

5.12 OMAVELOXOLONE, Capsule 50 mg, Skyclarys[®], BIOGEN AUSTRALIA PTY LTD.

1 Purpose of submission

- 1.1 This Category 1 submission requested a General Schedule, Authority Required (Telephone/Online) listing of omaveloxolone for the treatment of Friedreich's ataxia (FA) in adults and adolescents aged 16 years and older.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC). The key components of the clinical issue addressed by the submission are summarised in Table 1.

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

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	<p>Primary</p> <ul style="list-style-type: none"> Change in the modified Friedreich's ataxia rating scale (mFARS) score at week 48 Safety outcomes <p>Key secondary</p> <ul style="list-style-type: none"> Patient Global Impression of Change (PGIC) responses at week 48 Clinical Global Impression of Change (CGIC) responses at week 48 <p>Other secondary</p> <ul style="list-style-type: none"> 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, p3 of the submission

2 Background

Registration status

- 2.1 The Therapeutic Goods Administration (TGA) granted orphan drug status for omaveloxolone on 14 May 2024.
- 2.2 The submission was made under the TGA/PBAC Parallel Process. The sponsor submitted an application for omaveloxolone to the TGA on 26 June 2024 via the Comparable Overseas Regulator (COR-B) pathway. The COR-B submission was based on the European Medicines Agency (EMA) approved Marketing Authorisation

Application (MAA) with Australian-specific appendices. The TGA Delegate's Overview was received prior to the March 2025 PBAC meeting.

- 2.3 The proposed TGA indication is for the treatment of FA in adults and adolescents aged 16 years and older.
- 2.4 Omaveloxolone was granted a marketing authorisation for the treatment of people with FA aged 16 and older by the European Medicines Association (EMA) in February 2024 and the United States (US) Food and Drug Administration (FDA) in February 2023. The approved EMA and FDA indications are similar and aligned with the proposed TGA indication.

3 Requested listing

Essential elements of the requested listing

MEDICINAL PRODUCT medicinal product pack	DPMQ AEMP	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OMAVELOXOLONE					
Initial treatment					
Omaveloxolone, 50 mg capsule (oral)	Published price DPMQ: \$ [REDACTED] AEMP: \$ [REDACTED]	1	90	5	Skyclarys
Maintenance treatment					
Omaveloxolone, 50 mg capsule (oral)	Published price DPMQ: \$ [REDACTED] AEMP: \$ [REDACTED]	1	90	5	Skyclarys

Category / Program: Section 85 - General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Indication: Friedreich's ataxia
Treatment Phase: Initial treatment of Friedreich's ataxia
Clinical criteria:
The patient must have a mutation in the frataxin (FXN) gene
AND
The patient must have a clinical symptom of Friedreich's ataxia,
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. Patients with a history of clinically significant cardiac disease must show evidence that their disease is hemodynamically stable prior to initiating treatment (e.g. echocardiogram, electrocardiogram), records must be no more than 3 months old.

Public Summary Document - March 2025 PBAC Meeting

Prescribing Instructions:

Application for authorisation of initial treatment must be in writing (lodged via postal service or electronic upload) and must include a completed authority prescription form which includes the confirmation of genetic diagnosis of Friedreich's ataxia

Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au

Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos

Or mailed to:

Services Australia
Complex Drugs
Reply Paid 9826
HOBART TAS 7001

Note

No increase in the maximum number of repeats may be authorised.

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

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 of Friedreich's ataxia

Clinical criteria:

Patient must have previously received PBS-subsidised treatment with this drug for this condition

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.

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 12 months old.

Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au

Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos

Or mailed to:

Services Australia
Complex Drugs
Reply Paid 9826
HOBART TAS 7001

Note

No increase in the maximum number of repeats may be authorised.

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

Source: Tables 1.6- 1.9, pp41-50 of the submission.

AEMP=approved ex-manufacturer price; DPMQ=dispensed price for maximum quantity

- 3.1 Although the submission requested a special pricing arrangement (SPA), no effective price was proposed in the submission. Instead, the submission stated that the SPA at the time of PBS listing would be informed by feedback and discussion on the proposed PBS restrictions, clinical evidence and cost-effectiveness. The submission noted there are no registered treatments for FA, the unmet need in FA is high, and acknowledged that incremental cost-effectiveness ratios (ICERs) in the submission were high, which the submission considered was expected in rare diseases with a high clinical need.
- 3.2 The proposed restriction requires all patients to have a confirmed genetic diagnosis of a mutation in the frataxin (FXN) gene. This is consistent with the clinical trial which required patients to have 'genetically confirmed FA'. Genetic testing is funded by the states and territories through public hospital clinics or via the Medicare Benefits Schedule (MBS) item 73434 (i.e., gene variants associated with neuromuscular disorders including the FXN gene).
- 3.3 The proposed restriction is for FA patients aged 16 years and older which is in line with the requested TGA indication. The submission did not propose an upper age limit; however, this did not align with the key MOXIe Part 2 trial which only included patients up to 40 years of age. The submission stated that this would cause inequity of access, and it was a small population. Australian data in Table 2 below suggest approximately 20% of patients are above 40 years of age. 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. The pre-PBAC response

stated late onset disease is very rare and although that the pathogenesis of late onset disease (reduction in frataxin and impaired Nrf2 signalling) was the same as in patients with an earlier onset, the time to diagnosis is impacted by initial misdiagnosis. Further, the pre-PBAC response stated that determining retrospectively when a patient was diagnosed based on historical records can be challenging, as medical records from earlier decades may be incomplete.

- 3.4 The submission noted a clinical trial is underway in children with FA to evaluate the pharmacology, efficacy, and safety of omaveloxolone in FA patients ≥ 2 to < 16 years of age (NCT06054893).
- 3.5 The submission did not propose a modified Friedreich's ataxia rating scale (mFARS) range in the requested restriction. This was a key eligibility criterion in the MOXle Part 2 trial (mFARS ≥ 20 and ≤ 80). The mFARS range of 20 to 80 captures a range of FA disease severity (mFARS of 20 reflective of mild severity at the time of presentation, and an mFARS of 80 reflective of more severe disease). The submission, Pre-Sub-Committee Response (PSCR) and pre-PBAC response argued that mFARS was designed for use in clinical studies rather than in clinical practice, and that the results from the supportive MOXle Part 1 study 'support' the efficacy of omaveloxolone in a population with an mFARS score < 20 . The PSCR and pre-PBAC response stated that most patients present with symptoms consistent with a mFARS score ≥ 20 at diagnosis as the process is long (typically 24 months or 6.7 years for a non-neurological presentation)¹, but that if a minimum mFARS was implemented in the PBS restriction, it would deny or delay treatment in approximately 4.6% to 6.3% of the FA population.
- 3.6 Additional severity criteria (such as mFARS score) relating to more detailed FA symptoms/levels of disability would more closely reflect the eligibility criteria in the key MOXle Part 2 trial. A criterion that remains silent with respect to mFARS may be pragmatic in providing flexibility to patients and doctors when discussing treatment options. However, this would need to be weighed against the lack of evidence of efficacy and safety in some FA patients that would not have been eligible to enrol in the key trial. Further, patients with less severe disease may be unnecessarily exposed to additional toxicity with minimal or no meaningful clinical benefit from a high-cost drug.
- 3.7 Overall, 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 MOXle Part 2 trial. The DUSC considered that another option would be to include additional criteria that described the severity of FA, and which better aligned the proposed restriction with the eligibility criteria of the MOXle Part 2 trial.
- 3.8 The requested restriction requires evidence that patients with clinically significant cardiac disease are hemodynamically stable prior to initiating treatment with

¹ Indelicato E, et al. Onset features and time to diagnosis in Friedreich's ataxia. *Orphanet J Rare Dis.* 202;15(1):198

omaveloxolone, with records no older than 3 months. The submission intends that the requirement for such evidence of stable cardiac disease remains in the treatment continuation listing and that the evidence needs to be no older than 12 months. This ensures that continuation is not exclusionary and inflexible.

- 3.9 The submission did not propose restricting treatment with omaveloxolone by pes cavus status. The submission argued that 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. However, the primary full analysis set (FAS) was based on patients without pes cavus. Furthermore, recognising the small patient numbers with pes cavus (n=20), subgroup analyses indicated there was no significant improvement with omaveloxolone in patients with pes cavus (refer to efficacy section further below). The ESC considered that the restriction should not specify pes cavus status.
- 3.10 The submission noted that no specific continuation or stopping criteria based on treatment response were proposed. The arguments presented in the submission included i) mFARS was not designed for use in clinical practice, ii) the mFARS overall score is a sum of 5 subscales and changes in mFARS scores have different impacts on different people, and iii) the decision to permanently discontinue treatment with omaveloxolone for a particular patient needs to be taken in consultation between the patient and the treating physician. The ESC considered that it would be appropriate to include a continuing criterion which stated that ‘Patient must continue to demonstrate clinical benefit’. The pre-PBAC response considered that this was appropriate.
- 3.11 The PSCR stated that the sponsor was planning to commence an early access program in late January 2025. The sponsor stated that it would request a separate initiation listing for grandfathering at the time of PBS listing. The Secretariat noted that a separate grandfather restriction would not be required given that the proposed initial treatment restriction wording allows access for patients initiated on omaveloxolone prior to PBS listing.
- 3.12 The submission stated that cascade testing of the extended family members could identify older or younger siblings with the disease at an earlier stage, but pre-symptomatic genetic testing should be considered on a case-by-case basis. Given that routine genetic testing is not recommended in asymptomatic siblings, and that treatment guidelines do not recommend treating presymptomatic patients, the submission argued this is not an issue for the proposed PBS restriction. The Medicare Benefits Schedule (MBS) Item 73434 indicates that a relative of a patient with a confirmed pathogenic or likely pathogenic germline variant associated with a neuromuscular disorder would be eligible for the MBS item (criterion b).

4 Population and disease

- 4.1 FA is a rare, autosomal recessive and progressive multisystem neurodegenerative movement disorder, affecting both 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 associated with earlier symptom onset and more rapid progression, with more severe co-morbidities such as diabetes and cardiovascular disease².
- 4.2 Frataxin deficiency leads to mitochondrial dysfunction, suppression of nuclear factor erythroid 2 like 2 (Nrf2) activity, impaired iron metabolism, oxidative stress, and other metabolic abnormalities. As FA progresses, symptoms may include difficulty swallowing, speech problems, fatigue, skeletal abnormalities (such as scoliosis and pes cavus), muscle weakness, reflex loss and sensory impairment.
- 4.3 The mean age of onset of the classical FA, the most common form, is between 10 and 16 years, late-onset (LOFA) and very late-onset (VLOFA) FA develops after the ages of 25 and 40 years, respectively³. The average life expectancy of a patient with FA is between 30 and 40 years of age. FA cases of early symptom onset can also occur. Some people have presented with symptoms before the age of 5 years, including infants as young as one year old. Cardiac complications are a leading cause of death in people with FA⁴.
- 4.4 Diagnosis of FA usually occurs during childhood or adolescence and is based on clinical suspicion of symptoms (gait ataxia, balance and coordination disturbances) confirmed by genetic testing for GAA expansion in the FXN gene. In Australia, diagnosis is usually confirmed with a paediatric neurologist in close collaboration with a paediatric geneticist. 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.
- 4.5 A genetic counsellor should 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.

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.

- 4.6 Table 2 summarises the age distribution of FA patients in the Australian Friedreich's Ataxia Clinical Outcome Measures Study (FACOMS) at the time they entered the registry.

Table 2: Australian FACOMS – distribution by age

Stratification	Description	n	N	%
Age ^a	< 16 years (current age, visit 1)	50	202	24.8
	16-40 years (current age, visit 1)	111	202	55.0
	>40 years (current age, visit 1)	41	202	20.3
	≥16 years (current age, visit 1)	152	202	75.2

Source: Table 1-7, p44 of the submission.

FACOMS=Friedreich's Ataxia Clinical Outcome Measures Study.

^a Age at current visit (Visit 1)

- 4.7 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. The submission stated the potential benefits of omaveloxolone in people with FA include slowing disease progression by improving muscle function, mobility, visual function, cardiac function and quality of life.

