7.03 OMAVELOXOLONE, Capsule 50 mg, Skyclarys®, BIOGEN AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The standard re-entry resubmission requested a General Schedule, Authority Required (telephone/online) listing of omaveloxolone for the treatment of Friedreich's ataxia (FA) in people aged 16 years and older. Omaveloxolone was previously considered by the PBAC in March 2025.

1.2 Listing was requested on the basis of a revised cost-utility analysis versus best supportive care (BSC). The key components of the clinical issue are summarised in Table 1.

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

Component	Description
Population	People aged 16 years and older with Friedreich's ataxia (FA)
Intervention	Omaveloxolone is administered orally once daily as three 50 mg capsules (i.e., 150 mg in total).
Comparator	Best supportive care (placebo as a proxy)
Outcomes	Primary • Change in the modified Friedreich's ataxia rating scale (mFARS) score at week 48 • Safety outcomes Key secondary • Patient Global Impression of Change (PGIC) responses at week 48 • Clinical Global Impression of Change (CGIC) responses at week 48 Other secondary • Change in performance on a 9-hole peg test (9-HPT) at week 48 • Change in performance on a 25-foot timed walk test at week 48 • Frequency of falls • Change in peak work during maximal exercise testing at week 48 • Change in the Friedreich's Ataxia-Activities of Daily Living (ADL; FA-ADL) score
Clinical claim	In people with FA, omaveloxolone is superior in terms of efficacy and inferior with respect to safety, compared best supportive care (BSC).

Source: Table 1.1, p8 of the resubmission
Blue shading indicates information previously considered by the PBAC.

2 Background

Registration status

2.1 The Therapeutic Goods Administration (TGA) granted orphan drug status for omaveloxolone on 14 May 2024. Omaveloxolone was approved by the TGA in May 2025 and was listed on the Australian Register of Therapeutic Goods (ARTG) on 26 June 2025 for the treatment of FA in adults and adolescents aged 16 years and older.

Previous PBAC consideration

2.2 At the March 2025 PBAC meeting, the PBAC did not recommend omaveloxolone to be listed on the PBS for the treatment of FA in patients aged 16 years and older. The PBAC noted the high clinical need for treatments for this condition but considered that the data presented did not convincingly support the claims that omaveloxolone was superior in terms of effectiveness compared to BSC. Further, the PBAC advised that omaveloxolone was not cost-effective with an incremental cost-effectiveness ratio (ICER) of > $1,055,000 per quality adjusted life year (QALY) gained. The PBAC noted that this was based on the proposed published price, and although the submission indicated the effective price would be lower, it was not provided by the sponsor. The PBAC also considered that the estimated financial impact of listing omaveloxolone on the PBS was very high (approximately $900 million to < $1 billion over 6 years), although this was also based on the proposed published price (paragraph 7.1, omaveloxolone Public Summary Document [PSD], March 2025 PBAC meeting).

2.3 A summary of key PBAC concerns raised regarding the previous submission and how the resubmission addressed these are presented in Table 2.

Table 2: Summary of key matters of PBAC concern

	Matter of concern (omaveloxolone PSD, March 2025 PBAC meeting)	How the resubmission addresses it
PBS restriction	The ESC advised that it may be appropriate to restrict the use of omaveloxolone to patients diagnosed before the age of 40 years inclusive given patients over 40 years of age were excluded from the trial and as very late onset FA has a different disease course compared to classical FA, which has an onset during childhood and is the focus of this submission (para 3.3). The ESC considered that it would be appropriate to include a criterion stating that 'Patient must have a mFARS rating scale between 20 and 80' in the restriction to be consistent with the eligibility criterion in the MOXIe Part 2 trial (para 3.7). The ESC considered that it would be appropriate to include a continuing criterion which stated that "Patient must continue to demonstrate clinical benefit' (para 3.10).	The resubmission partially addressed the issues relating to the PBS restriction. The proposed initial supply restriction included a mFARS score of 20 to 80, aligning with the pivotal trial. In addition, the proposed continuing supply restriction included the criterion "Patient must continue to demonstrate clinical benefit". However, the proposed restriction did not include an upper age limit. The resubmission stated that this was to avoid introducing inequities. The resubmission argued that this approach was consistent with many other PBS listings that do not apply a maximum age, despite not including those patients in the clinical trials.
Clinical evidence	Whilst recognising the unmet need, the PBAC considered that the data did not convincingly support the claims of superior comparative effectiveness compared to BSC. In particular, the PBAC noted the uncertainty in magnitude and duration of improvement, particularly in patients with different disease severity (para 6.59 & 7.1).	The resubmission did not present updated data.

	Matter of concern (omaveloxolone PSD, March 2025 PBAC meeting)	How the resubmission addresses it
Economic model	The PBAC advised that omaveloxolone was not cost-effective with an ICER of > $1,055,000 per QALY gained. The PBAC noted that this was based on the proposed published price, and although the submission indicated the effective price would be lower, it was not provided by the sponsor (para 7.1). The ESC raised the following concerns: i) The approach utilised to model mortality was not appropriate as it resulted in a life expectancy that was longer than that published in literature (para 6.67). ii) The utility values applied did not relate mFARS to utility values for the full range of utility values applied in the economic model (para 6.68). iii) The assumption that the full treatment effect was maintained indefinitely while patients were on treatment was not appropriate (para 6.65).	The resubmission partially addressed the issues relating to the economic model. A revised base case was presented in the resubmission which addressed several key issues noted by the PBAC and ESC, including: (i) a lower published price plus an effective price that was [redacted]% lower than the published price (see below), (ii) updated utility data from a vignette study which reflected quality of life across the entire spectrum of mFARS scores, and (iii) revised mortality inputs which reduced overall survival in the model consistent with previous evaluator advice. The resubmission did not incorporate treatment waning in the base case analysis.
Financial estimates	The DUSC considered that the treatment continuation rate should consistent across the financial estimates and the economic model (Table 22).	While the resubmission changed the treatment (dis)continuation rate in the financial estimates, the applied values were not consistent with the economic model.
Pricing and RSA	A price reduction is required as the PBAC noted that the ICER was outside the range usually considered cost-effective (para 7.4).	The resubmission provided a reduced published price (from $[redacted] to $[redacted]). The proposed effective price is $[redacted] per pack. For expenditures that exceed the expected expenditure caps, a [redacted] cost-sharing rebate mechanism between the sponsor and the Government was proposed. Despite the revised price, the base case ICER presented by the resubmission was > $1,055,000per QALY gained.

Source: Table ES 1, ppxvi-xvii in the resubmission
DUSC = Drug Utilisation Sub-Committee; FA = Friedreich's ataxia; ICER = incremental cost-effectiveness ratio; mFARS = modified Friedreich's ataxia rating scale; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document; RSA = risk-sharing arrangement.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	№.of Rpts	Available brands
OMAVELOXOLONE					
Initial and continuing treatment					
Omaveloxolone, 50 mg capsules, 90	Published: $[redacted] Effective: $[redacted]	1	90	5	Skyclarys

Source: Table 1.7, p46 of the resubmission
DPMQ = dispensed price for maximum quantity.
Blue shading indicates information previously seen by the PBAC.

Category / Program: Section 85 - General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)

Indication: Friedreich's ataxia
Treatment Phase: Initial treatment
Clinical criteria:
The patient must have a mutation in the frataxin (*FXN*) gene
AND
The patient must have a score of 20 to 80 on the modified Friedreich Ataxia Rating Scale (mFARS),
AND
Patients with a history of clinically significant cardiac disease must show evidence that their disease is haemodynamically stable prior to initiating treatment (e.g. echocardiogram, electrocardiogram), records must be no more than 3 months old,
AND
The treatment must be given concomitantly with best supportive care for this condition
Treatment criteria:
Patient must be under the management of a specialist with experience and expertise in the management of Friedreich's ataxia. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit
Population criteria:
Patient must be 16 years of age or older.
Prescribing Instructions: The following must be documented in the patient's medical records: (a) Genetic diagnostic report confirming the presence of the Frataxin (*FXN*) gene mutation; and (b) Echocardiogram or electrocardiogram results confirming that the patient's cardiac disease is haemodynamically stable (if applicable). **Note** Clinically significant cardiac disease is defined as; (i) congenital or acquired valvular disease (ii) pericardial constriction (iii) restrictive or congestive cardiomyopathy (iv) coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina) (v) hospitalisation for heart failure in the last five years (vi) atrial fibrillation or arrhythmia
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. **Note** No increase in the maximum number of repeats may be authorised. **Note** No increase in the maximum quantity or number of units may be authorised. **Note** Special Pricing Arrangements apply.

Source: Table 1.9, p54 of the resubmission.
Blue shading indicates information previously seen by the PBAC.

Category / Program: Section 85 - General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Indication: Friedreich's ataxia
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,

AND
Patient must continue to demonstrate clinical benefit,
AND
Patients with a history of clinically significant cardiac disease must show evidence that their disease is haemodynamically stable prior to continuing treatment (e.g. echocardiogram, electrocardiogram), records must be no more than 12 months old,
AND
The treatment must be given concomitantly with best supportive care for this condition
Treatment criteria:
Patient must be under the management of a specialist with experience and expertise in the management of Friedreich's ataxia. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a unit
Prescribing Instructions: **Note** Clinically significant cardiac disease is defined as; (i) congenital or acquired valvular disease (ii) pericardial constriction (iii) restrictive or congestive cardiomyopathy (iv) coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina) (v) hospitalisation for heart failure in the last five years (vi) atrial fibrillation or arrhythmia **Note** The decision to permanently discontinue treatment with omaveloxolone for a particular patient needs to be taken in consultation with the patient and the treating physician and agreed by all parties.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. **Note** No increase in the maximum number of repeats may be authorised. **Note** No increase in the maximum quantity or number of units may be authorised. **Note** Special Pricing Arrangements apply.

Source: Table 1.10, p57 of the resubmission
Blue shading indicates information previously seen by the PBAC.

3.1 The resubmission proposed a SPA with an effective ex-manufacturer price (EMP) of $[redacted] per pack which represented a [redacted]% reduction from the published price.

3.2 The resubmission revised the proposed PBS restrictions as per previous ESC and/or PBAC advice and included:

- a criterion in the initial supply restriction stating that patient must have a modified Friedreich's ataxia rating scale (mFARS) score of between 20 and 80. This was consistent with the eligibility criterion in the MOXIe Part 2 trial (paragraph 3.7, omaveloxolone PSD, March 2025 PBAC meeting). The ESC considered that this inclusion was appropriate.

- a criterion in the continuing supply restriction which stated that a patient must continue to demonstrate clinical benefit (paragraph 3.10, omaveloxolone PSD, March 2025 PBAC meeting). Although this aligned with what had been proposed by the ESC in March 2025, the ESC noted that patients are expected to experience continued disease progression despite receiving treatment. Therefore, the ESC considered that a criterion based on mFARS score might be more appropriate, e.g. stating that treatment should be discontinued if the mFARS score increased by more than 2 points annually, compared to the previous year, or if the mFARS score exceeded 80. The ESC noted that similar conditions for reimbursement had been recommended for omaveloxolone in Canada in July 2025[1]. The pre-PBAC response noted that mFARS is a research tool and is not generally used in clinical practice and stated that performing an assessment yearly would be burdensome for clinicians and patients. The pre-PBAC response stated that the criterion "Patient must continue to demonstrate a clinical benefit" was sufficient.

3.3 In the previous submission, no upper age limit was proposed for patient's eligibility to omaveloxolone. This did not align with the key MOXIe Part 2 trial which only included patients up to 40 years of age. In March 2025, the ESC advised that it may be appropriate to restrict the use of omaveloxolone to patients diagnosed before the age of 40 years inclusive given patients over 40 years of age were excluded from the trial and as very late onset FA has a different disease course compared to classical FA, which has an onset during childhood and was the focus of the previous submission (paragraph 3.3, omaveloxolone PSD, March 2025 PBAC meeting). The resubmission stated that an upper age limit for eligible patients was not proposed to avoid inequities and to align with other PBS listings that do not apply a maximum age, despite not including those patients in the clinical trials. In addition, the resubmission argued that the minimum mFARS score of 20 in the proposed PBS restriction ensures that all patients regardless of age of onset of FA demonstrate a comparable level of disease severity at initiation of treatment. The ESC considered that this was reasonable.

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

4 Population and disease

4.1 FA is a rare, autosomal recessive and progressive multisystem neurodegenerative movement disorder that affects the central and peripheral nervous systems, the musculoskeletal system, the myocardium, and the endocrine pancreas. FA is caused by guanine-adenine-adenine (GAA) trinucleotide repeat expansions in the *FXN* gene, resulting in a deficiency in the protein frataxin. A greater number of GAA repeats is

[1] https://www.cda-amc.ca/sites/default/files/DRR/2025/SR0864-Skyclarys_Rec.pdf

associated with earlier symptom onset and more rapid progression, with more severe co-morbidities such as diabetes and cardiovascular disease.[2]

4.2 Mitochondrial dysfunction, suppression of nuclear factor erythroid 2 like 2 (Nrf2) activity, impaired iron metabolism, oxidative stress, and other metabolic abnormalities are the results of frataxin deficiency. As FA progresses, symptoms may include difficulty swallowing, speech problems, fatigue, skeletal abnormalities (such as scoliosis and pes cavus (which is an abnormally high and rigid longitudinal arch of the foot that does not flatten when bearing weight)), muscle weakness, reflex loss, and sensory impairment.

