEZ/IVA was adequately supported.
- The claim that VNZ/TEZ/IVA has comparable safety to BSC was poorly supported by the data presented in the submission.

6.34 The ESC noted VNZ/TEZ/D-IVA offers the benefit of a single, once daily, fixed dose combination (FDC) treatment relative to ELX/TEZ/IVA (which requires twice daily dosing).

6.35 The PBAC considered that the claim of non-inferior comparative effectiveness versus ELX/TEZ/IVA and superior comparative effective versus BSC for patients with mutations response to VNZ/TEZ/D-IVA was reasonable.

6.36 The PBAC considered that the claim of non-inferior comparative safety versus ELX/TEZ/IVA was reasonable but the claim of non-inferior comparator safety versus BSC was not adequately supported by the data.

Economic analysis

6.37 The submission presented a CMA comparing VNZ/TEZ/D-IVA to ELX/TEZ/IVA. The presentation of a CMA was appropriate given the claim of non-inferior efficacy and safety of VNZ/TEZ/D-IVA.

6.38 The submission also claimed that VNZ/TEZ/D-IVA plus BSC was superior in terms of overall efficacy compared with BSC alone in people with at least one VNZ/TEZ/D-IVA-responsive *CFTR* mutation that is not responsive to ELX/TEZ/IVA. While the submission could have presented a cost-utility analysis (CUA) for the comparison against BSC, it did not do so. This is reasonable in this context in that a CUA is unlikely to be informative for decision-making given the small proportion of the population affected (the 0.3% of patients with mutations responsive to VNZ/TEZ/D-IVA).

6.39 The key components and assumptions of the CMA are presented in Table 11.

Table 11: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the submission, the effectiveness of VNZ/TEZ/D-IVA is demonstrated to be non-inferior to ELX/TEZ/IVA in terms of lung function, with superiority in terms of CFTR function restoration (measured via SwCl concentration)
Therapeutic claim: safety	Based on evidence presented in the submission, the safety of VNZ/TEZ/D-IVA is demonstrated to be comparable to ELX/TEZ/IVA
Evidence base	Randomised controlled trials of VNZ/TEZ/D-IVA vs ELX/TEZ/IVA following run-in period on ELX/TEZ/IVA (Study 102 and 103)
Equi-effective doses	VNZ/TEZ/D-IVA at the recommended age- and weight-based, once-daily dose is equi-effective with ELX/TEZ/IVA at the recommended age- and weight-based, twice-daily dose
Direct medicine costs	VNZ/TEZ/D-IVA $[redacted] per patient ELX/TEZ/IVA $[redacted] per patient

Source: Table 3.1, p128 of the submission.
CFTR = cystic fibrosis transmembrane regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; SwCl = sweat chloride; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.

6.40 The equi-effective doses applied in the submission were the daily recommended doses of VNZ/TEZ/D-IVA and ELX/TEZ/IVA. This was reasonable; dosing of VNZ/TEZ/D-IVA and ELX/TEZ/IVA was as per the respective PIs and the key trials provided with the submission.

6.41 The submission did not account for any additional costs or cost offsets except for the cost of monitoring due to liver function tests (LFTs). Given both ELX/TEZ/IVA and VNZ/TEZ/IVA have similar prescribing, administration and monitoring profiles, this was reasonable.

6.42 The results of the CMA are presented in Table 12 and are based on the proposed effective prices.

Table 12: Results of the cost-minimisation approach

Component	VNZ/TEZ/D-IVA	ELX/TEZ/IVA
Treatment cost		
Cost per pack (AEMP), 28 days	$[redacted]	$[redacted]
Duration	1 year (365.25 days)	1 year (365.25 days)
Total medicine cost per year	$[redacted]	$[redacted]
Monitoring cost		
Monitoring cost per year	$17.70	$17.70
Total cost of treatment per year	$[redacted]	$[redacted]

Source: Table 3.3, p130 and Table 3.4, p 130 of the submission.
AEMP = approved effective ex-manufacturer price; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor

6.43 To calculate the total annual cost of treatment, the submission included the costs of the CFTR modulator treatment and monitoring (annual liver function test, MBS Item 66512 = $17.70). The cost for other monitoring specific to the first year of treatment, i.e., liver function tests prior to initiation, every 3 months during the first year of treatment and ophthalmologist examinations, were not included. Given the chronic nature of the disease, inclusion of these costs will only have a minor impact on the total annual cost of the treatment and are not anticipated to differ between treatments. However, the submission included these monitoring costs in the financial estimates.