5 Comparator

- 5.1 Omaveloxolone is intended to be used as an adjunct to BSC in the requested patient population. The ESC considered that the nomination of BSC as the main comparator was appropriate. The comparator for omaveloxolone + BSC would be no active therapy for which placebo was a proxy in the key MOXle Part 2 trial. BSC involves the management of disease-related symptoms (cardiac, metabolic, respiratory, nutritional and orthopaedic support) via a multi-disciplinary clinic.
- 5.2 The submission noted that there are only two centres of excellence for the management of adults with FA in Australia which include the Monash Medical Centre in Melbourne and the Royal Brisbane & Women's Hospital in Queensland. There was no discussion of paediatric centres in the submission, although most patients present with clinical symptoms during their paediatric years, patients must be 16 years of age or older to access omaveloxolone under the proposed restriction.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician described the mFARS scale which was used to measure response in the MOXle Part 2 trial. The clinician stated that the least squares mean difference between the omaveloxolone and placebo arms from baseline to Week 48 of -2.40 points was clinically significant. The clinician stated that natural history studies have shown that patients aged 16 to 40 years of age with

FA generally progress at an average of 1.8 points annually on the mFARS scale (Patel et al., 2016). Therefore, a difference in the change from baseline of -2.40 points in mFARS in favour of omaveloxolone within the MOXIe trial represents both a statistically significant and clinically meaningful improvement for these patients relative to BSC, noting treatment 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 carers including reducing the amount of carer hours required and unpaid care provided by family.

- 6.2 In terms of the restriction, the clinician suggested eligibility for omaveloxolone be based on symptoms as identified in a clinical exam rather than mFARS scores. The clinician explained that patients with FA are typically identified when they present with clinical symptoms, followed by confirmed diagnosis with genetic testing, as opposed to receiving an mFARS score.
- 6.3 The clinician was not supportive of restricting the use of omaveloxolone to patients diagnosed with FA before the age of 40 to avoid inequities in a rare disease context.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from individuals (77), health care professionals (10) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals included patients with FA and parents, family members, partners or carers of people living with FA. Input described the impacts of this progressive condition, which reduces people's ability to undertake daily tasks, on quality of life and how important it was for patients to find treatments that would delay progression and improve daily functioning. Input from carers 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.
- 6.5 Input from health professionals was received from neurologists, clinical researchers/ investigators, physiotherapists and an occupational therapist. Clinicians noted that no disease modifying therapies are currently available and that those undergoing treatment receive supportive care only. The health professionals described the significant impact of this progressive neurodegenerative 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.

- 6.6 The PBAC noted the advice received from Friedreich's Ataxia Research Alliance (FARA) and Friedreich Ataxia Research Association. 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, diarrhea, and nausea.

Clinical trials

- 6.7 MOXle Part 2 represents the key evidence to support the clinical claim in the submission. This was a randomised, placebo-controlled, double-blind, trial assessing the efficacy and safety of omaveloxolone 150 mg once daily in FA patients 16-40 years of age for 48 weeks. 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 vs no pes cavus).
- 6.8 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 MOXle 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 phenotype⁵.
- 6.9 Additionally, to help inform the longer-term magnitude of benefits with omaveloxolone treatment, a *post hoc* propensity-matched unanchored indirect comparison analysis of MOXle Extension study data compared to an international natural history study (FACOMS) was presented in the submission.
- 6.10 The MOXle Part 2 trial represented the key evidence in support of the clinical claim in the submission. Details of the MOXle Part 2 trial are provided in Table 3.

⁵ Lynch, DR et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. *Annals of clinical and translational neurology* 2019; 6(1): 15-26.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MOXle Part 2 NCT02255435	Clinical study report: RTA 408 (Oma veloxolone) 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 (MOXle 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 April 25 2023; 100 (17_supplement_2)
Propensity score matched analysis	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
	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, pp62-63 of the submission.

6.11 The key features of the MOXle Part 2 trial are summarised in Table 4.

Table 4: Key characteristics of the key MOXle 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	<u>Demographics</u> Male: 53% Mean age: 24 yo White: 97% Mean mFARS: 40 <u>Inclusion Criteria</u> 16 to 40 yo with genetically confirmed FA -mFARS score ≥ 20 - ≤ 80 <u>Exclusion Criteria</u> Uncontrolled diabetes BNP > 200 pg/mL History of significant cardiac or hepatic disease.	ITT N = 103 Oma, n = 51; Placebo, n = 52 FAS (without pes cavus) N = 82 Oma, n = 40; Placebo, n = 42	<u>Primary Endpoint:</u> LSM change from baseline in mFARS score at 48 weeks <u>Secondary Endpoints:</u> 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.	<u>Selection Bias:</u> Unclear due to small sample size and imbalances for some baseline characteristics. <u>Performance Bias:</u> Unclear as AEs may have resulted in unblinding. <u>Detection Bias:</u> Unclear (see performance bias). <u>Attrition Bias:</u> High. <u>Reporting Bias:</u> Low.

Source: Section 2 of the submission and the MOXle Part 2 Clinical Study Report

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=beta natriuretic peptide; CGIC=Clinical Global Impression of Change; CI=confidence interval; DB=double blind; FA=Friedreich's ataxia; FAR-ADL=Friedreich's Ataxia Rating-Activities of Daily Living; FAS=full-analysis set; GAA=guanine-adenine-adenine; HbA1c=haemoglobin A1c; ITT=intention to treat; IWRS=interactive web response system; MC=multi-centre; MCID=minimal clinically important difference; mFARS=modified Friedreich's Ataxia Rating Scale; LSM=least squares mean; N=number of subjects; NR = not reported; OHP=Oregon Health Plan; PC=placebo controlled; PG=parallel group; PGIC=Patient Global Impression of Change; PO=orally; PP=per protocol; RCT=randomised controlled trial; SAE=serious adverse event; yo=years old.

- 6.12 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 Full Analysis Set [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 is unclear.
- 6.13 All patients and investigators with direct involvement in the conduct of the study were blinded to treatment assignments. However, the risk of bias in the assessment of subjective measures were considered unclear as adverse events (AEs) consistent with the known safety profile of omaveloxolone (such as an increase in ALT and AST levels), were more frequent in patients treated with omaveloxolone than patients in the placebo arm which may have resulted in unblinding.
- 6.14 The risk of confounding from differential attrition rates was considered high given the higher percentage of missing data in the omaveloxolone arm (15%) compared to placebo arm (2.3%) and the small sample size.
- 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%, respectively). The most common reason for treatment discontinuation was AEs (5.8%).

Comparative effectiveness

- 6.16 The primary endpoint in MOXle Part 2 was the change in modified FARS (mFARS) scores from baseline to Week 48. Table 5 and Table 6 summarise the scoring and assessments of mFARS.

Table 5: Overview of scoring of mFARS used in MOXle Part 2

Section	FARS	mFARS (range 0-99)
Upper limb coordination	0-36	0-36
Upright stability	0-36	0-36
Lower limb coordination	0-16	0-16
Bulbar function	0-11	0-11
Peripheral nervous system	0-26	–
Total score	0–125	0–99

Source: Table 2.14, p88 of the submission.

FARS= Friedreich's ataxia (FA) rating scale; mFARS=modified FARS

Table 6: Overview of the assessment of mFARS used in MOXle Part 2

Section	Evaluation	Number of assessments	Assessments
Upper limb coordination	Coordination of the arms and hands and tremor	10 assessments; scored 0–36	Finger to finger test (left/right) Nose to finger test (left/right) Dysmetria test – touching target (left/right) Rapid alternating movements (left/right) Finger taps (left/right)
Upright stability	Ability to sit, stand and walk	9 assessments; scored 0–36	Sitting posture Stance (eyes opened/closed, and feet together/apart) Gait Tandem walk Tandem stance; and stance on dominant foot
Lower limb coordination	Coordination of movement and function of lower limbs	4 assessments; scored 0–16	Heel along shin slide (left/right) Heel to shin tap (left/right)
Bulbar function	Speech, cough, facial strength	2 assessments; scored 0–11	Forceful cough Spontaneous speech (repeat specific sentences) Tongue atrophy Facial atrophy
Total score		0–99	

Source: Table 2-15, p89 of the submission.

mFARS=modified Friedreich's ataxia rating scale

6.17 Secondary endpoints were assessed using hierarchical testing. If the study was able to demonstrate statistical significance of a benefit for the primary outcome, then the key and other secondary endpoints would be analysed using a hierarchical approach to maintain the family-wise overall Type I error rate of 0.05. Hierarchical testing of the key secondary and secondary outcomes continued in the following order:

- Patient Global Impression of Change (PGIC) at Week 48
- Clinician Global Impression of Change (CGIC) at Week 48
- Change in nine-hole peg test (9-HPT) at Week 48
- Change in 25-foot walk test (T25-FWT) at Week 48
- Frequency of falls over 48 weeks
- Change in peak work during maximal exercise testing at Week 48
- Change in Activities of Daily Living (ADL) score at Week 48

6.18 The ESC noted that the submission nominated a minimally clinically 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 was concerned that a change of -1 point could be the result of random variation or measurement error.

6.19 The FAS primary analysis set was based on all patients without pes cavus who had at least 1 post-baseline measurement. The primary analysis utilised all mFARS values collected through Week 48, irrespective of whether a patient was receiving treatment.

6.20 Table 7 summarises the results for the primary outcome of mean change from baseline in mFARS for the FAS population in the key MOXle Part 2 trial. Figure 1 shows the change from baseline in mFARS over time in the FAS.

Table 7: Mean change in mFARS score from baseline at Week 48 in MOXle Part 2 (FAS)-patients without pes cavus

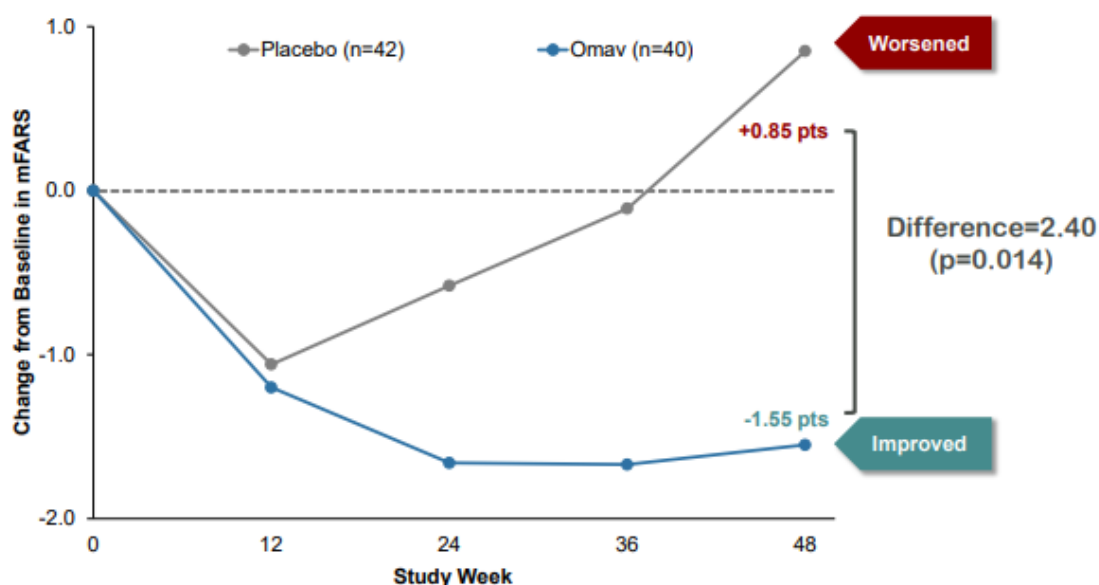
Measure	Omaveloxolone 150 mg (N=40)	Placebo (N=42)
Baseline score		
N	40	42
Mean (SD)	40.94 (10.39)	38.77 (11.03)
Median (range)	39.15	35.65
Week 48 score		
N	34	41
Mean (SD)	39.17 (10.02)	39.54 (11.57)
LS mean (SE)	-1.55 (0.69)	0.85 (0.64)
Median (range)	38.10	38.70
LS mean difference (SE) [95% CI];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

Source: Table 2-19, p99 of the submission.

