Medicinrådet

Bilag til Medicinrådets anbefaling vedr. omaveloxolone til behandling af Friedreichs ataksi hos voksne og unge ≥ 16 år

Nationalt dansk appendix til fælles nordisk rapport

Vers. 1.0

Bilagsoversigt

1. JNHB-rapport vedr. omaveloxolone til behandling af Friedreichs ataksi
2. Ansøgers notat til Rådet vedr. omaveloxolone til behandling af Friedreichs ataksi
3. Forhandlingsnotat fra Amgros vedr. omaveloxolone til behandling af Friedreichs ataksi
4. Ansøgers endelige ansøgning vedr. omaveloxolone til behandling af Friedreichs ataksi

Joint Nordic HTA-Bodies
Health Technology assessment report

Skyclarys (omaveloxolone)

Hard capsules

Assessed indication
Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

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Joint Nordic HTA-Bodies

Joint Nordic HTA-Bodies (JNHB) formerly known as FINOSE started as a bottom-up initiative by the HTA authorities in Finland, Norway and Sweden and was launched in Stockholm in 2018. The collaboration extended to comprise Denmark in 2023 and Iceland in 2024. In June 2024 FINOSE changed its name and became Joint Nordic HTA-Bodies (JNHB).

JNHB offers efficient and transparent joint health technology assessments of medicinal products in the five Nordic countries. The assessments include both relative effectiveness and health economics. Decisions on price and reimbursement as well as recommendations for use, are made at the national level in each country. By working together and sharing knowledge, JNHB aim to produce high-quality assessment reports that provide solid support for national decisions.

The basis for the collaboration is outlined in a Memorandum of Understanding, signed in April 2024 by the collaborating HTA bodies;

- Danish Medicines Council (DMC),
- Finnish Medicines Agency (Fimea),
- Landspitali- The National University Hospital of Iceland,
- Norwegian Medical Products Agency (NOMA) and
- Dental and Pharmaceutical Benefits Agency (TLV) in Sweden.

In this assessment of Skyclarys, NOMA was assessor, DMC co-assessor and TLV was reviewer. Skyclarys is an out-patient drug in Finland, which means that the product is not within Fimea's remit. Therefore, Fimea had an observer role during the assessment. Landspitali also had an observer role during the assessment.

Assessors: Ane Funderud (clinical assessor, NOMA), Pernille Winther Johansen (health economist, DMC)

Reviewers: Corizandy Gonzalez (TLV), Sara Massena (TLV)

Clinical experts: Kristina Flemming (University Hospital of North Norway), Kristoffer Haugarvoll (Haukeland University Hospital, Norway), Sebjørg Hesla Nordstrand (Oslo University Hospital) and fagudvalget vedr.sjældne medfødte sygdomme hos børn (DMC) (medicinraadet.dk). The clinical experts have been consulted on current clinical praxis and in interpretation of the clinical material. The JNHB group is not bound to the statements of the experts, interpretations and opinions on which the cost-effectiveness analysis should be based on.

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Summary

- Friedreich's ataxia (FA) is a hereditary neurodegenerative disease that is caused by mutations in the gene that encodes frataxin. Symptoms include poor coordination and spasticity, and gradually loss of ambulation as well as speech difficulties, visual and hearing impairments. As the disease progresses it leads to worsening of the symptoms, affecting daily functions and quality of life. Comorbidities such as cardiomyopathy and diabetes are also related to FA. The disease often has an early onset in childhood or young adulthood. Patients have a shortened lifespan with an average life expectancy of 37 years (~20 years from disease onset). Atypical FA with late onset and slower disease progression also exists but is rare compared to classical FA.
- Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.
- The active substance in Skyclarys, omaveloxolone, activates the Nrf2 pathway that is involved in cellular response to oxidative stress, which are suppressed in patients with Friedreich's ataxia.
- JNHB agrees with the company that best supportive care is the most relevant comparator as there are currently no disease modifying treatments available.
- Omaveloxolone is investigated in the MOXIe studies (MOXIe part 1, MOXIe part 2 and MOXIe OLE). The primary endpoint in the placebo-controlled main study MOXIe part 2 was change in mFARS (modified Friedreichs Ataxia Rating Scale). The mFARS measures disease progression in Friedreich's ataxia. Omaveloxolone resulted in a reduced (-2,4 points) mFARS progression compared to placebo (Least Squares mean difference, 95% CI -4.31; −0,5. p=0.014) after 48 weeks. The result is highly uncertain as the study lasted for only 48 weeks and is based on only 82 (42+40) patients.
- Results for 136 patients from the uncontrolled 3-year extension study MOXIe OLE were compared with an external control arm from the natural history study FA-COMS using propensity score matching. This resulted in a −3.6 points difference in mFARS progression (p = 0.0001) over 3 years, which corresponds to a 55 % reduction in disease progression for omaveloxolone compared to FA-COMS patients. In comparison the yearly progression of natural FA disease (for patients in the natural history study FA-COMS) is around 2 points increase in mFARS. The effect size is highly uncertain as it is based on non-randomized evidence. The reduction in mFARS compared to FA-COMS varied between the three years, -2,1 points in the first year, -1,3 in the second year and -0,2 in the third year. The estimate is a mean for a patient group with considerable individual variability in disease progression and age of onset.
- Non-randomized evidence leads to uncertainty in the effect size. Inability to include *pes cavus* as a covariate in the propensity score matching means risk of bias as the number of patients with *pes cavus* was limited in the MOXIe part 2 that constitutes the largest part of the MOXIe OLE population. *Pes cavus* is a foot deformity that might affect e.g. gait and thereby mFARS. Consequently, the effect is also more uncertain in patients with *pes cavus,* as well as in other groups that were excluded from the study population including patients above 40 years old and patients with clinically significant heart disease or uncontrolled diabetes.
- The drug cost of omaveloxolone is 1.8 million DKK per patient per year.

- The health economic analysis is a regression-based model, based on mFARS score comparing omaveloxolone plus standard of care (SoC) with SoC alone. Natural disease progression for SoC is estimated from the natural history study FA-COMS, where patients were divided into four age-subgroups based on disease onset.
- The effect of omaveloxolone in the health economic analysis is based on the propensity score matched analyses comparing MOXIE OLE and FA-COMS over 3 years and applies a reduction in disease progression throughout the time horizon of the model (relative mFARS progression: 0,45 in scenario 1 and 0.90 in scenario 2).
- There is no direct data to support the effect of omaveloxolone on mortality. Mortality is based on external data and the relation between mortality and mFARS score is estimated through several steps. Mortality is associated with disease progression (disability stage) based on the natural history study EFACTS. Disability stage is then crosswalked to disease ataxia state, which is then related to mFARS based on data from FA-COMS.
- HRQoL is also based on external data from FA-COMS or EFACTS and a linear relation between HRQoL and mFARS is assumed.
- The resource use for health care professional visits and home modifications, aids and medical device are related to mFARS categories (0-10, 10-20 etc.). Thus, by slowing disease progression omaveloxolone reduces the resource use for these resources that are related to mFARS score.
- Resource use for comorbidities is unrelated to mFARS score.
- In the JNHB base-case scenarios the costs per QALY gained for omaveloxolone + SoC is 22 and 52 million/DKK compared to SoC alone and the QALYs gained are 0.32 and 0.78 over a lifetime period.
- The treatment effect of omaveloxolone from year 4, the estimation of HRQoL, mortality risk, and hospital resource use are all highly uncertain and the main drivers of the health economic results.
- The treatment effect is based on non-randomized data over three years. The effect size is uncertain, and it is uncertain if the treatment effect is maintained throughout the model horizon or if the effect is waning. Treatment waning is indicated as there seems to be an almost similar steepness in the curves for disease progression for omaveloxolone and SoC after the first year of treatment. It is therefore difficult to choose a plausible estimate for the effect from year 4. To illustrate how the effect could affect the health economic result JNHB have performed two base case scenario analyses: one where the effect from year 4 will be based on all three years of data from MOXIe OLE (cost per QALY 22 million DKK), and one where the effect from year 4 will be based on the disease progression only in the third (last) year (cost per QALY 52 million DKK).
- The large range in the results indicates that the analysis is associated with large uncertainties. Other factors also influence the results greatly. Because of this, the result should be interpreted with caution, as the real costs per QALY cannot be said with certainty to be within the range.
- HRQoL is not estimated directly from the clinical studies investigating omaveloxolone, which introduces uncertainty. JNHB choose to use FA-COMS in their base case scenarios as this aligns the data for utility values with data for disease progression. JNHB sensitivity analyses using EFACTs data instead of FA-COMS data for HRQoL increases the QALY gain substantially in both scenarios.
- It is uncertain whether slowing of disease progression will lead to a reduction in hospital resource use over a lifetime horizon or if the resource use will merely be postponed

in time. The disease is still progressing for the average patient and the long-term effect of omaveloxolone on disease progression is essentially unknown.

Table of contents

1 Scope

This JNHB report is the result of a joint Nordic assessment of omaveloxolone (Skyclarys) for the treatment of Friedreich's ataxia.

The assessment is primarily based on the documentation presented by the company (Biogen).

The aim of the JNHB report is to support national decisions on price and reimbursement as well as recommendations for use, in Denmark, Iceland, Norway and Sweden regarding Skyclarys. The primary focus of this report is the assessment of relative effectiveness, safety and cost effectiveness of Skyclarys. The JNHB report may be complemented with national appendices with additional local information and conclusions.

P (population)	Patients with Friedreich's ataxia aged 16 years and older
I (intervention)	Omaveloxolone
C (comparison, comparators)	Best supportive care
O (outcomes)	mFARS Adverse events Health-related quality of life
HE	QALYs Costs Incremental cost-effectiveness ratio (ICER)

2 Medical background

2.1 Friedreich's ataxia

Aetiology
Friedreich's ataxia (FA) is an inherited degenerative neuromuscular disorder that in most patients is caused by increased number of guanine-adenine-adenine (GAA) repetitions in the frataxin gene (*FXN*). Normal alleles typically have 7-34 GAA repetitions, whereas in Friedreich's ataxia there can be as many as 66-1.700 repetitions, with resulting decreased production of frataxin. Friedreich's ataxia is an autosomal recessive disease that only develops if inherited from both parents.

Frataxin deficiency is associated with cell damage and death due to increased oxidative stress caused by accumulation of iron in the mitochondria, formation of free radicals and loss of ATP. Cells with high mitochondrial metabolism and that typically produce large amounts of frataxin, such as neurons, cardiomyocytes, and beta cells in the pancreas, are particularly vulnerable to oxidative damage in the case of frataxin deficiency. More GAA repetitions give less frataxin, and generally lead to more severe disease, with earlier onset and faster progression [1].

Symptoms
The major clinical manifestations of Friedreich ataxia are impaired neurological function and neurodegeneration, scoliosis, cardiomyopathy, and diabetes mellitus [1].

Loss and degeneration of neurons in both the central and peripheral nervous system lead to symptoms such as ataxia in all four limbs, balance problems, uncoordinated movements, spasticity and difficulty in walking. Other neurological symptoms include speech difficulties (dysarthria), swallowing difficulties (dysphagia), visual and hearing impairments and bladder

dysfunction. Musculoskeletal abnormalities, such as kyphoscoliosis (abnormal spine curvature) and *pes cavus* (high-arched foot deformity) are common. Scoliosis affects more than 90 % of patients with early onset FA and may require corrective surgery [2].

Heart disease in the form of cardiomyopathy, is also common, affecting up to 85 % of patients. This occurs as cardiomyocytes die and are replaced by fibroblasts and macrophages, leading to inflammation and fibrosis in the heart. Heart disease is the leading cause of death among Friedreich's ataxia patients, with approximately 30 % of those affected dying from heart failure [3].

Destruction and dysfunction of beta cells in the pancreas result in up to 30 % of individuals with Friedreich's ataxia developing insulin deficiency and resistance, leading to type 1 and type 2 diabetes mellitus, respectively.

Prognosis
Friedreich's ataxia is an incurable disease with a poor prognosis. The disease onset is typically in early adolescence, between 8 to 15 years of age, but can range from 2 years to 70 years [1]. Early onset is associated with faster disease progression and a worse prognosis, while atypical cases with late onset is linked to a milder course of the disease and a better prognosis [1]. The first symptoms of Friedreich's ataxia are often increasing balance issues and difficulty in walking, along with the gradual development of scoliosis and foot deformities [4]. As the disease progresses the symptoms have increasing impact on physical function and quality of life. When balance and coordination become poor, the patient experiences walking as very exhaustive. Most individuals will need a wheelchair approximately 10 years after diagnosis [1]. Assistance may become necessary to perform daily activities. With home aids and help from caregivers, it is still possible to live an active life. A patient representative explained that when the ability to speak and communicate with other people is affected, this has a very large negative impact on the daily life.

Reported mean life expectancy varies between 35 and 40 years [5]. Patients with atypical milder disease may live much longer. Cardiac dysfunction as a consequence of dilated cardiomyopathy and arrhythmias is widely accepted as the most common cause of mortality (half of all FA patients). Results from the European natural history cohort EFACTS, has shown that disability stage, history of arrhythmias and diabetes are independent predictors of mortality.

Epidemiology
FA is the most common form of inherited ataxias, but still a rare disease. It is most prevalent among people with origin in Europe, North Africa, the Middle East and South Asia. Within Europe, the reported prevalence is highest in Southwest and lowest in Northeast, with reported prevalences from 1:20,000 in Spain to 1:750,000 in Finland [6]. Clinical experts consulted by JNHB estimate slightly more than 30 patients in Norway, 30-50 in Denmark and closer to 25 than 75 in Sweden.

2.2 Skyclarys

2.2.1 Therapeutic indication

Skyclarys is indicated for the treatment of Friedreich’s ataxia in adults and adolescents aged 16 years and older.

2.2.2 Mechanism of action

Omaveloxolone has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in

the cellular response to oxidative stress. There is substantial evidence that Nrf2 levels and activity are suppressed in cells from patients with Friedreich's ataxia. The precise mechanism for clinical efficacy is however unknown [7].

2.2.3 Posology and method of administration

The recommended dose is 150 mg omaveloxolone (3 hard capsules of 50 mg each) once daily.

The capsules should be swallowed whole. For patients who are unable to swallow whole capsules, which may be relevant for FA patients, the SPC (Summary of Product Characteristics) suggests that the capsules may be opened, and the entire contents sprinkled on apple puree [7].

2.3 Current treatment options

2.3.1 Treatment guidelines in Denmark, Norway and Sweden

There are no national treatment guidelines for FA in the Nordic countries. Some medical experts mentioned an international guideline that is used for reference; Clinical management guidelines for Friedreich ataxia in Orphanet [8]. No curative or disease-modifying treatment is available for FA, and current clinical practice focuses on management of symptoms and comorbidities. Conventional medicines are used for example to treat spasticity, sleeping difficulties, depression, reflux, pain, osteopenia etc, as well as in treatment of cardiomyopathy and diabetes.

Norwegian medical experts mentioned that Q10-analogues (idebenone) previously have been used off-label to treat FA to a limited extent. An HTA of IFNγ-1b (Imukin) has recently been conducted in Norway based on off-label use in a limited number of FA patients (ID2021_125). Neither of these two therapies are described by any medical experts as part of SoC (Standard of Care).

Symptomatic non-pharmacological treatment includes physiotherapy and exercise, which is important in order to maintain physical functioning as the disease progresses. Other types of support include speech/hearing/communication support and devices, phycological support and psychotherapy, nutrition support such as gastrostomy, orthopedic treatment for scoliosis and foot deformities, orthoses, surgery when required for scoliosis, CPAP (Continuous Positive Airway Pressure) treatment for sleep apnoea syndrome.

Adaptive devices to assist ambulation and daily activities including wheelchair and walkers are gradually introduced when needed, as well as assistance from caregivers.

As FA is a multisystem disorder, disease management often includes a team of health care personnel including neurologist, physiotherapist, psychiatrist, cardiologist, diabetes therapy, speech therapist, orthopedist and nutritionist, as relevant. It is common that follow-up visits are coordinated such that the patient can have consultations with a team of different health care professionals the same day, when possible, especially for children and adolescents. Regular follow-up visits take place yearly or twice yearly, according to medical experts.

2.3.2 Comparator

There is no FA-specific treatment available in clinical practice today in Norway, Denmark or Sweden. The company describes that omaveloxolone is expected to be used alongside current standard of care (SoC) rather than replacing it, and that the relevant comparator is current SoC.

JNHB conclusion:
JNHB agrees with the company that no treatment in addition to best supportive care is the relevant comparator as there are currently no disease modifying FA treatments available. SoC is described in section 2.3.1.

3 Clinical efficacy and safety

The assessment of clinical efficacy and safety is mainly based on the evidence included in the submission dossier prepared by the company. The authoring team has checked the information retrieval included in the company's submission dossier for completeness against
- a search in ClinicalTrials.gov and PubMed
- the studies included in the European public assessment report (EPAR)

3.1 Clinical trials

Clinical efficacy and safety of omaveloxolone was investigated in the MOXIe trials (summarized in Table 1). Based on the dose-ranging MOXIe part 1, a dose of 150 mg daily was selected as the dose in the main study MOXIe part 2. Patients from part 1 and 2 could continue treatment in the open-label extension study MOXIe OLE. The marketing authorization application to EMA (European Medicines Agency) included a *post hoc* propensity score-matching analysis that compared efficacy data from MOXIe OLE to external natural history data from FA-COMS, also summarized in Table 1 below. Results from this analysis are used to inform the effect of omaveloxolone in the health economic model. Data from the FA-COMS is also used to inform natural disease progression in the model and is an option as source for health-related quality of life. The FA-COMS is run in the United States, Australia, Canada, India and New Zealand. EFACTS is a natural history study run in several European countries. It is used to inform mortality and is an option as source for health-related quality of life for FA patients in the health economic model.

An ongoing paediatric omaveloxolone study (NCT06054893), can possibly support an indication extension to include children. The study evaluates pharmacokinetics and safety of a single dose of omaveloxolone in children 2-16 years old. This study is not included in the current assessment.