6.44 In its consideration of ELX/TEZ/IVA in March 2025, the PBAC recalled it had initially recommended the listing of CFTR modulators with high and likely underestimated

incremental cost effectiveness ratios on the basis of high clinical need. The PBAC noted that, over time, requests for expanded populations (i.e., for younger patients and those with rarer mutations) have been recommended for listing. The PBAC noted the magnitude of clinical benefit is less certain in expanded populations, and this may result in use that is less cost-effective overall (para 7.8, ELX/TEZ/IVA, March 2025 PBAC minutes).

Drug cost/patient/year

6.45 The drug cost per patient per year for ELX/TEZ/IVA and VNZ/TEZ/D-IVA is $[redacted] (based on 100% compliance) (see Table 12). The financial estimates assumed 90% compliance for ELX/TEZ/IVA and VNZ/TEZ/D-IVA.

Estimated PBS usage & financial implications

6.46 This submission was not considered by the Drug Utilisation Sub Committee (DUSC). The submission used a combination of both epidemiological and market share approaches to estimate the extent of use and financial impact of listing VNZ/TEZ/D-IVA on the PBS. The sources of data utilised are shown in Table 13.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Only VNZ/TEZ/D-IVA-responsive patients	9 prevalent patients in Year 1 with 3.6% annual growth applied Year 2 to Year 6 Number of prevalent patients was sourced from a bespoke ACFDR data request based on 2023 data. Annual growth rate sourced from data reports 2020 to 2023.	The growth rate aligns with CF growth rate as per the ACFDR reports. The ESC noted limited information was provided in the submission to support the number of prevalent patients.
Scripts per patient per year	13.04 scripts x 90% compliance	The ESC noted no discontinuation rate was applied to the VNZ/TEZ/D-IVA patients.
Script equivalence	1:1	
Existing ELX/TEZ/IVA market	Total scripts dispensed from October 2023 and September 2024: 26,875 (PBS item reports) Scripts from March 2025 PBAC submission for ELX/TEZ/IVA (for patients who are 6 years or older): 1,756 for Year 1	Annual growth rate of 3.6%.
Number of patients currently enrolled in clinical trials	[redacted][1], reported by the submission	As per submission The ESC noted these patients were appropriately assumed to substitute for ELX/TEZ/IVA.
Transition from trial to PBS-subsidised therapy	2025: 33% 2026: 66% 2027-2030: 100%	As per submission
MBS costs	MBS Item 66512: $17.70 MBS Item 104: $98.95	

Source: Table 4.1, p132, Table 4.2 p132, Table 4.3, p 133, table 4.4, p 133, Table 4.5, p134, Table 4.6, p 134, Table 4.9, p 136 of the submission.
ACFDR = Australian Cystic Fibrosis Data Registry; CF = cystic fibrosis; ELX/TEZ//IVA = elexacaftor/tezacaftor/ivacaftor; IVA =ivacaftor; MBS = Medicare Benefits Schedule; mg = milligram; PBAC = Pharmaceutical Benefit Advisory Committee; PBS = Pharmaceutical Benefit Scheme; PSD = Public Summary Document, RPBS = Repatriation Pharmaceutical Benefit Scheme; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.
The redacted values correspond to the following ranges:
[1] *< 500*

6.47 The submission used an epidemiological approach to estimate the addition of new patients to the listing i.e., patients with VNZ/TEZ/D-IVA responsive (but not ELX/TEZ/IVA responsive) mutations. To estimate the scripts that would replace treatment with ELX/TEZ/IVA, the submission used a market share approach assuming a 70% replacement rate, a 95% uptake rate and 90% compliance rate.