4.3 The mean age of onset of classical FA (the most common form) is between 10 and 16 years. For late-onset and very late-onset FA, the disease generally develops after the age of 25 and 40 years, respectively. Some people have presented with symptoms before the age of 5 years, including infants as young as 1 year old.[3] Patients with FA have an average life expectancy of 30 to 40 years. Cardiac complications are a leading cause of death in people with FA.[4]

4.4 The mFARS is an assessment tool which evaluates FA patient's motor function in four key areas including bulbar (i.e., cerebellum and the lower part of the brainstem), upper and lower limb coordination, as well as upright stability. The mFARS is used as a standardised way to measure disease severity and track disease progression or improvement, with higher scores indicating more severe physical impairment.[5] Pes cavus makes performing some aspects of the mFARS challenging as two of the four subsections of mFARS include assessments of lower limb coordination and upright stability. Therefore, in the key trial, patients with pes cavus (limited to 20%) were excluded from the primary analysis.

4.5 Age distribution of FA patients in the Australian Friedreich's Ataxia Clinical Outcome Measures Study (FACOMS) is summarised in Table 3.

[2] Delatycki, MB *et al*. Friedreich ataxia-pathogenesis and implications for therapies. *Neurobiology of disease* 2019; 132: 104606.

[3] Cook, A *et al*. Friedreich's ataxia: clinical features, pathogenesis and management. *British Medical Bulletin* 2017; 124(1): 19-30.

[4] Hanson, E *et al*. Heart disease in Friedreich's ataxia. *World Journal of Cardiology* 2019; 11(1): 1.

[5] Rummey, C *et al*. Psychometric properties of the Friedreich Ataxia Rating Scale. *Neurology Genetics* 2019; 5(6): 371.

Table 3: Australian FACOMS — distribution by age and mFARS

Stratification	Description	n	N	%
Age (age at current visit – visit 1)	< 16 years	50	202	24.8
	16-40 years	111	202	55.0
	> 40 years	41	202	20.3
	≥16 years	152	202	75.2
mFARS[a]	Disease severity			
	≥ 20 to ≤ 80	184	202	91.1
Age and mFARS[a] < 20 (age at diagnosis)	Analysis for cascade testing			
	≥16 years[b]	7	152	4.6
	16-25 years (intermediate onset)	4	56	7.1
	> 25 years (late onset)	2	39	5.1

Source: Table 1.8, p48 of the resubmission; Attachment 4 of the resubmission
FACOMS = Friedreich's Ataxia Clinical Outcome Measures Study; mFARS = modified Friedreich's ataxia rating scale.
[a] Scores from the version of mFARS used in the Australian FACOMS ranged from 0 to 93, whereby the bulbar function section is scored from 0 to 5. The mFARS in the key trial MOXIe Part 2 scored on a scale of 0 to 99, with the bulbar function scored from 0 to 11. A higher score indicates more severe physical impairment.
[b] Age at current visit (Visit 1)
Blue shading indicates information previously seen by the PBAC.

4.6 Diagnosis of FA is based on presentation of symptoms (gait ataxia, balance, and coordination disturbances), confirmed by genetic testing for GAA expansion in the *FXN* gene. FA is usually diagnosed during childhood or adolescence. The clinical diagnosis of FA is performed through a number of tests including a review of a person's medical history, a medical examination, magnetic resonance imaging (MRI), and potentially an electrocardiogram or echocardiogram, with genetic testing providing a conclusive diagnosis. In Australia, diagnosis is usually confirmed with a paediatric neurologist in close collaboration with a paediatric geneticist.

4.7 A genetic counsellor should be involved in patient care, to provide emotional support, information about the test and results, and advice on testing siblings and other family members. Neurologists should liaise with their clinical genetic counterparts given the potential implications for family members of patients who undergo genetic testing including any reproductive choices they may make. Informed consent should be sought from all undergoing genetic testing.

4.8 Omaveloxolone is an orally bioavailable triterpenoid analogue and a potent activator of the transcription factor, Nrf2. Omaveloxolone selectively and reversibly binds to Keap1 (Kelch-like ECH-associated protein 1), allowing for nuclear translocation of Nrf2 and transcription of its target genes. Nrf2 controls the expression of genes involved in mitochondrial function, redox balance, and inflammation. Omaveloxolone is proposed to be used for the treatment of FA in adults and adolescents aged 16 years and older.

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

5 Comparator

5.1 The resubmission again nominated BSC as the main comparator. BSC for FA involves the management of disease-related symptoms (cardiac, metabolic, respiratory,

nutritional, and orthopaedic support) via a multi-disciplinary clinic. The ESC previously considered that the nomination of BSC as the main comparator was appropriate (paragraph 5.1, omaveloxolone PSD, March 2025 PBAC meeting).

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

6 Consideration of the evidence

6.1 The resubmission did not present any new clinical evidence and there were no new data cutoffs. Updated propensity score matched analyses, with a follow up of 5 years, were presented in the Pre-Sub-Committee Response (PSCR). Blue shading in tables in this section indicates information/data previously considered by the PBAC.

Sponsor hearing

6.2 There was no hearing for this item.

6.3 The PBAC recalled that there was a sponsor hearing in March 2025 at which the clinician described the mFARS scale which was used to measure response in the MOXIe Part 2 trial. The clinician stated that the difference of -2.40 points between the omaveloxolone and placebo arms at Week 48 was clinically significant compared to natural history studies which have shown that FA patients generally progress at an average of 1.8 points annually on the mFARS scale (Patel et al., 2016). The clinician stated that omaveloxolone potentially slowed disease progression by more than a year, allowing patients to continue to undertake daily activities and maintain independence for longer. Additionally, the clinician noted the reduction in mFARS score may also represent improvements to caregivers including reducing the amount of carer hours required and unpaid care provided by family.

Consumer comments

6.4 The PBAC noted and welcomed the input from individuals (46) and an organisation (1) via the Consumer Comments facility on the PBS website. The PBAC also recalled that in March 2025 input was received from individuals (77), health care professionals (10) and organisations (2).

6.5 The comments from individuals (in March and November 2025) included patients with FA and parents, family members, partners or caregivers of people living with FA. Input described the impacts of this condition, which consist of progressive symptoms affecting walking, balance, speech and coordination, reducing people's ability to undertake daily tasks and quality of life. The comments also described how important it was for patients to find treatments that would delay disease progression. The comments noted that, despite not being a cure, omaveloxolone has the potential to preserve functionality, reduce symptoms of disease (such as drooling and tremors) and delay life-limiting outcomes such as diabetes and disability. Input from caregivers highlighted the substantial difficulties and challenges in witnessing and supporting progressive FA decline. The potential benefits of omaveloxolone were described, including a slowing of disease progression, improvement in daily functioning, and

reduction in symptoms. This allowed patients to regain or retain independence and continuing working and participating in social and sporting activities, in addition to reducing caregiver burden. The input also stated omaveloxolone was well tolerated and that adverse events such as headache, nausea and diarrhoea were manageable.

6.6 The PBAC noted that advice received from the National Paediatric Medicines Forum which, noting the high unmet need for disease-modifying treatments in FA, supported the resubmission.

6.7 The PBAC again noted the input from health professionals received in March 2025 from neurologists, clinical researchers/investigators, physiotherapists and an occupational therapist. The health professionals described the significant impact of this progressive neurogenerative condition on quality of life, stating that FA slowly reduces the capacity for people to undertake daily tasks, walk, talk and swallow food. Vision and sight become impaired, there may be curvature of the spine, pain, limb spasticity, continence issues, muscle weakness, changes in sleep and fatigue and significant depression. Clinicians stated that the retention of functional capacities was crucial to quality of life and that omaveloxolone can slow the progression of the disease, allowing people to maintain their functional capacity, remain ambulant for longer and reduce/delay the need for carer assistance requirement. Clinicians stated that omaveloxolone has a favourable safety profile with very few people needing to cease treatment due to adverse events, but noted a need for monitoring for elevated liver enzymes and that withdrawal from the medication can result in accelerated degeneration.

6.8 Further the PBAC recalled the advice received from Friedreich's Ataxia Research Alliance (FARA) and Friedreich Ataxia Research Association in March 2025. Both organisations noted there are currently no approved treatments for FA in Australia. Additionally, both organisations noted that symptom management is not enough to fight this disease, as it does nothing to slow disease progression and results in high financial and social burden. Both organisations were supportive of the listing of omaveloxolone, noting the most important benefit of this treatment was the slowed progression of disease which resulted in retention of motor function, allowing individuals with FA to remain employed for longer, prevent falls that result in emergency room visits, and prolong individuals' abilities to independently perform activities of daily living, reducing the need for personal care assistants or reliance on family members. The comments also noted the side effects of omaveloxolone were minimal and include transient elevation of liver function enzymes, elevated cholesterol, headache, diarrhoea, and nausea.

Clinical studies

6.9 MOXIe Part 2 represents the key evidence to support the clinical claim in the resubmission. This was a randomised, placebo-controlled, double-blind trial assessing the efficacy and safety of omaveloxolone 150 mg once daily for 48 weeks in FA patients aged 16-40 years. A total of 103 FA patients with or without pes cavus

received omaveloxolone (n=51) or placebo (n=52) in the 'All Randomised' population. Randomisation was stratified by pes cavus status (pes cavus versus no pes cavus).

6.10 A total of 82 FA patients without pes cavus received omaveloxolone (n=40) or placebo (n=42). This was the study's pre-specified primary 'Full Analysis' set (FAS). Patients with pes cavus were limited to 20% of the total study population. The rationale for this approach was based on efficacy findings from the dose ranging study MOXIe Part 1 study and the hypothesis that the presence of this deformity may represent a different subtype of FA, with a different pathophysiology and clinical phenotype.

6.11 Details of the MOXIe Part 2 trial are provided in Table 4.

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
MOXIe Part 2 NCT02255435	Clinical study report: RTA 408 (Omaveloxolone) 408-C-1402 Part 2: A Clinical Study Report: Phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of Friedreich's ataxia.	5 November 2020
	Lynch DR, Chin MP, *et al*. Safety and efficacy of omaveloxolone in Friedreich ataxia (MOXIe study).	*Annals of Neurology* 2021; 89(2):212-225
	Hendrix S, Goldsberry A, *et al*. Efficacy of omaveloxolone in Friedreich's ataxia: Post-hoc analysis using global statistics test to strengthen secondary endpoint analyses [Conference abstract].	*Neurology* 2023; 100 (17_supplement_2)
	Zaoui P, Chin M, *et al*. Kidney effects in the moxie trial: A study of omaveloxolone in patients with Friedrich's ataxia [Conference Abstract].	*Nephrology dialysis transplantation* 2020; 35(supplement 3), iii526
	Boesch S, Delatycki M, *et al*. The MOXIe trial of omaveloxolone in Friedreich Ataxia: exploring the transient nature of treatment-emergent adverse events [Conference abstract].[a]	*Neurology* 2024; 102(17).
	Lynch DR, Boesch S, *et al*. Efficacy and safety results from part 2 MOXIe: A randomized, double-blind, placebo-controlled trial of omaveloxolone in Friedreich ataxia [Conference abstract].[a]	*Neurology* 2020; 95(4): E439.
Propensity score matched analysis	Clinical study report: RTA 408 post hoc propensity-matched analysis of Study 408-C-1402 extension and natural history.	24 August 2022.
	Lynch DR, Goldsberry A, *et al*. Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data.	*Annals of clinical and translational neurology* 2024; 11(1):4-16.

Source: Table 2.3, pp72-74 of the resubmission

Blue shading indicates clinical evidence previously seen by the PBAC.

[a] Although two conference abstracts were identified which were not included in the previous submission, data from these abstracts were not used in the resubmission.

6.12 The key features of the MOXIe Part 2 trial are summarised in Table 5.

Table 5: **Key characteristics of the key MOXIe Part 2 trial**

Design	Treatment regimens	Patient population	N	Efficacy outcomes	Safety outcomes	Risk of bias/applicability
MC, DB, PC, PG, Phase 2 RCT	Omaveloxolone 150 mg once daily for 48 weeks OR Placebo orally once daily for 48 weeks	Demographics Male: 53% Mean age: 24 yo White: 97% Mean mFARS score: 40 Inclusion criteria 16 to 40 yo with genetically confirmed FA -mFARS score ≥20 - ≤80 Exclusion criteria Uncontrolled diabetes BNP > 200 pg/mL History of significant cardiac or hepatic disease.	ITT N = 103 Oma, n = 51; Pla, n = 52 FAS (without pes cavus) N = 82 Oma, n = 40; Pla, n= 42	Primary endpoint: LSM change from baseline in mFARS score at 48 weeks Secondary Endpoints: LSM change in PGIC from baseline at 48 weeks LSM change in CGIC from baseline at 48 weeks	Any SAE; Discontinuation due to AE; Increased ALT; Increased AST.	Selection bias: Unclear due to small sample size and imbalances for some baseline characteristics. Performance bias: Unclear as AEs may have resulted in unblinding. Detection bias: Unclear (see performance bias). Attrition bias: High. Reporting bias: Low.

Source: Section 2 of the resubmission and the MOXIe Part 2 Clinical Study Report
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = beta natriuretic peptide; CGIC = Clinical Global Impression of Change; DB = double blind; FA = Friedreich's ataxia; FAS = full-analysis set; ITT = intention to treat; MC = multi-centre; mFARS = modified Friedreich's ataxia rating scale; LSM = least squares mean; oma = omaveloxolone; PC = placebo controlled; PG = parallel group; PGIC = Patient Global Impression of Change; Pla = placebo; RCT = randomised controlled trial; SAE = serious adverse event; yo = years old
Blue shading indicates information previously seen by the PBAC.