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

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



Source: Figure 2.4, p99 of the submission

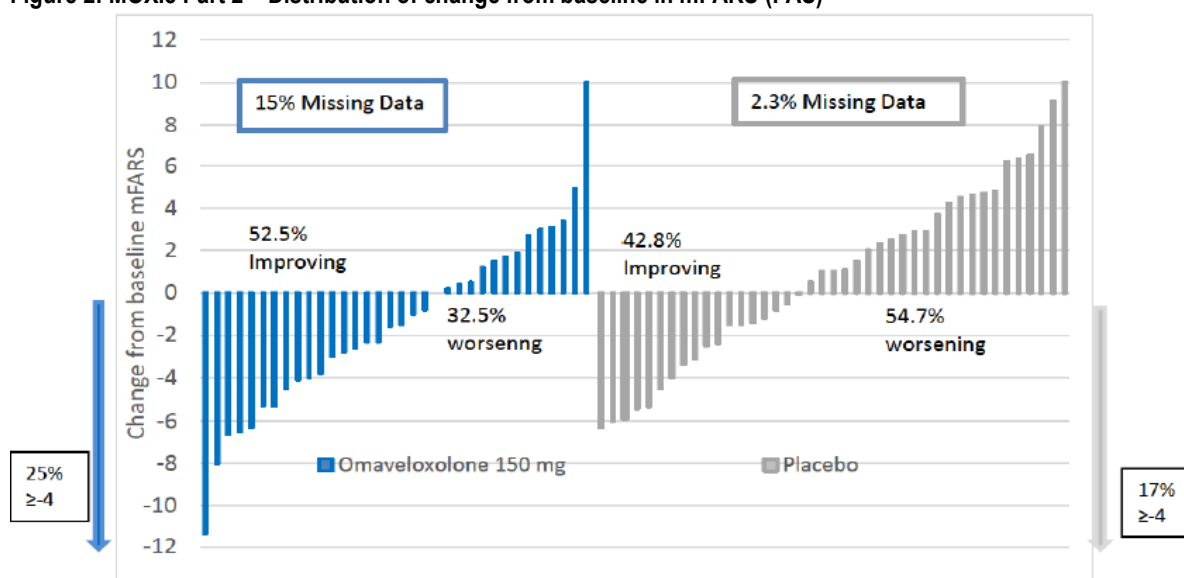
LS=least squares; mFARS=modified Friedreich's ataxia rating scale; Omav=omaveloxolone; SD=standard deviation

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 between the omaveloxolone and placebo arms was statistically significant (-2.40 points), the ESC questioned the clinical relevance of this small change (on a 99-point scale) and

whether it would result in benefits in terms of disease outcomes for the patient. The ESC noted that the mean mFARS at Week 48 were similar as the baseline score in the placebo arm (38.77) was lower than in the omeveloxolone arm (40.94). Patients in the omeveloxolone arm had a mean change from baseline in mFARS of -1.56 points compared to 0.85 points for patients in the placebo arm at Week 48. The change from baseline in neurological function favouring omeveloxolone over placebo was time dependent, with a progressively larger separation from placebo observed at each study visit over time.

- 6.22 The FAS restriction to patients without pes cavus is not in line with the ITT principle, although sensitivity analyses were conducted for a number of population sets including covariate adjustment for pes cavus in the ITT or in the total randomised population. In the total randomised population, treatment with omeveloxolone significantly improved mFARS by -1.94 points relative to that for placebo (n=103; p=0.0331).
- 6.23 Figure 2 summarises the distribution of change from baseline in mFARS across the treatment arms in MOXle Part 2

Figure 2: MOXle Part 2 – Distribution of change from baseline in mFARS (FAS)



Source: Figure 7, p58 of the FDA Clinical Review of omeveloxolone, September 2017, Application number: 216718Orig1s000, Reference ID 5133070.

FAS=Full Analysis Set (non-pes cavus patients); FDA=Food and Drug Administration; mFARS= modified Friedreich's Ataxia Rating Scale.

- 6.24 The ESC noted that whilst 52.5% of patients in the omeveloxolone arm compared to 42.8% in the placebo arm showed improvement from baseline in mFARS, the higher percentage of missing data in the omeveloxolone arm compared to the placebo arm (15.0% vs. 2.3%) decreased confidence in the results. The 15% of patients with missing data in the omeveloxolone arm could fall into either improvement or worsening categories. Overall, based on a worst-case scenario for omeveloxolone where all 15% of patients are assumed to have worsened, and recognising the low attrition rate in

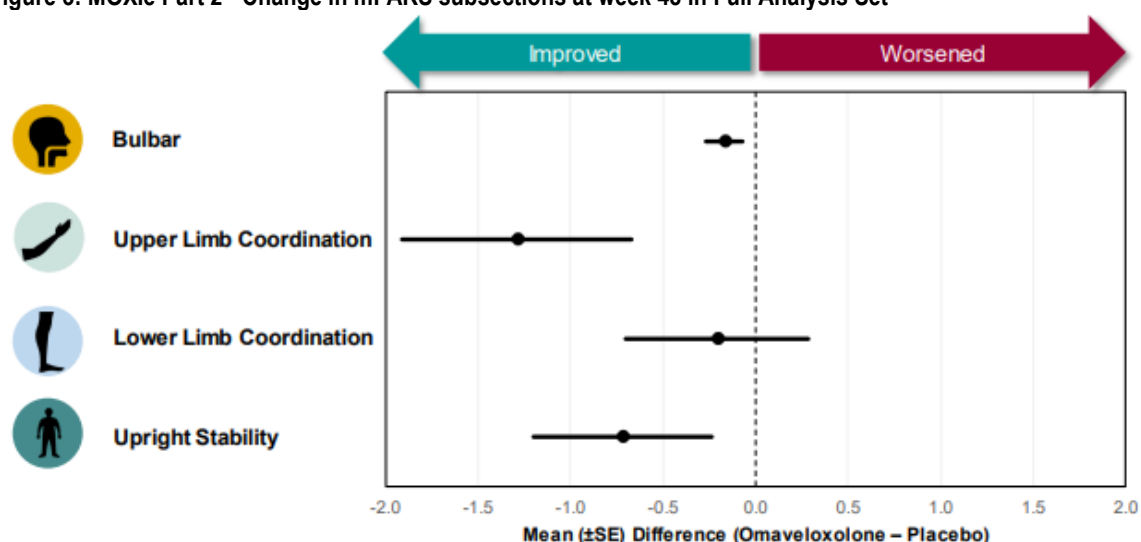
the placebo arm, the difference in mFARS would remain favourable to omaveloxolone, although the treatment effect would likely be modest.

6.25 Sensitivity tipping point analyses of missing data were presented in the MOXIe Part 2 CSR. Various shifts of the imputed data in the omaveloxolone group were explored. The ESC noted that generally, tipping point analysis is a reasonable, valid, somewhat subjective and well documented approach (also referred to ‘breakdown point’ in robust statistical theory) to assess the impact of imputation on analyses. The tipping point for the trial, where the treatment effect loses statistical significance, is a shift of +2 points (worsening) in the imputed data for missing mFARS values in the omaveloxolone arm at Week 48. This shift is more than twice the magnitude of worsening in the placebo arm (+0.85 points). Whilst these analyses suggest the primary analysis may be robust, the ESC agreed with the evaluation that concerns remain as to whether the decreased differences between the treatment arms resulting from worsening shifts for omaveloxolone are clinically meaningful.

6.26 The comparative treatment effect by mFARS component is presented in

6.27 Figure 3.

Figure 3: MOXIe Part 2 - Change in mFARS subsections at week 48 in Full Analysis Set



Source: Figure 2-6, p101 of the submission.

mFARS=modified Friedreich's ataxia rating scale; SE=standard error.

Difference Omaveloxolone minus Placebo (95% CI): Bulbar: -0.17 (-0.37, 0.04); Upper Limb Coordination: -1.29 (-2.51, 0.06); Lower Limb Coordination: -0.21 (-1.17, 0.76); Upright Stability: -0.72 (-1.67, 0.24)

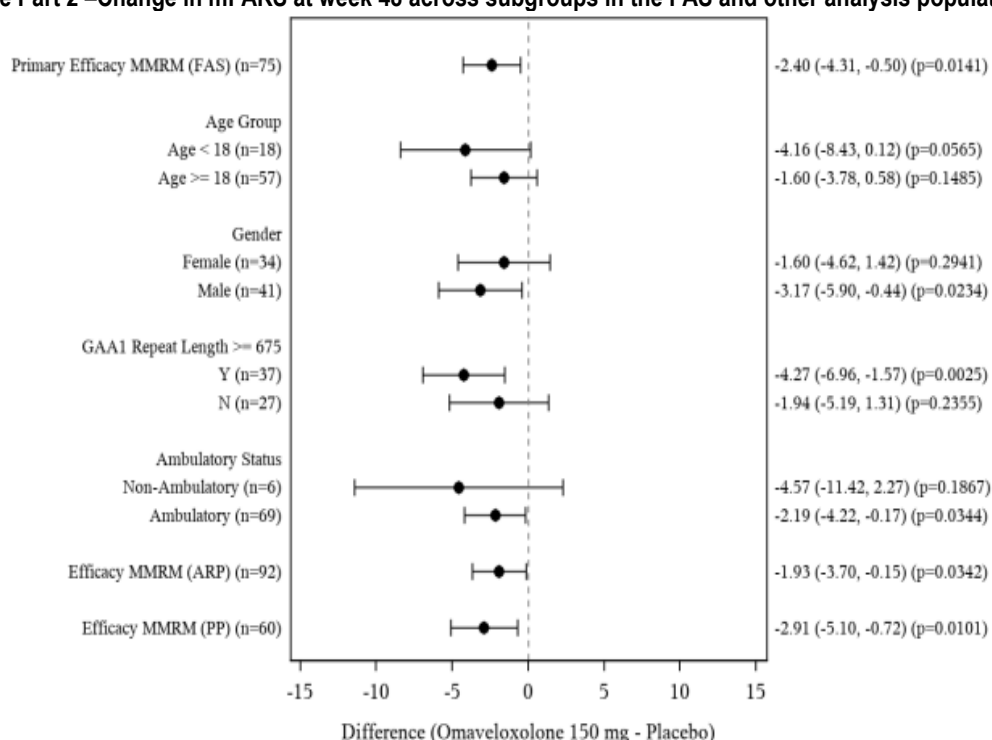
6.28 Treatment with omaveloxolone numerically improved each of the individual components of the mFARS assessment (bulbar, upper limb coordination, lower limb coordination, and upright stability) relative to placebo although the difference for lower limb coordination was not statistically significant. The largest treatment effects were observed for upper limb coordination and upright stability. The submission noted that importantly, the improvements in upright stability with omaveloxolone

relative to those for placebo demonstrate an effect on the mFARS component that defines important clinical milestones in FA, including loss of ambulation.

6.29 Pre-specified subgroup analyses of the MOXIe Part 2 trial (Figure 4) were presented for the primary efficacy endpoint of change from baseline in mFARS at Week 48 for the following subset categories:

- Age group: Age < 18 years, Age ≥ 18 years
- Gender: female, male
- GAA1 repeat length ≥ 675: yes, no
- Ambulatory status: non-ambulatory, ambulatory.

Figure 4: MOXIe Part 2 –Change in mFARS at week 48 across subgroups in the FAS and other analysis populations



Source: Figure 2-16, p139 of the submission

ARP=all randomized population; FAS=full analysis set; MMRM=mixed model for repeated measures; PP=per protocol; mFARS=modified Friedreich's ataxia rating scale.

Note: Data plotted are LS means differences between omaveloxolone and placebo patients estimated from a mixed model repeated measures (MMRM) analysis. The analysis used Visits 4, 12, 18, 24, 36, and 48. The number of patients (n) shown is the number of patients with an mFARS assessment at Week 48.