Table 14: Estimated use and financial implications (effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients responsive to VNZ/TEZ/D-IVA	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed for VNZ/TEZ/D-IVA responsive patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed from ELX/TEZ/IVA market (includes GF patients)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total number of scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total estimated number of patients treated[a]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of VNZ/TEZ/D-IVA						
Cost to PBS/RPBS less copayments	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Estimated financial implications for ELX/TEZ/IVA						
Cost to PBS/RPBS less copayments	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net financial implications						
Net cost to PBS/RPBS	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to MBS	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to PBS/RPBS/MBS	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]

Source: Table 4.20, p141; Table 4.26, p143; Table 4.27, p143; Table 4.28, p143; Table 4.37, p148; Table 4.43, p151 and Table 4.46, p152 of the submission.

ELX/TEZ//IVA = elexacaftor/tezacaftor/ivacaftor; IVA =ivacaftor; MBS = Medicare Benefits Schedule PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; VNZ/TEZ/D-IVA = vanzacaftor/tezacaftor/deutivacaftor.

[a] Assuming 11.74 scripts per patient per year as estimated by the submission (13.04 scripts x 90% compliance).

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$20 million to < $30 million*

[3] *500 to < 5,000*

[4] *$100 million to < $200 million*

[5] *$200 million to < $300 million*

[6] *net cost saving*

[7] *0 to < $10 million*

6.48 The total cost to the PBS/RPBS of listing VNZ/TEZ/D-IVA was estimated to be $200 million to < $300 million in Year 6, and a total of > $1 billion in the first 6 years of listing based on the effective price. Accounting for substitution for ELX/TEZ/IVA, the submission estimated a net cost to the PBS/ RPBS of 0 to < $10 million over 6 years which can be attributed due to the

addition of patients with VNZ/TEZ/D-IVA responsive (but not ELX/TEZ/IVA responsive) mutations to the listing.

6.49 The submission included the financial impact of providing listed access to <500 grandfathered patients. The submission assumed these people will transition to treatment with VNZ/TEZ/D-IVA and replace ELX/TEZ/IVA over 3 years after completion of the trial.

Financial Management – Risk Sharing Arrangements

6.50 The submission did not propose any Risk Sharing Arrangements (RSA). There is an RSA in place for the currently listed CFTR modulators (see Table 15). The pre-PBAC response noted VNZ/TEZ/D-IVA is a treatment option for approximately 9 people with CF who are not captured under the current RSA and while this represents a small incremental cost to the PBS, it proposed that VNZ/TEZ/D-IVA would join the current CFTR modulator RSA, .

Table 15: Current RSA for IVA, LUM/IVA, TEZ/IVA and ELX/TEZ/IVA (100% rebate for expenditure over the cap)

Cap Year	Cap Threshold	Total Commonwealth payment	% market share by drug	% of Cap reached
1 Year (Apr-22 – Mar 23)	$	$	LUM/IVA: %; TEZ/IVA: %; ELX/TEZ/IVA: %	%
2 Year (Apr-23 – Mar 24)	$	$	LUM/IVA: %; TEZ/IVA: % ELX/TEZ/IVA: %	%
3 Year (Apr-24 – Mar 25)*	$	$	LUM/IVA: %; TEZ/IVA: % ELX/TEZ/IVA: %; IVA %	%
4 Year (Apr-25 – Mar 26)**	$	$	LUM/IVA: %; TEZ/IVA: % ELX/TEZ/IVA: %; IVA %	%
5 Year (Apr-26 – Mar 27)	$			

Source: provided by Department

ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; LUM/IVA = lumacaftor/ivacaftor; TEZ/IVA = tezacaftor/ivacaftor

*Year 3 now has 12 months of data but has unadjusted data and is subject to change once EOFY adjustments have occurred