3.1.1 Methods of the clinical trials

Table 1. Summary of relevant trials

Study NCT-number primary reference	**Study design**	**Treated study population**	**Intervention**	**Key endpoints**
MOXIe part 1 NCT02255435 Lynch et al 2019 [9]	- Dose-finding - International - Randomized - Double-blind - Placebo-controlled	- Genetically confirmed FA 16 – 40 years old mFARS 10-80	Omaveloxolone 2,5-300 mg daily	- Change from baseline in peak work in Watts/kg during exercise testing on a stationary bicycle at 12 weeks (primary endpoint)
MOXIe part 2 Main study NCT02255435 Lynch et al 2021 [10]	- International - Randomized - Double-blind - Placebo-controlled	- Genetically confirmed FA - 16–40 years old - mFARS 10-80 - Severe *pes cavus* limited to 20 % of patients	Omaveloxolone 150 mg daily	- Change in mFARS at week 48 (primary endpoint)
MOXIe OLE NCT02255435 Lynch et al 2023 [11]	- Open-label - Extension study - International	Patients from MOXIe part 1 (n=57) and part 2 (n=92)	Omaveloxolone 150 mg daily	- Safety/tolerability - Efficacy: mFARS, ADL, 9-HTP, T25-FW (explorative endpoints)
FA-COMS NCT03090789	- Natural history study - International	- Individuals with clinical diagnosis or genetic confirmed FA	No intervention	- FARS, mFARS

		- 4-80 years old - Estimated n=2.000 (~1.000 by today)		
EFACTS NCT02069509 Reetz et al 2015 [12]	- Natural history study - European	-Genetically confirmed FA -Estimated n=1.200	No intervention	- SARA

mFARS (modified Friedreich's Ataxia Rating Scale), tool for evaluation of FA disease progression in clinical studies (described in section 3.1.2), ADL (activities of daily living), 9-HPT (9-hole peg test), test that measures fine motor skills, T25-FW = timed 25-foot walk test, SARA (Scale for Assessment and Rating of Ataxia)

MOXIe part 2

The main study MOXIe part 2 was a double-blind, placebo-controlled phase II trial conducted at 11 clinical sites, 7 in the United States, 1 site in Australia and three in European countries (1 site each in Austria, Italy and United Kingdom). Patients aged 16 to 40 years with a genetically confirmed FA diagnosis and mFARS (modified Friedreich's Ataxia Rating Scale, measures FA disease progression) score 10-80 were randomized 1:1 to receive 150 mg omaveloxolone (N=51) or placebo (n=52) daily for 48 weeks. Ability to complete maximal exercise testing was required and exclusion criteria included clinically significant heart disease, uncontrolled diabetes and use of antioxidant supplements. Randomization was stratified by *pes cavus* status and patients with *pes cavus* were limited to 20 % of the total randomized population, based on findings from MOXIe part 1 where *pes cavus* resulted in unreliable mFARS measurements. The *pes cavus* foot deformity likely affects the ability to perform certain clinical assessments included in mFARS. The primary outcome was change from baseline in mFARS at week 48 for the full analysis set (FAS); all patients without *pes cavus* with at least one post-baseline measurement. Secondary outcomes included patient and clinician assessment of improvement (PGIC, CGIC), fall frequency, activities of daily living (ADL) and SF-36 Health Survey. Outcomes are described in section 3.1.2.

MOXIe OLE

Patients from MOXIe part 1 and part 2 could continue treatment in MOXIe OLE that assessed long-term safety and efficacy over 144 weeks. All patients received omaveloxolone 150 mg daily, after a 4-week drug washout period, until omaveloxolone was available through commercial channels or until patient withdrawal. Patients and investigators remained blinded to prior treatment in MOXIe part 1 or 2 throughout the extension. Endpoints included different measures for safety and tolerability, and efficacy endpoints (mFARS, ADL, 9-HPT and T25-FW). Modified FARS was measured biannually.

FA-COMS

FA-COMS is a global multicenter natural history study. It is run in the United States (9 sites), Canada (2 sites) and at one site each in Australia, New Zealand and India, and includes patients of all ages (4-80 years old) with genetically confirmed FA. The study is still ongoing, and 1.000 patients have been enrolled so far. Patients are evaluated annually on FARS, mFARS and quality of life-assessments including SF-36. As the largest FA register FA-COMS is a well-known cohort.

EFACTS

EFACTS (Patient Registry of the European Friedreich's Ataxia Consortium for Translational Studies) is a multicenter observational study that includes patients with genetically confirmed FA at 16 clinical centers in several European countries (Austria, Belgium, Czechia, France, Germany, Greece, Ireland, Italy, Spain, United Kingdom). Participants are assessed annually for disease progression (SARA) and quality of life (ADL and EQ-5D) among other outcomes. In addition, participants provide biological for research purposes.

3.1.2 Description of outcomes

FA rating scales

Modified FARS
Modified Friedreich's Ataxia Rating Scale (mFARS) was the primary endpoint in MOXIe part 2 and a main outcome in MOXIe OLE. It is a tool for evaluation of FA disease progression that assesses changes in patients' speech, arm/hand function, balance, and ability to stand. Compared to SARA (Scale for the Assessment and Rating of Ataxia), that is more commonly used in clinical settings, mFARS is more complex and time consuming. Modified FARS was developed from the well validated and known FARS for use in clinical trials and commonly used in recent clinical trials (EPAR). Modified FARS consists of four subscales; bulbar function, upper limb coordination, lower limb coordination and upright stability. A total of 18 assessments are scored within the range 0-2 to 0-5, and scoring is based on a composite score of all the subscales with a maximum score of 93 points, with increasing number of points indicating a higher disease severity or worsening of neurological function. It is an objective physician-assessed examination, but there might be high day-to-day intra-patient variability in the results. Progression in mFARS at natural disease varies widely between patients but the mean change is 2 points per year according to the FA-COMS disease register. FA patients are typically scored between 25-30 at diagnosis, and 60-70 when ambulation is lost.

SARA
Scale for Assessment and Rating of Ataxia (SARA) is widely used in clinical practice, also in the Nordic countries as confirmed by the medical experts. As mentioned in the previous section SARA is both less time-consuming and less granular than mFARS, but measures similar disease aspects and correlates with mFARS.

Other clinical outcomes

PGIC and CGIC
PGIC (Patient Global Impression of Change) and CGIC (Clinical Global Impression of change) measure the patient and clinician opinion on change in overall health status. They are 7-point scales that require the patient and clinician, respectively, to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention. Scores less than 4 represent some measure of improvement, scores greater than 4 represent some measure of worsening and a score of 4 represents no change.

9-HTP
The 9-hole peg test (9-HPT) measures fine motor skills of the hands. The test involves first placing nine pegs into nine holes on a board and then to remove them, using one hand at a time. The time required to complete the task is measured.

T25-FW
In the timed 25-foot walk (T25-FW) the time it takes a patient to walk 25 feet is measured.

Health related quality of life

SF-36
The SF-36 (36-item short form health survey) total score is a 0-100 scale where eight different health aspects are assessed: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions.

FA-ADL
ADL (Activities in Daily Living) assesses the patient's ability to perform daily activities. Nine different aspects of daily living are assessed by the patient and scored 0-5 resulting in a possible total score from 0 to 36 where higher scores reflect a poorer ability. FA-ADL is adjusted to cover the specific challenges of FA patients and cover multiple aspects of FA, including speech, personal hygiene, walking, and bladder function, and is a relevant measure for FA patients.

3.1.3 Study results

MOXIe part 2
In total 103 patients were randomized in MOXIe part 2 (ARP, all randomized population, 51 to omaveloxolone and 52 to placebo). The FAS (full analysis set) population consisted of 40 and 42 patients respectively without *pes cavus*. At week 48 there were 34 and 41 patients in the omaveloxolone and placebo arms that had mFARS assessed respectively. In the omaveloxolone arm 86 % completed treatment, and in the placebo-arm 96 % completed treatment. Baseline and demographic characteristics for the patients are shown in Table 2.

Table 2. Baseline and demographic characteristics from MOXIe part 2 [10]

Parameter	Full Analysis Set (FAS)		All randomized patients (ARP)		*Pes cavus* patients	
	Placebo n = 42	Omaveloxolone n = 40	Placebo, n = 52	Omaveloxolone, n = 51	Placebo, n = 10	Omaveloxolone, n = 10
Female, n (%)	14 (33)	24 (60)	17 (33)	31 (61)	3 (30)	7 (70)
Mean age (SD)	23.6 (7.8)	24.2 (6.5)	24.1 (7.8)	23.4 (6.1)	26.0 (8.2)	19.9 (2.6)
Median age	21.0	23.0	21.0	22.0	27.0	20.0
<18 yr, n (%)	13 (31)	7 (18)	15 (29)	9 (18)	2 (20)	2 (20)
Race, White, n (%)	40 (95.2)	40 (100)	50 (96.2)	50 (98)	10 (100)	9 (90)
mFARS, mean (SD)	38.8 (11)	40.9 (10.4)	37.9 (10.8)	40.8 (10.2)	34.4 (9.3)	41.1 (9.9)
Peak work, W/kg, mean (SD)	1.2 (0.6)	1.1 (0.5)	1.2 (0.6)	1.1 (0.6)	1.4 (0.7)	1.1 (0.8)
ADL, mean (SD)	9.9 (4.8)	10.7 (4.8)	9.9 (4.7)	11.0 (4.5)	9.8 (4.4)	12.2 (3.4)
Age at onset, mean (SD)	15.1 (5.3)	15.9 (5.7)	15.3 (5.3)	14.8 (5.7)	16.4 (5.3)	10.9 (3.6)
Duration, yr, mean (SD)	4.7 (4.7)	4.8 (4.0)	4.4 (4.4)	4.7 (3.8)	3.0 (2.7)	4.6 (3.2)
GAA1 repeat length, mean (SD)	693.8 (277.2)	739.2 (214.9)	676.2 (267.9)	736.8 (206.8)	585.6 (206.6)	736.6 (200.1)
Ambulatory, n (%)	39 (93)	37 (93)	49 (94)	46 (90)	10 (100)	8 (80)
History of cardiomyopathy, n (%)	12 (29)	19 (48)	15 (29)	25 (49)	3 (30)	6 (60)
History of scoliosis, n (%)	32 (76)	29 (73)	37 (71)	39 (77)	5 (50)	10 (100)
Scoliosis surgery, n (%)	7 (17)	12 (30)	10 (19)	16 (31)	3 (30)	4 (40)

Mixed models repeated measures (MMRM) was used to analyse the change from baseline mFARS for omaveloxolone compared to placebo in MOXIe part 2. After 48 weeks patients on omaveloxolone had a 1.55 decrease, and patients on placebo had increased (worsened) 0.85 points on the mFARS scale, see Figure 1. The mean difference between the treatment arms was −2.40 (95% CI -4.31, −0.5) for the FAS population (primary endpoint), which was statistically significant (p=0.014). The difference was also statistically significant for the ARP population including patients with *pes cavus* (difference -1,94, p=0,033).

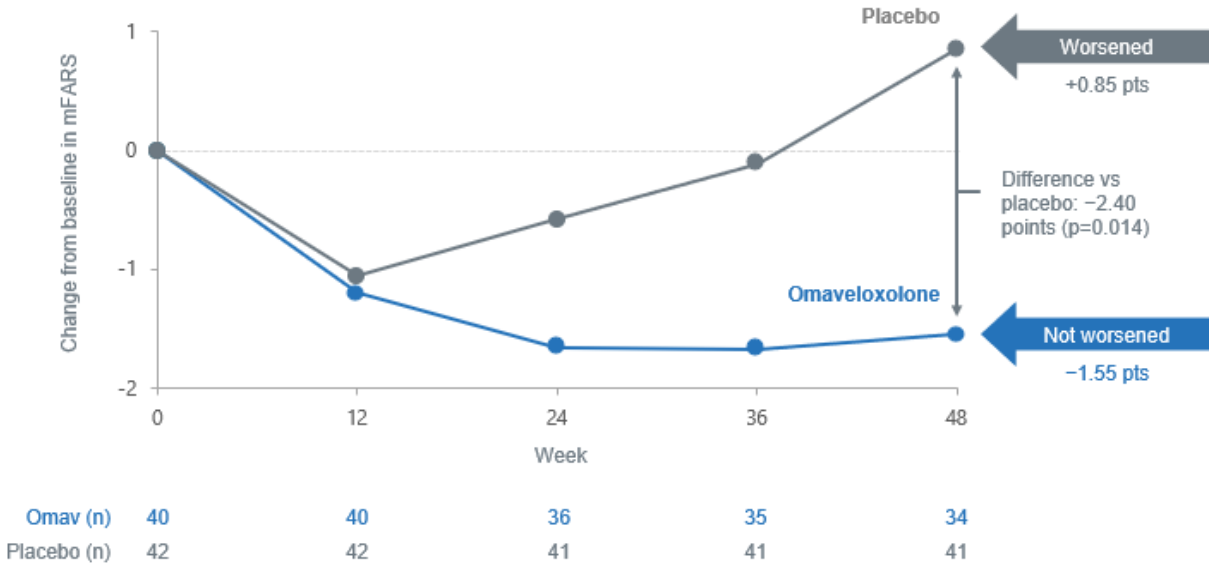

Figure 1 Mean change from baseline in mFARS score over 48 weeks (FAS population)

Figure 2 shows changes in the four mFARS subscales and indicates improvement for all subscales.

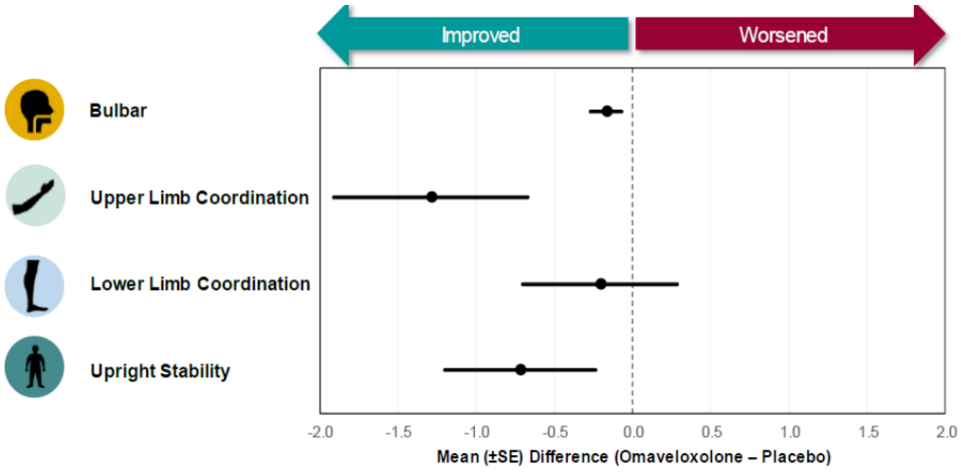

Figure 2 Analysis of changes in mFARS subscales at week 48 from MOXIe part 2 (FAS population)

Pre-specified subgroup analyses of the primary end-point did not identify major differences between subgroups. See Figure 3.

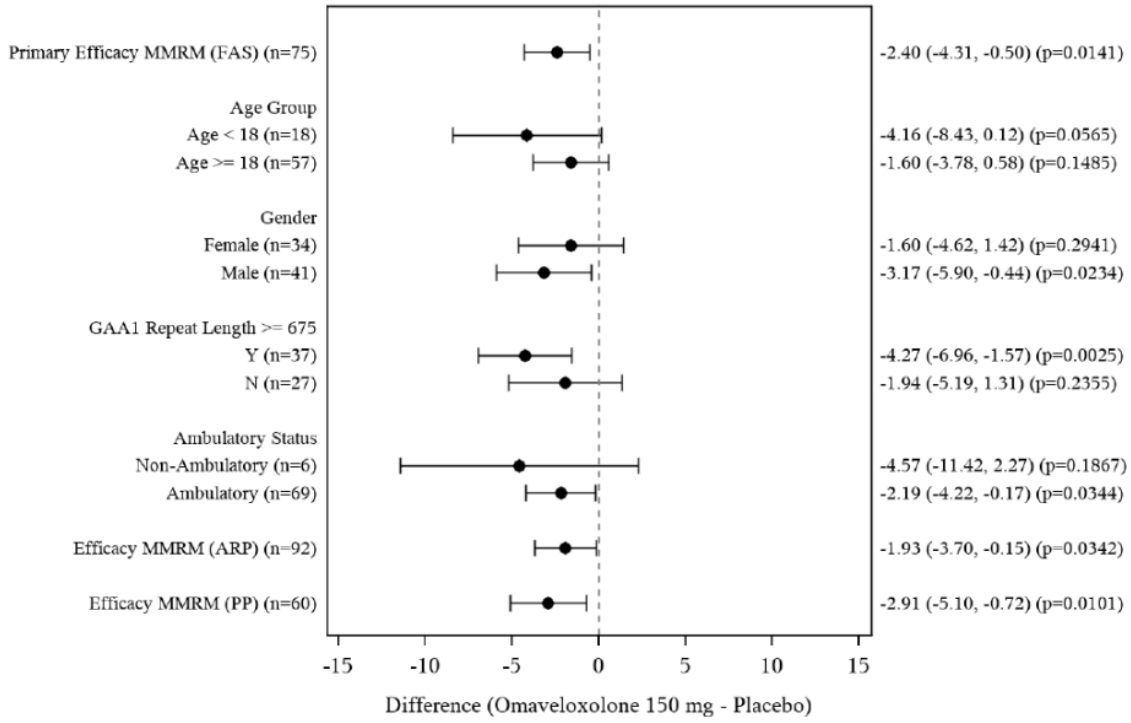

Figure 3 Change in mFARS at week 48 in pre-specified subgroups
ARP, all randomized population, FAS, full analysis set, MMRM, mixed model for repeated measures, PP, per protocol. LS (Least Squares) differences estimated from a MMRM analysis using visit 4, 12, 24, 36 and 48.

MOXIe OLE

Of the 172 patients from MOXIe part 1 and 2 there were 149 patients that enrolled in the extension study MOXIe OLE and received omaveloxolone treatment. Of these, 43 patients continued omaveloxolone treatment from MOXIe part 2 ("omav-omav population"). The remaining 106 patients were termed "treatment-naive" as they had either received placebo in MOXIe part 2 (n=49) or placebo or omaveloxolone in MOXIe part 1 (12 weeks of treatment more than 12 months ago) ("placebo-omav population").

At the time of the analyses (24 March 2022 database lock) the median treatment duration was 144 weeks (25-177 weeks). 133 (89.3%) patients had then been exposed to the study drug for more than 48 weeks in MOXIe OLE, 125 (83.9%) patients for more than 96 weeks, and 69 (46.3%) patients for more than 144 weeks. Twentysix patients terminated early from treatment, of which 10 did so due to adverse events and 15 upon patient decision. The company has confirmed that no later data cuts from MOXIe OLE are currently available.

Secondary outcomes from MOXIe part 2

Secondary outcomes included patient and clinician global impression of change (PGIC and CGIC, defined as key secondary endpoints), walk test, frequency of falls over 48 weeks and FA-ADL. Secondary outcomes assessed in MOXIe part 2 numerically favoured omaveloxolone. Only FA-ADL showed a statistically significant difference. See Table 3.

Table 3 Secondary endpoints and post hoc analyses of FAS patients who improved or worsened in primary and secondary measures at Week 48 of MOXIe Part 2 (FAS) (table from submitted documentation)

Outcome	Change from baseline to Week 48[†]		LS (Least Square) mean difference, omaveloxolone vs placebo	P value
	Omaveloxolone (n=40)	Placebo (n=42)		
PGIC	3.90	4.33	–0.43	0.13
CGIC	3.93	4.06	–0.13	0.52
9-HPT, 1/s	–0.0014	–0.0001	–0.0013	0.18
T25-FW, 1/s	–0.0169	–0.0226	0.0058	0.46
Frequency of falls (over 48 weeks), median	3.0	8.5	0.30	0.30
Peak work, W/kg	0.03	0.09	–0.06	0.22
FA-ADL	–0.17	1.14	–1.30	0.04

9-HPT, 9-hole peg test; CGIC, Clinician Global Impression of Change; FA-ADL, Friedreich Ataxia Activities of Daily Living; FAS, full analysis set; LS, least squares; PGIC, Patient Global Impression of Change; T25-FW, timed 25-foot walk test.
Notes: [†]Mean changes for PGIC and CGIC responses and p values were analysed using an analysis of covariance. Mean changes and p values for 9-HPT, T25-FW, peak work, and FA-ADL were estimated using a mixed-model repeated measures analysis

Health-related quality of life

In MOXIe part 2 SF-36 was an exploratory endpoint on health-related quality of life in addition to FA-ADL. ADL was measured in MOXI OLE.