6.30 The treatment benefit associated with omaveloxolone over placebo appeared larger in the subgroup of patients <18 years of age in the FAS. Placebo-treated patients worsened by +2.17 points at Week 48, while omaveloxolone-treated patients improved by -3.42 points at Week 48 resulting in a placebo-corrected improvement of -4.16 points (n=20; p=0.0565). The sample size of the subgroup is too small to test for a treatment interaction by age. Other prespecified subgroup analyses favoured

omaveloxolone over placebo although a definitive conclusion is difficult due to the small sample sizes and high risk of confounding.

- 6.31 Notably, the MOXle Part 2 CSR also presented subgroup analysis by pes cavus. Results for mFARS change from baseline at Week 48 are presented in Table 8.

Table 8: MOXle Part 2 - mFARS change from baseline at Week 48 (pes cavus population)

	Omaveloxolone (N=10)	Placebo (N=10)
Least Square Means change (95% CI)	0.15 (-2.62, 2.91)	1.33 (-1.29, 3.96)
Least Square Means Difference in change Omaveloxolone minus Placebo	-1.19 (-5.19, 2.82)	

Source: Table 14.2.2.3, p453 of the MOXle Part 2 CSR.

- 6.32 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 is high uncertainty arising from the small sample size of the subset, a potential impact of foot structure on performance cannot be excluded.

- 6.33 Table 9 summarises the key secondary endpoints of global impression of change.

Table 9: PGIC and CGIC from baseline at Week 48 in MOXle Part 2

Measures	Full analysis set		All randomised population	
	Omaveloxolone 150 mg (N=40)	Placebo (N=42)	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
PGIC				
LS mean change from baseline	3.89	4.32	3.91	4.47
LS mean difference between groups; p-value	-0.43 (p=0.13)		-0.56 (p=0.028)	
CGIC				
LS mean	3.92	4.06	3.90	4.18
LS mean difference between groups ^a	-0.13 (p=0.526)		-0.28 (p=0.133)	

Source: Table 2-20, p102 of the submission.

CGIC=Clinician Global Impression of Change; FAS=full analysis set; LS=least squares; N=total number of participants in treatment arm; PGIC=Patient Global Impression of Change

^a Comparison of PGIC and CGIC change from baseline between in the omaveloxolone 150 mg arm and patients in the placebo arm was estimated using analyses of covariance, with the following fixed factors: site, pes cavus status, and treatment. Missing data were imputed using multiple imputation

- 6.34 In the FAS population, mean PGIC and CGIC scores at Week 48 numerically favoured the omaveloxolone arm but were not statistically different from placebo. The least squares mean treatment difference between treatment groups 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).
- 6.35 Omaveloxolone treatment did not statistically significantly improve the other secondary endpoints including 25-foot timed walk test, frequency of falls, or peak work relative to placebo. Numerically, frequency of falls favoured omaveloxolone. During the 48-week treatment period, omaveloxolone patients reported a median of 3.0 falls (range, 1 to 89), while placebo patients reported a median of 8.5 falls (range, 0 to 131). These estimates are imprecise.

- 6.36 Change in ADL scores from baseline at Week 48 was last in the hierarchy of statistical testing in the statistical analysis plan. The least squares mean difference between treatment groups was -1.30 points favouring omaveloxolone which reached nominal statistical significance relative to placebo ($p=0.04$). These results should be interpreted with caution given the small data sets and lack of adjustment for multiplicity in the statistical analyses.
- 6.37 To help inform the longer-term magnitude of benefits with omaveloxolone treatment versus BSC, results from an unanchored propensity matched indirect comparison between omaveloxolone treated patients in the MOXle Extension study and the FACOMS natural history data was presented in the submission.
- 6.38 For inclusion in the indirect comparison analysis, patients from the MOXle Extension study must have had a baseline and at least one post baseline mFARS within 3 months of baseline; and must have data for all variables included in the propensity score matching. For the propensity-matched analysis, the sample size was based on the 136 patients from MOXle Extension who had an on-treatment post-baseline mFARS assessment and were thus available for matching to 136 patients from the FACOMS natural history study.
- 6.39 The analysis of change from baseline in mFARS at Year 3 was performed based on a mixed model repeated measures (MMRM) model, including treatment group, baseline mFARS, visit, and interaction terms for visit-by-baseline and treatment group-by-visit as covariates.
- 6.40 The median treatment duration in MOXle Extension (exclusive of treatment duration in Part 1 or Part 2) was 2.76 years, with a maximum treatment duration of 3.4 years and a minimum treatment duration of 0.5 years (. The 136 patients matched from FACOMS had a median follow-up duration of 2.92 years, with a maximum follow-up duration of 3.5 years and a minimum follow-up of 0.6 years.
- 6.41 The covariates matched and not matched for the indirect comparison, and FACOMS covariates matched to the MOXle Extension dataset are summarised in Table 10 and Table 11, respectively.

Table 10: Covariates used for propensity score matching

Logistic regression covariate	Rationale for inclusion	Reference supporting importance of covariate	n (%) of FACOMS patients with data (N=810)	n (%) of MOXle extension patients with data (N=149)
Key covariates that were matched				
Age	Age is the primary determinant of phenotypic severity	Patel 2016	807 (99.6%)	149 (100%)
Age of FA onset	Surrogate for relative rate of progression and GAA repeat length	Patel 2016	801 (98.9%)	149 (100%)
Sex	Sexual dimorphisms inconsistently observed in ataxia studies	Friedman 2010	810 (100%)	149 (100%)
Gait score at baseline	Allows matching of patients at the same level of function	Rummey 2022	790 (97.5%)	149 (100%)
mFARS score at baseline	Allows matching of patients at the same level of function	Rummey 2022	789 (97.4%)	149 (100%)
Key covariates that were not matched				
GAA1 Repeat Length	Not included, not available for all patients	None provided	745 (92.0%)	131 (87.9%)
Pes cavus status ^a	Not included, not systematically recorded in FACOMS	None provided	432 (53.3%)	149 (100%)

Source: Table 2-43, p143 of the submission.

FA= Friedreich's ataxia; FACOMS= Friedreich's Ataxia Clinical Outcome Measures Study; GAA= guanosine adenosine adenosine; mFARS= modified Friedreich's ataxia rating scale.

^a The definition of pes cavus between the two studies was not consistent. Pes cavus was based on clinical judgment in FACOMS; however, MOXle 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.

Table 11: Demographics and baseline FACOMS covariates matched to MOXle Extension for propensity score calculation

	Matched FACOMS (n=136)	MOXle 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, p144 of the submission.

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

^a Assessment in FARS subsection E-Upright stability

^b Note number of patients in either cohort varied across other characteristics due to missing data

6.42 Baseline characteristics, particularly those used as covariates for determining the propensity scores (mFARS, Gait, and ADL), appeared balanced between the FACOMS and MOXle Extension groups

6.43 Prognostic covariates such as GAA1 repeat length and pes cavus were considered but not included due to incomplete GAA1 data for all patients and differences in the method of evaluation of pes cavus between studies⁶.

6.44 Results from the propensity score matched analysis for change in mFARS from baseline at 3 years are summarised in Table 12.

Table 12: Change from baseline in mFARS at 3 years: PSMA

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

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

6.45 Whilst the matched FACOMS patients progressed 6.6 mFARS points after three years, patients treated with omaveloxolone in MOXle 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 group compared to the matched control group.

6.46 The evaluation noted that indirect comparisons with natural history cohorts are generally difficult to interpret due to a high risk of confounding given the non-randomised nature of the comparison, selection biases of patients for comparisons from the natural history database, other comparability issues related to selection of patients due to missing information on known or unknown prognostic factors of disease progression, and attrition of patients during the comparison durations in both treated and natural history groups. Issues with the comparison included:

- additional important prognostic covariates such as GAA1 repeat length and pes cavus were considered but not included due to incomplete GAA1 data for all patients and differences in the method of evaluation of pes cavus between studies.
- there was no indication that differences in the collection of data regarding concomitant medications were matched or 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 MOXle Extension study and the FACOMS registry was unknown.
- selection bias: MOXle Extension patients may have been healthier at baseline or responded better to omaveloxolone than those who did not participate in the

⁶ The definition of pes cavus between the two studies was not consistent. Pes cavus was based on clinical judgment in FACOMS; however, MOXle 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.

extension study, which would bias measures of association towards a beneficial effect of omaveloxolone. Another concern is that the natural history study is likely to have less stringent inclusion and exclusion criteria, thus patients in the natural history study may be more likely to have severe FA, which would bias associations away from the null favouring omaveloxolone.

- on a related note, study participants in MOXle 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 remains a concern.
- the impact of differences in frequency of mFARS assessment between the two studies remains 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 MOXle Extension.
- *post-hoc* nature of the analysis.

Comparative harms

6.47 Overall AEs and treatment emergent AEs (TEAEs) in MOXle Part 2 are summarised in Table 13.

Table 13: 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 (3.9%)	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, p123 of the submission.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence intervals; Omav=omaveloxolone; RD=risk difference (calculated in the submission); SAE=serious adverse event; TEAE=treatment-emergent adverse event.

- 6.48 No deaths were reported in either treatment arm of MOXIE Part 2.
- 6.49 TEAEs related to study drug were higher in the omaveloxolone treatment arm (72.5%) compared to the placebo arm (36.5%). The proportion of patients who interrupted study drug administration because of a TEAE was greater in the omaveloxolone group (17.6%) than the placebo group (1.9%). The proportion of patients with AEs leading to permanent treatment discontinuation was approximately two-fold in the omaveloxolone arm compared to the placebo arm (7.8% vs. 3.8%). Serious TEAEs were reported in 5 (9.8%) omaveloxolone-treated patients, and 3 (5.8%) placebo-treated patients. TEAEs were mostly mild or moderate in severity in both treatment arms (>90%) and most TEAEs resolved within 2 months of the event start date.
- 6.50 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% vs. 1.9%), headache (37.3% vs 25.0%), nausea (33.3% vs 13.5%), fatigue (21.6% vs 13.5%), abdominal pain (21.6% vs 5.8%), and increased AST (21.6% vs 1.9%). Increased ALT, increased AST, and headache were considered by the investigators to be related to omaveloxolone.
- 6.51 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. More omaveloxolone-treated patients with normal baseline values had increases in ALT above the upper limit of normal (ULN) while taking omaveloxolone than placebo-treated patients.
- 6.52 The submission noted that ALT and AST levels returned to baseline levels after continuous treatment (Week 52 for ALT and Week 36 for AST), and that ‘this likely

reflects a coordination or physiological adaption to metabolic demand and energy homeostasis rather than liver injury’.

- 6.53 Within the (SOC) Cardiac disorders, 3 (5.9%) omaveloxolone treated patients and one (1.9%) placebo treated patient experienced serious TEAEs. Small mean increases in BNP were observed with omaveloxolone treatment relative to placebo and 2 (3.9%) patients had B-type natriuretic peptide (BNP) values that exceeded 200 pg/mL.
- 6.54 The submission presented a discussion on cardiac-related AEs associated with bardoxolone (another Nrf2 modulator) and noted the following:
- Although omaveloxolone and bardoxolone methyl are Nrf2 activators, and share a common pharmacophore, they exhibit differences in their structural and chemical properties. The EMA assessment report notes that available non-clinical data suggest that the pharmacology and safety profiles of omaveloxolone and other Nrf2 activators are similar (p230, Committee for Medicinal Products for Human Use (CHMP) report for omaveloxolone, 14 December 2023, EMA/CHMP/535977/2023).
 - Available non-clinical data suggest that there is no indication that the pharmacology and safety profiles of omaveloxolone cause adverse cardiac effects. Long-term Nrf2 activation at tolerable doses does not appear to cause adverse effects on the heart. Preclinical models indicate that increases in BNP expression in heart tissue are likely due to metabolic effects.
 - The patient population in the BEACON⁷ study of bardoxolone methyl (i.e., people with chronic kidney disease [CKD] and type 2 diabetes mellitus [T2DM]) is significantly different from the FA population. The FA patient population has a low likelihood of advanced CKD and cardiac diastolic dysfunction. Differences between the BEACON and MOXIe FA patient populations are recognised. However, elevated baseline BNP and prior hospitalisation for heart failure were among the major risk factors identified for the events in the bardoxolone study; consequently, patient with significant heart disease were excluded from the FA studies.
 - Notably, the cardiac morphology of preserved contractility and diastolic dysfunction for the BEACON patients differs from the morphology of end stage heart failure that is typical for FA, which is characterised by a reduced ejection fraction and low contractility. There has been no safety signal for heart failure presenting with fluid overload and increased blood pressure in clinical trials of omaveloxolone in FA, including in patients with mild to moderate cardiomyopathy. However, as a precaution, the sponsor proposed adequate BNP monitoring in the

⁷ Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events; Study 402-C-0903

draft PI label. It is unclear whether current MBS listings for BNP testing (heart failure and PAH) could be used for monitoring patients receiving omaveloxolone.