**Year 4 contains 2 months of unadjusted data only.

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7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for vanzacaftor with tezacaftor and with deutivacaftor (VNZ/TEZ/D-IVA) for the treatment of cystic fibrosis in patients aged 6 years and older who have at least one mutation in the cystic fibrosis transmembrane regulator (*CFTR*) gene that is responsive to VNZ/TEZ/D-IVA potentiation based on clinical and/or in vitro assay data. The PBAC was of a mind to recommend VNZ/TEZ/D-IVA on receipt of the TGA Delegate's Overview which was not available at the time of PBAC consideration. The PBAC considered VNZ/TEZ/D-IVA was non-inferior to elexacaftor with tezacaftor and with ivacaftor (ELX/TEZ/IVA) in terms of efficacy (as measured by lung function) and safety and would provide a once daily treatment option for patients with responsive mutations. Additionally, the PBAC noted VNZ/TEZ/D-IVA would provide access to a CFTR modulator for a very small number of patients (<10) who have mutations that do not respond to ELX/TEZ/IVA. The PBAC considered VNZ/TEZ/D-IVA would be cost effective if it were cost minimised to ELX/TEZ/IVA and should be included in the risk sharing arrangement currently in place for CFTR modulators with no increase in expenditure caps.

7.2 The PBAC acknowledged the consumer comments strongly supported the listing for VNZ/TEZ/D-IVA. The PBAC noted VNZ/TEZ/D-IVA would provide access to a once daily treatment for patients over 6 years of age that can currently access ELX/TEZ/IVA and would provide treatment for a small number of additional patients that cannot currently access a CFTR modulator.

7.3 The PBAC considered the proposed restriction criteria were appropriate but that some amendments may be required, depending on the final TGA approval in terms of how responsive mutations are included in the Product Information (see paragraph 3.4). The PBAC noted flow on changes would be required to the administrative note for other CFTR modulators to include VNZ/TEZ/D-IVA in the list of CFTR modulators (see paragraph 3.3).

7.4 The PBAC noted the submission nominated ELX/TEZ/IVA + BSC as the comparator for patients with a mutation that is responsive to both ELX/TEZ/IVA and VNZ/TEZ/D-IVA, and BSC alone as the comparator for patients with a mutation that is responsive to VNZ/TEZ/D-IVA only. The PBAC considered the nominated comparators were appropriate, noting only a small number of patients (<10) were likely to have a mutation that is responsive to VNZ/TEZ/D-IVA only.

7.5 The PBAC noted the clinical evidence for VNZ/TEZ/D-IVA was from two head-to-head studies comparing VNZ/TEZ/D-IVA to ELX/TEZ/IVA in patients aged 12 years and older (Study 102 and Study 103, 52 weeks) and one single arm study of VNZ/TEZ/D-IVA in patients aged 6 to 11 years (Study 105, 24 weeks). The PBAC noted the majority of patients had prior treatment with a CFTR modulator, with the majority having received ELX/TEZ/IVA (> 85% in Study 102, > 67% in Study 103, > 79% in Study 105). Additionally, the submission presented one randomised study of VNZ + TEZ/D-IVA versus placebo or TEZ/IVA in patients aged 18 years and older (Study 101, 4 weeks) and two non-clinical studies to provide evidence of *in vitro* responsiveness of mutations to VNZ/TEZ/D-IVA (Study U015 and Study U020).

7.6 In Study 102 and Study 103, the PBAC noted the difference between the treatment arms in least squares (LS) mean change in $ppFEV_1$ from baseline (after the 4-week run in period) through Week 24 or Week 52 was less than the minimal clinically important difference of 3 percentage points in both studies which supported non-inferiority of VNZ/TEZ/D-IVA and ELX/TEZ/IVA. The PBAC noted that at Week 24, treatment with VNZ/TEZ/D-IVA resulted in larger improvements in sweat chloride (SwCl) compared to ELX/TEZ/IVA as measured by the LS mean difference and this treatment effect was maintained at Week 52.