No relevant differences in SF-36 between the treatment arms in MOXIe part 2 were detected. See Table 4. There was a statistically significant difference in ADL scores between omaveloxolone and placebo at week 48. LS (Least Squares) mean difference (SE) was -1.30 (0.62), p = 0.04.

Table 4 SF-36 and ADL scores results – MOXIe Part 2 CSR

	SF-36		ADL	
	Omaveloxolone (n=40)	Placebo (n=42)	Omaveloxolone (n=40)	Placebo (n=42)
Baseline				
n	40	42	40	42
Mean (SD)	70.55 (22.16)	68.95 (20.57)	10.738 (4.77)	9.87 (4.83)
Week 24				
n	36	41	36	41
Mean (SD)	75.252 (23.14)	71.42 (20.52)	10.36 (4.48)	10.48 (5.03)
Week 36				
n	-	-	36	41
Mean (SD)			11.03 (4.77)	10.60 (4.80)
Week 48				
n	36	41	36	41
Mean (SD)	68.92 (21.56)	68.68 (19.62)	10.56 (4.72)	11.07 (5.00)
LS mean change from baseline				
n	36	41	36	41
	-2.69 (23.04)	0.488 (21.98)	-0.17 (± 0.450)	1.14 (± 0.421)

Mean (SD/SE)			(p = 0.71)	(p = 0.009)
LS mean difference between groups Mean (SE)	Not reported		-1.30 (± 0.629) (p = 0.04)	

3.1.4 Safety results

Table 5 summarizes adverse events in MOXIe part 2 and OLE. The most common AEs that occurred more frequently with omaveloxolone versus placebo were headache, nausea, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), fatigue, diarrhoea and abdominal pain (Table 5). Most adverse events were mild or moderate. Serious AEs occurred in < 10% of patients receiving omaveloxolone in Part 2 or in the OLE. These serious AEs were not considered to be related to the study treatment except one event of palpitations and tachycardia that was discussed to possibly be related [13]. In MOXIe part 2, four patients (7,8 %) discontinued due to adverse events in the treatment group and two patients (3,8 %) in the placebo group.

Table 5 Adverse events in MOXIe Part 2 and OLE (from submitted documentation)

Adverse event, n (%)	MOXIe Part 2		MOXIe OLE	
Summary of AEs	**Omaveloxolone (n=51)**	**Placebo (n=52)**	**Omav-omav (n=43)**	**Placebo-omav (n=106)**
≥1 AE	51 (100)	52 (100)	39 (90.7)	103 (97.2)
≥1 SAE	5 (9.8)	3 (5.8)	4 (9.3)	6 (5.7)
Discontinuation due to AE	4 (7.8)	2 (3.8)	1 (2.3)	8 (7.5)
AEs occurring in > 20 % of patients in any treatment arm of Part 2 or OLE				
Contusion	17 (33.3)	19 (37.3)	2 (4.7)	12 (11.3)
Headache	19 (37.3)	13 (25.0)	5 (11.6)	19 (17.9)
Upper respiratory tract infection	14 (28)	15 (29)	9 (20.9)	15 (14.2)
Excoriation	13 (25.5)	12 (23.1)	2 (4.7)	15 (14.2)
Nausea	17 (33.3)	7 (13.5)	7 (16.3)	17 (16.0)
ALT increased	19 (37.3)	1 (1.9)	4 (9.3)	24 (22.6)
Fatigue	11 (21.6)	7 (13.5)	5 (11.6)	12 (11.3)
Diarrhoea	10 (19.6)	5 (9.6)	3 (7.0)	13 (12.3)
Abdominal pain	11 (21.6)	3 (5.8)	7 (16.3)	9 (8.5)
AST increased	11 (21.6)	1 (1.9)	1 (2.3)	9 (8.5)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse event.

Elevation of B-type natriuretic peptide (BNP) was observed in MOXIe. Due to possible risk of heart failure due to fluid overload in diabetic patients observed in another study on a similar compound, it is recommended in the SPC for omaveloxolone that BNP is monitored prior to and periodically during omaveloxolone treatment.

In the SPC it is also recommended that ALT, AST, and bilirubin should be monitored prior to initiation of omaveloxolone, monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated, based on findings from MOXIe [7].

3.2 JNHB discussion

Efficacy

Efficacy of omaveloxolone in slowing FA deterioration was demonstrated in the MOXIe trial as evaluated by EMA through the MA application. The primary endpoint measurement tool (mFARS) is commonly used in recent clinical trials of FA and considered to robustly reflect disease progression [13]. The relative efficacy estimate in the health economic model is also based on mFARS. Modified FARS primarily evaluates physical function and does not cover e.g. function in daily activities like the secondary endpoint ADL. Improvements in most secondary endpoints in MOXIe part 2 were modest but support the benefit of omaveloxolone. The MOXIe study did not measure the effect on important comorbidities such as cardiomyopathy and diabetes, nor on mortality. Based on the mechanism of action it could be considered plausible that omaveloxolone also would affect cells in other organs than the nervous system, that mFARS reflects, but it cannot be ruled out that e.g. the timing of cell damage could be less gradual than for the nerve degeneration and require e.g. earlier treatment.

The mFARS progression in the omaveloxolone arm was less than in the placebo arm after 48 weeks, (−2.40, 95% CI -4,31, −0,5, p=0,014). A mean disease progression of 2-point increase in mFARS is generally expected yearly from a FA population on SoC, based on results from the FA-COMS study. As the main study MOXIe part 2 was of small size and short duration, there is significant uncertainty in the mFARS effect size. The placebo effect seen in MOXIe part 2 also makes it more difficult to interpret the results. In the placebo group in MOXIe part 2, the mean mFARS increased only 0.85 points after 48 weeks and even showed a decrease during the first months. See Figure 1. Clinical experts and patients explain that postponing disease progression with one year or more can be of significance for the patient. Even smaller changes in mFARS can sometimes have large effect on the daily life depending on the functions that are affected. The clinical relevance of the relative effect is further discussed in section 3.3.2.

There is a large inter-patient variety in how the FA disease progresses, e.g. depending on age of onset, but the study population is too small to make conclusions regarding effect in subgroups. However, results from mFARS subdomains and subgroup analysis in general indicated broad effect for different physical functions and patient subgroups including age and GAA1 repeats. Patients < 18 years old showed large variability and improvement but were only represented by 18 from a total of 75 patients. Very few patients with late onset (> 24 years) and no patients with very late onset (> 40 years) disease were included. Effect in these groups is therefore to a large extend unknown.

Patients with *pes cavus* were limited to 20 % of the MOXIe part 2 population and excluded from the FAS population analysed for the primary endpoint. The reason for this was findings from MOXI part 1 suggesting that mFARS might not be a reliable tool in these patients as *pes cavus* could affect e.g. assessments dependent on the foot. Patients with *pes cavus* are however not excluded from the approved therapeutic indication for omaveloxolone. This was based on EMAs evaluation that patients with *pes cavus* also had an effect on mFARS, although smaller, and on lack of evidence that patients with *pes cavus* represent a different aetiological FA group. However, this adds uncertainty to effect results in patients with *pes cavus*. More patients with *pes cavus* are included in the analyses of 3-year data for MOXIe OLE.

Long-term efficacy is highly relevant for omaveloxolone, which is a potentially life-long treatment. The extension study MOXIe OLE lasted for 3 years and included several endpoint measures for safety and tolerability, including mFARS and ADL. It was however an extension

study primarily designed to enable continued access to omaveloxolone until commercial availability. The uncontrolled design limits efficacy results. The results from MOXIe OLE will be covered in the next section (section 3.3).

Safety

In the EPAR it is concluded that available safety data from the clinical development program show that omaveloxolone is generally well tolerated. Clinical experts describe that the most commonly reported adverse events normally will not require treatment discontinuation. The safety documentation is, however, based on a small population (MOXIe studies) with limited follow-up time. The restricted population with limited experience with cardiac disease and diabetes mellitus further limits the relevance of the safety results.

JNHB conclusion

The submitted MOXIe trial part 2 documents relative effect against the relevant comparator for this assessment (standard of care). Modified FARS is an appropriate endpoint for disease progression. How omaveloxolone affect comorbidities and mortality is however not documented in the MOXIe study.

The effect size is highly uncertain due to small patient population and short duration. To estimate relative effect against standard of care over a longer timeframe the company has submitted a propensity score matching analysis where the 144-week MOXIe OLE study is compared to an external control arm from the natural history study FA-COMS. The analysis is described in section 3.3.

3.3 Indirect comparisons

3.3.1 Submitted analysis

The company has submitted a propensity score (PS) matched analysis on data from MOXIe OLE using the natural history study FA-COMS as an external control arm performed according to ICH E10 guideline [14] and NICE DSU guidance [15]. Propensity score matching is used to emulate randomisation by identifying control individuals which are similar to the treated individuals based on their propensity score. Propensity scores for matching were estimated using logistic regression based on the following covariates: sex, baseline age, age of disease onset, baseline mFARS and baseline gait score.

The primary endpoint for the analysis was change in mFARS score from baseline at year 3 analysed using mixed model repeated measures analysis. The analysis was a supporting analysis in the MA application for omaveloxolone and was published in 2024 [11]. Below is a summary of the documentation submitted by the company for the analysis.

Comparability of MOXIe OLE and FA-COMS

Eight of 11 study sites in FA-COMS were also participating sites in MOXIe, increasing the likelihood for similar SoC, mFARS assessment and population characteristics. The time period of FA-COMS overlaps with the MOXIe trials, as does age at enrolment; 16-40 in MOXIe and all ages in FA-COMS. Modified FARS is a main outcome in both studies.

Table 6. Comparability of study designs of MOXIe OLE and FA-COMS

	MOXIe OLE	FA-COMS
Location	United States, Australia, Europe (Austria, United Kingdom, Italy)	United States, Australia, New Zealand, Canada, India
Time period	2017-ongoing	2003-ongoing

Patient number	N = 149 (43 and 49 patients that had received omaveloxolone or placebo respectively in MOXIe part 2 + 57 patients from MOXIe part 1)	More than 1.000 to date. Estimate to enroll 2000 in total. Of these 810 had consented to share data outside FA-COMS
Endpoint	mFARS (key endpoint) Assessed every 24 weeks	mFARS was collected Assessed yearly
Duration of follow-up	3 years Data from 24. March 2022 interim database lock	Data current as of 24. March 2021
Intervention	Omaveloxolone 150 mg daily	Non-interventional study (SoC)
Inclusion criteria	• Male or female patients who completed treatment in MOXIe Part 1 or 2, which enrolled patients 16 - 40 years of age. • Genetically confirmed FA	• Male and female children and adults 4-80 years old • Genetically confirmed FA
Exclusion criteria	• History of clinically significant left-sided heart disease and/or clinically significant cardiac disease • Uncontrolled diabetes (HbA1c >11.0%) • B-type natriuretic peptide value >200 pg/mL • Cognitive impairment that may preclude ability to comply with study procedures	• Signs or symptoms of severe cardiomyopathy (such as congestive heart failure)

Analysis populations

Figure 4 gives an overview of the MOXIe OLE population and prior participation in MOXIe part 1 and 2, and the FA-COMS population.

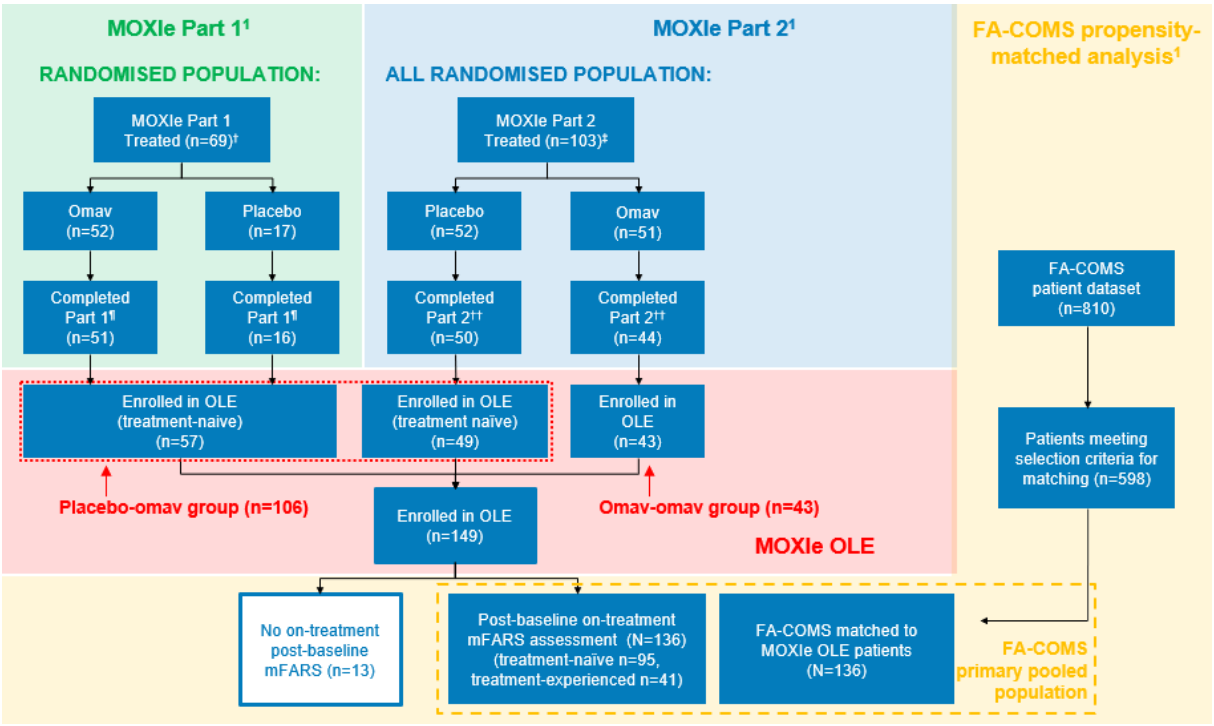

Figure 4. Overview of MOXIe populations and external control group FA-COMS (from submission dossier)

For inclusion in the PS-matched analysis patients had to have a baseline mFARS measurement, at least one post-baseline mFARS measurement within 3 years after baseline, and values for all PS covariates. This resulted in 136 patients from MOXIe OLE and 598 patients from FA-COMS.

Three different MOXIe OLE populations were matched with FA-COMS (three separate PS matchings):

- the pooled MOXIe OLE population (n=136)
- patients that had received omaveloxolone in MOXIe part 2 prior to MOXIe OLE (omav-omav population, n=41)
- patients that had *not* received omaveloxolone in MOXIe part 2 prior to MOXIe OLE (placebo-omav population, n=95)

A sensitivity population from FA-COMS was also defined (n=278); the subset of patients with mFARS within the range observed at baseline in MOXIe OLE (mFARS 8-74) and age at baseline in MOXIe OLE (16-41).

PS matching

Propensity score (PS) matching aims to emulate randomization by identifying control individuals which are similar to treated individuals based on a propensity score. The propensity score was estimated using logistic regression with covariates corresponding to the identified and available prognostic factors. The propensity score is a linear combination of covariates and matching on propensity implies that that matched patients are required to have similar propensity scores rather than a caliper match on a set of covariates. The matching was carried out as optimal 1:1 matching without replacement.

Selection of covariates for the PS score model was based on established prognostic factors that were available in both studies. According to the company the factors were identified through review of published literature, based on knowledge of factors previously established as prognostic and the view of clinical experts, statisticians, and representatives from FARA (Friedreich Ataxia Research Alliance). The selected covariates were sex, baseline age, age of FA onset, baseline mFARS score, and baseline gait score. Number of GAA1 repeats and presence of *pes cavus* were also identified as potential covariates. The company explains that these were not included due to insufficient available data, and for *pes cavus* also due to the fact that presence of *pes cavus* was not evaluated in the same manner in the two studies.

Assumptions that were made and met:

- *Strongly ignorable treatment assignment:* The treatment assignment must be independent of the change from baseline in mFARS score over time given the covariates used in the analysis. There is a positive probability of being in the omaveloxolone or the FACOMS population, that is the propensity score estimated from the logistic regression model must be strictly greater than 0 and less than 1.
- *Stable-unit treatment value assumption:* The outcomes of one individual are not affected by the group assignment of another.

Diagnostic assessment

Diagnostic assessments were performed to assess the quality of the matching. The standardised difference of the means of the propensity score, and for each covariate was well below the 0.5 boundary for all three populations (Table 7). Additionally, the ratio of the variances of the propensity score was close to 1, greater than 0.8, and less than 1.25 for all 3 populations. The ratio of the variances of the residuals for most covariates met the criteria for an acceptable match. The ratio of the variances of the residuals for age and age of FA onset covariates however fall below 0.5 in these populations, that the company explains is due to age variability in FA-COMS. In total the diagnostic results indicate that propensity matching was acceptable for all three populations.

Table 7. PS matching diagnostics (from submission dossier)

Diagnostic	Criteria for good or acceptable match	Pooled (match 1)	Placebo-omavelox-olone (match 2)	Omaveloxolone-omaveloxolone (match 3)
Standardized Difference of the Means of the Propensity Score	<0.5	0.0055	0.0090	0.0012
Standardized difference of the means of covariates				
Sex	<0.5	0	0	0
Baseline gait	<0.5	0.0672	0.0802	0.0325
Baseline mFARS	<0.5	0.0826	0.1103	0.0828
Age	<0.5	0.0375	0.0902	0.1357
Age at FA onset	<0.5	0.0292	0.0645	0.0424
Ratio of the variances of the propensity score	Close to 1; >0.8 and <1.25	1.0243	1.0411	0.9974
Ratio of the variances of the residuals for covariates				
Sex	0.5 to 2	0.9999	1.0044	0.9993
Baseline gait	0.5 to 2	0.5751	0.5022	0.5599
Baseline mFARS	0.5 to 2	0.6068	0.4986	0.5479
Age	0.5 to 2	0.3428	0.3305	0.2005
Age at FA onset	0.5 to 2	0.3194	0.2852	0.4325

Results

Table 8 shows demographic and baseline characteristics after matching for MOXIe OLE population and the matched and non-matched FA-COMS population. The PS covariates appear as balanced after matching (the five bottom characteristics in the table). Among the other characteristics statistically significant differences (based on two-sample t-test) were found for weight, height and heart beats, but evaluated as not clinically meaningful by consulted clinical experts. For GAA1 and GAA2 repeat lengths there were also statistically significant differences. The company explained that a ceiling effect of GAA length makes the difference not clinically significant.