6.55 Overall, due to the observations of congestive heart failure in the bardoxolone study, and the cardiovascular risk in FA patients, cardiotoxicity remains a safety concern with omaveloxolone.

Benefits/harms

6.56 A summary of the comparative benefits and harms for omaveloxolone versus placebo (proxy for BSC) is presented in Table 14.

Table 14: Summary of the comparative benefits and harms for omaveloxolone versus placebo (proxy for best supportive care) – MOXle 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: Sections 2.5 and 2.6 of the submission

ADL=activities of daily living; AEs=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI = confidence interval; LS=least squares; Oma=omaveloxolone; PGIC=patient global impression of change.

^aIn 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).

6.57 On the basis of direct evidence presented by the submission:

- 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 after 48 weeks of treatment in patients without pes cavus (n = 82, FAS). There is some uncertainty regarding the clinical meaningfulness of these changes which may impact patients differently.
- 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 significant.
- for every 100 FA patients treated with omaveloxolone in comparison with placebo, 10 additional patients will experience a SAE, 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

6.58 The submission described omaveloxolone as superior in terms of effectiveness and inferior in terms of safety compared to BSC. The ESC considered the submission's clinical claims to be reasonable, but noted the following:

- 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 MOXle Part 2 trial.
- The key MOXle Part 2 trial showed that omaveloxolone was superior to placebo (as a proxy for BSC) in terms of the primary endpoint of change from baseline in mFARS at Week 48. Although the difference in mFARS at Week 48 between the omaveloxolone and placebo arms was statistically significant (-2.40 points), the ESC questioned the clinical relevance of this small change (on a 99-point scale) and whether it would result in benefits in terms of disease outcomes for the patient.
- The higher percentage of missing data in the omaveloxolone arm compared to the placebo arm for the primary endpoint (15.0% vs. 2.3%) decreases confidence in the primary results as they were based on the assumption that data were missing at random. The ESC noted that 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 is high uncertainty arising from unreliability of the small sample size of the subset, an impact of foot structure on performance cannot be excluded.
- The evidence 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 exercised 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.

- 6.59 Whilst recognising the unmet need, the PBAC considered that the data did not convincingly support the claims of superior comparative effectiveness. In particular, the PBAC noted the uncertainty in magnitude and duration of improvement, particularly in patients with different disease severity. The PBAC considered that claim of inferior comparative safety was reasonable.

Economic analysis

- 6.60 The submission presented a modelled economic evaluation, comparing treatment with omaveloxolone versus best supportive care for patients diagnosed with FA, aged over 16 years. The type of economic evaluation presented was a cost-utility analysis. Key components of the model are summarised in Table 15.

Table 15: 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), based on previous literature. ⁸
Outcomes	Life years and QALYs.
Time horizon	Lifetime time horizon (84 years) vs 4 years of follow-up in the omaveloxolone arm and 13 years follow up in the BSC arm. The ESC noted that the observed data was immature and substantially shorter than the time horizon, introducing uncertainty into the model. A shorter time horizon may be preferable to reduce the amount of uncertainty in the economic analysis and as the average life expectancy of a FA patient is 35 to 40 years.
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). The ESC noted that the natural history data was immature and hence, extrapolations based on this observed data were substantially uncertain. Mortality was related to disease progression (not treatment status) and was modelled using extrapolations of OS data from patients in the EFACTS registry, with HRs applied for different disease stages. The final modelled curves were adjusted for general population mortality using the competing risks approach (i.e. the highest instantaneous risk of dying is applied from either OS extrapolations or general population mortality). The ESC noted that as the vast majority of FA patients experience disease-related mortality, if the function is an accurate representation of mortality rate, the unadjusted extrapolated OS curves should be sufficient to model OS for FA, however the unadjusted OS curves modelled a substantial proportion of the populations alive in the final year of the model which was implausible.
Treatment effect	The treatment effect of omaveloxolone was (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. The assumption of that the full treatment effect is maintained indefinitely while patients remain on treatment (i.e. there is no development of treatment resistance) was uncertain and not justified in the submission. The model was substantially sensitive to alternative assumptions of treatment effect waning. Cohort specific treatment effects based on age were not applied in the model.
Utilities	Based on a regression model which related mFARS to utility values. This was based on mean EQ-5D and SARA scores (converted to mFARS) per year for patients enrolled in EFACTS over five years. The ESC noted the five data points used in the regression model was insufficient to relate the full spectrum of mFARS scores applied in the model to utility values which introduced further uncertainty in the model.
Costs	Costs include omaveloxolone acquisition costs, medical appointments, hospitalisation, home modifications, medical devices, AE management costs and carer costs. The ESC advised the inclusion of costs for carer, home modification and certain medical aids (walker, wheelchairs, specialised mattress, electric beds) was not reasonable in the base case analysis as the PBAC guidelines specify to only include direct medical costs.

Source: Constructed during the evaluation.

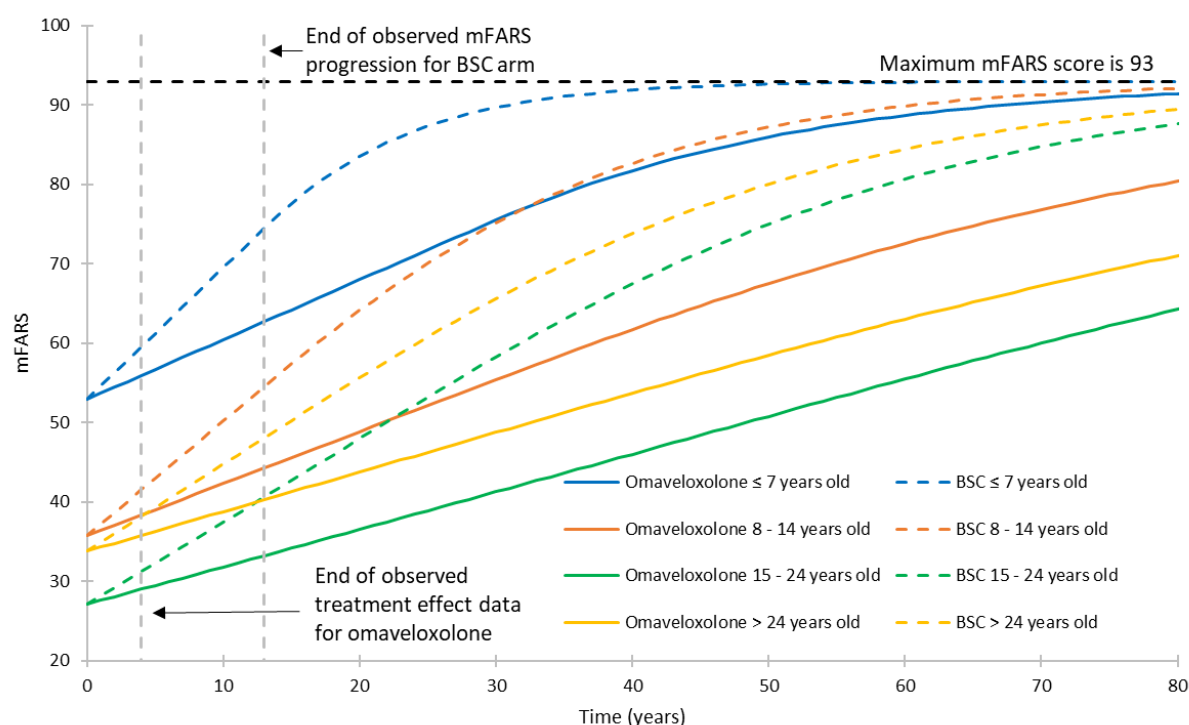
⁸ Rummey C, Corben LA, Delatycki M, Wilmot G, Subramony SH, Corti M, et al. Natural History of Friedreich Ataxia. *Neurology*. 2022;99(14):e1499-e510.

AE=adverse event; BSC=best supportive care; EFACTS=European Friedreich's Ataxia Consortium for Translational Studies; EQ-5D=EuroQol 5 dimensions; FA=Friedreich's Ataxia; FACOMS=Friedreich's Ataxia Clinical Outcome Measures; HR=hazard ratio; mFARS=modified Friedreich's Ataxia rating scale; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; SARA=Scale for the Assessment and Rating of Ataxia; TTD=time to treatment discontinuation.

- 6.61 Patients enter the model and are assigned into one of four 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.
- 6.62 The submission nominated a lifetime time horizon. This was essentially 84 years as the model stops once each age of onset cohort reaches 100 years old and the youngest age of onset cohort (≤ 7 years) enters the model at 16 years. While the time horizon was sufficient to capture all important differences between the two modelled arms, observed data in both arms was relatively short and immature, meaning disease progression and mortality extrapolations are uncertain. The ESC considered that a shorter time horizon would be preferable to reduce the amount of uncertainty in the economic analysis. Further, the ESC noted that the time horizon was exceeded the average life expectancy of patients with FA, which is 35 to 40 years.
- 6.63 In the BSC arm, disease progression (measured by mFARS scores) was modelled based on mFARS progressions by age of onset cohort observed in the FACOMS registry for 13-years. Beyond the 13 years of observed data, disease progression was estimated by extrapolating the observed data using a logistic distribution (as opposed to a linear function) based on clinician advice that slowing of progression at worsening mFARS scores is expected. The ESC considered that the submission's extrapolations, based on clinician advice with a low level of detail, were uncertain. Other than linear extrapolations, alternative extrapolation distributions were not provided or tested in the submission. The effect of the adopted extrapolation approach in the BSC arm of the model was unclear as the treatment effect of omaveloxolone (discussed below) is applied to this extrapolated curve. Hence, any changes to the extrapolation of progression rates in the BSC arm would also change the extrapolation of progression rates in the omaveloxolone arm.
- 6.64 The treatment effect of omaveloxolone was applied as a rate ratio calculated based on the relative change in mFARS scores in both arms of the propensity matched comparison of omaveloxolone patients in the MOXle extension study to matched patients enrolled in the FACOMS. The rate ratio (0.45) was applied to the yearly change in mFARS score in the BSC arm to derive the yearly change in mFARS score in the omaveloxolone arm. The propensity matched analysis was uncertain due to concerns relating to confounding, selection biases and missing mFARS data (this was discussed in paragraph 6.46).
- 6.65 In the base case analysis, the submission applied this rate ratio treatment effect to all patients in the omaveloxolone arm while they remained on treatment, without any waning. Once a patient ceased treatment (as per a time to treatment discontinuation

curve derived from the MOXle part 2 and extension trials), they lost all treatment effect. The assumption that the full treatment effect was maintained indefinitely whilst patients remain on treatment (i.e. that there is no development of treatment resistance) was uncertain and not adequately justified in the submission, with no effectiveness data provided beyond the four years of the extension study. Given patients are on treatment for a mean duration of 16 years in the model, the ESC considered that some waning may be expected. Linearly decreasing the treatment effect from Year 4 to 18 increased the ICER by 1% (the incremental quality-adjusted life year (QALY) gained decreased from 1.16 to 0.81). The pre-PBAC response stated that if there was a waning of treatment effect, then those patients no longer benefitting from treatment would be likely to discontinue treatment. It was noted that this was not captured in the economic model.

Figure 5: Comparison of modelled mFARS progression for omaveloxolone and BSC arm patients



Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment provided with the submission.