7.7 In Study 105 (a single arm study), the PBAC noted that $ppFEV_1$ was maintained and SwCl reduced over 24 weeks in patients treated with VNZ/TEZ/D-IVA.

7.8 In Study 101, treatment with VNZ/TEZ/D-IVA resulted in improved $ppFEV_1$ and SwCl compared to placebo and TEZ/IVA at Week 4.

7.9 The PBAC noted Study U015 and Study U020 provided evidence of the *in vitro* responsiveness of mutations to VNZ/TEZ/D-IVA, including mutations that are not responsive to ELX/TEZ/IVA. Additionally, the PBAC noted the claim in the submission that mutations that are responsive to ELX/TEX/IVA, TEZ/IVA or IVA are also response to VNZ/TEZ/D-IVA.

7.10 The PBAC considered that VNZ/TEZ/D-IVA was likely to be non-inferior to ELX/TEZ/IVA in terms of $ppFEV_1$ and may be superior in terms of SwCl; however, the PBAC noted the claim was uncertain for rare mutations and for some populations (i.e. CF patients under 12 years of age). The PBAC considered the claim that VNZ/TEZ/D-IVA was superior to BSC in patients with at least one VNZ/TEZ/D-IVA responsive mutations that is not responsive to ELX/TEZ/IVA was uncertain but, on balance, likely to be reasonable.

7.11 The PBAC noted the safety profile of VNZ/TEZ/D-IVA and ELX/TEZ/IVA were similar and considered the claim that VNZ/TEZ/IVA has non-inferior safety to ELX/TEZ/IVA was adequately supported. The PBAC considered the claim that VNZ/TEZ/IVA has non-inferior safety to BSC was not adequately supported by the data presented in the submission.

7.12 The PBAC considered the cost minimisation approach (CMA) comparing VNZ/TEZ/D-IVA to ELX/TEZ/IVA presented in the submission was reasonable. The PBAC noted the CMA was based on the following equi-effective doses: on VNZ/TEZ/D-IVA at the recommended age- and weight-based, once-daily dose and ELX/TEZ/IVA at the recommended age- and weight-based, twice-daily dose.

7.13 The PBAC noted the submission used an epidemiological approach to estimate the number of new patients that would be treated with VNZ/TEZ/D-IVA and a market share approach to estimate the ELX/TEZ/IVA scripts that would be replaced with VNZ/TEZ/D-IVA scripts. The PBAC considered that the methodology for estimating the utilisation of VNZ/TEZ/D-IVA and the estimated financial impact was reasonable.

7.14 The PBAC advised that VNZ/TEZ/D-IVA should be included in the existing risk sharing arrangement for CFTR modulators with no increase in expenditure caps (see paragraph 6.50).

Outcome:
Deferred

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.

September Addendum to the July 2025 PBAC Minutes:

4.03 VANZACAFTOR WITH TEZACAFTOR AND WITH DEUTIVACAFTOR

Pack containing 84 tablets vanzacaftor 4 mg with tezacaftor 20 mg and with deutivacaftor 50 mg

Pack containing 56 tablet vanzacaftor 10 mg with tezacaftor 50 mg and with deutivacaftor 125 mg

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10 Background

10.1 At its July 2025 meeting, the PBAC was of a mind to recommend vanzacaftor with tezacaftor and with deutivacaftor (VNZ/TEZ/D-IVA) for the treatment of cystic fibrosis in patients aged 6 years and older who have at least one mutation in the cystic fibrosis transmembrane regulator (CFTR) gene that is responsive to VNZ/TEZ/D-IVA potentiation based on clinical and/or in vitro assay data, however deferred making this recommendation as the TGA Delegate's Overview was not available at the time of PBAC consideration.

10.2 The TGA Delegate's Overview was provided following the July 2025 PBAC meeting and the Delegate is supportive of registration.