6.13 Patients were randomised in a 1:1 ratio to 48 weeks of omaveloxolone (150 mg daily) or placebo. Acknowledging the standard approach of randomisation, the small number of patients per treatment arm (approximately 40 patients per arm in the FAS [without pes cavus] and approximately 50 patients per arm in the total randomised population) resulted in some imbalances in baseline characteristics that could potentially confound the comparative efficacy. The overall direction of the impact of confounding was unclear.

6.14 All patients and investigators involved in the conduct of the study were blinded to treatment assignment. However, the risk of bias due to unblinding, as a result of adverse events (AEs) that were consistent with the known safety profile of omaveloxolone (such as an increase in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels), remained unclear. Furthermore, the risk of confounding from differential attrition rates was considered potentially high given the higher percentage of missing data in the omaveloxolone arm (15%) compared to the placebo arm (2.3%) and the small sample size of the analysis set.

6.15 Most patients completed treatment through to Week 48 (91.3%), although there was a higher treatment discontinuation rate in the omaveloxolone arm compared to the placebo arm (13.7% versus 3.8%). The most common reason for treatment discontinuation was due to an AE (7.8% versus 3.8%).

6.16 To help inform the longer-term magnitude of benefits with omaveloxolone treatment, the same indirect comparison as presented in the previous submission was

reproduced in the resubmission. This was a post hoc propensity-matched unanchored indirect comparison analysis of the MOXIe Extension study compared with the natural history FACOMS study.

Comparative effectiveness

6.17 The primary endpoint in MOXIe Part 2 was the change in mFARS scores from baseline to Week 48 (99-point scale).

6.18 As in the previous submission, the resubmission nominated the minimally clinical important difference (MCID) of a change in baseline of less than or equal to -1 point in mFARS (on a 99-point scale). The ESC has previously raised the concern that a change from baseline of less than or equal to -1 point in mFARS on a 99-point scale could be the result of random variation or measurement error (paragraph 6.18, omaveloxolone PSD, March 2025 PBAC meeting). In consideration of the resubmission, the ESC noted that the Canadian Drug Expert Committee (CDEC) had also noted that there was no defined MCID for mFARS and therefore there was uncertainty regarding how important the difference between omaveloxolone and placebo, demonstrated in the MOXIE Part 2 trial, was to patients. Overall, the CDEC noted that although mFARS has limitations, it is a validated tool for assessing neurologic function across the four domains (bulbar, upper limb coordination, lower limb coordination and upright stability) and recommended its use for evaluating the response to treatment with omaveloxolone.[6] The pre-PBAC response noted that clinical experts advised the CDEC that "a change in 2 points in the mFARS score is considered clinically meaningful, but also that the stabilisation of disease over a long period would be considered beneficial given the progressive nature of FA".[6]

6.19 The primary analysis was based on the FAS which included all patients without pes cavus who had at least one post-baseline measurement, irrespective of whether a patient was receiving treatment.

6.20 Table 6 summarises the results for the primary outcome of mean change from baseline in mFARS for the FAS population in the key MOXIe Part 2 trial. Figure 1 shows the change from baseline in mFARS over time in the FAS.

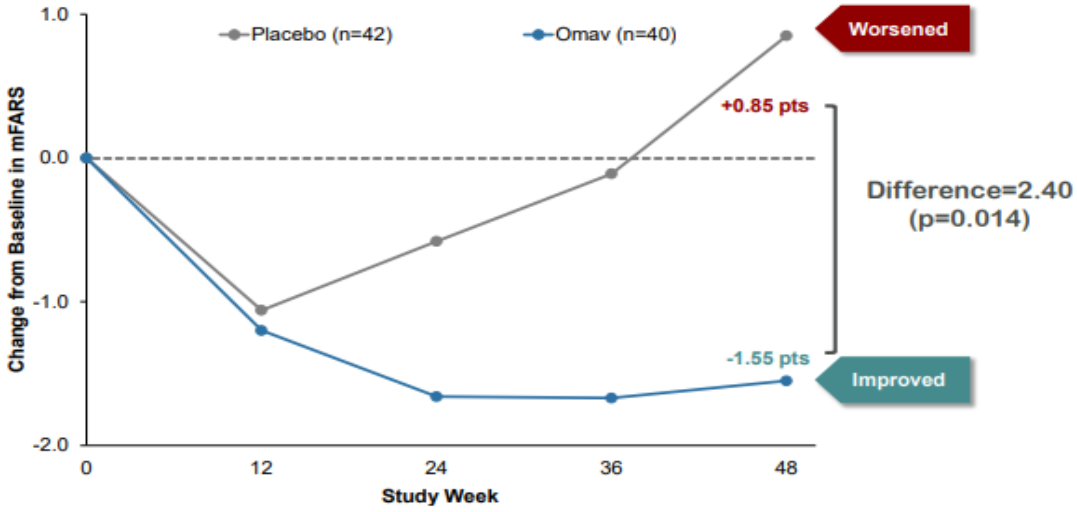
[6] Canada's Drug Agency (CDA-AMC). Reimbursement Recommendation: omaveloxolone (Skyclarys). July 2025; Volume 5, Issue 7.

Table 6: Mean change in mFARS score from baseline at Week 48 in MOXIe Part 2 (FAS)-patients without pes cavus

Measure	Omaveloxolone 150 mg (N=40)	Placebo (N=42)
Baseline score		
N	40	42
Mean (SD)	40.94 (10.39)	38.77 (11.03)
Median (range)	39.15	35.65
Week 48 score		
N	34	41
Mean (SD)	39.17 (10.02)	39.54 (11.57)
LS mean (SE)	-1.55 (0.69)	0.85 (0.64)
Median (range)	38.10	38.70
LS mean difference (SE) [95% CI]; p-value	-2.40 (0.96) [-4.31, -0.50]; 0.0141	

Source: Table 2.19, p112 of the resubmission.
CI = confidence intervals; FAS = full analysis set; LS = least squares; mFARS = modified Friedreich's ataxia rating scale; N = number of participants in treatment arm/with available data; SD = standard deviation; SE = standard error.
Note: LS means calculated from mixed model repeated measures. LS mean difference refers to difference in LS means change from baseline of omaveloxolone – placebo
Blue shading indicates data previously seen by the PBAC.

Figure 1: MOXIe Part 2 - Change from baseline over time in mFARS by visit (FAS)



Source: Figure 2.4, p99 of the resubmission
FAS = full analysis set; mFARS = modified Friedreich's ataxia rating scale; Omav = omaveloxolone
This figure has been previously seen by the PBAC.

6.21 The study met its primary efficacy objective. For the FAS with no pes cavus (N=82), there was a statistically significant difference of -2.40 points in mFARS at Week 48 (on a scale of 99) favouring the omaveloxolone arm compared to the placebo arm (p=0.0138). Although the difference in mFARS at Week 48 (-2.40 points) between the omaveloxolone and placebo arms was statistically significant, the ESC previously considered this was a small change on a 99-point scale, and considered it was uncertain whether it would result in benefits in terms of disease outcomes for the patient (paragraph 6.21, omaveloxolone PSD, March 2025 PBAC meeting).

6.22 In the total randomised population (N=103) that included patients with pes cavus, treatment with omaveloxolone significantly improved mFARS by -1.94 points relative to that for placebo (p=0.0331).

6.23 Whilst 52.5% of patients in the omaveloxolone arm compared to 42.8% in the placebo arm showed improvement from baseline in mFARS, the higher percentage of missing data in the omaveloxolone arm compared to the placebo arm (15.0% versus 2.3%) decreased confidence in the results. The 15% of patients with missing data in the omaveloxolone arm could fall into either improvement or worsening categories. Overall, based on a worst-case scenario presented in the resubmission for omaveloxolone where all 15% of patients were assumed to have worsened, and recognising the low attrition rate in the placebo arm, the difference in mFARS would remain favourable to omaveloxolone, although the treatment effect would be modest.

6.24 Tipping point sensitivity analyses of missing data (also referred to 'breakdown point' in robust statistical theory), where various 'shifts' of the imputed data in the omaveloxolone group were presented in the MOXIe Part 2 clinical study report (CSR). The ESC previously noted that generally, tipping point analysis was a reasonable, valid, somewhat subjective and well documented approach to assess the impact of imputation on analyses (paragraph 6.25, omaveloxolone PSD, March 2025 PBAC meeting). The tipping point for the trial, where the treatment effect loses statistical significance, was a shift of +2 points (worsening) in the imputed data for missing mFARS values in the omaveloxolone arm at Week 48. Recognising that this shift was more than twice the magnitude of worsening in the placebo arm (+0.85 points), and that these analyses suggested the primary analysis might be robust, the ESC previously agreed with the evaluation that concerns remained as to whether the decreased differences between the treatment arms resulting from worsening shifts for omaveloxolone were clinically meaningful (paragraph 6.25, omaveloxolone PSD, March 2025 PBAC meeting).

6.25 Treatment with omaveloxolone numerically improved each of the individual components of the mFARS assessment (bulbar, upper/lower limb coordination, and upright stability) relative to placebo although the difference for lower limb coordination was not statistically significant. The largest treatment effects were observed for upper limb coordination and upright stability. The resubmission noted that the improvements in upright stability with omaveloxolone, relative to those for placebo, demonstrated an effect on the mFARS component that defines important clinical milestones in FA, including loss of ambulation.

6.26 In the subset of patients with severe pes cavus (n=20), the improvement with omaveloxolone in mFARS relative to placebo was not statistically significant (-1.19 points; p=0.5379). Whilst there was high uncertainty arising from the small sample size of the subset, a potential impact of foot structure on performance could not be excluded.

6.27 Analysis of secondary endpoints based on the FAS indicated that the mean Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) scores at Week 48 numerically favoured the omaveloxolone arm but were not statistically different from placebo. The least squares mean difference between treatment arms for PGIC was -0.43 (p=0.1300) and for CGIC was -0.13 (p=0.5259). Higher scores in PGIC and CGIC indicate worsening. In the total randomised population, a nominally positive p-value was observed with PGIC (p=0.0282) but not for CGIC (p=0.1328).

6.28 The least squares mean difference between treatment arms for change in Activities of Daily Living (ADL) scores from baseline at Week 48 was -1.30 points, favouring omaveloxolone relative to placebo, which reached nominal statistical significance (p=0.04). These results should be interpreted with caution given the small data sets and lack of adjustment for multiplicity in the statistical analyses.

6.29 An unanchored propensity matched indirect comparison to help inform the relative longer-term magnitude of benefit with omaveloxolone treatment versus BSC was presented in the previous submission and reproduced in the resubmission. The analysis compared omaveloxolone treated patients in the MOXIe Extension study and the FACOMS natural history cohort.

6.30 Analysis of change from baseline in mFARS at Year 3 was based on a mixed model repeated measures (MMRM) model. For the propensity-matched analysis, the sample size was based on the 136 patients from the MOXIe Extension study who had post-baseline mFARS assessment data and were thus available for matching to 136 patients from the FACOMS natural history cohort.

6.31 The median treatment duration in MOXIe Extension (exclusive of treatment duration in Part 1 or Part 2) was 2.76 years. The 136 patients matched from FACOMS had a median follow-up duration of 2.92 years.

6.32 Demographics and baseline FACOMS covariates which were matched to MOXIe Extension for propensity score calculation are summarised in Table 7.

Table 7: Demographics and baseline FACOMS covariates matched to MOXIe Extension for propensity score calculation

	Matched FACOMS (n=136)	MOXIe Extension (N=136)
Covariates		
Age in years, mean (SD)	26.2 (13.7)	26.6 (7.3)
Age at FA onset in years, mean (SD)	15.2 (10.2)	15.5 (5.3)
Sex, n (%)	70 (51.5%)	70 (51.5%)
mFARS	41.0 (16.1)	42.2 (12.6)
Gait[a]	2.7 (1.69)	2.8 (1.36)
Other characteristics [b]		
White n (%)	125 (96.2%)	133 (97.8%)
BMI (kg/m^2)	22.0 (5.7)	24.0 (5.2)
ADL total score	11.8 (5.9)	12.5 (4.9)
GAA1 repeat length	589.7 (245.5)	720.9 (269.6)
GAA2 repeat length	862.8 (232.4)	727.6 (296.9)

Source: Table 2.44, p157 of the resubmission.
BMI=body mass index; FA=Friedreich's ataxia; FACOMS= Friedreich's Ataxia Clinical Outcome Measures Study; GAA= guanosine adenosine adenosine; mFARS= modified Friedreich's ataxia rating scale; SD = standard deviation
[a] Assessment in FARS subsection E-Upright stability
[b] Note number of patients in either cohort varied across other characteristics due to missing data
Blue shading indicates data previously seen by the PBAC.

6.33 Covariates for determining the propensity scores (mFARS, Gait, and ADL) appeared balanced between the FACOMS and MOXIe Extension groups. However, the resubmission noted that prognostic covariates such as GAA1 repeat length and pes cavus were considered but not included for matching due to incomplete GAA1 data for all patients and differences in the method of evaluation of pes cavus[7] between studies.

6.34 Results from the propensity score matched analysis for change in mFARS from baseline at 3 years are summarised in Table 8.