Table 8. Demographics and baseline characteristics of the pooled population in the MOXIe extension, the propensity-matched population from FA-COMS, and the non-matched population of FA-COMS

Characteristic	Statistic	Matched FA-COMS	MOXIe OLE	Non-Matched FA-COMS
Ethnicity (n [%])	n	136	136	455
	Hispanic or Latino	6 (4.4%)	6 (4.4%)	12 (2.6%)
	Not Hispanic or Latino	129 (94.9%)	130 (95.6%)	432 (94.9%)
	Not reported	1 (0.7%)	0	11 (2.4%)
	p-value	0.99		
Race (n [%])	n	130	136	428
	White	125 (96.2%)	133 (97.8%)	412 (96.3%)

	Non-White	5 (3.8%)	3 (2.2%)	16 (3.7%)
	p-value	0.43		
Height (cm)	n	89	136	276
	Mean (SD)	165.1 (14.7)	169.3 (10.4)	156.7 (19.2)
	p-value	0.020		
Weight (kg)	n	95	136	299
	Mean (SD)	61.0 (20.7)	69.1 (16.7)	52.4 (21.4)
	p-value	0.0018		
BMI (kg/m^2)	n	89	136	270
	Mean (SD)	22.0 (5.7)	24.0 (5.2)	20.2 (5.4)
	p-value	0.0069		
Systolic Blood Pressure (mmHg)	n	82	136	252
	Mean (SD)	121.4 (15.0)	121.1 (13.5)	118.8 (14.2)
	p-value	0.90		
Diastolic Blood Pressure (mmHg)	n	82	136	252
	Mean (SD)	73.2 (10.5)	75.3 (8.7)	69.5 (9.1)
	p-value	0.15		
Heart Rate (beats/min)	n	82	136	250
	Mean (SD)	85.2 (15.4)	79.8 (12.6)	86.2 (14.7)
	p-value	0.0089		
ADL Total Score	n	124	136	432
	Mean (SD)	11.8 (5.9)	12.5 (4.9)	11.6 (7.0)
	p-value	0.28		
GAA1 Repeat Length	n	129	119	439
	Mean (SD)	590 (246)	721 (270)	664 (225)
	≥ 675, n (%)	54 (41.9%)	66 (55.5%)	233 (53.1%)
	p-value	<0.0001		
GAA2 Repeat Length	n	121	116	426
	Mean (SD)	863 (232)	728 (297)	942 (209)
	p-value	0.0001		
Age (years)	n	136	136	462
	Mean (SD)	26.2 (13.7)	26.6 (7.3)	22.4 (13.8)
	Min, max	6, 64	16, 41	5, 73
	p value	0.76		
Age at FA onset	n	136	136	462
	Mean (SD)	15.2 (10.5)	15.5 (5.3)	12.3 (8.6)
	p value	0.81		
Sex (n [%])	n	136	136	462
	Female	70 (51.5%)	70 (51.5%)	234 (50.6%)
	Male	66 (48.5%)	66 (48.5%)	228 (49.4%)
	p value	1		
mFARS	n	136	136	462
	Mean (SD)	41.0 (16.1)	42.2 (12.6)	44.8 (18.1)

	Min, max	5.3, 77.0	8.2, 73.5	2.0, 91.0
	p value	0.50		
Gait (assessment #7 in FARS section E [upright stability])	n	136	136	462
	Mean (SD)	2.7 (1.69)	2.8 (1.36)	2.3 (1.69)
	p value	0.58		

Efficacy

Results for the primary endpoint of the analysis, change from baseline in mFARS at year 3, was statistically significantly different between patients from MOXIe OLE and FA-COMS. After 3 years, in the pooled population, matched FA-COMS patients had progressed 6.6 mFARS points whereas patients treated with omaveloxolone in MOXIe extension had progressed 3.0 points (difference = −3.6 points; $p = 0.0001$). This corresponds to a 55 % reduction in disease progression of omaveloxolone compared to SoC. See Figure 5 and Table 9. Median treatment duration for the 136 patients from the MOXIe study was 144 weeks (between 25 and 177 weeks). The 3-year data point only includes data for 60 % of the population. A sensitivity analysis using an unmatched population with age and mFARS restricted to the same range as in MOXIe OLE showed similar results (not shown).

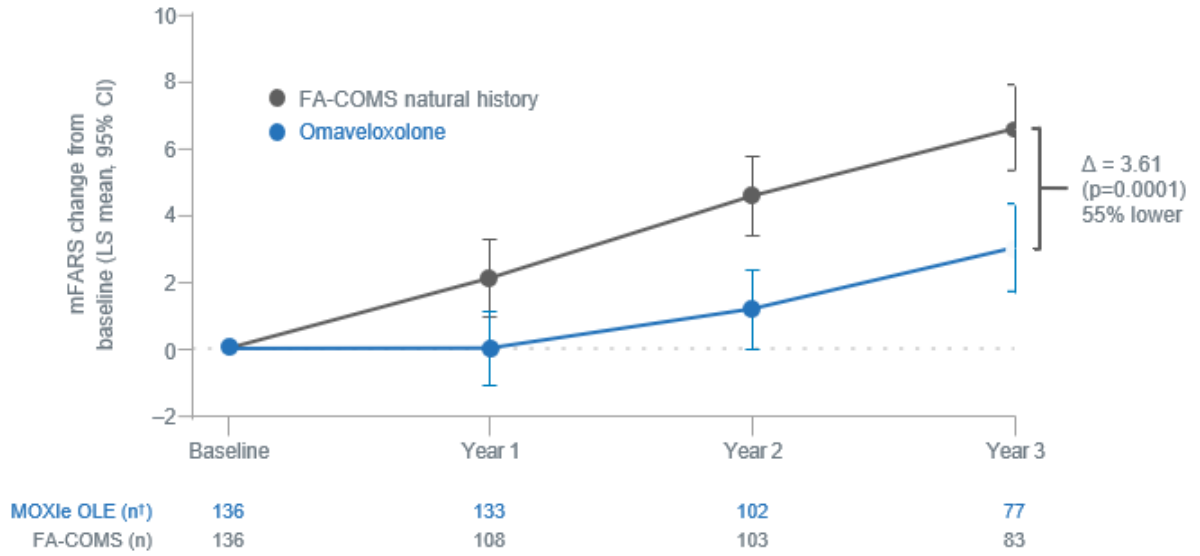

Figure 5. PS-analysis: LS (least squares) mean change in mFARS from baseline over time (primary pooled population)

Table 9. PS-analysis: LS (least squares) mean change in mFARS from baseline and difference over 3 years (primary pooled population) (table from EPAR)

	Baseline		mFARS change from baseline					
			Year 1		Year 2		Year 3	
	N	Mean (SD)	N	LS mean (± SE)	N	LS mean (± SE)	N	LS mean (± SE)
MOXIe OLE	136	42.223 (12.6019)	133	0.015 (0.5556)	102	1.179 (0.5949)	77	3.004 (0.6638)
FA-COMS	136	41.030 (16.1017)	108	2.113 (0.5909)	103	4.584 (0.5930)	83	6.611 (0.6459)
Difference				-2.098 (0.8115) p=0.0101		-3.405 (0.8401) p<0.0001		-3.607 (0.9263) p=0.0001

When the results are stratified according to prior omaveloxolone in MOXIe part 2 or not , the progression after 3 years compared to FA-COMS is mean -4.09 ($p < 0.01$) for placebo-omav

(Figure 6) and -3.76 (p = 0.04) omav-omav (Figure 7), respectively, compared to matched FA-COMS patients.

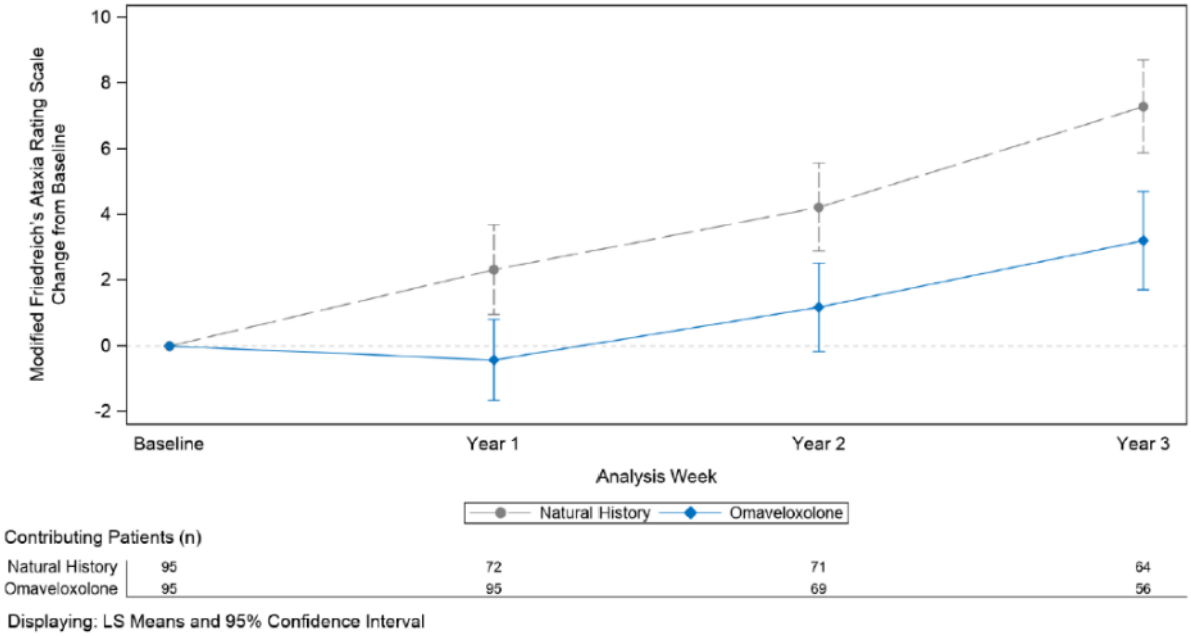

Figure 6. PS analysis: LS mean change in mFARS over time (placebo-omav population)

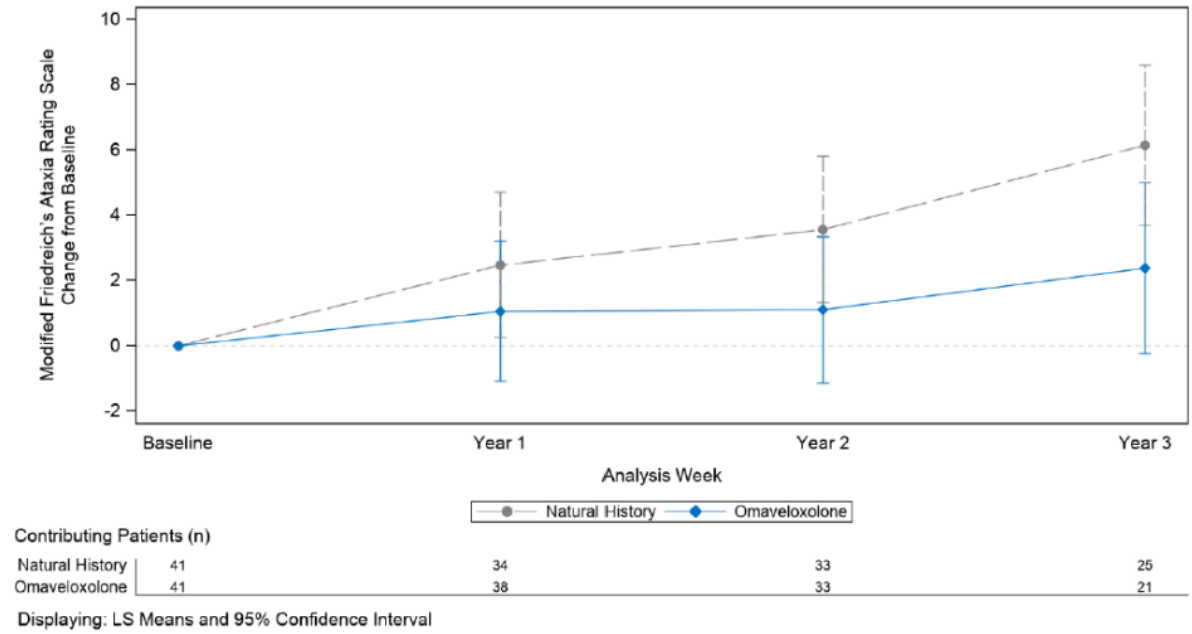

Figure 7. PS analysis: LS mean change in mFARS over time for patients with no prior omaveloxolone use (omav-omav population) (patients that had received prior omaveloxolone in MOXIe part 2)

3.3.2 JNHB discussion

Assessment of indirect comparison

In non-randomized evidence, there is a high risk of confounding bias and thus violation of the underlying assumption of exchangeability. Exchangeability is an assumption that studies as similar enough to be compared, i.e. that if patients from one treatment were substituted into another, the same treatment effect would be expected. Comparison of the two studies show overlapping inclusion and exclusion criteria, study location and time period of study conduction, supporting similar populations. A possible risk of bias is that different patients will volunteer to participate in MOXIe than in FA-COMS, for example as a randomized controlled trial can be more demanding to participate in than a registry trial.

The selection criteria for patients to be included in the PS matching analysis (at least one post-baseline mFARS measurement within 3 years after baseline, and values for all chosen PS covariates) further increases the risk of selection bias. These criteria reduced the FA-COMS patient from 810 to 589 eligible patients. The MOXIe OLE patient population was reduced from 149 to 136 due to the same restrictions.

The method for selection of covariates for the PS model used for matching seems sufficient to identify relevant prognostic factors and effect modifiers, and no critical additional factors were identified by Nordic medical experts consulted by JNHB. One medical expert mentioned that surgeries performed for scoliosis and similar conditions could be of possible significance. Omission of GAA repeats and *pes cavus* have been explained and discussed by the company. GAA repeats were not included due to lack of data, but it was available for around 90 % of the patients included in the analysis from both studies. JNHB therefore questions if it would have been feasible to at least perform a sensitivity analysis with GAA repeats included in the PS model. The company explained that there were also differences in how the GAA1 repeat length data was collected between studies. Strong correlation with age of onset also reduces the need for including it. There was a slight difference in number of GAA repeats after matching, most of which is probably not clinically significant as it is above the ceiling for clinically relevant differences, i.e. the length where when the maximum clinical manifestations has been reached, as explained by the company, supported by literature [16]. As GAA repeats is an important factor that correlates with early disease onset and severity of disease, excluding it introduces uncertainty in results due to potential residual confounding.

Comparison of patient demographics and characteristics after matching (Table 8), indicates balanced populations, also for factors that were not included as covariates in the PS model. The MOXIe OLE population was slightly heavier (weight, mean 69 kg for MOXIe OLE and 61 kg for matched FA-COMS patients). One medical expert mentioned that overweight could for example affect gait, but that the difference here probably not will be of significance in this regard.

The comparison of patient characteristics does not include study location and concomitant treatments. As MOXIe and FA-COMS was run in different countries worldwide there could potentially be differences in standard of care that could affect mFARS. The risk of this could be considered as small however, as both studies included mostly patient in the United States (9/14 and 7/11 sites in FA-COMS and MOXIe respectively).

The percentage of patients with *pes cavus* cannot be compared due to lack of information. For the same reason *pes cavus* was not a covariate in the PS model as described above. Lack of information is partially a consequence of the absence of standardized measuring methods. The literature suggests that more that 50 % of FA-patients develop *pes cavus* [8], which could be an estimate for the FA-COMS population. The MOXIe OLE population includes fewer *pes cavus* patients as they were limited to 20 % in MOXIe part 2 that constitute 2/3 of the MOXIe

OLE population. The reason for the limitation was findings in MOXIe part 1 that patient with *pes cavus* scored poorer on mFARS as described in section 3.1.1.

As described in the Practical Guideline for Quantitative Evidence Synthesis from HTA Coordination Group [17], three assumptions must be met when using non-randomised data and PS matching to adjust for confounding: positivity, overlap and balance.

- Positivity assumption: This means that patients in both groups must be theoretically eligible for both treatments of interest. Inclusion and exclusion criteria indicate that MOXIe population could be part of FA-COMS. The company reports that the following is met; a positive probability of being in the omaveloxolone or the FA-COMS population, that is the propensity score estimated from the logistic regression model must be strictly greater than 0 and less than 1.

- Overlap assumption: Sufficient overlap means that the distribution of patients among the different propensity scores must be similar. This assumption cannot be directly assessed as the company has not submitted documentation such as histograms or similar that enables evaluation of overlap.

- Balance assumption: The populations compared must be sufficiently balanced after adjustment for confounding. Standardized difference of the means of all the covariates was below the 0.5 boundary chosen in the submitted analysis for all three populations, see Table 7. According to the above-mentioned guideline a cut-off of 0,1-0,25 is more common. The company explained that a 0.5 boundary balances a trade-off between covariate balance, sample size and model performance, which is especially important in real world studies on rare disease with a limited number of patients. The standardized difference of the means of propensity score was nevertheless well below the 0,5 boundary for all three populations. The same was true for the standardized difference of the means of each covariate. Additionally, the ratio of the variances of the propensity score was close to 1, greater than 0.8, and less than 1.25 for all 3 populations.

In conclusion the PS analysis is performed with suitable methods and the analysis is in accordance with current guidelines.

Assessment of comparability with the Nordic patient population

The baseline patient characteristics for the MOXIe OLE population (n=136), is overall representative of Nordic patients according to consulted medical experts, and when comparing them to results from a Norwegian study from 2014 where FA patients were characterized [18]. See Table 8. This includes 1:1 male:female ratio, mean age of around 26 years and number of GAA1 and GAA2 repeats. The reported age of disease onset in the Norwegian study population was mean 10 years, and around 15 years in MOXIe OLE, implying more severe disease in the Norwegian population. Whether this is a real difference is not possible to judge due to the small Norwegian population (N=30). A potential difference could be of importance for efficacy, as the age of onset predicts disease progression and severity. Subgroup analysis in MOXIe part 2 indicated however that the number of GAA repeats, that is known to correlate with age of onset, does not influence effect, but the study is too small to conclude on result from subgroups.

One medical expert also pointed out that the Norwegian population includes a significant number of patients with ancestors from North Africa and the Middle East where the FA prevalence is relatively high. These are not optimally represented by the MOXIe OLE population where 98 % were white. The possible significance of this is unknown. As the MOXIe study is run primarily in the United States there might be differences compared to the Nordic population in e.g. treatment practice of SoC, but the differences are probably marginal and of minor importance for the results.

Patients above 40 years of age are not included in MOXIe, and the effect of omaveloxolone in this group is consequently unknown. In clinical practice most of these patients have a late onset milder disease. Medical experts consulted by JNHB do not see any obvious reasons why these patients should not benefit from omaveloxolone. Other groups in clinical practice are also excluded from the study such as patients with severe cardiomyopathy, uncontrolled diabetes, and mFARS above 80 (advanced disease).

Consulted Nordic medical experts estimate that around 50 % of patients in clinical practice develop *pes cavus*, based on literature. The percentage in MOXIe OLE is by design closer to 20 % as described above, which could lead to an effect estimate that is too high for the Nordic population.

The comparison table (Table 8) also show patient characteristics for the total FA-COMS population. This population is used to estimate mFARS progression for the SoC arm in the health economic model. From the table the population seems in general to be representative for the Nordic FA population. As the inclusion in the FA-COMS is not restricted (except severe cardiomyopathy) it is also likely that it is representative of the overall FA population (includes all ages).