11 PBAC Outcome

11.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of vanzacaftor with tezacaftor and with deutivacaftor (VNZ/TEZ/D-IVA) for the treatment of cystic fibrosis in patients aged 6 years and older who have at least one mutation in the cystic fibrosis transmembrane regulator (*CFTR*) gene that is responsive to VNZ/TEZ/D-IVA potentiation based on clinical and/or *in vitro* assay data.

11.2 The PBAC noted the TGA Delegate was supportive of registering VNZ/TEZ/D-IVA for the following indication: "VNZ/TEZ/D-IVA is indicated for the treatment of those who meet the diagnostic criteria of cystic fibrosis (CF) in patients aged 6 years and older who have at least one non-Class 1 mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive, based on clinical study or in vitro evidence." The PBAC noted registration was pending advice from the Advisory Committee on Medicines and finalisation of the Product Information, Consumer Medicines Information and conditions of registration.

11.3 The PBAC advised the inclusion of the following wording in the relevant Prescribing Instruction is appropriate, consistent with the ELX/TEZ/IVA listing, depending on the final approved Product Information: 'Mutations that are not listed in the TGA approved PI but considered to be responsive to vanzacaftor/tezacaftor/ deutivacaftor can be accepted with a confirmation that these patients do not harbour two Class I mutations'.

11.4 The PBAC advised that flow-on changes will be required for the administrative advice for the existing PBS listing for CFTR therapies to include VNZ/TEZ/D-IVA, i.e. 'For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor and vanzacaftor/tezacaftor/ deutivacaftor.' The PBAC advised that the clinical criterion 'The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy for this condition' should be added across all ELX/TEZ/IVA and VNZ/TEZ/D-IVA listings to prevent concomitant use of CF therapies.

11.5 The PBAC reiterated its previous consideration that the CMA presented in the submission was reasonable (see paragraph 7.12) and that VNZ/TEZ/D-IVA should be included in the existing risk sharing arrangement for CFTR modulators with no increase in expenditure caps (see paragraph 7.14**Error! Reference source not found.**).

11.6 The PBAC advised that VNZ/TEZ/D-IVA is not suitable for prescribing by nurse practitioners

11.7 The PBAC advised that VNZ/TEZ/D-IVA should be exempt from the Early Supply rule as it currently does not apply to Section 100 Highly Specialised Drugs Program listings.

11.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because VNZ/TEZ/D-IVA is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ELX/TEZ/IVA or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

11.9 The PBAC recommended that VNZ/TEZ/D-IVA should not be treated as interchangeable with

any other drugs.

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

Outcome:
Recommended

12 Recommended listing

12.1 Add new medicinal product:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VANZACAFTOR + TEZACAFTOR + DEUTIVACAFTOR					
Vanzacaftor 4 mg + tezacaftor 20 mg + deutivacaftor 50 mg, 84	NEW (Public) NEW (Private)	1	1	5	Alyftrek
Vanzacaftor 10 mg + tezacaftor 50 mg + deutivacaftor 125 mg, 56	NEW (Public) NEW (Private)	1	1	5	
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: ☒ Medical Practitioners					
Benefit type: ☒ Authority Required (FULL assessment) in writing only via OPA/post/HPOS upload)					
Authority type: ☒ Complex Authority Required (CAR)					
Prescribing rule level:					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor and vanzacaftor/tezacaftor/ deutivacaftor.					
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826					