Table 8: Change from baseline in mFARS at 3 years: PSMA

	Matched FACOMS (N=136)	MOXIe Extension (N=136)
Baseline, mean (SD)	41.0 (16.1)	42.2 (12.6)
mFARS change from baseline at Year 3, LS mean (SE)	6.61 (0.65)	3.00 (0.66)
Differences at Year 3	-3.61 (0.93); p=0.0001	

Source: Table 2.45, p158 of the resubmission.
FACOMS = Friedreich's Ataxia Clinical Outcome Measures Study; LS = least squares; mFARS = modified Friedreich's ataxia rating scale; PSMA = propensity-score matched analysis; SD = standard deviation; SE = standard error
Blue shading indicates data previously seen by the PBAC.

6.35 Whilst the matched FACOMS patients progressed 6.6 mFARS points after three years, patients treated with omaveloxolone in MOXIe Extension progressed 3.0 points (difference in LS means (SD) -3.6 (0.66) points; nominal p=0.0001). Progression in mFARS was reduced by 55% in the omaveloxolone treatment arm compared to the matched control arm.

[7] The definition of pes cavus between the two studies was not consistent. Pes cavus was based on clinical judgment in FACOMS; however, MOXIe Extension defined a flashlight test such that if light was visible under the arch of the foot while standing the patient was deemed as having pes cavus.

6.36 The PSCR presented updated data from the propensity score matched analysis that demonstrated that there was an 8-point difference, which was equivalent to a 67% reduction in cumulative mFARS progression, at 5 years. The ESC noted that this analysis was based on a smaller group of patients receiving omaveloxolone (43 versus 136) and that no absolute values at baseline were presented. In addition, the ESC considered that the updated data had the same potential limitations as the original 3-year analysis (see paragraph 6.37). The pre-PBAC response stated that the 43 patients included in the 5 year follow up data had received omaveloxolone in the MOXIE Part 2 trial as well as the open label extension and reflected real-world clinical outcomes.

6.37 The following issues with the indirect comparisons were identified in the March 2025 evaluation (paragraphs 6.46, omaveloxolone PSD, March 2025 PBAC meeting):

- Additional important prognostic covariates such as GAA1 repeat length and pes cavus were not included due to incomplete data and differences in the method of evaluation, respectively.
- There was no indication that differences in the collection of data regarding concomitant medications were adjusted for. Recognising there are no approved treatments for FA, there was use of antioxidants, vitamins, and/or minerals in both studies, administered as BSC in an attempt to slow symptoms of disease progression. The comparability of clinical care of patients including physical therapy and training exercise, occupational therapy, routine orthopaedic care, gait aid provisions etc., between the MOXIe Extension study and the FACOMS registry was unknown.
- There was potential selection bias. MOXIe Extension patients may have been healthier at baseline or responded better to omaveloxolone than those who did not participate in the extension study, which would bias measures of association towards a beneficial effect of omaveloxolone. Another concern was that the natural history study was likely to have less stringent inclusion and exclusion criteria, thus the included patients might be more likely to have severe FA, which would bias associations away from the null favouring omaveloxolone.
- Study participants in MOXIe Extension were excluded if they had a history of clinically significant cardiac disease, uncontrolled diabetes, B-type natriuretic peptide value > 200 pg/mL, and cognitive impairment that may preclude ability to comply with study procedures. Thus, participants in the extension study were likely healthier and more able to comply with completion of mFARS assessments compared to the FACOMS study patients. This would bias associations away from the null and possibly favour omaveloxolone.
- Study participants and researchers were not blinded to treatment status and the data collection processes differed between the two studies. Thus, there could be differences in the way study staff measured or recorded outcomes that biased the study effect estimates. The main outcome (mFARS) is a clinician-observed/performance-based outcome with standardised instructions. Misclassification remained a concern.

- The impact of differences in frequency of mFARS assessment between the two studies remained unknown. In the FACOMS natural history study, mFARS assessment was conducted on an annual basis, whereas mFARS was scheduled to be performed every 24 weeks in MOXIe Extension.
- The *post-hoc* nature of the analysis.

Comparative harms

6.38 AEs and common treatment-emergent AEs (TEAEs) from MOXIe Part 2 are summarised in Table 9.

Table 9: Overall AEs and TEAEs in MOXIE Part 2 (Safety population)

AE	Omaveloxolone 150 mg (N=51)	Placebo (N=52)	RD (95% CI)
Patients with at least one AE	51/51 (100%)	52/52 (100%)	0.00 (0.00, 0.00)
Patients with at least one drug-related AE	37/51 (72.6%)	19/52 (36.5%)	0.36 (0.17, 0.55)
Patients with at least one severe AE	5/51 (9.8%)	0/52 (0%)	0.10 [0.02, 0.18)
Patients with at least one SAE	5/51 (9.8%)	3/52 (5.8%)	0.04 (-0.06, 0.14)
Patients with at least one drug-related SAE	1/51 (2.0%)	0/52 (0%)	0.02 (-0.02, 0.06)
Patients with AEs leading to permanent treatment discontinuation	4/51 (7.8%)	2/52 (3.8%)	0.04 (-0.05, 0.13)
TEAEs ≥ 20% of patients in either treatment arm			
Nausea	17/51 (33.3%)	7/52 (13.5%)	0.20 (0.04, 0.36)
Abdominal pain	11/51 (21.6%)	3/52 (5.8%)	0.16 (0.03, 0.29)
Diarrhoea	10/51 (19.6%)	5/52 (9.6%)	0.10 (-0.04, 0.24)
Fatigue	11/51 (21.6%)	7/52 (13.5%)	0.08 (-0.07, 0.23)
ALT increased	19/51 (37.3%)	1/52 (1.9%)	0.35 (0.20, 0.51)
AST increased	11/51 (21.6%)	1/52 (1.9%)	0.20 (0.07, 0.32)
Headache	19/51 (37.3%)	13/52 (25.0%)	0.12 (-0.06, 0.30)

Source: Summarised from Table 2.34, p136 of the resubmission.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence intervals; RD = risk difference; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Blue shading indicates data previously seen by the PBAC.

6.39 The incidence of drug-related TEAEs (72.6% versus 36.5%), serious TEAEs (9.8% versus 5.8%), and TEAEs leading to permanent treatment discontinuation (7.8% versus 3.8%) was consistently higher in the omaveloxolone arm than in the placebo arm. TEAEs were mostly mild or moderate in severity in both treatment arms (> 90%) and most TEAEs subsequently resolved within 2 months of the event start date. No deaths were reported in either treatment arm of MOXIe Part 2.

6.40 The most common TEAEs (≥ 20% incidence in either treatment arm) with ≥ 5% difference in incidence in the omaveloxolone arm compared with the placebo arm were increased ALT (37.3% versus 1.9%), increased AST (21.6% versus 1.9%), headache (37.3% versus 25.0%), nausea (33.3% versus 13.5%), fatigue (21.6% versus 13.5%), and abdominal pain (21.6% versus 5.8%). Increased ALT, increased AST, and headache were considered by the investigators to be related to omaveloxolone. A peak of mean absolute ALT and AST levels was observed at Week 2 in the omaveloxolone treatment arm with a subsequent decrease in values through Week 48 toward baseline.

6.41 Within the Cardiac disorders category, three (5.9%) omaveloxolone treated patients and one (1.9%) placebo treated patient experienced serious TEAEs. Small mean increases in B-type natriuretic peptide (BNP) were observed with omaveloxolone treatment relative to placebo and two (3.9%) patients had BNP values that exceeded 200 pg/mL.

6.42 The resubmission noted that the clinical circumstances underlying the increased frequency of heart failure events observed in patients with Stage 4 chronic kidney disease (CKD) and cardiac diastolic dysfunction treated with bardoxolone, another Nrf2 modulator, in the BEACON study[8] were unlikely to apply to the FA patient population who have low risk for advanced CKD and diastolic dysfunction. The EMA assessment report noted that available non-clinical data suggest that the pharmacology and safety profiles of omaveloxolone and other Nrf2 activators are similar (Committee for Medicinal Products for Human Use [CHMP] report for omaveloxolone, EMA/CHMP/535977/2023). Considering this, in addition to the observations of congestive heart failure in the bardoxolone study and the cardiovascular risk in FA patients, cardiotoxicity remained a safety concern with omaveloxolone.

Benefits/harms

6.43 A summary of the comparative benefits and harms for omaveloxolone versus placebo (proxy for BSC) is presented in Table 10.

[8] Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events; Study 402-C-0903

Table 10: Summary of the comparative benefits and harms for omaveloxolone versus placebo (proxy for best supportive care) – MOXIe Part 2

Benefits			
(Full Analysis Set) - patients without pes cavus			
	Oma 150 mg N=40	**Placebo N=42**	**LS mean difference (SE) Oma minus placebo**
Mean change in mFARS from baseline at Week 48			
Mean score (SD) at baseline	40.94 (10.39)	38.77 (39.3)	–2.40 (0.96)[a]
Mean score (SD) at Week 48	39.17 (10.02)	39.54 (11.57)	
Mean change in PGIC from baseline at Week 48			
LS mean change from baseline at Week 48	3.89	4.32	–0.43 (p=0.13)
Mean change ADL from baseline at Week 48			
LS mean change from baseline at Week 48	-0.17	1.14	–1.3 (nominal p=0.04)
Patients with pes cavus			
	Oma 150 mg N=10	**Placebo N=10**	**LS mean difference (95% CI) Oma minus placebo**
LS mean change in mFARS from baseline at Week 48	0.15 (-2.62, 2.91)	1.33 (-1.29, 3.96)	-1.19 (-5.19, 2.82)
Harms (Safety population – all randomised patients)			
Event	**Oma 150 mg, n/N**	**Placebo, n/N**	**Risk difference (95% CI) Oma minus placebo**
Patients with at least one severe AE	5/51	0/52	0.10 (0.02, 0.18)
ALT increased	19/51	1/52	0.35 (0.20, 0.51)
AST increased	11/51	1/52	0.20 (0.07, 0.32)

Source: Paragraph 6.56, Table 14, p25, omaveloxolone PSD, March 2025 PBAC Meeting

ADL = activities of daily living; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; LS = least squares; mFARS = modified Friedreich's ataxia rating scale; Oma = omaveloxolone; PGIC = patient global impression of change; PSD = Public Summary Document; SD = standard deviation.

[a] In the subset of patients with severe pes cavus (n=20), the improvement with omaveloxolone in mFARS relative to placebo was not statistically significant (-1.19 points; p = 0.5379)

Blue shading indicates data previously seen by the PBAC.

6.44 On the basis of direct evidence presented in the resubmission, after 48 weeks of treatment:

- omaveloxolone significantly improved mFARS (mean difference of -2.4, p=0.014) and ADL (mean difference of -1.3, p=0.04) relative to placebo in patients without pes cavus (n = 82, FAS). There was some uncertainty regarding the clinical meaningfulness of these changes.
- in patients with pes cavus (n=20), the improvement with omaveloxolone in mFARS relative to placebo was not statistically significant (-1.19 points; p = 0.5379).
- there was a trend favouring omaveloxolone compared to placebo in terms of PGIC, but the improvement was not statistically significant.
- for every 100 FA patients treated with omaveloxolone in comparison with placebo, 10 additional patients will experience a serious AE, 35 additional patients will experience an increase in ALT levels above normal, and 20 additional patients will experience an increase in AST levels above normal.

Clinical claim

6.45 The resubmission again described omaveloxolone as superior in terms of effectiveness and inferior in terms of safety compared to BSC.

6.46 Overall, while noting the rarity and severity of the condition and the absence of clinically effective alternatives, the ESC considered that the available evidence suggested that omaveloxolone potentially slowed disease progression. However, the ESC noted that the following uncertainties regarding the clinical evidence identified in the March 2025 submission remained (paragraph 6.58, omaveloxolone PSD, March 2025 PBAC meeting):

- Acknowledging the rarity of the condition, the patient numbers were small, making the efficacy results imprecise. Comparative superiority can only be concluded within the short time frame of 48 weeks in the key MOXIe Part 2 trial.
- The difference in change from baseline in mFARS at Week 48 (-2.40 points) favoured omaveloxolone over placebo (as a proxy for BSC) which was statistically significant. However, the precision of the measured change (-2.40 points) and whether it would result in benefits in terms of disease outcomes for the patient remained somewhat uncertain.
- The higher percentage of missing data in the omaveloxolone arm compared to the placebo arm for the mFARS primary endpoint (15.0% versus 2.3%) decreased confidence in the primary results as they were based on the assumption that data were missing at random. The impact of the missing data could mean that the difference between omaveloxolone and placebo was smaller than presented.
- Although the trial was double-blinded, there was a high risk of unblinding due to AEs associated with omaveloxolone such as an increase in transaminase levels. This could have further biased the results away from the null towards favouring omaveloxolone over placebo.
- Results for the key secondary outcomes of PGIC and CGIC were only directionally favourable for omaveloxolone and not statistically significant. These results did not provide strong support for the results of the primary outcome.
- In the subset of patients with severe pes cavus (n=20), the improvement with omaveloxolone in mFARS relative to placebo was not statistically significant (-1.19 points; p=0.5379). Whilst there was high uncertainty arising from unreliability of the small sample size of the subset, an impact of foot structure on performance could not be excluded.
- The 3-year follow up data presented to support the longer-term comparative effectiveness of omaveloxolone versus BSC was based on an unanchored propensity matched indirect comparison between the MOXIe Extension single arm study and the FACOMS registry data. There were several limitations associated with the indirect comparison analyses and caution should be excised in the interpretation of the results. These limitations included the residual high risk of confounding that could arise from measured and non-measured important covariates and biases arising from the selection of patients for the indirect comparison. The ESC, noting the updated 5-year data presented in the PSCR, considered that uncertainty in long term effects remained, because, as for the 3-year analysis, it compared omaveloxolone-treated patients in the MOXIe Extension single arm study with a comparator arm derived from registry data.