BSC=best supportive care; FACOMS= Friedreich's Ataxia Clinical Outcome Measures Study; FARS=modified Friedreich's Ataxia rating scale; IPD=individual patient data.

Note: The economic model was based on an upper bound mFARS score of 93 rather than an upper bound of 99 as implemented in the MOXle trial program (part 2 and extension), however there were no apparent meaningful differences in the results between the two versions of mFARS in the FACOMS IPD dataset.

6.66 Mortality risk was determined by mFARS score, not adjusted directly by treatment. As omaveloxolone slows the progression of mFARS, an indirect effect on overall survival (OS) associated with omaveloxolone is implicit. Modelling OS by mFARS score involved several steps. Firstly, OS Kaplan Meier data from Indelicato et al. (patients enrolled in the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS)

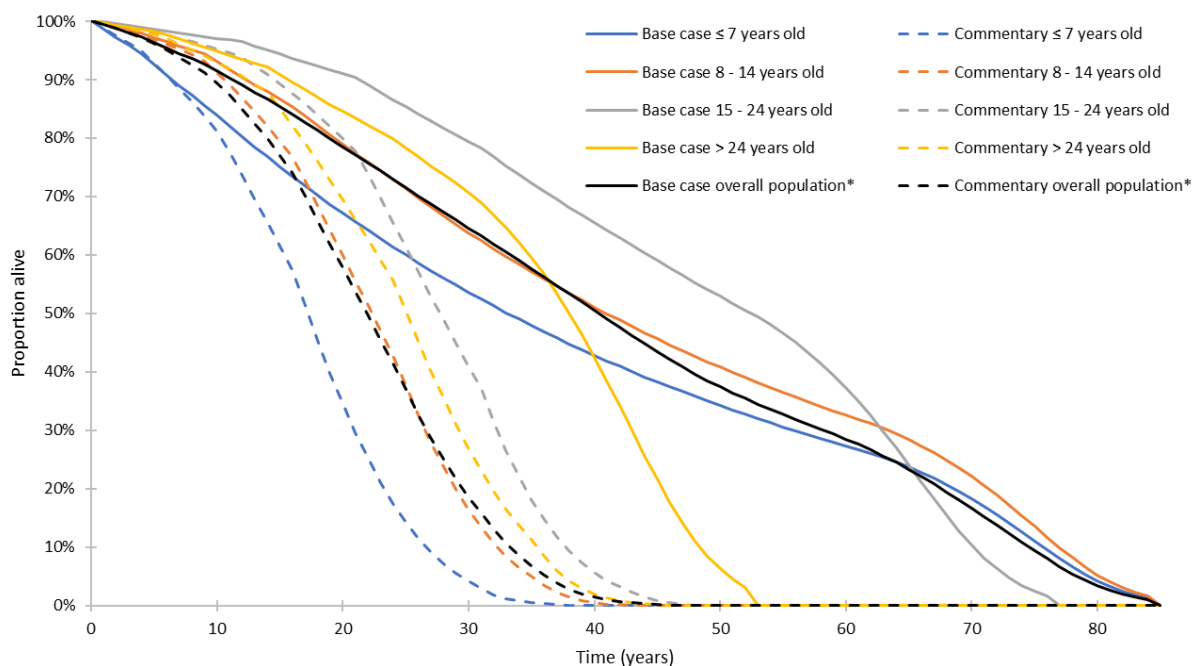
registry) was extrapolated.⁹ The ESC agreed with the evaluation that the extrapolation of this immature OS data (where 87% of patients remained alive at the end of the 11-year observation period), introduced substantial uncertainty into the economic model. Additionally, Indelicato et al. enrolled prevalent patients and therefore the findings may be biased by inclusion of a survivor cohort (those who have survived since their FA diagnosis until the time the study observation period started); which would overestimate FA mortality for incident patients, i.e. the modelled population.

- 6.67 The ESC also noted the majority of the extrapolated OS curves were implausible, with better survival hazards at older ages than occur in the general population. This meant that although the remaining transformation steps were reasonable, because they were applied to an implausible survival extrapolation, the generated curves required further adjustment. The submission claimed incorporation of background mortality, via the application of a competing risks approach, rectified the survival projections (for each model cycle the highest instantaneous risk of death is applied from either (i) the unadjusted parametric functions or (ii) the risk of death in the age and sex matched general population). This approach suggests that patients who survive until the disease-related mortality hazard is reduced to match the risk in the general population, are no longer at risk from dying from FA related complications. The ESC noted that this occurred for approximately 38% of modelled patients. The ESC considered that this was not reasonable as the vast majority of FA patients experience disease-related mortality, therefore the application of a risk function that accurately models disease-related mortality should be sufficient to generate OS curves.¹⁰ The ESC noted that (i) the unadjusted OS curves (exponential function) resulted in a substantial proportion of the population alive in the final year of the model (noting all age cohorts are 100+ years by this time) and (ii) the adjusted OS curves, which applied background-mortality, were overly optimistic, generating a mean life-expectancy of 64 years (or 43 years from symptom onset) in the BSC arm. The majority of literature indicates that the life-expectancy for FA patients is around 35 to 40 years.⁹ An alternative modelling approach explored by the evaluation, which did not involve extrapolating the OS Kaplan Meier data in Indelicato et al. but applied FA mortality hazard ratios to general population mortality resulted in a life-expectancy of 43 years (22 years from symptom onset) in the BSC arm, which is more aligned with clinical expectation. A comparison of the submission base case and evaluation OS curves in the BSC arm is presented in Figure 6. This alternative OS modelling approach increased the ICER by 1% (the incremental QALYs decreased from 1.16 to 0.97). The pre-PBAC response stated that the 1% change to the ICER suggested that the model was not particularly sensitive to the method of estimating mortality by disease stage and that the treatment benefits of omaveloxolone remain consistent across a range of mortality assumptions.

⁹ Indelicato E, Reetz K, Maier S, et al. Predictors of Survival in Friedreich's Ataxia: A Prospective Cohort Study. *Movement Disorders*. 2024;39(3):510-518. doi:<https://doi.org/10.1002/mds.29687>

¹⁰ Tsou AY, Paulsen EK, Lagedrost SJ, et al. Mortality in Friedreich Ataxia. *Journal of the Neurological Sciences*. 2011/08/15/ 2011;307(1):46-49. doi:<https://doi.org/10.1016/j.jns.2011.05.023>

Figure 6: Comparison of base case BSC OS curves and the evaluation's alternative curves



Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment provided with the submission.

BSC=best supportive care; OS=overall survival.

* Overall population weighted 27% ≤7 years, 45% 8 – 14 years, 18% 15 – 24 years and 11% >24 years as per the economic model.

6.68 The MOXIe extension trial did not capture quality of life data. Instead, utility values applied in the model were sourced from an external study which reported the mean EQ-5D and Scale for the Assessment and Rating of Ataxia (SARA) scores (which were converted to mFARS) per year for patients enrolled in the EFACTS registry over five years.¹¹ A linear regression was conducted by the submission, which estimated a 0.012 decrement for each increase in mFARS, was based off mean EQ-5D and SARA scores. The ESC noted that the five data points used to inform the regression (with an EQ-5D range of 0.53 - 0.59 and a mFARS range of 55 - 61) were insufficient to relate mFARS to utility values for the full range of utility values applied in the economic model. The evaluation re-calibrated the linear regression so that the data points were based on ambulatory and non-ambulatory patients in Reetz et al. (instead of the pooled mean of these patients used in the submission's regression), resulting in a 0.009 decrement for each increase in mFARS score. This analysis increased in the ICER by 1% the incremental QALYs decreased from 1.16 to 0.93); however, given the small range of data points and lack of alternative published estimates, the utility values remain as a key area of uncertainty which substantially affected the ICER. The pre-PBAC response agreed with the evaluation that a linear relationship between EQ-5D and mFARS may not fully capture the non-linear association between quality of life and disease

¹¹ Reetz K, Dogan I, Hilgers R-D, et al. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 4-year cohort study. *The Lancet Neurology*. 2021/05/01/ 2021;20(5):362-372. doi:https://doi.org/10.1016/S1474-4422(21)00027-2.

progression but stated that it was unclear whether deriving a regression model based on the ambulatory and non-ambulatory subgroups was more methodologically sound compared to the method used in the submission.

- 6.69 The economic model 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. Noting 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.
- 6.70 The key model drivers are presented in Table 16.

Table 16: Key drivers of the model

Description	Method/Value	Impact Base case: \$█/QALY gained
Treatment effect	The submission assumed no treatment effect waning in the base case analysis while patients remained on treatment. This was not justified. No evidence of a treatment effect maintenance was provided beyond 4 years of the MOXle extension trial, noting the mean treatment duration was 16 years in the model. Assuming linear treatment waning from Year 4 to Year 18 may be more reasonable.	High, favours omaveloxolone. Assuming linear treatment waning from Year 4 to Year 18 decreased the incremental QALYs to 0.81 and increased the ICER to \$█/QALY gained.
Utility values	Based on a linear regression which estimated a 0.012 decrement for each increase in mFARS. The five data points used to form the regression was insufficient to relate mFARS to utility values for the full range of utility values applied in the economic model. Re-calibrating the linear regression so that the data points were based on ambulatory and non-ambulatory patients in Reetz et al. ¹¹ (instead of the pooled mean of these patients used in the submission's regression) is a more reasonable approach.	High, favours omaveloxolone. Including ambulatory and non-ambulatory patients in Reetz et al. ¹¹ as separate data points in the regression decreased the incremental QALYs to 0.93 and increased the ICER to \$█/QALY gained.
OS modelling	Based on the extrapolation of very immature OS data from patients in the EFACTS registry and adjusting the OS curve with the competing risks approach with general population mortality (i.e. the highest instantaneous risk of death is applied from either the extrapolated OS curve or general population mortality). ⁹ The adjustment for general population mortality was not reasonable as the unadjusted curve should be sufficient to model FA OS where the majority of patients experience disease-related mortality. Error! Bookmark not defined. However, the final unadjusted OS curves were implausible and modelled a substantial proportion of the populations alive in the final year of the model.	Moderate, favours omaveloxolone. Using a different OS modelling approach ^a decreased the incremental QALYs to 0.97 and increased the ICER to \$█/QALY gained.

Source: Constructed during the evaluation.

EFACTS=European Friedreich's Ataxia Consortium for Translational Studies; FA=Friedreich's Ataxia; HR=hazard ratio; ICER=incremental cost-effectiveness ratio; KM=Kaplan Meier; mFARS=modified Friedreich's Ataxia rating scale; OS=overall survival; QALY=quality-adjusted life year.

^a An alternative modelling approach explored by the evaluation, which did not involve extrapolating the OS KM data in Indelicato et al. but applied FA mortality HRs to general population mortality.

The redacted values correspond to the following ranges:

1 > \$1,055,000

6.71 The submission conducted a stepped analysis presented in Table 17. Transforming avoided change in mFARS to survival gains resulted in a substantial increase in the ICER (Step 1 to 2). However, this is expected given the small change in mFARS over the short time horizon (three-years) is unlikely to result in any substantial survival gain. As expected, extrapolating survival out to a lifetime time horizon resulted in a substantial decrease in the ICER (Step 4 to 5) and transforming this to QALYs further reduced the ICER (Step 5 to 6) as the majority of omaveloxolone benefit is reducing mFARS progression which delays quality of life deterioration in the model. However, as raised above (paragraph 6.68), the applied utility values are a key uncertainty in the economic evaluation.