HOBART TAS 7001
Restriction Summary [new1] / Treatment of Concept: [new1A]
Indication: Cystic fibrosis
Treatment Phase: Initial treatment
Clinical criteria:
Patient must have at least one mutation in the CFTR gene that is considered responsive to vanzacaftor/tezacaftor/deutivacaftor potentiation based on clinical and/or in vitro assay data
AND
Clinical criteria:
The treatment must be given concomitantly with standard therapy for this condition
AND
Clinical criteria:
Patient must have either chronic sinopulmonary disease or gastrointestinal and nutritional abnormalities, prior to initiating treatment with this drug
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy for this condition
Treatment criteria:
Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.
AND
Treatment criteria:
Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.
Population criteria:
Patient must be at least 6 years of age.
Prescribing Instructions: For the purposes of this restriction, the list of mutations considered to be responsive to vanzacaftor/tezacaftor/deutivacaftor is defined in the TGA approved Product Information (PI). Mutations that are not listed in the TGA approved PI but considered to be responsive to vanzacaftor/tezacaftor/deutivacaftor can be accepted with a confirmation that these patients do not harbour two Class I mutations.
Prescribing Instructions: This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.
Prescribing Instructions: The authority application must be via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the pathology report substantiating the specific mutation considered to be responsive to vanzacaftor/tezacaftor/deutivacaftor as listed in the TGA approved PI - quote each of the: (i) the specific mutation, and if the specific mutation is not listed in the TGA approved PI, confirmation that the patient does not harbour two Class I mutations (ii) name of the pathology report provider, (iii) date of pathology report, (iv) unique identifying number/code that links the pathology result to the individual patient; and (2) current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.
Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

Restriction Summary [new2] / Treatment of Concept: [new2A]
Indication: Cystic fibrosis
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
The treatment must be given concomitantly with standard therapy for this condition.
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy for this condition
Treatment criteria:
Must be treated by a specialist respiratory physician with expertise in cystic fibrosis or in consultation with a specialist respiratory physician with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.
AND
Treatment criteria:
Must be treated in a centre with expertise in cystic fibrosis or in consultation with a centre with expertise in cystic fibrosis if attendance is not possible due to geographic isolation.
Population criteria:
Patient must be at least 6 years of age.
Prescribing Instructions: This pharmaceutical benefit is not PBS-subsidised for this condition in a patient who is currently receiving one of the strong CYP3A4 inducers outlined in the Product Information.
Prescribing Instructions: The authority application must be via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include current CYP3A4 inhibitors, CYP3A4 inducers and IV antibiotics.
Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

Pending the final TGA approval, the restrictions may be subject to further changes.

12.2 Flow on changes to the combination CFTR modulator PBS listings for cystic fibrosis (CF):

- Amend an administrative advice in the **elexacaftor + tezacaftor + ivacaftor (&) ivacaftor** (12936W, 12938Y, 13276R, 13266F, 14280N, 14228W, 14279M, 14227T) restrictions to include reference to this drug.

Administrative Advice:
For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, ~~and~~ elexacaftor/tezacaftor/ivacaftor *and vanzacaftor/tezacaftor/ deutivacaftor.*

- Remove and replace an administrative advice in the **lumacaftor + ivacaftor** (11463H, 11466L, 11464J, 11465K, 11866M, 11841F, 11851R, 11848N, 13798F, 13795C) and **tezacaftor + ivacaftor** (11863J, 11833T, 11854X, 11834W) restrictions with a new administrative advice, for consistency purposes across all PBS CFTR modulator listings.

Administrative Advice:
~~For the purposes of this restriction, CFTR modulators, regardless if they are available as a single drug or in combination, are currently: elexacaftor, ivacaftor, lumacaftor, tezacaftor.~~

For the purposes of this restriction, PBS-subsidised 'CFTR modulator' means ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor and vanzacaftor/tezacaftor/ deutivacaftor.

- Add a new clinical criterion to the **elexacaftor + tezacaftor + ivacaftor (&) ivacaftor** (12936W, 12938Y, 13276R, 13266F, 14280N, 14228W, 14279M, 14227T) restrictions to prevent concomitant use of CF therapies.

Clinical criteria:
The treatment must be the sole PBS-subsidised cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy for this condition

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

13 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.

14 Sponsor's Comment

Vertex welcomes the recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) for the PBS listing of ALYFTREK® (vanzacaftor/tezacaftor/deutivacaftor; VNZ/TEZ/D-IVA) for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one mutation in the cystic fibrosis transmembrane regulator (CFTR) gene that is considered responsive to VNZ/TEZ/D-IVA potentiation based on clinical and/or *in vitro* assay data. This is an important step in achieving reimbursed access for eligible patients in Australia.