6.47 The PBAC previously considered that the data did not convincingly support the claims of superior comparative effectiveness. In particular, the PBAC noted the uncertainty in the magnitude of the clinical benefit and duration of improvement (paragraph 6.59, omaveloxolone PSD, March 2025 PBAC meeting).

6.48 In consideration of the resubmission, the PBAC considered that omaveloxolone was likely to be clinically superior compared to BSC. The PBAC considered that a 2-point change in mFARS score was likely to be clinically meaningful in the context of the proposed use. Further, the PBAC noted the 3- and 5-year data and considered that it provided some evidence of a duration of effect for some patients. The PBAC considered that given the progressive nature of FA, any stabilisation of disease would likely be beneficial for patients and their caregivers.

6.49 The PBAC again considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.50 The resubmission presented an economic evaluation that compared treatment with omaveloxolone + BSC to BSC only, in patients diagnosed with FA and aged over 16 years. The type of economic evaluation presented was a cost-utility analysis and the key components are summarised in Table 11.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary
Cohorts modelled	Four cohorts were modelled depending on the age of symptom onset (≤7 years, 8 – 14 years, 15 – 24 years and > 24 years).
Outcomes	Life years and QALYs.
Time horizon	Lifetime time horizon (84 years) versus 4 years of follow-up in the omaveloxolone arm and 13 years follow up in the BSC arm. Given the relatively short duration of follow up, immature trial data and average life expectance of FA patients, the ESC previously noted that a shorter time horizon may be more appropriate. The ESC noted that the alternate approach utilised for modelling mortality meant that the economic model presented in the resubmission was less sensitive to shorter time horizons.
Methods used to generate results	Regression based analysis which relates disease progression (measured as mFARS in the model) to costs and outcomes.
Health states	Patients were either alive or dead, with no other health states defined. Operationally, in the omaveloxolone arm, alive patients were divided into 'on treatment' and 'off treatment' for the purposes of assigning costs and treatment effect.
Cycle length	1 year
Transition probabilities	Disease progression transition probabilities were based on a regression analysis of natural history registry data. In the BSC arm these were applied directly. In the omaveloxolone arm, a treatment effect (relative risk) was applied to the transition probabilities, derived from a propensity matched analysis (which compared patients in the MOXIe extension study to matched patients enrolled in the FACOMS registry). Mortality was related to disease progression (not treatment status) and was modelled by applying HRs due to FA, based on disability stage to general population mortality curves for each age of onset cohort. Patients on treatment were modelled through a TTD curve based on the proportion of patients remaining on treatment in the MOXIe part 2 trial (13%) in the first year and a 5.6% discontinuation rate in subsequent years based on the annual TTD rate in years 2 – 4 of the MOXIe extension trial.
Treatment effect	The treatment effect of omaveloxolone (derived from the propensity matched analysis) was applied to all omaveloxolone patients while on treatment with no on-treatment waning for the duration of the model. Once patients cease treatment, omaveloxolone has no further treatment effect. In March 2025, the ESC noted that treatment effect waning may be reasonable due to insufficient evidence to justify a constant treatment effect. However, treatment effect, applied as a rate ratio, remained unchanged from the previous submission. Further, it may have been more reasonable to calculate the rate ratio based on available data for changes in mFARS score for each of the first 3 years instead of a rate ratio based on a cumulative change in mFARS score over 3 years. The rate ratio calculated in Year 3 could then be extrapolated over the lifetime of the model. The ESC noted that the individual rate ratios derived from the updated 5-year data were highly variable and did not follow a particular trend. The ESC considered that this may be due to the small number of patients receiving omaveloxolone (n = 43).
HRQoL	Utility values, based on mFARS score ranges, derived from a time-trade-off (TTO) study conducted in December 2024, were applied in the base case analysis.
Costs	Costs include omaveloxolone acquisition costs, medical appointments, hospitalisation, home modifications, medical devices, AE management costs and carer costs. As noted by the ESC previously, the inclusion of costs for carer, home modification and certain medical aids (walker, wheelchairs, specialised mattress, electric beds) may not be reasonable in the base case analysis as the PBAC guidelines specify to only include direct medical costs.

Source: tabulated during the evaluation.
AE = adverse event; BSC = best supportive care; ESC = Economics sub-committee; FACOMS = Friedreich's Ataxia Clinical Outcomes Measures Study; HRQoL = Health related quality-of-life; HRs = hazard ratios; mFARS = modified Friedreich Ataxia Rating Scale; QALYs = quality-adjusted life-years; TTD = time to treatment discontinuation; TTO = time-trade-off
Blue shading represents results previously considered by the PBAC.

6.51 The structure of the model and lifetime time horizon nominated in the base case analysis remained unchanged from the previous submission. While the structure was deemed reasonable for decision making, the ESC previously noted that a shorter time horizon may be more appropriate due to the overall uncertainty in the economic analysis and because the time horizon exceeds the average life expectancy of a patient with FA which is approximately 35-40 years (paragraph 6.62, omaveloxolone PSD, March 2025 PBAC meeting). However, due to the approach utilised to model mortality, the ESC noted that the economic model presented in the resubmission was not sensitive to shorter time horizons. The economic model also revised the utility values applied and proposed an effective price for omaveloxolone.

6.52 Patients were assigned into one of 4 cohorts based on the age of onset of FA symptoms: ≤7 years, 8 – 14 years, 15 – 24 years and > 24 years. The distribution of patients in each of these cohorts (27%, 45%, 18% and 11%, respectively) was based on the proportion of Australian patients in each of these cohorts in the Friedreich's Ataxia Clinical Outcome Measures (FACOMS) registry.

6.53 The transition probabilities in the economic model related to progression of FA (as measured by mFARS scores) and mortality. A treatment effect associated with omaveloxolone treatment was applied to model the progression of mFARS score.

6.54 In the BSC arm, the trajectory for mFARS progression was based on 13 years of natural history data for mFARS progression for each age of symptom onset cohort as observed in the FACOMS registry. The observed data was not used directly in the model. Instead, a multivariate regression model, based on 13 years of observed data, was employed to extrapolate the observed data over the modelled lifetime time horizon. A linear model was fitted to the observed data in the base case analysis based on goodness of fit using AIC/BIC values and visual inspection. Other than linear extrapolations, alternative extrapolation distributions were not provided or tested in the resubmission. Beyond 13 years, a logistic model was employed for extrapolation of data based on clinician input which was not adequately justified in the resubmission. Overall, the modelled curves provided a reasonably good fit to the observed data, noting that the resubmission did not provide the regression equation utilised in the multivariate regression model.

6.55 The mFARS progression trajectory for patients in the omaveloxolone + BSC arm was estimated by applying a treatment effect to the mFARS progression trajectory in the BSC arm. The treatment effect was applied as a rate ratio, which was based on the average relative reduction in mFARS scores from a propensity match analysis (PSMA)[9] which compared patients in the MOXIe extension study (which had 3 years of follow-up data) to those in the FACOMS registry. The limitations of the indirect comparison and issues raised by the ESC in March 2025 are noted in paragraph 6.37.

6.56 The resubmission applied a constant rate ratio of 0.454, based on the cumulative change in mFARS score over 3 years. The rate ratio was derived by comparing mFARS progression across the treatment arms over 3 years. However, differences across the arms in terms of mFARS progression reduced considerably within the 3 years of observed data. In the final year (Year 3), mFARS progression in the omaveloxolone arm was 90% of that in the BSC arm (or a rate ratio of 0.9). Applying individual rate ratios for each year and extrapolating the rate ratio observed in Year 3 across the lifetime of the model (assuming no treatment effect waning), increased the ICER by [redacted]%, from the base case ICER of $ > $1,055,000 / QALY gained to $> $1,055,000 /QALY gained.

6.57 The resubmission applied the constant treatment effect of 0.454 over the modelled time horizon. However, treatment effect waning was observed over the first 3 years as evident from the mFARS progression data. The ESC previously noted that patients in the economic model are on treatment for a mean duration of 16 years (13.1 years if survival is accounted for) and compared to the relatively short duration of follow up of 4 years in the MOXIe extension study. The assumption that the full treatment effect is maintained indefinitely while patients remained on treatment was not adequately justified. The ESC previously noted that some waning is likely to be expected (paragraph 6.65, omaveloxolone PSD, March 2025 PBAC meeting) and the application of a linear waning of treatment effect from year 4 to 18 increased the ICER by [redacted]% to $> $1,055,000/QALY. Treatment effect waning has a minimal impact on the ICER when the alternate rate ratios calculated in the evaluation are used.

6.58 The PSCR stated that the updated 5-year data resulted in a rate ratio of 0.321, and that the updated data indicated that the treatment effect applied in the resubmission (RR = 0.454) was conservative and potentially underestimated the treatment effect of omaveloxolone. The ESC noted that the individual rate ratios for each year for the updated data were highly variable and did not follow a particular trend (see Table 12), which may be due to the small sample size of patients receiving omaveloxolone (n = 43). The ESC considered that applying the individual rate ratios and assuming the treatment effect observed in Year 5 would be maintained across the modelled time horizon would not be reasonable due to the variability of the data. The ESC considered that application of the 3-year individual rate ratios, the data for which included substantially more omaveloxolone patients (n = 136), with a treatment waning effect from Year 4 to 18 may be more appropriate. The pre-PBAC response stated that, aside from Year 4, the 5-year data were less variable than the 3-year data and that the 5-year data suggested a slower waning of effect compared to the 3-year data.

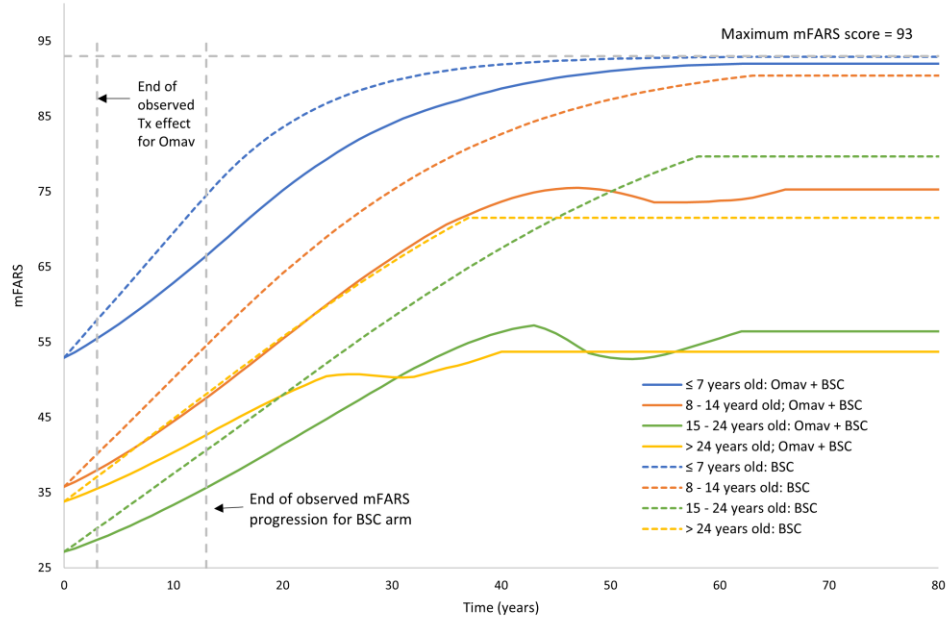
Table 12: Individual rate ratios derived from the updated 5-year data, based on yearly changes in mFARS scores

	3-year data (n = 136)	5-year data (n = 43)	Ratio applied in the economic model
Year 1	0.01	0.03	0.454
Year 2	0.47	0.28	0.454
Year 3	0.90	0.20	0.454
Year 4	-	1.14	0.454
Year 5	-	0.44	0.454
Average	0.454	0.321	-

Source: Compiled from information provided in the PSCR, and pre-PBAC response.
mFARS = modified Friedreich Ataxia Rating Scale

6.59 The mFARS progression trajectory for both treatment arms by age of onset cohorts is presented in Figure 2. The mFARS scores of patients in the 8-14 years old, 15-25 years old and > 24 years old cohorts reduced at different time points over the time horizon. This was not observed in the economic model presented in the previous submission. However, the resubmission argued that this was a result of patients that discontinued treatment (and were likely to have worse mFARS scores) dying at a higher rate. Thus, the surviving population, i.e., patients that were alive and remained on treatment, were likely to have lower mFARS scores, thereby reducing the overall mFARS scores of the cohort. The ESC considered that this approach was reasonable.

Figure 2: mFARS progression for age of onset cohorts for both treatment arms



Source: *constructed during the evaluation,* from the "Attachment 9 – Cost utility analysis (CUA) workbook (Section 3)" workbook included in the resubmission.
BSC = best supportive care; mFARS = modified Friedreich Ataxia Rating Scale; Omav = omaveloxolone; Tx = treatment

6.60 The approach to modelling OS was changed as ESC previously raised several concerns regarding the approach utilised in the previous submission (paragraph 6.67, omaveloxolone PSD, March 2025 PBAC meeting). In the previous submission, OS data from the EFACTS registry was extrapolated and adjusted for general population

mortality using the competing risks approach. In March 2025, the ESC noted that the unadjusted OS curves resulted in better survival rates at older ages compared to the general population which was not plausible and that the use of the competing risks approach was not appropriate as most patients would die of FA. Further, the adjusted OS curves resulted in a mean life expectancy of 64 years in the BSC arm, which was noted to be inconsistent with published literature which reported a shorter life expectancy of 35 to 40 years for patients with FA. In the resubmission, mortality risk was determined directly by applying hazard ratios (HRs) for FA, sourced from Indelicato et. al.[10], to general population mortality curves for each age of onset cohort. A HR of 2.01, assumed to increase by a factor of 2.01 with each disability stage, was applied to general population mortality curves, adjusted for the proportion of males (54%) in the Indelicato study. It was assumed that patients in disability stage 1 would have survival rates equal to that of the general population which the evaluation considered was reasonable.