Table 17: 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	\$█	\$0	\$█
Change in mFARS	1.99	4.04	-2.05
Incremental cost/change in mFARS score avoided			\$█ ¹
Step 2: mFARS scores transformed to survival			
Costs	\$█	\$0	\$█
Life years	2.83	2.83	0.00
Incremental cost/life year gained			\$█ ²
Step 3: Include disease management costs^b			
Costs	\$█	\$90,777	\$█
LYG	2.83	2.83	0.00
Incremental cost/life year gained			█ ²
Step 4: Include AE costs			
Costs	\$█	\$90,813	\$█
LYG	2.83	2.83	0.00
Incremental cost/life year gained			\$█ ²
Step 5: Extrapolate survival and costs to lifetime time horizon			
Costs	\$█	\$646,846	\$█
LYG	16.63	16.26	0.37
Incremental cost/life year gained			\$█ ²
Step 6: Apply utility weights to life years			
Costs	\$█	\$646,846	\$█
QALYs	10.58	9.42	1.16
Incremental cost/extra QALY gained (base case)			\$█ ²

Source: Adapted during the evaluation from Table 3.35 of the submission.

mFARS=modified Friedreich's Ataxia rating scale; QALYs=quality-adjusted life years.

^a Costs include only omaveloxolone acquisition costs and outcomes from the propensity matched analysis.¹²

^b Including medical appointments, hospitalisation, disease aids, home modification and carer costs.

The redacted values correspond to the following ranges:

¹ \$455,000 to < \$555,000

² > \$1,055,000

6.72 The results of the economic analysis by age of onset cohort indicates that the cost-effectiveness of omaveloxolone is primarily driven by the patients in the 8 – 14 years age of onset cohort (which also happens to be the largest cohort). However, this should be interpreted with caution as cohort specific treatment effects were not applied in the model.

¹² Lynch DR, Goldsberry A, Rummey C, Farmer J, Boesch S, Delatycki MB, 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.

Table 18: Results of the economic analysis by age of onset cohort

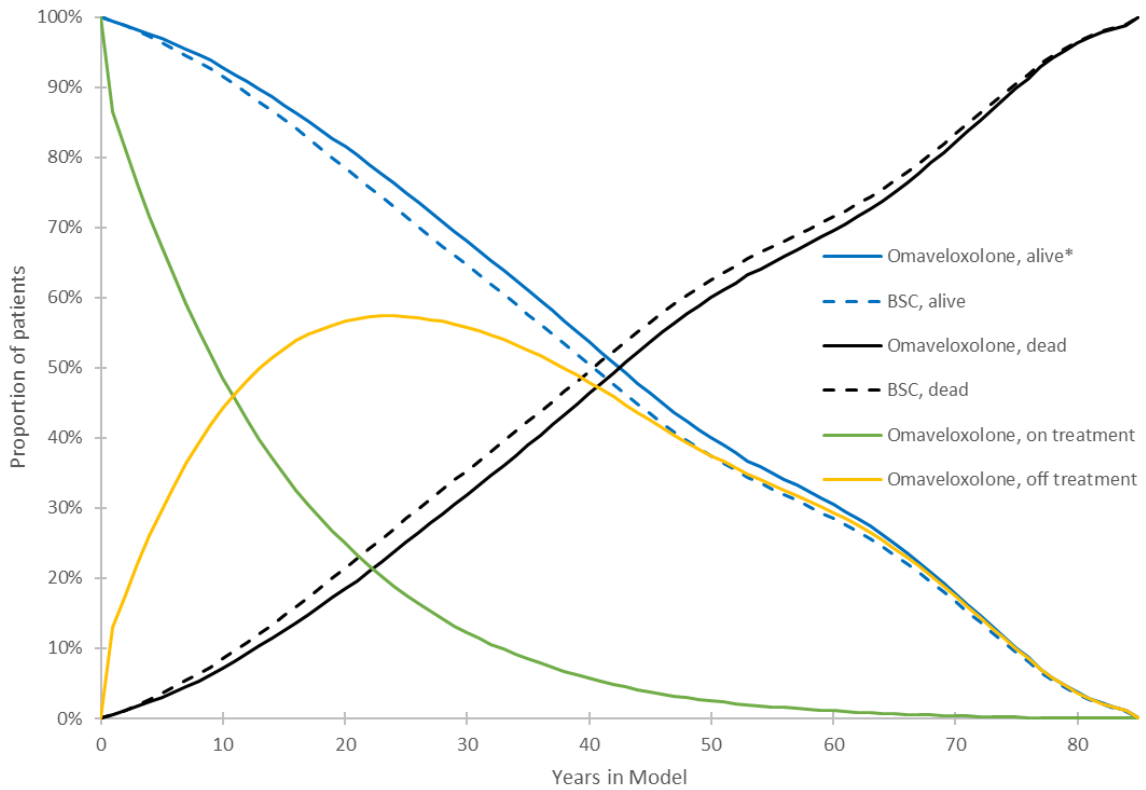
Population	Omaveloxolone	BSC	Increment
Overall population			
Costs	\$█	\$646,846	\$█
QALYs	10.58	9.42	1.16
Incremental cost/extra QALY gained (base case)			\$█ ¹
≤7 years age of onset cohort (27% of total population)			
Costs	\$█	\$745,901	\$█
QALYs	6.76	5.81	0.95
Incremental cost/extra QALY gained			\$█ ¹
8 – 14 years age of onset cohort (45% of total population)			
Costs	\$█	\$656,105	\$█
QALYs	11.05	9.73	1.32
Incremental cost/extra QALY gained			\$█ ¹
15 – 24 years age of onset cohort (18% of total population)			
Costs	\$█	\$553,978	\$█
QALYs	14.28	13.13	1.15
Incremental cost/extra QALY gained			\$█ ¹
>24 years age of onset cohort (11% of total population)			
Costs	\$█	\$517,195	\$█
QALYs	12.01	10.99	1.02
Incremental cost/extra QALY gained			\$█ ¹

Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment. BSC=best supportive care; QALYS=quality-adjusted life years. Traces of health state membership over the time horizon are presented in Figure 7. There is minimal incremental difference in survival over the time horizon. The majority of omaveloxolone benefit is through the preservation of quality of life through the slowing of mFARS progression (this was presented in Figure 5).

The redacted values correspond to the following ranges:

¹ > \$1,055,000

Figure 7: Health state membership over the time horizon



Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment. BSC=best supportive care.

Note: *=Omaveloxolone alive health state is the sum of the proportion of patients in the omaveloxolone on and off treatment (sub) health states.

6.73 The disaggregated costs and outcomes are presented in Table 19. The vast majority of incremental costs are attributable to omaveloxolone acquisition.

Table 19: Health care resource items: disaggregated summary of cost impacts

Resource/health state	Omaveloxolone	BSC	Increment	% increment
Costs				
Omaveloxolone	\$█	\$0	\$█	█%
AE management costs	\$341	\$36	\$304	0%
GP, specialist visits and hospitalisation	\$251,087	\$293,076	-\$41,989	-1%
Disease management aids	\$28,190	\$43,622	-\$15,432	-0%
Co-morbidity costs	\$303,353	\$297,002	\$6,351	0%
Carer costs	\$10,675	\$13,111	-\$2,435	-0%
Total	\$█	\$646,846	\$█	█%
Outcomes				
Life-years (undiscounted)				
On omaveloxolone	13.71	0.00	13.71	813%
Off omaveloxolone	30.02	42.04	-12.03	-713%
Total	43.73	42.04	1.69	100%
QALYs (discounted)				
On omaveloxolone	6.04	0.00	6.04	522%
Off omaveloxolone	4.54	9.42	-4.88	-422%
Total	10.58	9.42	1.16	100%

Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment. AE=adverse event, BSC=best supportive care; GP=general practitioner.

6.74 The results of key sensitivity analyses are presented in Table 20. While some of the parameters tested in sensitivity analyses did not appear to have a substantial effect on the economic analysis, the ESC noted the impact is masked to some extent due to the high base case ICER. If the base case ICER is reduced (through a special pricing arrangement of omaveloxolone as proposed in the submission), parameters would have larger effect on the economic analysis.

Table 20: Results of key sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	% Change
Base case		1.16		
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes		3.41		
• 3.5% costs and outcomes		1.53		
Time horizon (base case 84 years)				
• 20 years		0.71		
• 40 years #4		1.09		
Treatment effect waning (base case: no waning)				
• Linear decrease to no treatment effect from Year 4 to 8		0.58		
• Linear decrease to no treatment effect from Year 4 to 13		0.71		
• Linear decrease to no treatment effect from Year 4 to 18 #5		0.81		
OS extrapolations				
• Evaluation's OS modelling approach ^a #3		0.97		
Utility values (base case: linear regression of EQ-5D data by SARA score reported in Reetz et al. ¹)				
• Evaluation alternative utility regression ^b #2		0.93		
Carer, walker, wheelchair, specialised mattress, electric bed and home modification costs (base case: included)				
• Exclude #1		1.16		
Multivariate analyses				
#1 and #2		0.93		
#1, #2 and #3		0.80		
#1, #2, #3 and #4		0.79		
#1, #2, #3, #4 and #5		0.58		

Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment. EQ-5D=EuroQol 5 dimensions; ICER=incremental cost-effectiveness ratio; OS=overall survival; QALY=quality-adjusted life year; SARA=Scale for the Assessment and Rating of Ataxia.

^a An alternative approach to model mortality was explored by the evaluation which involved assuming patients who had a disability score of 1 as having a mortality risk in line with the Australian general population and applying a HR of 2.01 who every worsening disability score.

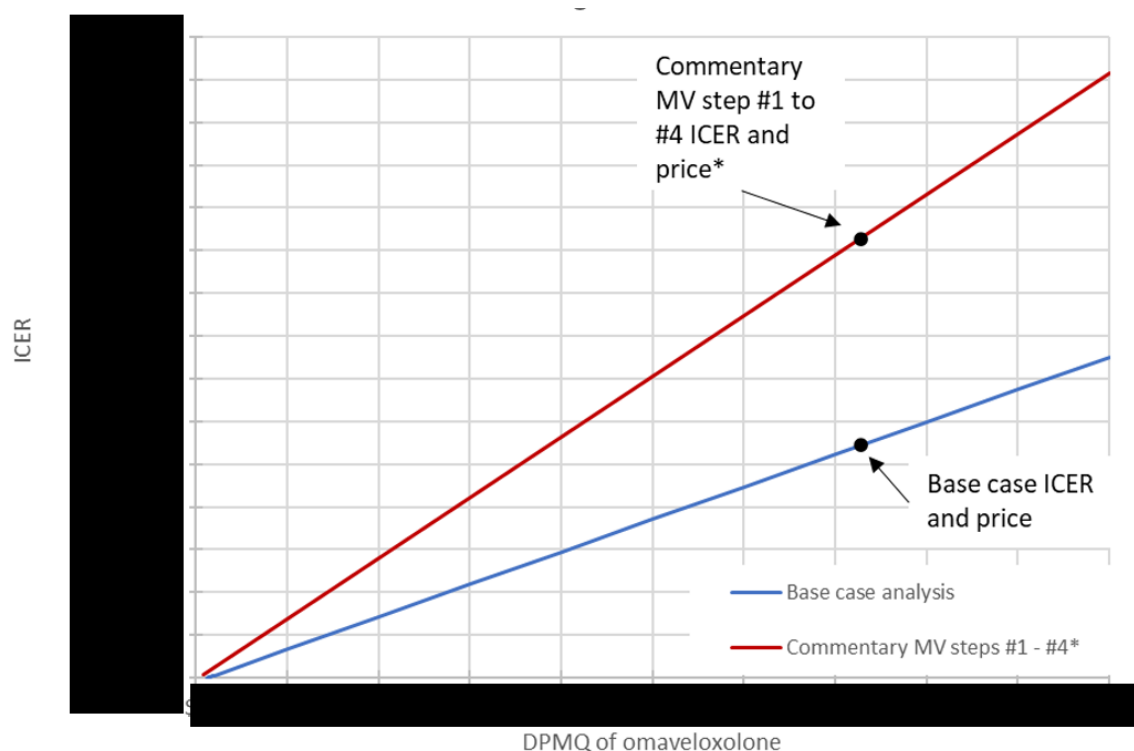
^b An alternative utility regression was explored by including EQ-5D data by SARA scores for ambulatory and non-ambulatory patients reported in Reetz et al.¹¹

The redacted values correspond to the following ranges:

¹ > \$1,055,000

6.75 Given that the submission indicated that a special pricing arrangement would be implemented at the time of PBS listing, the evaluation performed additional sensitivity analyses varying the cost of the omeveloxolone with the base case and Evaluation's multivariate analysis. The results are presented in Figure 8. The ESC noted the impact of varying the assumed price of omeveloxolone on the ICER was large, however it was unclear how informative these analyses were, as no effective price was proposed in the submission.