Assessment of relative efficacy results

Patients in MOXIe OLE progressed 3.0 points in mFARS in three years, and the PS matched patients from FA-COMS progressed 6,6 points (-3,61 points difference), which corresponds to 55 % less progression in mFARS after 3 years (relative progression is 0,454). The company refer to this as a rate ratio. JNHB choose to use "relative progression" at it does not seem to be constant rate ratio. Relative efficacy was not analysed for outcomes other than mFARS.

JNHB considers that the PS matching analysis is appropriate in methods and assumptions to estimate relative efficacy based on the single armed MOXIe OLE study and the natural history study FA-COMS. However, an effect estimate from a non-randomized analysis inherently includes high uncertainty, because of risk of bias. Randomized evidence from MOXI part 2 also exists and should preferably have been included in the estimation of relative efficacy, even if MOXIe part 2 is limited by few participants and only 48 weeks of follow-up time. In support of using MOXIe OLE data, the PS matching analysis shows similar 1-year effect size as seen in MOXIe part 2.

The small study population in MOXIe OLE further increases uncertainty in the effect size. It should however be kept in mind that the rarity of the disease makes it difficult to achieve a large population for FA. Out of the 136 patients in MOXIe OLE data is only available for 77 patients for the 3-year time point. Reasons for this are primarily shorter follow-up than 3 years, but also discontinuation due to adverse events or patient decision. This includes a risk of bias, if e.g. more patients that do not experience effect have decided to discontinue treatment.

The yearly effect seems to vary between the three years of the study. From the effect curves (Figure 5) it seems that the effect is highest in the first year and then is reduced over time, as curves seems to be more parallel closer to 3 years. The difference in the results for the omav-omav and the placebo-omav population (Figure 6 and Figure 7) adds uncertainty in using the pooled population for the effect estimate, even if the larger patient number of the pooled population is a strength, and illustrate the inherent uncertainty in the effect results. The omav-omav population is however small. In conclusion the effect size of omaveloxolone and how it develops in the long-term must be interpreted with great caution. Data show that the disease progression can be reduced at least within the first year of treatment, whereas it is more uncertain if it is further reduced over the remaining years of treatment.

The clinical relevance of the results is difficult to assess due to the uncertainty, and variability between patients. The PS-analysis showed a maximum reduction in mFARS of around 2 points

in the first year which would correspond to around one year of natural disease progression (no progression), but the reduction in the third year would corresponds to around one month of natural disease progression. The average yearly reduction in progression over the 3 years corresponds to 7 months of natural disease progression. The efficacy results could be described as modest, but medical experts explain however that even small changes could be of importance to patients. As FA is a disease that gradually progresses over years, even a relatively small effect over a few years could potentially mean a significant long-term difference. This also implicates that early treatment initiation is of importance. Whether the effect size will be lasting is however highly uncertain.

JNHB conclusion:
The indirect comparison based on 136 omaveloxolone-treated patients in MOXIe OLE compared to PS matched natural history controls, resulted in 55 % less progression in mFARS over 3 years. The estimate is based on non-randomized evidence from a relatively small population and includes high uncertainty. The effect size and whether it changes over time is uncertain. The prediction of long-term effects is therefore difficult.

The analysis population is in general representative of the Nordic FA patient population and the methods and assumptions are appropriate. The effect in groups that were excluded from the MOXIe study is unknown, which includes patients above 40 years old, patients with severe cardiomyopathy and uncontrolled diabetes, patients with mFARS above 80 (advanced disease) as well as in patients with *pes cavus*.

Relative efficacy is based on mFARS only, which is an appropriate outcome for the disease progression but does not include risk of important comorbidities.

4 Cost-effectiveness methods

The following chapter is based on the dossier submitted by the company. All assumptions described are based on the dossier if not otherwise stated. The conclusions boxes after each section give a short assessment of the choices related to key parameter inputs, methods used, simplifications and scientific judgements made by the company.

4.1 Company model description

The health economic analysis explores the cost-effectiveness of omaveloxolone for treatment of FA in patients aged 16 or older. As omaveloxolone is expected to be used in addition to SoC, the analysis is comparing omaveloxolone + SoC with SoC alone. The cost-utility analysis is conducted using a regression-based model with a life-time horizon. The structure of the company's model is shown in Figure 8.

Patients in the model are divided into subgroups according to age at time of diagnosis. The subgroups are: onset younger than 8 years, onset at 8-14 years, onset at 15-24 years and onset age above 24 years. The distribution of patients in the subgroups and the population's characteristics are based on the FA-COMS database.

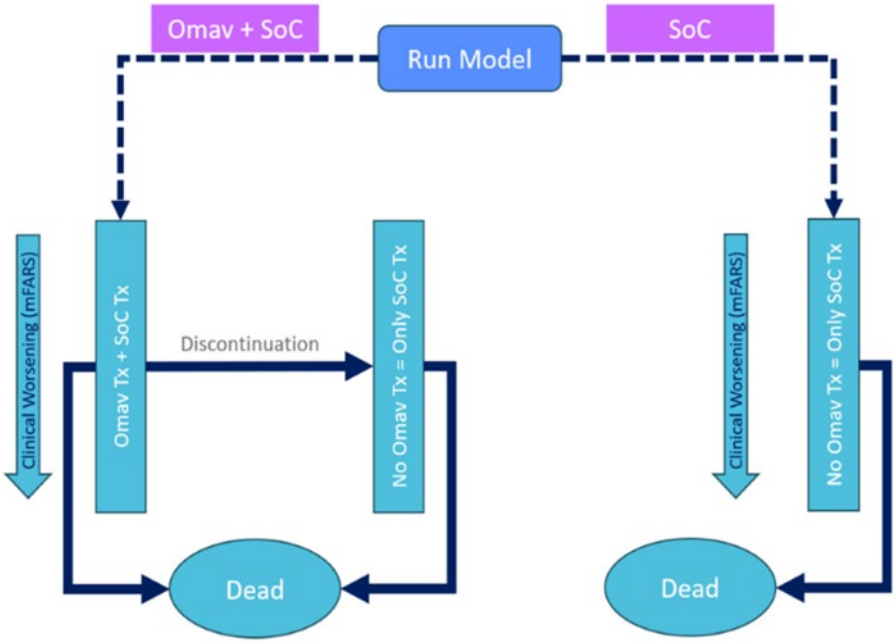

Figure 8. Structure of the company's regression-based model

The model estimates the treatment effect over a life-time period and since the patients in the model have different starting ages, their time in the model also varies. The time spent in the model for the different age subgroups is described in Table 10. An annual discount rate of 3.5 % was used for both costs and health effects for all years.

Table 10. Specifications of the different age groups in the model

Age at diagnosis	Mean age at model entry	Years followed in the model	Proportion of total population at model start
< 7 years old	16 years old	84 years	34%
8 – 14 years old	16 years old	84 years	40%
15 – 24 years old	25,3 years old	74,7 years	18%
> 25 years old	48,2 years old	51,8 years	8%

The regression-based model uses the following patient characteristics: age of onset, baseline age, gender distribution, baseline mFARS score and baseline gait score to predict the mFARS score for patients treated with SoC alone.

In the model, the patients in the SoC-arm are assumed to have a natural disease progression derived and extrapolated from FA-COMS data. In the omaveloxolone-arm, patients are assumed to have slower disease progression due to the effect of omaveloxolone estimated from the propensity scoring matched analyses, see section 3.3.1. Omaveloxolone is assumed to be a lifelong treatment, but discontinuation is possible if, e.g., adverse events occur, or the treatment's effect decreases over time.

JNHB discussion

JNHB finds the lifetime perspective of the model to be reasonable for this chronic condition to capture the costs and effects of treatment with omaveloxolone. The company's choice of a regression-based model seems reasonable due to the different patients' outcomes, based on the age of diagnosis. The division of patients into subgroups based on age at diagnosis also seems like a reasonable approach as progression of disease is strongly influenced by onset of disease. The distribution of patients between the onset age groups is similar to the patients expected to

be candidates for the treatment in Nordic clinical practice, according to medical experts JNHB has consulted.

In the company's analysis, it is assumed that treatment with omaveloxolone will be discontinued due to adverse events or decreased treatment effect over time. As disease progression speed varies between patients, it is difficult to predict how the individual patient's disease progression will be and therefore difficult to assess when the effect of omaveloxolone is diminishing. This can potentially mean that the treatment will not be discontinued, even if the treatment effect has decreased.

JNHB conclusion:
JNHB concludes that the model structure is suitable to evaluate the decision problem. JNHB concludes that the distribution of patients between the onset age groups is similar to the patients expected to be candidates for the treatment in Nordic clinical practice.

4.2 Effectiveness outcomes

4.2.1 Clinical effectiveness

Natural disease progression
Natural disease progression is informed by the change in mFARS over time. The progression of mFARS over time in the SoC-arm is informed by data from the FA-COMS database. Different mFARS trajectories are estimated for each onset subgroup during the observation period.

The change in mFARS for each sub-group is estimated using a multivariable linear model and subsequently used to extrapolate natural disease progression for the entire time horizon. The company explored both a linear and non-linear logistic model. The linear model was found to match the observed data from FA-COMS best as it had both a lower AIC and BIC. Therefore, the multivariable linear model was used in the company's model to estimate mFARS progression for the SoC group, from the baseline age of each cohort to 13 years later.

For the period after 13-years observation a logistic extrapolation was used to account for the expected reduction of disease progression at worsening disease stages. The extrapolation is shown in Figure 9.

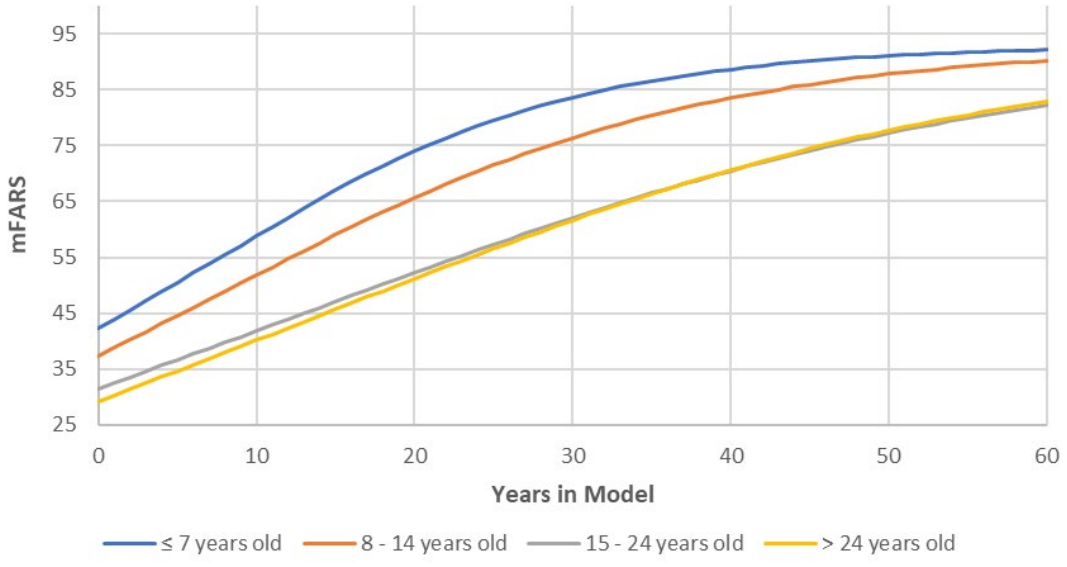

Figure 9. Modelled SoC mFARS Trajectory (With Logistic Extrapolation) for Each Age of Onset Subgroup

Treatment effect

The treatment effect over the model's time horizon is derived from the propensity score-matched analysis. In the analysis patients receiving omaveloxolone in the MOXIe OLE study (pooled population) are compared to matched patients from the FA-COMS. The cumulative change in mFARS over 3 years for patients from the natural history study are compared to those receiving omaveloxolone. Based on this analysis, the company calculates a relative progression that is applied throughout the entire time horizon, which means the effect of omaveloxolone is assumed to be the same from year 4 in the model. The relative progression is assumed to be the same for all age at onset subgroups, as the number of patients in each subgroup in the MOXIe OLE study is considered to be too low to estimate the difference for each subgroup separately.

The relative progression is defined as the change in mFARS for patients on omaveloxolone + SoC after 3 years divided by the change in mFARS for patients on SoC alone after 3 years. This results in a relative progression of 0,454, see Table 11. In the model, for each cycle in the omaveloxolone arm the mFARS change in the SoC arm is multiplied with 0,454 and added to the mFARS value in the omaveloxolone arm of the previous cycle. The modelled mFARS for all subgroups combined can be seen in Figure 10.

Table 11. Company's calculation of relative progression used to estimate treatment effect

	Omaveloxolone	Placebo
Cumulative change over 3 years resulted from propensity score matched analysis	3.004	6.611
Relative progression	3.004/6.611 = 0.454	

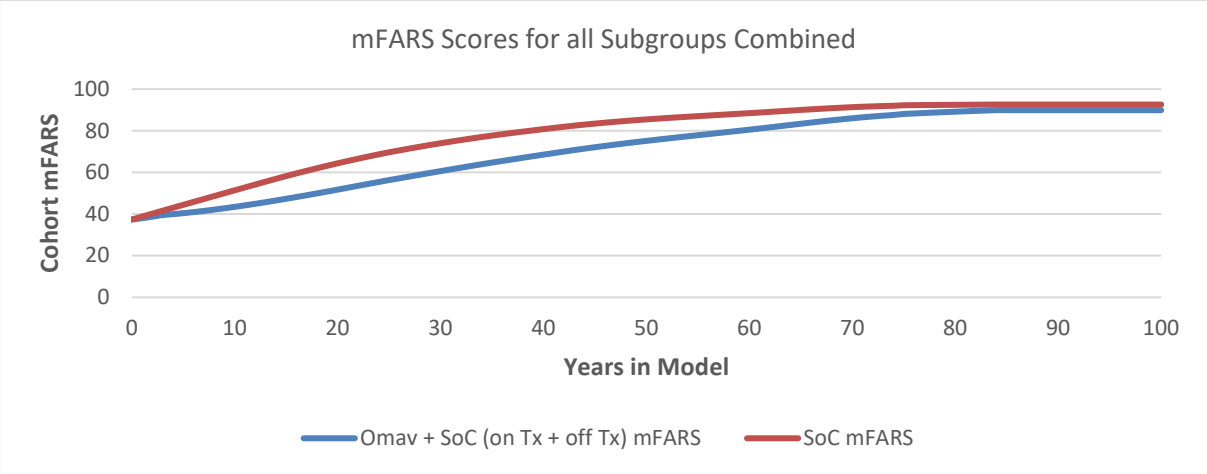

Figure 10. Modelled mFARS progression for all age sub-groups combined

Discontinuation

In the model, treatment discontinuation with omaveloxolone is based on the MOXIe OLE-study and includes only the group that completed MOXIe part 2 and was enrolled in MOXIe OLE. In this study 13 % of patients discontinued treatment during the first year and 5.6 % discontinued annually in the subsequent years of the study. In the company base case, 13 % is assumed to discontinue the first year, while 5.6% of patients are assumed to discontinue treatment annually for the remaining time horizon. When a patient discontinues treatment, no further effect is assumed to occur, thereby having the same mFARS development as the patients treated with SoC.

Mortality

No deaths were recorded in either MOXIe Part 2 or OLE. In the model, mortality is modelled as a risk associated with age and mFARS score. The risk of mortality is applied at the end of

each model cycle before treatment discontinuation is calculated. Disease specific mortality risk is always bounded below the general population mortality informed by Norwegian life tables from Statistics Norway [19].

Mortally is estimated based on data reported in Indelicato et al. [5], based on 12-years data from 631 FA patients from the EFACTS study and thereafter linked to mFARS from FA-COMS.

An OS curve for the full FA population was generated combining published Kaplan-Meier survival curves based on prognostic factors from Indelicato et al. [5]. To predict long-term mortality, various distributions are fitted to the OS curve, see Figure 11.

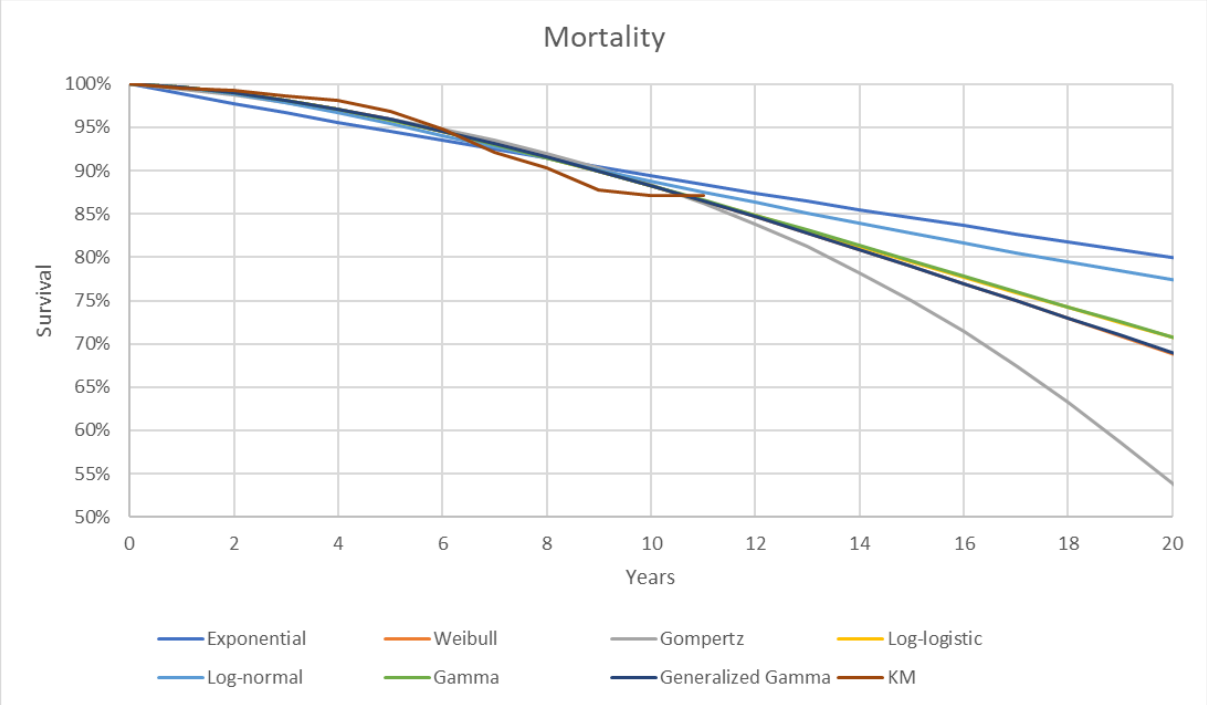

Figure 11. Overall survival Kaplan-Meier and fitted distributions for overall FA population in Indelicato et al. (2023)

The company argues that none of the distributions fit the KM curve well, but the log-logistic distribution has the best statistical fit according to AIC/BIC. The company chooses the exponential distribution as they find it to be more clinical plausible as patients will move from one mortality curve to another based on disability stage, and that could result in clinical implausible scenarios with a log-logistic distribution.