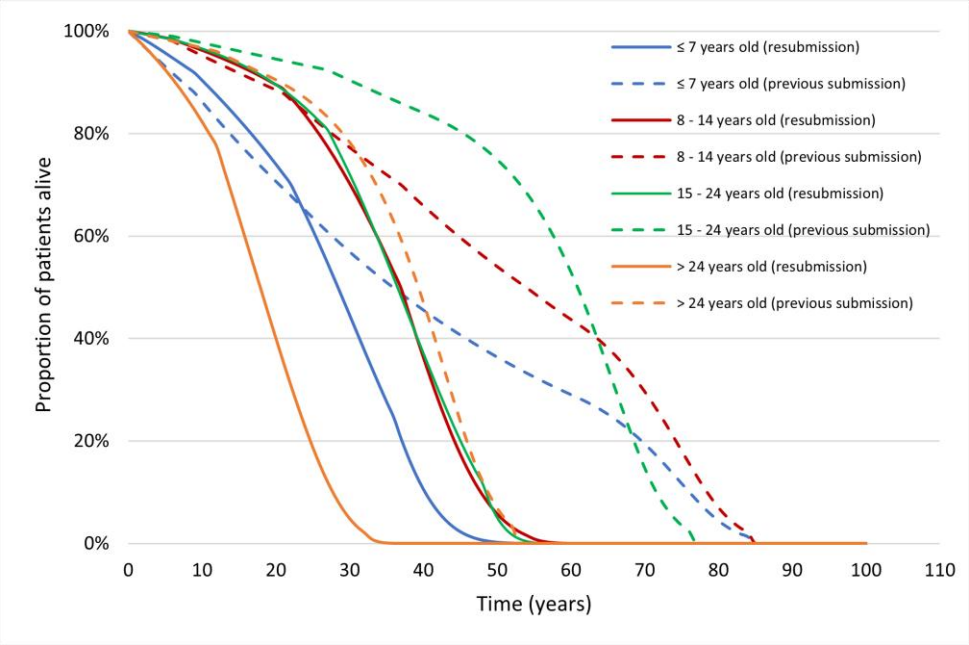
6.61 Survival by disability stage was then linked to mFARS score ranges (in increments of 10) by calculating the HR for each mFARS score range based on the distribution of patients by mFARS score in each disease ataxia stage. This was done by cross-walking disability stages with disease ataxia stages and was reasonable. The resulting HRs for each disease ataxia stage were then applied to the mortality curves by age of onset, adjusted for the starting age of each cohort (16 in the ≤ 7 years old and 8 – 14 years old cohorts, 25 in the 15 – 24 years old cohort and 49 in the > 24 years old cohort) to generate the survival curves by mFARS score for each cohort.

6.62 Since omaveloxolone treatment only slows the progression of disease and does not directly impact survival, the resulting survival gain between the two arms was not substantial. The modelled survival for patients in the omaveloxolone + BSC arm was 27.8 years and 26.6 years for patients in the BSC arm (compared to 44.2 years and 42.6 years in the previous submission). The ESC considered that the approach utilised in the resubmission resulted in more plausible survival curves and substantially reduced the uncertainty in modelled mortality compared to the previous submission. However, the HRs for mortality due to FA, by disease stage, applied to the general population mortality curves were based on a prospective cohort study[7] in which the median baseline age of participants was 31 years old. In the modelled population, 71.4% of patients (patients in the ≤ 7 years old cohort and 8-14 years old cohort) entered the model at 16 years of age. Thus, it was unclear whether the HRs derived from this cohort of patients would be applicable to the modelled population.

6.63 A comparison of the survival curves between the resubmission and the previous submission, for each age of onset cohort in the omaveloxolone + BSC arm, is presented in Figure 3.

[10] Indelicato E, Reetz K, Maier S, Nachbauer W, Amprosi M, Giunti P, et al. Predictors of Survival in Friedreich's Ataxia: A Prospective Cohort Study. Movement Disorders. 2024;39(3):510-8.

Figure 3: Comparison of modelled OS curves from the resubmission and previous submission for age of onset cohorts (omaveloxolone + BSC arm)



Source: constructed during the evaluation, from the "Attachment 9 – Cost utility analysis (CUA) workbook (Section 3)" workbook included in the resubmission (July 2025) and the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment provided with the submission (November 2024).

6.64 The previous submission estimated utility values based on a linear regression model as the MOXIe extension trial did not capture quality of life data. Five data points, with an EQ-5D range of 0.53 to 0.59 and mFARS range of 55 to 61, were utilised to inform the regression model. In March 2025, the ESC noted that the five data points were insufficient to relate mFARS scores to utility values for the full range of utility values applied in the economic model (paragraph 6.68, omaveloxolone PSD, March 2025 PBAC meeting). Therefore, the resubmission presented results from a vignette-based time trade-off (TTO) utility study which estimated the utility weights of patients across all ranges of mFARS scores (0-93) as. The study included 5 health state vignettes, (based on mFARS ranges of 0-19, 20-39, 40-59, 60-79 and 80-93). The description of each health state was based on a review of published literature and ADL scores and was further refined based on clinician input. The mFARS 80-93 health state was valued worse than death by all participants in the TTO study (utility value = -0.18). The ESC considered that the values applied in the base case analysis appeared to reasonable in the absence of alternative utility values for the full range of mFARS scores. The resubmission did not include any disutilities in the economic model, which, given the low incidence of AEs in the trial, was also reasonable.

6.65 The economic model again included costs associated with omaveloxolone acquisition, medical appointments, hospitalisation, medical devices and aids (wheelchairs, electric beds, specialised mattresses), home modifications, AE management and carers. Utilisation was mainly based on clinician feedback. While the inclusion of these costs

(other than drug costs), were not model drivers, the inclusion of carer and certain medical aids (such as walkers, wheelchairs, specialised mattress and electric beds) and home modification costs was not reasonable in the base case analysis as the PBAC guidelines specify to only include direct medical costs.

6.66 The key drivers of the economic model are presented in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1] per QALY gained.
Treatment effect	A rate ratio of 0.454, calculated from the cumulative change in mFARS score over the first 3 years of treatment, was applied in the base case analysis. It may have been more appropriate to apply rate ratios for each of the first 3 years and then extrapolate the rate ratio calculated in Year 3 over the lifetime of the model.	High, favours omaveloxolone. When rate ratios for Years 1-3 were calculated and applied, the ICER increased by [redacted]% to $[redacted][1] per QALY.
Treatment effect waning	The resubmission assumed no treatment effect waning whilst patients remained on treatment (mean treatment duration in the model was 13 years). This was not justified. No evidence of treatment effect maintenance was provided beyond 4 years of the MOXIe extension trial.	High, favours omaveloxolone When treatment waning is incorporated from Year 4 to 18, the ICER increases to $[redacted][1] per QALY.
Utility values	Utility values derived from a TTO study with 5 health states based on mFARS scores.	Moderate, favours omaveloxolone. Applying the upper limits of the 95% CI increases the ICER to $[redacted][1] per QALY.

Source: tabulated during the evaluation

CI = confidence interval; ICER = incremental cost-effectiveness ratio; mFARS = modified Friedreich Ataxia Rating Scale; TTO = time-trade-off

The redacted values correspond to the following range:

[1] > $1,055,000

6.67 The results of the stepped economic analysis are presented in Table 14.

Table 14: Results of the stepped economic evaluation

Step and component	Omaveloxolone	BSC	Increment
Step 1: Propensity matched analysis costs and outcomes (3-year time horizon) [a]			
Costs	$ [redacted]	$0	$ [redacted]
Change in mFARS	[redacted]	[redacted]	[redacted]
Incremental cost/change in mFARS score avoided			$ [redacted] [1]
Step 2: mFARS scores transformed to survival			
Costs	$ [redacted]	$0	$ [redacted]
Life years	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			$ [redacted] [2]
Step 3: Include disease management costs [b]			
Costs	$ [redacted]	$91,013	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			$ [redacted] [2]
Step 4: Include AE costs			
Costs	$ [redacted]	$91,049	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			$ [redacted] [2]
Step 5: Extrapolate survival and costs to lifetime time horizon			
Costs	$ [redacted]	$546,625	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			$ [redacted] [3]
Step 6: Apply utility weights to life years			
Costs	$ [redacted]	$546,625	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained (base case)			**$** [redacted] [3]
Previous submission [c]			
Costs	$ [redacted]	$646,846	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/ extra QALY gained			**$** [redacted] [3]

Source: Adapted during the evaluation from Table 3.35 of the resubmission, pp 247-249.
AE = adverse event; BSC = best supportive care; mFARS = modified Friedreich Ataxia Rating Scale; QALYs = quality-adjusted life-years.
Blue shading represents results previously considered by the PBAC.
[a] Costs include only omaveloxolone acquisition costs and outcomes from the propensity matched analysis.
[b] Including medical appointments, hospitalisation, disease aids, home modification and carer costs.
[c] Based on a proposed published price of $ [redacted] and a different approach for modelling mortality and utility weights.
The redacted values correspond to the following ranges:
[1] *$255,000 to < $355,000*
[2] *$955,000 to < $1,055,000*
[3] *> $1,055,000*

6.68 The ICER ($955,000 to < $1,055,000/QALY) is substantially lower than that presented in the previous submission (> $1,055,000/QALY). This was primarily due to the application of the proposed effective EMP of omaveloxolone. Further, the approach utilised to model mortality in the resubmission resulted in a lower life expectancy.

6.69 The disaggregated results for costs and health outcomes are presented in Table 15. The largest contributor to the incremental costs were omaveloxolone acquisition costs and patients accrued the most benefit while on omaveloxolone treatment.

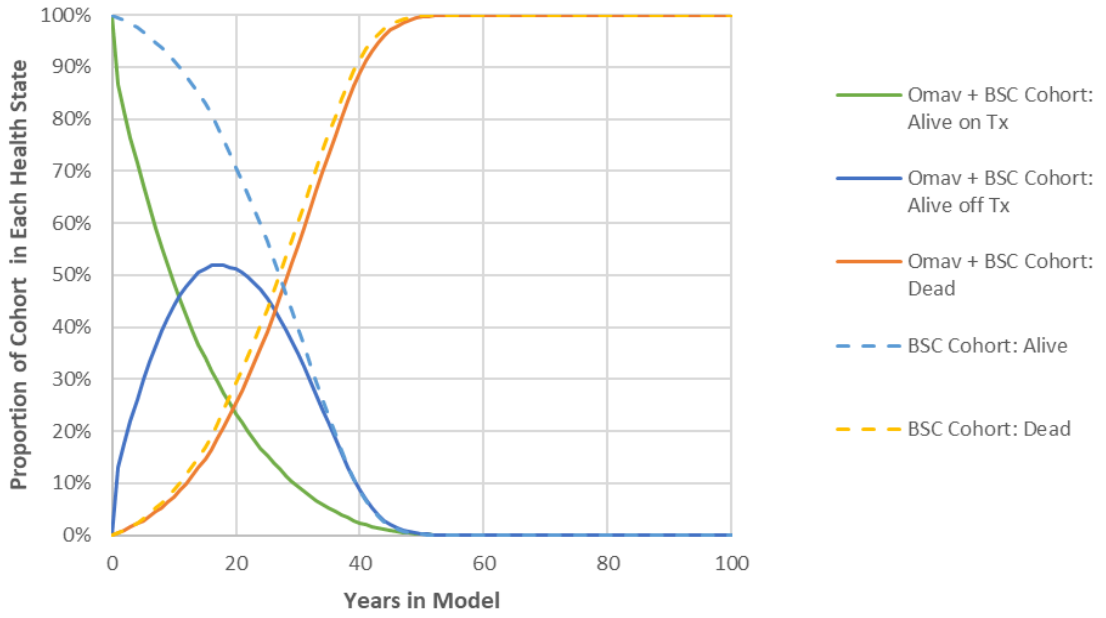
Table 15: Disaggregated summary of costs and outcomes included in the economic evaluation

Resource item	Omaveloxolone	BSC	Incremental cost	% incremental cost
Costs				
Omaveloxolone	$[redacted]	$0	$[redacted]	[redacted]%
AE management costs	$341	$36	$304	0.0%
GP, specialist visits and hospitalisation	$196,080	$230,239	-$34,159	-1.9%
Disease management aids	$25,651	$41,416	-$15,766	-0.9%
Co-morbidity costs	$271,070	$264,775	$6,295	-0.1%
Carer costs	$8,043	$10,158	-$2,115	0.3%
Total	**$[redacted]**	**$546,625**	**$[redacted]**	**100%**
Outcomes				
LYs: on omaveloxolone	12.56	0.00	12.56	1032%
LYs: off omaveloxolone	14.72	26.06	-11.34	-932%
Total LYs (undiscounted)	**27.28**	**26.06**	**1.22**	**100%**
QALYs: on omaveloxolone	7.82	0.00	7.82	258%
QALYs: off omaveloxolone	6.18	10.97	-4.79	-158%
Total QALYs (discounted)	**10.58**	**9.42**	**3.04**	**100%**

Source: tabulated during the evaluation from the "Attachment 9 - Cost utility analysis (CUA) workbook (Section 3)" attachment.
AE = adverse event; BSC = best supportive care; LYs = life-years; QALYs = quality-adjusted life-years

6.70 A Markov trace for the entire modelled population is presented in Figure 4.

Figure 4: Health state membership over the model time horizon



Source: Figure 3.14, p245 of the resubmission.
BSC = best supportive care; Omav = omaveloxolone; Tx = treatment

6.71 The results of key univariate and multivariate sensitivity analyses are summarised in Table 16. The ICER was most sensitive to the treatment effect applied, the assumption of treatment effect waning, and utility values applied to the health states based on mFARS score ranges.