Figure 8: The effect of varying price of omaveloxolone on the ICER with the base case and Evaluation's MV analysis



Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment. DPMQ=dispensed price for maximum quantity; ICER=incremental cost-effectiveness ratio; MV=multivariate.

* Evaluation's multivariate analysis, excluding carer, walker, wheelchair, specialised mattress, electric bed and home improvement costs, including alternative modelling approaches for health utilities and mortality, reducing the time horizon to 40 years and assuming linear treatment waning from year 4 to Year 18.

6.76 The ESC considered that the PBAC would not be in a position to consider the cost-effectiveness of omaveloxolone as the proposed effective price was not included in the submission. The ESC noted only the proposed published price was provided with the submission and use of this price in the economic model resulted in (i) an ICER substantially outside the range usually considered cost-effective by the PBAC, (ii) the ICER being driven by the omaveloxolone price (for which the proposed value was unknown) and (iii) the sensitivity analyses being difficult to interpret due to the artificially high omaveloxolone price masking the impact on the ICER when changing other inputs. The ESC further noted, in the context of FA being a rare disease, that without an estimate of the ICER, the PBAC would be unable to assess the level of uncertainty that may be reasonable with respect to the economic model structure and inputs, and ultimately the uncertainty in the ICER that may be acceptable. The pre-PBAC response stated that notwithstanding ESC's concerns regarding the PBAC's ability to assess the level of uncertainty of the economic model, it is the case that price is just one of many considerations the PBAC are required to decide on. The pre-PBAC acknowledged that a PBAC recommendation at a base case ICER of > \$1,055,000 million per QALY gained was unlikely [REDACTED].

Drug/cost/patient/year

6.77 The published omaveloxolone acquisition cost per patient is reported in Table 21. The costs per year were broadly consistent across the trial (noting its short duration), economic and financial sections of the submission. No other medicines were included in the economics or financial analyses.

Table 21: Omaveloxolone cost per patient

	MOXle Part 2	Economic Model	Financial Estimates
Mean dose (daily, mg)	129 ^a	130 ^b	129 ^a
Mean duration	43 weeks (trial duration was 48 weeks)	14 years	Indefinitely for those on treatment for 2+ years. ^c
Cost/patient/month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost/patient/year	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Constructed during the evaluation from the "Attachment 10 - Cost utility analysis (CUA) workbook (Section 3)" attachment provided with the submission.

PI=product information; RDI=relative dose intensity.

^a Mean dose based on the PI dose (150 mg daily) × RDI reported in the trial, 86%.

^b In the economic analysis, the submission applied an RDI of 87%, it is unclear where this was sourced from.

^c A treatment discontinuation rate of 14% was applied for patients in their first year of treatment, for patients in the second or above year of treatment no discontinuation rate was applied.

Estimated PBS usage & financial implications

6.78 This submission was considered by DUSC. An epidemiological approach was used to estimate the financial impact of listing omaveloxolone on the PBS. The key components of the financial analyses are presented in Table 22.

Table 22: Data sources and parameter values applied in the utilisation and 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.	The prevalence rate in the Australian setting is uncertain. The use of the FARA prevalence estimate (1 in 30,000) had a substantial impact on the financial estimates ^a . The DUSC considered the prevalence rate applied may be reasonable in the absence of an alternative estimate, but it is highly uncertain.
Proportion of FA patients aged over 16 years	75%. Proportion of patients aged over 16 years in the Australian FACOMS registry.	The DUSC noted that the FACOMS registry is not population-based and therefore may not be representative of the Australian population with FA.
Treatment naïve patients	Prevalent patients who have not been treated due to not taking up treatment in previous years.	No incident patients were included in the financial estimates.
Treatment utilisation		
Uptake rate	█% in Year 1 increasing to █% in Year 6. Assumption based on uptake in other submission that address high unmet clinical need.	-
Treatment continuation rate	█% for patients in their first year of treatment, █% for patients in subsequent years. Discontinuation rate observed in the MOXle Part 2 clinical trial (which lasted 48 weeks).	The assumption of 0% discontinuation rate for patients in Year 2+ of treatment was inconsistent with the economic model (which applied a 5.6% discontinuation rate from the MOXle extension trial). The DUSC considered that the treatment continuation rate should be consistent across the financial estimates and the economic model.
Scripts per year per patient	10.5. Assuming a dosage of 150 mg per day × 87% RDI ^b Each script contains 90 × 50mg capsules.	-
Costs		
Omaaveloxolone	\$█. Proposed AEMP of \$█ with Section 85 dispensing fees.	-
Patient copayment	\$14.40. 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.	The submission did not include costs for BNP monitoring, despite the draft PI indicating that BNP monitoring should be performed prior to and on treatment with omaaveloxolone. It is unclear if current MBS item numbers for BNP monitoring (66585, 66586, 66830 and 66829) could be used for omaaveloxolone patients.

Source: Constructed during the evaluation from the "Attachment 12 - Utilisation and cost model (Section 4)" attachment provided with the submission.

ABS=Australian Bureau of Statistics; AEMP=approved ex-manufacturer price; FA=Friedreich's Ataxia; FACOMS=Friedreich's Ataxia Clinical Outcome Measures Study; fara=Friedreich's Ataxia Research Association; MBS=Medicare Benefits Schedule; PBAC=Pharmaceutical Benefits Advisory Committee; PI=product information; PSD=Public Summary Document; RDI = relative dose intensity; RPBS=Repatriation Pharmaceutical Benefits Scheme; UK=United Kingdom.

^a The source behind the fara estimate is unclear.

^b RDI sourced from the MOXle Part 2 clinical trial. The submission stated the RDI was due to temporary treatment discontinuations or dose de-escalation.

^c PBS items 13266F, 13276R, 12936W and 12938Y. Weighted 30% general services (\$31.60), 1% general safety net services (\$7.70), 63% concessional ordinary services (\$7.70) and 6% concessional free services (\$0.00).

6.79 The estimated number of patients treated with omaveloxolone and the net cost to the PBS per year are presented in Table 23.

Table 23: Estimation of use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of omaveloxolone (proposed published price)						
Cost to PBS/RPBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Copayments	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Cost to PBS/RPBS less copayments	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net financial implications						
Net cost to PBS/RPBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to MBS	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Net cost to Australian Government	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³

Source: Table 4.8 of the submission

^a Assuming 10.5 scripts per patient per year as estimated by the submission.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$100 million to < \$200 million

⁴ net cost saving

⁵ \$0 to < \$10 million

6.80 The total cost to the PBS of listing omaveloxolone was estimated to be \$100 million to < \$200 million in Year 6, and a total of \$900 million to < \$1 billion over the first 6 years of listing. The submission expected that the listing of omaveloxolone would not change the extent of use of other medicines.

6.81 The submission estimated the prevalent population each year without explicitly estimating new incident patients. This evaluation considered that this may be reasonable given the low prevalence rate.

6.82 The DUSC considered the main area of financial uncertainty was the prevalence rate of FA in Australia. The PSCR argued the submission conducted a systematic review which reported FA prevalence rates across different countries and regions (as no Australian prevalence rate data were identified).¹³ The average of the prevalence estimates (1 in 43,458) from Western Europe countries, including Spain, Portugal, the United Kingdom, Greece, and Italy, was then applied to Australian Bureau of Statistics (ABS) population projections (medium series). The DUSC noted the applicability of this prevalence estimate to the Australian setting was uncertain, noting that the majority of studies which reported FA prevalence were relatively outdated (ranging from 1981 to 2014) or conducted in regions where demographics were not necessarily applicable

¹³ 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*. 2022/10/03 2022;38(10):1739-1749. doi:10.1080/03007995.2022.2112870

to Australia. The evaluation noted that the best alternative estimate may come from the Friedreich Ataxia Research Association which estimated that 1 in 30,000 people in Australia and New Zealand suffer from FA. **Error! Bookmark not defined.** Applying this prevalence value had a substantial effect on the financial estimates. However, the DUSC, noting that the FA Research Association estimate does not reference a source, considered that, in the absence of further information regarding how this estimate was derived, it was unreliable for decision making. Overall, the DUSC considered that, given the lack of alternative options, using the estimate derived in the submission may be reasonable, albeit highly uncertain. The submission stated that a risk-sharing arrangement would address the uncertainty regarding the number of patients eligible for treatment (see paragraph 6.85).

- 6.83 The DUSC noted that the proportion of patients aged over 16 years in the Australian FACOMS registry (75%) was used to estimate the eligible population for omeveloxolone. The DUSC noted that the FACOMS registry is not population-based and therefore may not be representative of the Australian population with FA. The DUSC further noted that this assumption had not been tested in a sensitivity analysis. The pre-PBAC response stated that the Australian FACOMS registry was integrated to estimate the proportion of patients aged ≥ 16 years and, while it is not population-based, it is the most accurate Australian estimate available with regards to the proportion of patients aged ≥ 16 years.

Quality Use of Medicines

- 6.84 The DUSC considered that the submission reasonably 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 omeveloxolone on the PBS;
 - Routine pharmacovigilance activities and;
 - A long-term post market safety study which started in 2024.

Financial Management – Risk Sharing Arrangements

- 6.85 The submission stated that the sponsor expects to engage in a Risk Sharing Arrangement to share the risk regarding the number of patients eligible for omeveloxolone treatment. No specific details were provided in the submission.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend omeveloxolone for treatment of Friedreich’s ataxia (FA) in adults and adolescents 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 best supportive care (BSC). Further, the PBAC advised that omaveloxolone was not cost-effective with an incremental cost-effectiveness ratio (ICER) of > \$1,055,000 million 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 considered that financial impact estimate 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.

- 7.2 The primary reason for this outcome was the economic evaluation.
- 7.3 The PBAC noted the consumer input which strongly supported the submission. The PBAC noted that the input highlighted the high need for treatments for FA. The PBAC noted the debilitating symptoms of FA on patients and the burden on patients and carers. The PBAC noted that the slowing of disease progression and the retention of functional capacities was a crucial factor in improving patient quality of life and that this outweighed any adverse events experienced with omaveloxolone treatment.
- 7.4 The PBAC noted that the base case ICER in the economic analysis was > \$1,055,000 million per quality-adjusted life year (QALY), which was calculated using the proposed published price of omaveloxolone. The PBAC noted that the submission indicated that the sponsor intends to request a special pricing arrangement; however, an effective price was not proposed in the submission. The PBAC noted that the use of the published price in the economic model resulted in an ICER which was:
- substantially outside the range usually considered cost effective by the PBAC; and
 - driven by the omaveloxolone price (for which the effective price was not provided). This made interpretation of the sensitivity analyses difficult due to the artificially high omaveloxolone price masking the impact on the ICER when changing other inputs.
- 7.5 Overall, the PBAC considered that, in the context of FA being a rare disease, without a meaningful estimate of the ICER, it was unable to assess the level of uncertainty that may be reasonable with respect to the economic model structure and inputs, and ultimately the uncertainty in the ICER that may be acceptable.
- 7.6 The PBAC noted that the estimated financial impact, when using the published price, was approximately \$900 million to < \$1 billion over the first 6 years, which was unacceptably high.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

9 Sponsor's Comment

Biogen welcomes the PBAC acknowledgement of the high clinical need for people living with Friedreich ataxia. Biogen believes that the MOXIe trial demonstrated that omaveloxolone provides a clinical benefit to people with Friedreich ataxia by slowing the progression of the disease. Omaveloxolone was approved by the TGA in Australia in May 2025. Omaveloxolone is registered in over 15 countries, including the UK, Canada, Germany, US and Brazil. Biogen would like to take this opportunity to thank the Friedreich ataxia community and healthcare professionals who contributed submissions (89 in total) through the consumer comments process.

Biogen remains committed to working with the PBAC and Department of Health to provide access to omaveloxolone for people with Friedreich ataxia.