When using an exponential distribution, the mortality risk is assumed to be constant. A log-logistic distribution is used in a scenario analysis. The estimated survival curves based on the exponential distribution are presented in Figure 12. Patients discontinuing omaveloxolone are assumed to have the same mortality risk as patients on SoC alone.

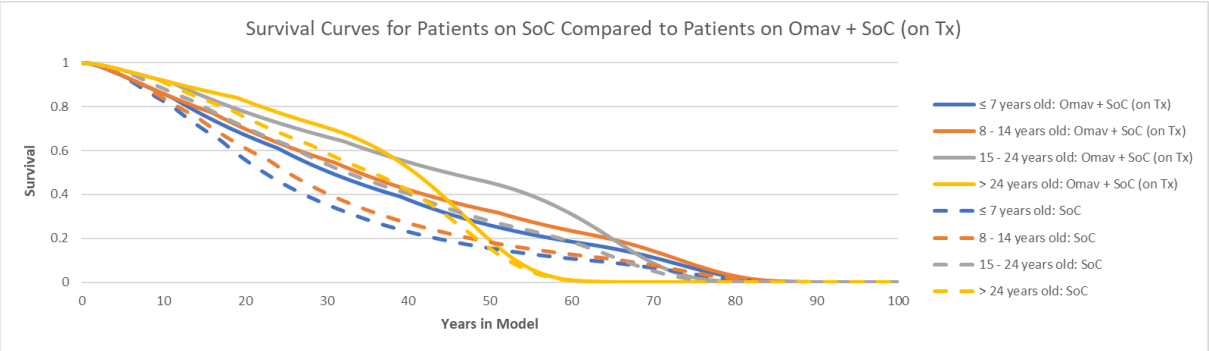

Figure 12. OS curves for omaveloxolone plus SoC and SoC patients in each subgroup with exponential distribution

To link the survival derived from Indelicato et al. (2023) to mFARS scoring, data from FA-COMS was used and hazard ratios (HRs) by mFARS category were estimated.
In Indelicato et al., HR of OS based on disability scores (1-7) were reported and cross-walked to disease ataxia stage, which is an almost similar staging system (1-6). Since both disease ataxia stage and mFARS were measured in FA-COMS, the company made an analysis of FA-COMS to generate a distribution of disease ataxia stage by mFARS categories.
The distribution of disease ataxia stage by mFARS category was used to create a weighted average of the reported HRs by disability stage to generate the HRs by mFARS category, which are presented in Table 12.

Table 12. Mortality HR by mFARS category

mFARS Category	HR vs. overall FA population
0–10	0.130
10–20	0.214
20–30	0.291
30–40	0.411
40–50	0.711
50–60	1.283
60–70	1.847
70-80	2.594
80–90	3.690
90+	3.965

The OS curves for the omaveloxolone + SoC for the four age subgroups are presented in Figure 13 and for SoC alone in Figure 14.

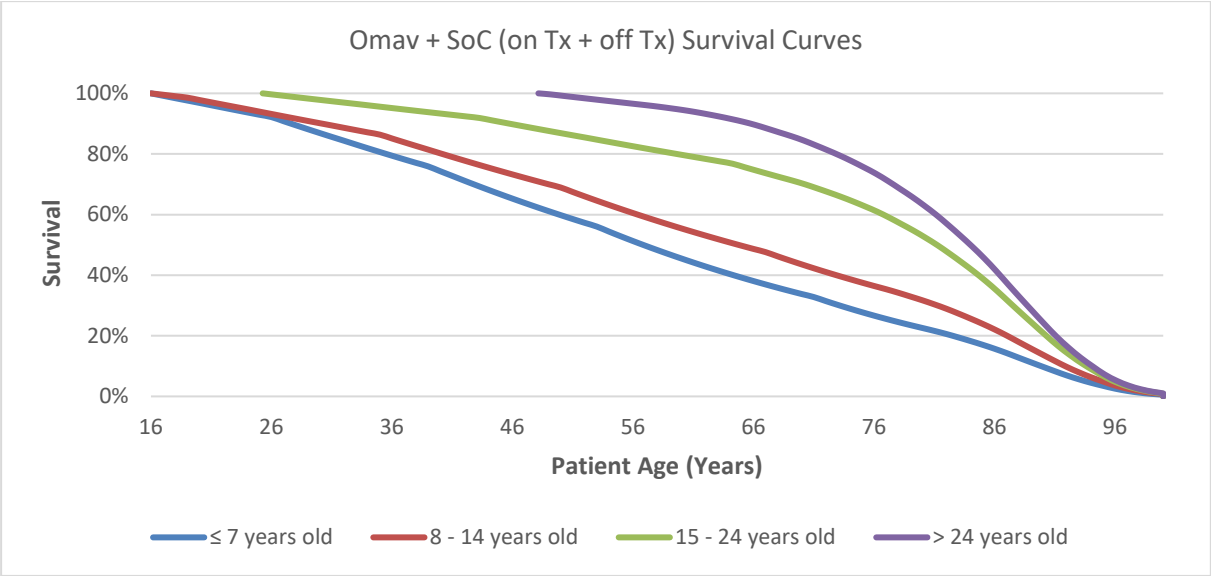

Figure 13. Estimated survival for patients treated with omaveloxolone + SoC in company's analysis. Survival is based on exponential survival curves, general population mortality, and estimated HR for different mFARS categories

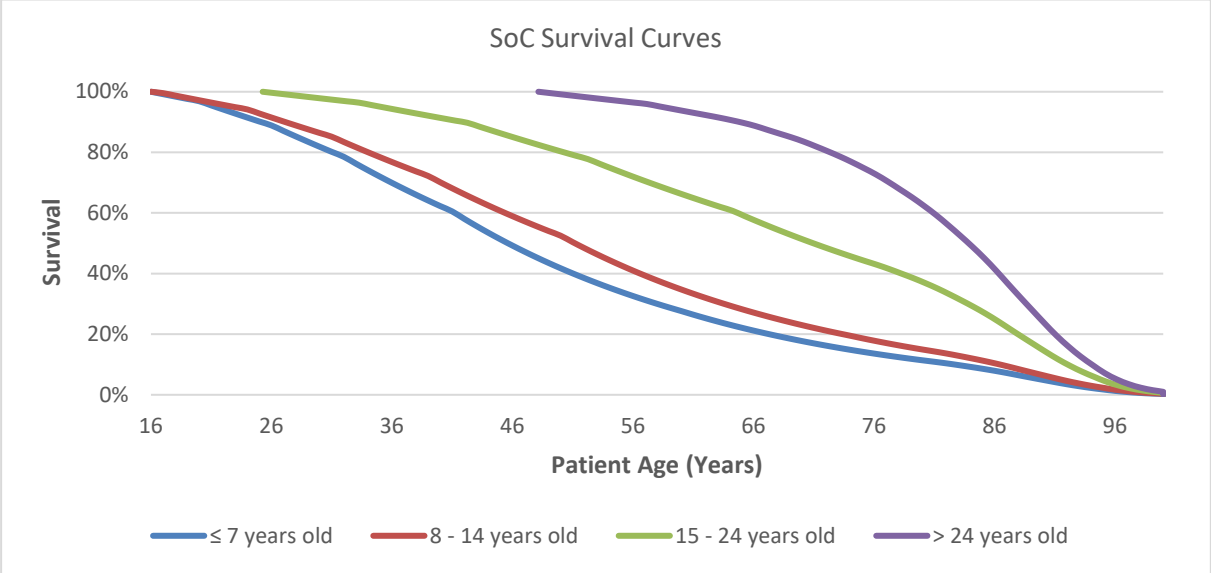

Figure 14. Estimated survival for patients treated with SoC in company's analysis. Survival is based on exponential survival curves, general population mortality, and estimated HR for different mFARS categories

JNHB discussion

Natural disease progression based on the FA-COMS population is acceptable as the FA-COMS population is considered to represent Nordic FA patients as discussed in section 3.3.2. To estimate the natural mFARS progression over time, a logistic extrapolation is made. When using this, the progression of mFARS over time is assumed to decrease. The modelled mFARS trajectories for the disease progression are however highly uncertain, as the disease progression differs between patients and it is difficult to describe an average disease course.

To model the treatment effect of omaveloxolone, the company estimates a relative progression based on change in mFARS between intervention and comparator over the first three years of treatment. There is high uncertainty in the effect estimate as it is derived from indirect comparison of non-randomized evidence based on relatively few patients. The company's estimated relative progression is kept constant throughout the time horizon. When looking at the curves in Figure 5, it is uncertain whether the treatment effect can be considered constant or if the effect is larger in the first year(s) of treatment. The difference in slope for omaveloxolone

and FA-COMS seem to be largest in the first year and then more similar between year 2 and 3 of treatment for the pooled population. This could imply that the effect of omaveloxolone is larger during the first year of treatment. The extrapolation from year 4 of the obtained effect based on all three years could therefore be considered to overestimate the long-term effect of omaveloxolone when the course of the curves is considered for the long term. The course of the curves must be considered as highly uncertain as discussed in section 3.3.2.

In the company's analysis a relative progression of 0.454 based on difference in mFARS progression from baseline to year three is estimated. They argue that a change based on all three years will give a more reliable estimate for the extrapolation from year 4 as fewer patients inform the last time points. If the calculation is based on difference in mFARS between year one and year three, the estimated relative progression with omaveloxolone is 0.665 and if based on difference in mFARS between year two and year three, the estimated relative progression is 0.900. The large difference between the estimated difference in cumulative change clearly shows the great uncertainty in the effect estimate. Different scenarios are performed to address this uncertainty about the effect from year 4.

The modelling of discontinuation seems reasonable, but it is uncertain whether the 5.6%annual discontinuation rate is applicable throughout the entire time horizon. Especially when considering the different progression of disease between the age subgroups, but also between patients in general, the discontinuation rate is associated with large uncertainty. It is possible that patients and clinicians will be hesitant to discontinue the treatment as no other treatments are available and the burden of side effects is limited compared to the severity of the disease. Clinical experts also assume that most adverse events that would require discontinuation will occur during the first few years.

There are no data on long-term effect of omaveloxolone beyond MOXIe OLE, i.e., 3 years. Data from MOXIe OLE suggest that the effect of omaveloxolone may diminish over time. Based on this, when extrapolating the effect, it could be relevant to include a waning effect. As the model includes a yearly discontinuation rate, the effect of omaveloxolone is already some extent reduced over time, and the scenario 2 also show results of a reduced effect, but if the patients continue treatment with omaveloxolone even though the treatment effect decreases over time, the effect will be overestimated, and the cost underestimated resulting in an underestimated ICER. Clinical experts agree that it could be difficult to judge whether or not a patient has benefitted from the treatment or whether the effect is reduced over time, and therefore difficult to potentially decide to stop treatment. JNHB do not investigate this issue further but is aware that this potentially could lead to cost of omaveloxolone being underestimated.

There is considerable uncertainty about the estimates of mortality. There are no data on the effect of omaveloxolone on mortality, and limited data available on mortality in FA in general. The estimates derived are indirect. Disability stage has been shown to be an independent predictor of mortality. Clinical experts state that it is reasonable to assume a correlation between disease progression measured with mFARS and mortality, but that the exact correlation is uncertain. Comorbidities are also strongly influencing mortality.

JNHB conclusion:
JNHB concludes that the effect estimate is highly uncertain, and it is uncertain whether the treatment effect can be considered constant or if the effect is larger in the first year(s) of treatment. Due to this, JNHB are conducting two scenarios: one where the effect from year 4 will be based on all three years (as in the company's base case) and one where the effect from year 4 will be based only on the third year.

JNHB concludes that the modelling of treatment discontinuation is reasonable, but the estimated discontinuation rate is associated with uncertainty. JNHB do not investigate this issue further

JNHB concludes that there is considerable uncertainty in the way mortality is estimated in the model since the correlation between mFARS and mortality is uncertain. In a sensitivity analysis the parametric functions log-logistic is tested instead of the exponential distribution is tested to see the influence on the results. This sensitivity analysis will not account for the possibility of structural uncertainty related to the assumed correlation between mFARS and mortality.

4.2.2 Health related quality of life

The company has not included health related quality of life (HRQoL) data from the MOXIe study, but instead two different approaches using external literature have been used to estimate quality of life in the model. In the base case EQ-5D data from the EFACTs database was used, and in a scenario SF-36 data from the FA-COMS database was used. In the model the company has also made it possible to include caregivers' disutility. As caregiver disutility is not to be included in the assessment in Denmark, this will not be presented in the assessment report.

EQ-5D from EFACTS

A linear regression with EQ-5D-3L values and SARA scores based on data from EFACTS, was conducted. The data consist of 5 data points reporting the average value yearly over 5 years. The SARA scores from EFACTS were cross-walked to mFARS scores using an algorithm published by Rummey et al [20]. The regression parameters are detailed in Appendix A

In Figure 15 the estimated linear relation between EQ-5D-3L and mFARS is shown. The regression parameters are listed inTable 13. The intercept is greater than 1 in the linear regression, which the company argues is not a problem as the utility generated in the model are always less than 1 due to the initial mFARS in each patient subgroup.

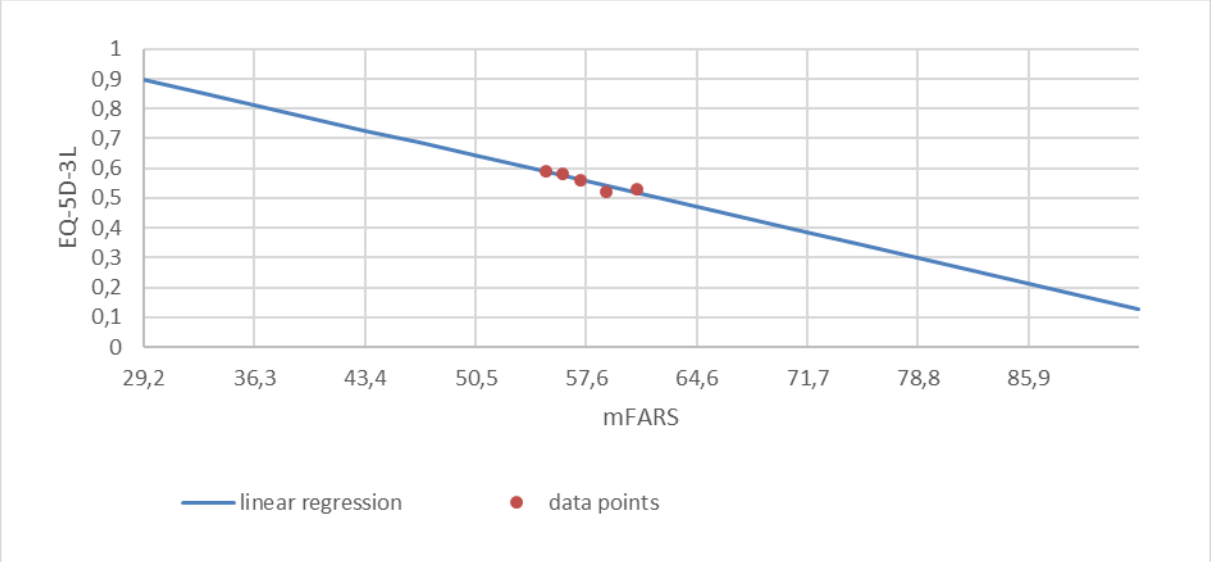

Figure 15. Estimated relation between EQ-5D-3L and mFARS in the model, based on EFACTS study

Table 13. Utility regression parameters

Parameter	Value	SE
Intercept	1.252	0.179
Slope	-0.012	0.003
Mean age of source population	33.7 years old	-
R-squared	0.834	0.014
F-statistic	11.118	
Residual degrees of freedom	3	
Regression of sum of squares	0.003	
Residual sum of squares	<0.001	

SF-36 from FA-COMS

Based on SF-36 and mFARS data from FA-COMS a regression analysis was performed to estimate patient utility at different disease stages. The SF-36 data was mapped to EQ-5D-3L using a published mapping algorithm from Rowen et al. [21] which was estimated with a generalized least squares (GLS) model. Thus, patient-level SF-36-data and mFARS from the same visits were used to predict the patient's EQ-5D-3L from mFARS by performing a linear regression analysis on mapped data. Figure 16 shows the estimated relation between mFARS and EQ-5D-3L based on FA-COMS and underlying dataset.

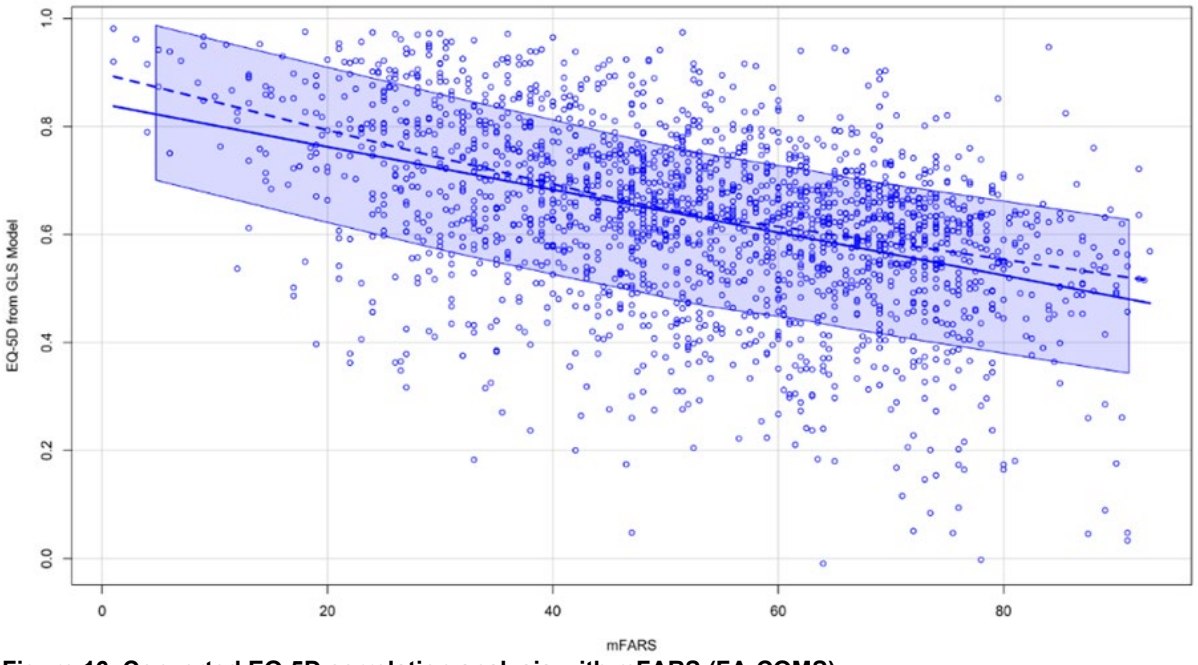

Figure 16. Converted EQ-5D correlation analysis with mFARS (FA-COMS)

Age adjustment

The model assumes that patient utility changes with patient age as demonstrated by the general population utility. The model uses the average age in the utility source, the current age of the patient in the model for each age of onset subgroup and the baseline gender distribution for each age of onset subgroup (assumed constant over the model time horizon) to adjust patient utility by age.