Table 16: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% Change
Base case	$ [redacted]	**1.28**	$ [redacted][1]	**-**
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes	$ [redacted]	3.04	$ [redacted][2]	- [redacted]%
• 3.5% costs and outcomes	$ [redacted]	1.62	$ [redacted][1]	- [redacted]%
Time horizon (base case 84 years)				
• 10 years	$ [redacted]	0.47	$ [redacted][3]	[redacted]%
• 20 years	$ [redacted]	0.91	$ [redacted][3]	[redacted]%
• 40 years **#4**	$ [redacted]	1.27	$ [redacted][1]	[redacted]%
Extrapolation of mFARS progression trajectory in BSC arm (base case: logistic model)				
• Linear model	$ [redacted]	1.31	$ [redacted][1]	- [redacted]%
Treatment effect (base case: same as year 3)				
• Year 1, 2 and 3 rate ratio calculated from the propensity matched analysis **#5**	$ [redacted]	0.61	$ [redacted][3]	[redacted]%
Treatment effect waning (base case: no waning)				
• Linear waning to no treatment effect from Year 4 to 18 **#6**	$ [redacted]	0.95	$ [redacted][3]	[redacted]%
Treatment costs (base case: RDI = 87%)				
• Assuming 100% RDI due to non-returnable monthly supply	$ [redacted]	1.28	$ [redacted][3]	[redacted]%
Utility values (Biogen TTO study)				
• Lower limits of 95% CI	$ [redacted]	1.35	$ [redacted][1]	- [redacted]%
• Upper limits of 95% CI **#7**	$ [redacted]	1.25	$ [redacted][1]	[redacted]%
Carer costs (base case: included cost per week for 14% of patients applied as the cost per year)				
• Exclude **#1**	$ [redacted]	1.28	$ [redacted][1]	[redacted]%
• Cost per year applied correctly	$ [redacted]	1.28	$ [redacted][1]	- [redacted]%
Home modifications (base case: included)				
• Excluded **#2**	$ [redacted]	1.28	$ [redacted][1]	[redacted]%
Medical aids (base case: included)[e]				
• Exclude, apart from catheters and feeding tubes **#3**	$ [redacted]	1.28	$ [redacted][1]	[redacted]%
Multivariate analyses				
#1, #2, #3	$ [redacted]	1.28	$ [redacted][1]	[redacted]%
#1 - #4	$ [redacted]	1.27	$ [redacted][1]	[redacted]%
#1 - #5	$ [redacted]	0.61	$ [redacted][3]	[redacted]%
#1 - #6	$ [redacted]	0.56	$ [redacted][3]	[redacted]%
#1 - #7	$ [redacted]	0.54	$ [redacted][3]	[redacted]%

Source: tabulated during the evaluation, from the "Attachment 9 - Cost utility analysis (CUA) workbook (Section 3)" attachment.
BSC = best supportive care; CI = confidence interval; ICER = incremental cost-effectiveness ratio; mFARS = modified Friedreich Ataxia Rating Scale; RDI = relative dose intensity; TTO = time-trade-off
The redacted values correspond to the following ranges:
[1] *$955,000 to < $1,055,000*
[2] *$855,000 to < $955,000*
[3] *> $1,055,000*

6.72 The ESC considered that the multivariate analysis #1-#6 (i.e. incorporating the amendments labelled #1 to #6 in Table 16) represented the most appropriate base case. The ESC noted that this analysis appropriately excluded carer, home modification and medical aid costs, applied a more appropriate time horizon of 40 years, applied the individual yearly rate ratios derived from the 3-year follow up data and applied a treatment waning effect from Year 4 to Year 18. The ESC noted that this resulted in an ICER of > $1,055,000per QALY gained.

Drug cost/patient/year

6.73 The drug cost/patient/year as estimated in the economic and financial analyses is presented in Table 17. The discontinuation rate for Years 4 to 6 on treatment differed between the economic and financial model (6% versus a discontinuation rate between 1 and 3%, respectively). The ESC considered that the application of different rates between the economic and financial models was not justified and resulted in a different mean treatment durations. The ESC considered that the discontinuation rate in the financial estimates should be consistent with the economic model (i.e. 6% from Year 2 onwards).

Table 17: Omaveloxolone cost per patient

	MOXIe Part II	Economic Model	Financial Estimates
Mean dose (daily, mg)	129[a]	130[b]	129[a]
Mean duration	43 weeks (trial duration was 48 weeks)	13.1 years	4.96 years[c]
Cost/patient/month	$[redacted]	$[redacted]	$[redacted]
Cost/patient/year	-	$[redacted]	$[redacted]

Source: tabulated during the evaluation, from the "Attachment 9 - Cost utility analysis (CUA) workbook (Section 3)" attachment provided with the resubmission.

Blue shading represents results previously considered by the PBAC.

[a] Mean dose based on the PI dose (150 mg daily) × RDI reported in the trial (86%), sourced from the MOXIe part II trial.

[b] In the economic analysis, the resubmission applied an RDI of 87%, sourced from the MOXIe extension study, the resubmission has not described the inconsistency between the RDIs applied in the economic and financial analyses.

[c] Based on the truncated mean derived from the financial analysis and a RDI of 86%.

Estimated PBS usage & financial implications

6.74 This resubmission was not considered by DUSC. An epidemiological approach was used to estimate the financial impact of listing omaveloxolone on the PBS. Following advice from DUSC in March 2025, the resubmission provided revised utilisation estimates.

6.75 The key components of the financial analyses are presented in Table 18.

Table 18: Key inputs for the financial estimates

Data	Value and Source	Comment
Eligible population		
FA prevalence	1 in 43,458. Average of prevalence rates reported in Spain, Portugal, UK, Greece and Italy.[11]	This was an area of uncertainty in the previous submission. However, the DUSC considered that the value may be reasonable, albeit uncertain, due to the lack of available options (para 6.82, omaveloxolone PSD, March 2025 PBAC meeting).
Proportion of FA patients over 16 years	75%. Australian FACOMS registry.	The DUSC noted that this registry is not population-based and may be unrepresentative of the Australian population with FA. However, the pre-PBAC response stated that it is the most accurate Australian estimate available with regards to the proportion of patients aged ≥ 16 years (para 6.83, omaveloxolone PSD, March 2025 PBAC meeting).
Proportion of FA patients with mFARS 20 – 80	91%. Australian FACOMS registry.	This input was added due to the inclusion of the relevant clinical criterion in the proposed PBS restriction. The value was reasonable, noting the limitations with the registry data mentioned above.
Grandfathered patients	The resubmission estimated that there would be [redacted][1] patients enrolled in an Early Access Program which would be grandfathered on to the PBS listing. These patients were subtracted from the eligible prevalent pool in Year 1.	While these patients were not included in the previous submission, this approach was reasonable.
Treatment utilisation		
Uptake rate	[redacted]% in Year 1, increasing to [redacted]% in Year 6. Assumption.	Uptake was increased from [redacted]% in Year 1 and [redacted]% in Year 6 in the March 2025 submission. The resubmission stated that this was due to the lack of alternative treatment options.
Discontinuation rate	13%, 6%, 6%, 3%, 1%, and 1% for Years 1, 2, 3, 4, 5, and 6 on treatment, respectively. Years 1 – 3 based on the economic model and Years 4 – 6 based on an assumption (discontinuing rate halving every year).	Discontinuation in the March 2025 submission was 0% from Year 2 onwards. The PBAC agreed with the DUSC Advice from March 2025 that the discontinuation rate should be consistent with the economic model (i.e. 6% from Year 2 onwards).
Scripts per patient per year	10.5. Assuming a dosage of 150 mg per day × 87% compliance. Each script contains 90 × 50 mg capsules.	This unchanged from the previous submission.
Costs		
Proposed medicine	$[redacted] per 90 × 50 mg capsules.	-
Patient copayment	$14.02. Weighted PBS copayment (by beneficiary type) of PBS items elexacaftor/tezacaftor/ivacaftor for cystic fibrosis.[c] Assuming no RPBS scripts.	-
Monitoring costs	$14.16 (MBS item 66512). As per the PI, for monitoring of lipids, liver and cardiac function. Three times in the first year of treatment, annually thereafter.	-

Source: Constructed during the evaluation from the "Attachment 12 - Utilisation and cost model (Section 4)" provided with the resubmission.
Blue shading represents financial inputs previously considered by the PBAC.

AEMP = approved ex-manufacturer price; FA = Friedreich's Ataxia; FACOMS = Friedreich's Ataxia Clinical Outcome Measures Study; MBS = Medicare Benefits Schedule; mFARS = modified Friedreich's Ataxia rating scale; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = product information; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme; UK = United Kingdom.
The redacted values correspond to the following ranges:
[1] *< 500*

6.76 The estimated number of patients treated with omaveloxolone and the net cost to the PBS per year are presented in Table 19.

Table 19: Estimated use and cost of omaveloxolone

	2026	2027	2028	2029	2030	2031
Initiating patients	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Continuing patients	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Total patients on treatment	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Scripts per year (10.5 per patient)[a]	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2
Cost to PBS/RPBS ($)	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3
PBS copayment ($)	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4
Cost to the PBS/RPBS less copayments ($)	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3
Net cost to the MBS, revised[b] ($)	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4
Net cost to the PBS, MBS, revised[b] ($)	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3	[redacted] 3
March 2025 submission						
Total patients on treatment	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Scripts per year	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Net cost to the PBS/RPBS ($)	[redacted] 5	[redacted] 6	[redacted] 7	[redacted] 7	[redacted] 7	[redacted] 8

Source: Constructed during the evaluation from the "Attachment 12 - Utilisation and cost model (Section 4)" provided with the resubmission.
MBS=Medicare Benefits Schedule; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme.
Blue shading represents financial inputs previously considered by the PBAC.
[a] Except for grandfathered patients in their first year of PBS-subsidised treatment who receive two fewer scripts than treatment-naïve patients.
[b] MBS 66512 ($14.16) service four times in the first year of treatment, annually thereafter per patient on treatment. Additional five services for 29% of patients in their initiating year for increased monitoring based on the MOXIe trial. However the resubmission miscalculated additional MBS services, this was revised during the evaluation.
The redacted values correspond to the following values:
[1] *< 500*
[2] *500 to < 5,000*
[3] *$80 million to < $90 million*
[4] *$0 to < $10 million*
[5] *$120 million to < $130 million*
[6] *$150 million to < $160 million*
[7] *$160 million to < $170 million*
[8] *$170 million to < $180 million*

6.77 The total cost to the PBS of listing omaveloxolone was estimated to be $80 million to < $90 million in Year 1 of listing, decreasing to $80 million to < $90 million in Year 6, and totalling $500 million to $600 million over the first 6 years of listing. This was reduced from a total of $900 million to < $1 billion over the first 6 years of listing in

[11] Buesch K, Zhang R. A systematic review of disease prevalence, health-related quality of life, and economic outcomes associated with Friedreich's Ataxia. Current Medical Research and Opinion. 2022;38(10):1739-49.

the March 2025 submission. The resubmission expected that the listing of omaveloxolone would not change the extent of use of other medicines.

6.78 The ESC noted that the key changes in the resubmission included:

- Restricting use of omaveloxolone to patients with a mFARS score of 20 to 80;
- Implicitly including grandfathered patients;
- Increasing the uptake rate (from [redacted]% - [redacted]% in the previous submission) to [redacted]% - [redacted]%;
- Applying continuous treatment discontinuation rate; whereas the previous submission assumed no discontinuation for patients in Year 2+ of treatment. The ESC considered that the discontinuation rate should align with that applied in the economic model (i.e. 6% from Year 2 onwards).

6.79 Similar to the previous submission, the Australian FA prevalence estimate remained a main area of uncertainty in the resubmission. The resubmission has maintained the estimate used in the previous submission as the DUSC considered that the value may be reasonable, albeit uncertain, due to the lack of available options (paragraph 6.82, omaveloxolone PSD, March 2025 PBAC meeting).

6.80 Sensitivity analyses performed on the financial estimates are presented in Table 20, below. Similar to the previous submission, the FA prevalence has the largest impact on the financial estimates.