Adverse events disutility

For each adverse event included in the model, a disutility and a duration associated with each adverse event is estimated. The values selected for this analysis are based on earlier submissions to the National Institute for Health and Care Excellence (NICE) in other neuromuscular disease areas. Based on these submissions only influenza is assumed to be associated with a decrease in quality of life. The assumed disutility and duration of each adverse events are displayed in Table 14.

Table 14. Disutility and duration of each adverse event in the health economic model

AE	Disutility	Duration	QALY loss per episode
Nausea	0	11 days	0
Diarrhoea	0	20 days	0
Oropharyngeal pain	0	20 days	0
Influenza	-0.08	1 day	-0.000219

JNHB discussion

No differences were detected in SF-36 between the treatment arms in MOXIe part 2 as described in section3.1.3, MOXIe part 2 also measured the patients ADL score. For the patients treated with omaveloxolone there where a statistically significant improvement in ADL score at week 48, which indicates an effect of omaveloxolone on the patient's quality of life. The company has no explanation for the lack of difference in SF-36 between the two treatment arms, but an explanation could be the relatively short timeframe for the study whereby the generic instruments are not sensitive enough to capture minor differences or that generic instruments (as EQ-5D and SF-36) do not adequately capture specific symptoms related to FA, such as bulbar dysfunction.

According to clinical experts and patients, it is reasonable to assume a correlation between mFARS score and quality of life. They explain that even minor changes on the score can impact the quality of life to a large extent. The form of the exact correlation is, however, unknown.

Instead of using SF-36 from MOXIe, the company has used two alternative approaches to estimate utility values.

In the estimation of utilities based on the EFACTS study, the company assumed a linear relation between EQ-5D-3L and mFARS. This approach results in patients with an mFARS of 30 having a utility value corresponding to that of the general population. This is not considered realistic when the impairment caused by the disease is considered, although JNHB also recognizes that values below 30 are not impacting the results. The linear regression is based on very limited data with only 5 datapoints spanning a narrow range of mFARS values (Figure 15), which also makes the approach even more uncertain. The estimated values span from ~0,9 for mFARS of ~30 to ~0,25 for mFARS of ~80.

The company also included utility values based on data from FA-COMS. The use of this data gives a lower utility score for the patients with a low mFARS score than the general Nordic population and is probably more clinical plausible for values in the lower end of the mFARS spectrum. The utility values estimated for patients with a high mFARS seems to be high and they are higher, compared to the EFACTS data which has a steeper curve. The values span from ~0.75 for mFARS of ~30 to ~0.55 for mFARS of ~80. As FA is a severe disease that leads to impaired neurological function and neurodegeneration, and a high mFARS score is an expression of great functional impairment, this could indicate that the estimated curve when using FA-COMS has a slope that is not steep enough and thus overestimates the quality of life for

patients with a high mFARS score. This could essentially lead to underestimation of the difference in quality of life from low mFARS to high mFARS. Data from FA-COMS includes more observations than the EFACTS data and spans a broader range of mFARS values.

In general, both approaches used to estimate utility values for the analysis are associated with high uncertainty. In addition, the EFACTS study was carried out in Europe, while FA-COMS is multinational. This could potentially mean that the patients in EFACTS are more comparable to the Nordic patients. Both approaches assume a linear relation between the patient's quality of life and mFARS score. this may not be true in a disease as FA, where specific functions, such as ability to speak, may have a large impact on the patient's quality of life compared to other functions.

In both approaches it was necessary to map data in order to obtain the estimates that were to be included in the analysis. In the analysis using EFACTS, SARA score is mapped to mFARS, whereas SF-36 is mapped to EQ-5D in the analysis using FA-COMS, adding uncertainty to both approaches. Since FA-COMS is used by the company and by JNHB for estimating disease progression it is consistent to use the same source for utility values as well.

JNHB considers it unlikely that long-term nausea and diarrhoea do not influence quality of life, but uses the company's assumption, since the overall impact in the results, is limited.

JNHB conclusion:
JNHB concludes that the approaches used to estimate utilities in the economic model are associated with large uncertainty. The analyses are very sensitive to changes in the utility values as only limited survival gain is estimated from treatment with omaveloxolone.

The assumption of a linear relation between the patient's quality of life and mFARS score is uncertain.

JNHB uses data from the FA-COMS in their main scenarios and conducts sensitivity analyses with utilities estimated from the EFACTS study.

4.3 Costs and resource utilization

The company has included direct cost associated with treatment acquisition, disease management, management of adverse events, and indirect costs associated with education, transportation and caregivers' cost.

4.3.1 Dosage/Administration

Omaveloxolone is administered orally once a day, at a dose of 150 mg (3 hard capsules of 50 mg each). See Table 15 for packaging cost for omaveloxolone.

The company does not include any administration cost in the model, as omaveloxolone is an oral treatment. Based on MOXIe part 2, a relative dose intensity (RDI) of 86.9 % is assumed.

Table 15. Cost and details of packaging of omaveloxolone

Drug	Drug form	Drug strength	Pack size	Cost per pack (DKK)
Omaveloxolone	Hard capsules	50 mg	90	173.175,66

4.3.2 Costs for health care and use of resources and other directs costs

The company has used expert opinions to inform the resource use of patients based on changes in ADL score. They argue that this metric is more suitable than mFARS as it captures changes in disease severity that can be linked to changes in resource use. The clinical experts were asked to define a baseline patient and then specify the number of additional annual medical visits or one-of costs the patients would accrue for an increase in ADL score. To make it possible to use the estimates from the clinical experts in the model mFARS was categorized by increments of 10, from 0-10 to 90+. Based on patient counts from FA-COMS, distributions of ADL scores per category (0-1, 2, 3, 4) were estimated within each mFARS category.

Healthcare professional visits

The company uses resources reported by Giunti et al. [22] and expert opinion to estimate det use of these resources. The estimated annual number of visits to health care professionals is listed in Table 16 and the unit costs in Table 17.

Table 16. Healthcare resource use by mFARS category per year

	mFARS									
Visits per year	**0-10**	**10-20**	**20-30**	**30-40**	**40-50**	**50-60**	**60-70**	**70-80**	**80-90**	**90+**
Neurologist	2.05	2.18	2.58	3.03	3.88	4.80	5.72	7.23	8.49	10.00
Cardiologist	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Primary Care Physician	1.00	1.00	1.06	1.13	1.17	1.29	1.48	1.82	2.12	3.30
Orthopedic Specialist	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Occupational Therapist	2.09	2.99	3.93	4.83	5.76	6.80	8.28	9.47	9.85	9.65
Dietician	1.00	1.00	1.04	1.06	1.07	1.11	1.18	1.38	1.67	2.65
Physiotherapist	8.00	11.20	13.12	14.83	15.29	14.14	11.51	10.78	10.54	10.17
Speech therapist	2.09	3.78	4.82	5.26	5.90	7.21	8.91	10.86	12.24	12.83
Palliative care physician	0.00	0.00	0.01	0.03	0.16	0.70	1.69	2.52	3.84	5.48
Home health nurse	0.00	0.00	0.05	0.14	0.41	1.60	3.79	6.24	10.21	16.35
Hospitalizations	0.00	0.05	0.28	0.57	1.03	1.78	2.66	3.41	3.90	5.65

Table 17. Unit costs for healthcare resource use in health economic model

Healthcare resource	Unit costs (DKK)	Source
Neurologist	558.19	Honorartabel Neurologi (senere konsultation)
Cardiologist	702.69	Honorartabel Intern Medicin (Vurdering af patient ved enkeltstående konsultation - kardiologi)
Primary Care Physician	156.39	Honorartabel (om almen praksis) Konsultation
Orthopedic Specialist	1,044	Overlæger, løntrinaflønnede (ikke-ledende) - timeomkostninger - tabel 2, Værdisætning af enhedsomkostninger 1.8 enhedsomkostninger 1.8
Psychiatrist	1,038.9	Honorartabel Psykiatri (Individuel psykoterapi)
Occupational Therapist	423	Ergoterapeuter - timeomkosniger - tabel 2, Værdisætning af enhedsomkostninger 1.8

Dietician	702.69	Honorartabel Intern Medicin (Vurdering af patient ved enkeltstående konsultation - gastroenterologi)
Nurse Practitioner	462	Sygeplejersker - timeomkostninger - tabel 2, Værdisætning af enhedsomkostninger 1.8
Physiotherapist	347	Fysioterapeuter - timeomkostninger - tabel 2, Værdisætning af enhedsomkostninger 1.8
Speech therapist	1,044	Overlæger, løntrinaflønnede (ikke-ledende) - timeomkostninger - tabel 2, Værdisætning af enhedsomkostninger 1.8
Palliative care physician	1,044	Overlæger, løntrinaflønnede (ikke-ledende) - timeomkosniger - tabel 2, Værdisætning af enhedsomkostninger 1.8
Home health nurse	1,149.78	Sygebesøg fra 17 km til 20 km + evt. kørselsgodtgørelse for alle kørte km (based on average distance 20 km reported in document)
Endocrinologist	1,044	Overlæger, løntrinaflønnede (ikke-ledende) - timeomkostninger - tabel 2, Værdisætning af enhedsomkostninger 1.8
Hospitalizations	42,170	DRG 2024, 01MA07 Dissemineret sklerose og cerebellar ataksi

Comorbidities

The company included resource use and comorbidity costs in the model. The prevalence of cardiomyopathy, scoliosis and diabetes are based on these studies respectively; Hanson et al [23], Rummey et al. [2] and Cnop et al. [24]. The comorbidities include cardiomyopathy, scoliosis and diabetes. The company assumes that the treatment with omaveloxolone will have no impact on the comorbidities or the resources needed to handle these. These assumptions mean that the only difference between costs related to comorbidities will be due to difference in estimated survival. The estimated resource use related to each comorbidity is listed in Table 18 and the unit costs are listed in Table 17.

Table 18. Resource use for each comorbidity per year

Visits per year	Cardiomyopathy	Scoliosis	Diabetes
Neurologist	2.00	2.00	0.00
Cardiologist	3.00	0.00	0.00
Primary Care Physician	0.00	0.00	3.00
Orthopedic Specialist	0.00	3.00	0.00
Dietician	0.00	0.00	12.00
Physiotherapist	0.00	8.00	0.00
Palliative care physician	2.00	0.00	0.00
Home health nurse	4.00	0.00	0.00
Endocrinologist	0.00	0.00	3.00
Hospitalizations	2.00	1.00	0.00

Adverse events

The model includes costs related to managing adverse events. Clinical experts were consulted when selecting relevant adverse events to include and the frequencies are based on MOXIe part 2. The adverse events included in the model are listed in Table 19. All adverse events are assumed to occur during the first year of treatment.

Table 19. Adverse events included in the health economic model, incidence from MOXIe part 2

Adverse event	Omaveloxolone	SoC	Costs	Source
Nausea	5.9 %	0.0 %	7,818 DKK	DRG 2024, 06MA11
Diarrhea	2.0 %	1.9 %	7,818 DKK	DRG 2024, 06MA11
Oropharyngeal pain	2.0 %	0.0 %	1,331 DKK	DRG 2024, 03MA09
Influenza	7.9 %	0.0 %	2,107 DKK	DRG 2024, 03MA98

Home modifications, aids, and medical devices

Costs for home modifications, aids, and medical devices are also included in the model. The resources are informed by the observational study of Giunti et al [22]. The calculated increase in resource use for increase in mFARS category is presented in Table 20 and the unit costs associated with home modifications are listed in Table 21.

Table 20. Frequency of home modifications, aids, and medical devices by mFARS category per year

	mFARS									
	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90+
Cane/Walker	0.00	0.05	0.10	0.17	0.30	0.29	0.08	0.01	0.00	0.00
Wheelchair	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Adaptive bath/shower	1.05	0.05	0.29	0.26	0.39	0.44	0.66	0.82	0.73	0.35
Change home flooring	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Door widening	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Electric bed	1.00	0.00	0.05	0.03	0.09	0.22	0.33	0.21	0.04	0.03
Handrail and grabrail	0.05	0.10	0.34	0.41	0.66	0.74	0.84	0.75	0.72	0.33
Hoists	0.00	0.00	0.08	0.04	0.23	0.56	1.02	0.91	0.75	0.37
Ramps	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Specialized mattress	0.00	0.00	0.05	0.03	0.16	0.47	0.82	0.54	0.52	0.35
Stair lift	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Stair rail	0.00	0.40	0.33	0.38	0.40	0.33	0.09	0.01	0.00	0.00
Home improvement	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Feeding tube	0.00	0.00	0.00	0.01	0.00	0.00	0.01	0.03	0.08	0.39
Catheter	0.00	0.00	0.02	0.06	0.09	0.14	0.26	0.31	0.21	0.39

Table 21. Home modifications, aids, and medical devices by mFARS category

Healthcare resource	Unit costs (DKK)	Source
Cane/Walker	1,159	Giunti, Greenfield et al. [22], Inflated to 2024 DKK
Wheelchair	23,183	
Adaptive bath/shower	55,654	Giunti, Greenfield et al. [22], Inflated to 2024 DKK
Changes to home flooring	16,925	

Door widening	20,720	
Electric bed	19,061	
Handrail and grabrail	2,776	
Hoists	18,259	
Ramps	27,800	
Specialized mattress	6,798	
Stair lift	12,978	
Stair rail	705	
Extensive home improvement	359,601	
Feeding tube	462	Assumed as a nurse practitioner visit
Catheter	462	Assumed as a nurse practitioner visit

4.3.3 Indirect costs

In the company's base case, the analysis adapts a limited societal perspective, which includes costs for education support and travel costs. In addition, costs related to productivity loss and caregiver costs are also included in the model, but only in a scenario analysis and not the base case.

Education

The model also includes educational support, which is defined as help in school. This is only assumed for patients there are 18 years old or younger. Education support is estimated to result in a yearly cost of 2,123 DKK, based on a study by Giunti et al. [22].

Transportation

Cost of transportation is estimated based on average transport cost included in the DMP Enhetskostnads database, which has been multiplied with the average number of physician visits per year based on patient mFARS score. This results in a cost of 149.2 DKK for transportation back and forth.

Productivity loss

In the model cost associated with productivity has been included but only as a scenario and not the base case. Based on the study by Giunti et al. employment rates for FA patients are assumed to be 13% and average work hours per week are assumed to be 23.6.

Caregiver cost

In the model, the company has made it possible to include caregiver costs. They assume that 14% of required caregiver hours are performed by professional caregivers while the rest is performed by informal caregivers. The estimated number of caregiver hours needed is stated in Table 22.

Table 22. Resource use and costs of professional and informal caregiver based on mFARS category

	mFARS									
	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90+
Proportion of patients requiring caregiving	18%	58%	76%	92%	98%	100%	100%	100%	100%	100%
Average caregiver hours per week	6.0	7.1	11.0	14.7	29.3	69.7	133.3	158.4	166.7	168.0

JNHB discussion

The company has estimated a high number of visits to different healthcare professionals, especially for the patients with higher mFARS scores. Different clinical experts have been consulted and all agree that the number of consultations with neurologists, cardiologists, and orthopedists is overestimated. Consultations with these physicians will be limited to one visit on average every year independent of mFARS score.

The consulted clinical experts also expressed that palliative care would be handled by other physicians than those the patient is in contact with in relation to other examinations. It is difficult to validate the exact number for other health care visits. Clinical experts and patients agree that the number of other visits may relate to disease progression (mFARS score). In addition, consulted clinical experts point out that the unit costs used to estimate the costs of consultation with a neurologist, cardiologist and psychiatrist are based on unit cost for consultation with a specialist and not in a hospital. In Danish clinical practice, patients with FA will be monitored exclusively in the hospital. The real unit costs are expected to be higher, but since the number of hospital visits is reduced in the JNHB analysis, a change will have minimal impact and is therefore not carried out.

As omaveloxolone is assumed not to affect the incidence of comorbidities, as no data indicates a correlation, the difference between the omaveloxolone arm and the SoC arm is very limited, and changes made to frequency or cost have minimal impact on the results.

According to clinical experts consulted, all adverse events related to the treatment with omaveloxolone can be handled with an outpatient visit to the hospital. Changing this assumption will have little to no impact on the result and are therefore not executed.

The costs associated with home modifications, aids, and medical devices have very little impact on the result.

The indirect costs included in the economic model have very little impact on the result. Changes to any parameter related to the indirect costs have minimal impact on the results due to the limited effect of omaveloxolone on mFARS, therefore no changes are considered, and costs and methods are not validated.

JNHB conclusion:

JHNB find that the application of an RDI is associated with uncertainty, as dose reduction is recommended only in few cases. To examine the impact on the result a sensitivity analysis where the RDI for omaveloxolone is 100 % is performed.

JNHB reduces the number of visits with health care professionals to 1 each year for neurologists, cardiologists, and orthopedists for all patients regardless their mFARS score. JNHB excludes palliative care.

The company's estimation of health care resource use, particularly the number of visits to health care professionals, is uncertain.

The rest of the parameters presented in this section have minimal impact on the results.

5 Results of the cost-effectiveness analysis

In JNHB's scenario analyses omavaloxolone + SoC is compared with SoC alone. As the analysis is associated with large uncertainty, the JNHB's base case consists of two scenarios, where the estimated effect of omaveloxolone from year 4 is based on two different time periods from the studies. The ICER in the two scenarios ranges from 22.0 – 51.7 million DKK. QALYs gained are 0.32 – 0.77. Changing the input for utility values from FA-COMS to EFACTS change the QALY gain to 0,64-1.53 and the cost per QALY gained to 11.1-26.2 mil. DKK. The JNHB assessment presented in detail in section 5.2.

The company's base case is presented in section 5.1.

5.1 The company's base case

The company assumes omaveloxolone treatment improves both survival and health-related quality of life and their result in the model is 10.9 million DKK per QALY gained. The company estimates an incremental QALY gain of 1.53, and an incremental cost increase of 16.7 million DKK.

5.1.1 Key assumptions in the company base case scenario

- Natural disease progression for SoC is based on FA-COMS data
- Relative mFARS progression for omaveloxolone compared to SoC is based on MOXIe OLE compared to FA-COMS data using propensity scoring analysis over 3 years. The effect from year 4 is assumed not to change during the model horizon.
- For HRQoL there is assumed a linear relation between mFARS and EQ-5D-3L and the linear model is estimated based on EFACTS study data
- Mortality is related to mFARS based on data from EFACTS and FA-COMS
- Omaveloxolone has no impact on comorbidities
- Costs for health care and use of resources are linked to mFARS
- Comorbidities costs are not related to mFARS.

5.1.2 Results in the company base case scenario

In the company's base case, shown in Table 23, the cost per QALY amounts to 10,9 mil. DKK.