Table 20: Sensitivity analyses on the net financial impact to the PBS

Analyses	2026	2027	2028	2029	2030	2031	% change
Base case	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	[redacted]%
FA prevalence and incidence (base case: prevalence: 1 in 43,458)							
1 in 38,462 (Canada)	$[redacted][2]	$[redacted][3]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	[redacted]%
1 in 44,187 (Western Europe)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	-[redacted]%
1 in 46,016 (Average of all estimates)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][4]	$[redacted][4]	$[redacted][4]	-[redacted]%
Uptake rate (base case: [redacted]% - [redacted]%)[a]							
Previous submission uptake rate[d]	$[redacted][4]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	-[redacted]%
Treatment discontinuation rate (base case: 13% - 1%[c])							
13% in Year 1, 6% in Year 2+[e]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][4]	$[redacted][4]	-[redacted]%

Source: Constructed during the evaluation from the "Attachment 12 - Utilisation and cost model (Section 4)" provided with the resubmission.
mFARS = modified Friedreich's Ataxia rating scale; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document.
Note: Analyses performed in italics are those performed during the evaluation.
[a] Uptake of [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, and [redacted]% in Years 1, 2, 3, 4, 5, and 6, respectively.
[b] Uptake presented in the PBAC submission of elexacaftor/tezacaftor/ivacaftor for cystic fibrosis (Elexacaftor with Tezacaftor and with Ivacaftor, and Ivacaftor PSD, March 2024 PBAC meeting).
[c] 13% in Year 1 on treatment, 5.6% for Years 2 and 3 and 3%, 1%, and 1% for Years 4, 5, and 6, respectively.
[d] [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% in Years 1, 2, 3, 4, 5, and 6, respectively.
[e] Consistent with the economic model.
The redacted values correspond to the following values:
[1] $80 million to < $90 million
[2] $90 million to < $100 million
[3] $100 million to < $200 million
[4] $70 million to < $80 million

Quality Use of Medicines

6.81 The resubmission again outlined the following quality use of medicine practices:

- Regular treatment monitoring with serology tests;
- Dose adjustments based on monitoring tests;
- Genetic diagnosis required for access to omaveloxolone on the PBS;
- Routine pharmacovigilance activities; and
- A long-term post market safety study which started in 2024.

Financial Management – Risk Sharing Arrangements

6.82 To account for the uncertainties regarding the size of the eligible patient population and, thus, the financial impact to the PBS, the resubmission proposed a [redacted] cost sharing arrangement between the sponsor and the Government in the event that the PBS expenditure exceeds the estimated financial impact of omaveloxolone in Table 19. The ESC considered that a [redacted]% rebate may not be sufficient given the uncertainties in the prevalence of FA and the potential for use in patients with a mFARS score outside of the 20 to 80 range.

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

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule, Authority Required (telephone/online) listing of omaveloxolone on the PBS for the treatment of Friedreich's ataxia (FA) in adults and adolescents aged 16 years and over. The PBAC noted the high unmet need for treatments for FA. The PBAC considered that omaveloxolone was likely to be clinically superior compared to best supportive care (BSC). The PBAC considered that the magnitude of benefit was uncertain, and likely to be modest; however, given the progressive nature of FA, any stabilisation of disease would be beneficial for patients and their caregivers. The PBAC considered that the economic model was structurally sound but the treatment effect of omaveloxolone was overestimated. The PBAC advised that amendments would be required to a number of inputs to make the model suitable for decision making. Noting that the incremental cost effectiveness ratio (ICER) was extremely high and uncertain, the PBAC recommended that a significant price reduction would be required. The PBAC considered that the utilisation estimates presented in the resubmission, with minor amendments, were acceptable.

7.2 The PBAC noted the consumer input received with this resubmission and with the original submission in March 2025 which strongly supported the submission. The PBAC noted that the input highlighted the high need for treatments for FA, the debilitating effect of symptoms of FA on patients and the burden on patients and caregivers. The PBAC considered that the slowing of disease progression and the retention of functional capacities was a crucial factor in patient quality of life and that this would generally outweigh the impact of adverse events with omaveloxolone treatment.

7.3 The PBAC considered that the proposed comparator, best supportive care (BSC), which consisted of the management of disease-related symptoms, was reasonable.

7.4 The PBAC noted that the resubmission was primarily based on the results of the MOXIE Part 2 trial which compared omaveloxolone with placebo (as a proxy for BSC) over 48 weeks. Supporting longer term data with a 3-year follow up was provided in the form of an unanchored propensity matched indirect comparison between omaveloxolone patients in the open label extension study of the MOXIE Part 2 trial and BSC patients from a natural history cohort. The PBAC noted that the resubmission did not present any new clinical data, but that updated propensity matched indirect comparison data with a follow up of 5 years was presented in the Pre-Sub-Committee response (PSCR).

7.5 The PBAC recalled that it had previously considered that the data presented did not convincingly support the claim that omaveloxolone was superior in terms of effectiveness compared to BSC. The PBAC also previously noted that although the difference in the mFARS score at Week 48 of -2.40 points was statistically significant, there were uncertainties associated with the clinical meaningfulness of this change

and whether it would result in benefits in terms of disease outcomes for the patient. However, at the November 2025 meeting the PBAC, the PBAC considered that a 2-point change in mFARS score was likely to be clinically meaningful in the context of the proposed use of omaveloxolone. The PBAC noted the 3- and 5-year follow up data and considered, notwithstanding the issues associated with the indirect treatment comparisons outlined in paragraph 6.37, that omaveloxolone appeared to provide an ongoing benefit for some patients. The PBAC also considered that given the progressive nature of FA, any stabilisation of disease would be beneficial for patients and their caregivers. Overall, the PBAC considered that omaveloxolone was likely to be superior compared to BSC in the treatment of FA and would result in stabilisation of disease for a period of time for some patients.

7.6 The PBAC again considered that omaveloxolone was inferior compared to BSC in terms of safety, noting that omaveloxolone was associated with cardiotoxicity, increased liver enzymes and headache.

7.7 The PBAC noted that the resubmission presented a revised economic model which incorporated some of the changes suggested by ESC in March 2025. These included (i) revised mortality inputs which appropriately reduced overall survival in the model; (ii) updated utility data which reflected quality of life across the entire spectrum of mFARS scores; and (iii) an effective price. The PBAC noted that the base case ICER presented in the submission was more than (> $1,055,000) per quality adjusted life year (QALY) gained. The PBAC considered that a number of the inputs into the model required amendment, including:

- Costs associated with carers, home modifications and medical aids were included. The PBAC acknowledged these costs but considered that they should be excluded from the base case analysis consistent with PBAC guidelines;
- The time horizon of 84 years was long, particularly when considering the average life expectance of patients with FA is 30 to 40 years. The PBAC advised that the time horizon should be reduced to 40 years;
- An average treatment effect was applied, calculated from the cumulative change in mFARS score over the first 3 years of treatment. The PBAC advised that individual rate ratios should be applied for the first 3 years, with the rate ratio calculated in Year 3 applied over the lifetime of the model;
- The model assumed a constant treatment effect over the time horizon which was not justified in the resubmission. The PBAC advised that there should be linear waning applied from Year 4 to Year 18.

7.8 The PBAC noted that the above changes significantly increased the ICER to over (> $1,055,000) per QALY (see Table 16) and considered that omaveloxolone was not cost-effective at the price proposed in the resubmission. The PBAC considered that omaveloxolone would be cost effective with a price reduction that resulted in an ICER

of $255,000 to < $355,000 per QALY when applying the changes advised in paragraph 7.7.

7.9 The PBAC considered that the submission targeted a well-defined population and the utilisation estimates provided were reasonable.

7.10 The PBAC considered that a risk sharing arrangement (RSA) would be required with [redacted]% reimbursement for expenditure above the utilisation estimates (based on the reduced price required as outlined in paragraph 7.8) to manage the total financial expenditure and to mitigate the uncertainty associated with the duration of treatment, continuing treatment in non-responders and the potential for use in patients with mFARS scores outside the range of 20 to 80.

7.11 The PBAC considered that where a price reduction was not possible to achieve an acceptable ICER as outlined in paragraph 7.8, a combination of a price reduction and an RSA may be utilised. The PBAC advised that while an RSA was not a preferred approach for achieving cost-effectiveness, it may be a mechanism to cap the cost per patient in the context of this rare condition, the high clinical need, and the relatively high degree of certainty in the number of eligible patients.

7.12 The PBAC considered that the initial and continuing restrictions proposed in the resubmission were broadly acceptable. The PBAC considered that:

- the inclusion of the criterion requiring a modified Friedreich's ataxia rating scale (mFARS) score of between 20 and 80 prior to initiation was appropriate;
- for the initial treatment phase, treatment must be prescribed by a specialist with expertise in the management of FA or by a medical practitioner in consultation with a specialist with expertise in the management of FA. Continuing treatment must be prescribed by a specialist or either medical or nurse practitioner in consultation with a specialist with expertise in FA;
- the criterion that continuing patients did not have a mFARS score that increased by more than 2 points annually or exceeded 80 was appropriate.
- a grandfather restriction was not required given the proposed initial restriction wording allows access for patients who have initiated on omaveloxolone prior to PBS listing.

7.13 The PBAC recommended that omaveloxolone should not be treated as interchangeable on an individual patient basis with any other drugs, according to s101(3BA) of the *National Health Act.*

7.14 The PBAC advised that continuing treatment with omaveloxolone is suitable for prescribing by nurse practitioners.

7.15 The PBAC recommended that the Early Supply Rule should apply.

7.16 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

Specifically, the PBAC found that in the circumstances of its recommendation for omaveloxolone:

a) The treatment is not expected to provide a substantial improvement in efficacy, over BSC, based on the results of the MOXIE Part 2 trial;

b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no effective treatments for this patient population;

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

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
OMAVELOXOLONE					
omaveloxolone 50 mg capsule, 90	NEW MP	1	90	5	Skyclarys
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Benefit type: ☒ Authority Required (Telephone/ Online PBS Authorities System)					
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: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: The modified Friedreich's Ataxia Rating Scale (mFARS) referenced in this restriction can be accessed from the following literature publication: Rummey C et al. Psychometric properties of the Friedreich Ataxia Rating Scale. Neurol Genet. 2019 Oct 29;5(6):371					
	Restriction Summary [new1] / Treatment of Concept: [new1A]				
Indication: Friedreich ataxia					

Treatment Phase: Initial treatment
Clinical criteria:
The condition must have a mutation in the frataxin (FXN) gene,
AND
Clinical criteria:
Patient must have/have had a modified Friedreich's Ataxia Rating Scale (mFARS) score between 20 to 80 inclusive prior to commencing treatment with this drug
AND
Clinical criteria:
Patient must have evidence that their cardiac disease is haemodynamically stable if they have a history of clinically significant cardiac disease
AND
Clinical criteria:
The treatment must be given concomitantly with best supportive care for this condition.
Treatment criteria:
Must be treated by a specialist with expertise in the management of Friedreich's ataxia; or
Must be treated by a medical practitioner in consultation with a specialist with expertise in Friedreich's ataxia.
AND
Population criteria:
Patient must be at least 16 years of age.
Prescribing Instructions: The following must be documented in the patient's medical records: (a) Genetic diagnostic report confirming the presence of the Frataxin (FXN) gene mutation; and (b) Echocardiogram or electrocardiogram results, within the 3 months prior to initiating treatment, confirming that the patient's cardiac disease is haemodynamically stable (if applicable).
Prescribing Instructions: The following must be provided at the time of the authority application and documented in the patient's medical records: (a) mFARS score prior to commencing treatment with this drug (i.e. at baseline)
Prescribing Instructions: Clinically significant cardiac disease is defined as either one of the following: (i) congenital or acquired valvular disease (ii) pericardial constriction (iii) restrictive or congestive cardiomyopathy (iv) coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina) (v) hospitalisation for heart failure in the last five years (vi) atrial fibrillation or arrhythmia
Restriction Summary [new2] / Treatment of Concept: [new2A]
Indication: Friedreich ataxia
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
Patient must continue to demonstrate clinical benefit
AND
Clinical criteria:

Patient must have evidence that their cardiac disease is haemodynamically stable if they have a history of clinically significant cardiac disease
AND
Clinical criteria:
The treatment must be given concomitantly with best supportive care for this condition
Treatment criteria:
Must be treated by a specialist with expertise in the management of Friedreich's ataxia; or
Must be treated by either (i) medical practitioner, (ii) nurse practitioner in consultation with a specialist with expertise in Friedreich's ataxia.
Prescribing Instructions: For the purposes of administering this restriction, demonstrating clinical benefit to this medicine is defined as either: (i) no deterioration of mFARS score by more than 2 points annually compared to the previous year; OR (ii) current mFARs score doesn't exceed 80.
Prescribing Instructions: The following must be documented in the patient's medical records: (a) Echocardiogram or electrocardiogram results within the last 12 months confirming that the patient's cardiac disease is haemodynamically stable (if applicable).
Prescribing Instructions: At the time of each continuing authority application, the current mFARS score, measured within 4 weeks prior to the authority application date must be provided and recorded in the patient's medical records. Annually, prescribers must also provide the mFARS score that was included in the PBS authority application submitted a year ago for assessment of response.
Prescribing Instructions: Clinically significant cardiac disease is defined as either one of the following: (i) congenital or acquired valvular disease (ii) pericardial constriction (iii) restrictive or congestive cardiomyopathy (iv) coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina) (v) hospitalisation for heart failure in the last five years (vi) atrial fibrillation or arrhythmia

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

9 Context for Decision

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

10 Sponsor's Comment

Biogen welcomes the recommendation by the PBAC for reimbursement of omaveloxolone for people with Friedreich ataxia (FA). Omaveloxolone is the first-ever approved treatment for FA and received registration from the Therapeutic Goods Administration in June 2025.

The PBAC recommendation comes with conditions that will need further consideration and discussion with the Committee. Biogen is committed to exploring every opportunity to enable access to omaveloxolone for all patients who could benefit from this medicine and will continue engaging with the PBAC and the Department to find agreeable positions that support reimbursed access.

Biogen would like to take this opportunity to thank the FA community and healthcare professionals who supported the submission.