Table 23. Company base case results, DKK

	Omaveloxolone + SoC	SoC	Diff.
Omaveloxolone costs	17,187,584	0	17,187,584
Adverse events costs	811	149	662
Medical resource use cost	2,340,899	2,872,429	- 531,530
Comorbidity costs	1,762,173	1,715,711	46,462

Non-medical resource use costs	159,992	159,282	710
Informal caregiver costs	45,197	56,410	- *11,214*
Total costs	21,496,656	4,803,982	16,692,675
Life years (LY)	19.86	19.23	0.63
QALYs	12.57	11.04	1.53
Cost per LY gained			26,303,921
Cost per QALY gained			**10,937,763**

5.2 JNHB base case

Due to the uncertainty about the long-term effect, JNHB have performed two base case scenario analyses, where the difference in cumulative change is varied: one where the effect from year 4 will be based on all three years of data from MOXIe OLE, and one where the effect from year 4 will be based on the disease progression only in the third (last) year. The estimation of cost per QALY gained is 22 – 52 mil. DKK for the entire patient population according to the JNHB assessment. Changing the input for utility values from FA-COMS to EFACTS change the QALY gain to 0,64-1.53 and the cost per QALY gained to 11.1-26.2 mil. DKK.

Key changes in the JNHB base case scenarios compared to the company's base case scenario

- Two scenarios regarding relative effectiveness from year 4 are included.
  - Scenario 1 includes the same assumption regarding the effect as in the company base case, i.e., uses data from baseline to year 3 to estimate effect from year 4.
  - JNHB scenario 2 only uses the effect of the third (last) year to estimate the effect from year 4.
- Patients will independently of mFARS score only be examined once a year by a neurologist, orthopaedist and cardiologist
- No palliative care costs
- HRQoL is based on FA-COMS data

Table 24. Results from JNHB scenario 1: effect of omaveloxolone is based on a mean of all three years of data from MOXIe OLE, DKK

	Omaveloxolone + SoC	SoC	Diff.
Omaveloxolone costs	17,187,584	-	17,187,584
Adverse events costs	811	149	662
Medical resource use cost	824,351	1,089,866	- 265,514
Comorbidity costs	1,762,173	1,715,711	46,462
Non-medical resource use costs	159,992	159,282	710
Informal caregiver costs	45,197	56,410	-11,214
Total costs	19,980,108	3,021,418	16,958,690
Life years (LY)	19.86	19.23	0.63
QALYs	12.29	11.52	0.77
Cost per LY gained			26,723,102
Cost per QALY gained			**22,016,221**

Table 25. Results from JNHB scenario 2: effect of omaveloxolone is based on year 2-3 data from MOXIe OLE, DKK

	Omaveloxolone + SoC	SoC	Diff.
Omaveloxolone costs	16,817,031	-	16,817,031
Adverse events costs	811	149	662
Medical resource use cost	990,001	1,089,866	-99,865
Comorbidity costs	1,736,652	1,715,711	20,941
Non-medical resource use costs	181,104	180,086	1,017
Informal caregiver costs	51,703	56,410	-4,707
Total costs	19,777,302	3,042,222	16,735,079
Life years (LY)	19.49	19.23	0.27
QALYs	11.84	11.52	0.32
Cost per LY gained			62,784,296
Cost per QALY gained			**51,690,473**

5.2.1 JNHB sensitivity analyses

JNHB has conducted several sensitivity analyses to explore the impact of uncertainties identified.
The greatest effect on the ICER is the source used to estimate quality of life.

Table 26: JNHB sensitivity analyses based on Scenario 1 and 2, DKK

Sensitivity analyses	+/- Δ Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
JNHB scenario 1	**16,958,690**	**0.63**	**0.77**	**22,016,221**
Utilities based on EFACTS	16,958,690	0.63	1.53	11,112,068
Omaveloxolone RDI: 100 %	19,547,053	0.63	0.77	25,376,502
Mortality based on log-logistic curve	16,415,291	0.76	0.79	20,865,486
JNHB scenario 2	**16,735,079**	**0.27**	**0.32**	**51,690,473**
Utilities based on EFACTS	16,735,079	0.27	0.64	26,221,978
Omaveloxolone RDI: 100 %	19,267,639	0.27	0.32	59,512,916
Mortality based on log-logistic curve	16,002,532	0.29	0.32	49,606,002

5.3 Patient number

According to the company the estimated number of patients eligible for treatment with omaveloxolone are 29 in Norway. The company has only estimated the number of patients who are expected to be candidates for omaveloxolone in Norway. If the same approach as described by the company is applied to Denmark and Sweden, the number of patients will be 31 and 57, respectively.

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Appendix A

Table 27. Multivariable linear model of natural mFARS progression

Parameter	Beta Coefficient	SE*	p-value*	Lower 95% CI*	Upper 95% CI*
% Male	0.69	0.39	0.0799	-0.08	1.47
Baseline Gait Score	0.43	0.24	0.0675	-0.03	0.89
Baseline mFARS	0.85	0.023	<0.0001	0.80	0.89
Age at Onset Category: 8–14 years old	6.30	0.72	<0.0001	4.88	7.71
Age at Onset Category: 15–24 years old	5.58	0.74	<0.0001	4.13	7.02
Age at Onset Category: > 24 years old	4.74	0.82	<0.0001	3.12	6.35
Age at Onset Category: ≤ 7 years old	7.49	0.80	<0.0001	5.92	9.06
Time since baseline per year: age at onset ≤ 7 years old**	1.66	0.054	<0.0001	1.56	1.77
Time (Years) Since Baseline: 8–14 years old**	1.44	0.043	<0.0001	1.36	1.53
Time (Years) Since Baseline: 15–24 years old**	1.04	0.057	<0.0001	0.93	1.15
Time (Years) Since Baseline: > 24 years old**	1.10	0.076	<0.0001	0.95	1.25

Joint Nordic HTA-Bodies Health Technology assessment report of Skyclarys (omaveloxolone)

Company review

Biogen would like to express sincere gratitude for the thorough and comprehensive review of the submission for omaveloxolone for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. The company appreciates the opportunity to engage with the JHNB team and provide additional comments.

Biogen confirms that MOXIe Part 2 restricted the enrolment of subjects with pes cavus to 20% of the total trial population, and patients with pes cavus were not included in the FAS used for primary analysis (1). The number of patients with pes cavus was restricted in MOXIe Part 2 because the presence of pes cavus may represent a different subtype of FA, with a different pathophysiology and clinical phenotype. Furthermore, the presence of pes cavus likely interferes with patients' ability to perform clinical assessments requiring standing or pedalling (2). Since omaveloxolone treatment is not expected to affect the foot structure of a patient with FA, the presence of pes cavus undermines the predictive power of assessment tools (e.g. mFARS) to determine a difference between omaveloxolone and placebo; it was therefore necessary to restrict enrolment of subjects with pes cavus into MOXIe Part 2 (2).

Nonetheless, all patients, including those with pes cavus (n=20), were included in the "all randomised population" (ARP) in MOXIe Part 2 (N=103). In the ARP, consistent with the primary efficacy analysis using the FAS (which excluded patients with pes cavus), treatment with omaveloxolone resulted in a statistically significant least squares mean difference in mFARS of –1.94 versus placebo at Week 48 (p=0.0331), demonstrating that omaveloxolone is associated with a treatment benefit in all patients, including those with pes cavus (3).

JNHB suggested the possibility to include GAA repeat-length as covariate in the sensitivity analysis of the propensity score matching analysis. This was not done for the following reasons: First, there is a strong correlation between age of onset and GAA1 repeat length. Second, there were more missing values for GAA1 repeat length than for the other included covariates. Additionally, there were inconsistencies in how GAA1 repeat length data was collected, both between and within FACOMS and Study 1402. In Study 1402, the data was collected retrospectively at the site level, and there was no consistency in the kits and methods used for GAA1 data collection. Given these three reasons, and following the principle of parsimony, the goal was to create a robust approach for propensity matching while keeping as many subjects from Study 1402 in the analysis as possible.

The company take the opportunity to highlight that the treatment effect that should be considered for the analysis should consider the overall treatment effect observed during the entire trial follow-up period. As the reviewers pointed out, limited trial data is available for a rare disease such FA. Focusing solely on a partial timeframe reduces the patient population underpinning the estimate, potentially introducing additional uncertainty and limiting the robustness of the findings. Utilizing the full dataset would provide a more comprehensive and reliable assessment of the treatment effect, aligning with the principles of maximizing evidence utilization.

Factual checks:

- The base case is Denmark, and Danish costs are used throughout. However, in the indirect costs section, Norwegian costs are mentioned instead of the available Danish costs.
    - Education support reported 2,842 NOK vs the correct 2,123 DKK

    - Travel costs reported as 1,719NOK vs the correct 149.20 DKK
- The company would like to point out an inconsistency in the estimation the patients treated over the budget impact 5-year time horizon. In the company submission, the number of eligible patients was predicted to be 30-31 in the next five years. However, this number was mistakenly used as incident patient. The correct expected numbers of new patients treated per year are 24 patients in year 1, 5 in year 2, 1 in year 3 and 4 and none in year 5. These patients refer to the Norwegian setting.
- JHNB included the following question in the drafted assessment: "Could you please specify how many of the 59 patients for which there was not data available for the 3-year time point that had 1. not reached this time point, 2. discontinued due to AE, 3. discontinued due to patient decision or 4. for other reasons?"
    - At the latest data cut-off (17th August 2021), 125 of the 149 patients were continuing treatment. Of the 23 patients that had discontinued treatment at this point, 14 patients had withdrawn from the OLE, 9 patients discontinued due to adverse events, and one patient discontinued for other reasons (4)[1].

[1] Table 5: MOXIe OLE interim CSR

References:

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02.01.2025
CAF/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.01.2025
Leverandør	Biogen
Lægemiddel	Skyclarys (omaveloxolone)
Ansøgt indikation	Skyclarys (omaveloxolone) til behandling af voksne patienter med Friedreichs ataksi
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel. JNHB-rapport + nationalt appendix

Prisinformation

Amgros har forhandlet følgende pris på Skyclarys (omaveloxolone):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Skyclarys	50 mg (90 stk.)	173.175,66	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros indgår en aftale med leverandøren med aftalestart den 01.03.2025 og to år frem. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Skyclarys er det første lægemiddel til denne indikation og der er ingen behandlingsguidelines eller nogle kurative eller sygdomsmodificerende behandlinger tilgængelig i Danmark.

Tabel 2 viser lægemiddeludgiften pr patient for et års behandling.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Skyclarys	50 mg (90 stk.)	150 mg dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	JNHB (Danmark og Norge)	Link til vurdering
England	Under vurdering		Link til vurdering

Opsummering

[redacted]

Application for the assessment of omaveloxolone (Skyclarys®) for the treatment of Friedreich´s Ataxia in adults and adolescents of 16 years and older

For Health Technology Assessment of Medicinal Products through Joined Nordic Assessment

Company	Biogen	
Medicinal Product	*Omaveloxolone (SKYCLARYS®)*	
Relevant therapeutic indication	For the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older	
IDXXXX_XX (if the assessment is ordered from Bestillerforum RHF)	ID2024_12	
Submission track:	CUA: ☒	Simplified: ☐
Submission checklist complete	Yes	
Company representative	*Tine Eriksen* *Tine.eriksen@biogen.com*	
Second company contact	*Mikko Fernström* *mikko.fernstrom@biogen.com*	
Date of submission	12th of July 2024	

Version Control

Version	Date	Description of key changes
1.0	18/01/2021	1. First published version of a submission template by NoMA.
2.0	XX/XX/2023	2. Major revision and restructuring of the submission template together with updated submission guidelines.

Contents

List of Tables

List of Figures

Glossary of terms

Abbreviation	*Definition*
AE	Adverse events
AIC	Akaike information criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical, therapeutic chemical
AUC	Area under the curve
AUP	Apotekens utförsäljningspris
BARS	Brief Ataxia Rating Scale
BIA	Budget impact analysis
BIC	Bayesian information criterion
BMI	Body max index
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEAC	Cost effectiveness acceptability curve
CEM	Cost effectiveness model
CEPO	Carbamylated erythropoietin
CGIC	Clinician Global Impression of Change
CI	Confidence interval
CMA	Cost minimisation analysis
CPI	Consumer price index
CSR	Clinical study report
CUA	Cost utility analysis
DARE	Database of Abstracts of Reviews of Effects
DMP	Direktoratet for medisinske produkter
DRG	Diagnosis related group
DSA	Deterministic sensitivity analysis
DSU	Decision supporting unit
EED	Service Economic Evaluation Database
EMA	European Medicine Agency
EPAR	European Public Assessment Report
FA	Friedreich’s’ ataxia
FA-COMS	Friedreich's Ataxia Clinical Outcome Measures

FARS	Friedreich's ataxia rating scale
FXN	Frataxin
GBP	British pound
HTA	Health Technology Assessment
ICARS	International Cooperative Ataxia Rating Scale
ICD	Integrated clinical database
ICER	Incremental cost effectiveness ratio
IFN	Interferon
ISF	Innsatsstyrt finansiering
ITT	Intention to treat
IV	Intravenous
KOL	Key opinion leader
LN	Natural logaritm
LS	Least square
LS	least square
LY	Life years
MCS	mental component scale
NHS	National Health System (England)
NICE	National Institute for Health and Care Excellence
NINDS	National Institute of Neurological Disorders and Stroke
OLE	Open label extension
OS	Overall survivals
PCR	Polymerase Chain Reaction
PCS	physical component scale
PGIC	Patient Global Impression of Change
PICO	Population, intervention, comparator and outcome
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
QALY	Quality adjusted life years
RCT	Randomised clinical trial
RDI	Relative dose intensity
SARA	Scale for Assessment and Rating of Ataxia
SD	Standard deviation

SE	Standard error
SLR	Systematic literature review
STA	Single technology assessment
TTD	Time to treatment discontinuation
UK	United Kingdom
US	Unites States
VAT	Value added tax
9-HPT	9-hole peg test

1 Background

1.1 Overview

1.1.1 Intervention

Table 1: Summary table of the intervention

Medicinal product	Omaveloxolone (SKYCLARYS®)		
ATC-code	07XX25		
Nordic Article Number	VNR: 102493[a]		
Pharmaceutical class	Nrf2 activators		
Mode of action	Nrf2 (Nuclear factor erythroid 2-related factor 2) activators work by inducing the expression of cytoprotective proteins through the activation of the Nrf2 signalling pathway. This pathway plays a critical role in the cellular defence mechanism against oxidative stress and inflammation which is related to the underlying pathogenesis of Friedreich's Ataxia.		
	For the indication relevant for the submission, state:		
Indication approved by EMA	Treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.		
Posology	3 capsules of 50 mg each once daily		
Route of administration	Oral		
Duration of treatment	Until death or discontinuation due to adverse events		
Conditional approval	Yes: ☐	No: ☒	If yes, specify:
Does treatment require prior biomarker testing, companion diagnostics etc.?	Yes: ☒	No: ☐	If yes, specify: Targeted testing for the guanosine-adenosine-adenosine (GAA) expansion in the frataxin (FXN) gene using PCR or Southern blot techniques
	Information on the clinical documentation:		
Pivotal/main studies for the indication under review	MOXIe (part 1) (NCT02255435)		Current data cut: 13.06.2017
	MOXIe (part 2) (NCT02255435)		Current data cut: 31.10.2019
	MOXIe (OLE)		Current data cut: 24.03.2022[b]

Abbreviations: ATC = Anatomical Therapeutic Chemical; EMA = European Medicines Agency; FXN = frataxin; GAA = guanosine-adenosine-adenosine; Nrf2 = Nuclear factor erythroid 2-related factor 2; PCR = Polymerase chain reaction.

[a] *VNR number for DK/NO/IS. The VNR for SE and FI will be provided as soon as it is available.*

1.1.2 Submitted analysis

Table 2: Summary of the submitted analysis

Type of health economic analysis:	**Information about the submitted economic analysis:**				
	CUA☒	CMA ☐	BIA ☒		
Type of economic model, if CUA	PSM/AUC:			☐	
	Markov:			☐	
	Decision tree:			☐	
	Micro simulation/individual patient simulation:			☐	
	Other: regression-based model			☒	
Source of clinical evidence for relative efficacy	Head-to-head clinical study: ☐		Evidence synthesis: ☒		
Brief description of PICO in the health economic analysis	Population: Patients affected by Friedreich's ataxia aged 16 years and older Intervention: Omaveloxolone 150 mg once daily Comparator: Standard-of-care Outcome: QALYs and costs				
	If CUA	**NOK**	**If CMA**		
Result of the economic analysis (using AUP excl. VAT)	Cost pr. QALY:	18,092,625	Total cost of intervention:	N/A	
	Cost pr. LY:	41,276,278	Total cost of comparator:	N/A	
Result of the economic analysis (using relevant rebate excl. VAT for product under assessment)	Cost pr. QALY:	-	Total cost of intervention:	N/A	
	Cost pr. LY:	-	Total cost of comparator:	N/A	
Absolute shortfall	35.3				
	Information regarding budget impact analysis:				
	2025	**2026**	**2027**	**2028**	**2029**
Total eligible patient population	29	30	30	31	31
Patients expected to receive intervention	15	19	23	27	31
Result on budget impact (using AUP incl. VAT)	65,996,422	131,068,481	208,341,926	297,934,570	392,823,141

Abbreviations: AUC = Area-Under-Curve; AUP = Pharmacy's retail price; BIA = Budget impact analysis; CMA = Cost-minimization analysis; CUA = Cost-utility analysis; LY = Life-Year; N/A = Not Available; PICO = Population, Intervention, Comparison, and Outcome; PSM = Partitioned Survival Model; QALY = Quality-adjusted life year; VAT = Value Added Tax.

Notes: Omaveloxolone uptakes based on market assumptions

Table 3: Clinicians and/or key opinion leaders (KOL) contacted for preparation of the submission package.

KOL:	Advisory board:	Other (specify):
Dr. Susan Perlman (1-3)	N/A	N/A
Dr. David Lynch (4)	N/A	N/A

1.2 Description of the disease and patient population

Friedreich ataxia (FA) is a rare genetic neurodegenerative movement disorder (5, 6). The causative mutation is a trinucleotide (GAA) repeat expansion in the first intron of the gene encoding the protein frataxin (FXN), leading to impaired transcription of FXN (5, 6). FXN is an essential mitochondrial protein that is highly expressed in tissues rich in mitochondria such as the heart, skeletal muscle, liver, and neurons (7, 8). Organs containing these tissues are therefore particularly affected by FA.

FA is primarily a neurological disorder presenting with multiple manifestations that progress and lead to significant disability (9). As FA worsens, patients with FA show progressive sensory neuropathy and cerebellar degeneration. A key benchmark for identifying meaningful change in FA is, the progressive loss of ambulation and confinement to a wheelchair typically occur at the age of 25–30 years (5, 9).Other neurological manifestations of FA include speech and swallowing difficulties, which may contribute to aspiration pneumonia, a common cause of death in patients with FA (9). Urological symptoms, including urgency, hesitancy, incontinence, and retention, are also common in FA (10). Loss of hearing and vision are diagnosed most frequently in people with an FA duration of ≥20 years (11). These symptoms all considerably impair the quality of life of patients with FA (see Section 2.1.2).

Non-neurologic features of FA include cardiac involvement, diabetes mellitus, and skeletal abnormalities (9). Systemic symptoms commonly progress in concert with neurological symptoms (11); the increasing worsening of both components of the disease contributes to severe disability in the advanced stages. FA considerably shortens life expectancy but there is little to no published information on the end stages of the condition. In a retrospective study of 61 patients with FA who had died, most deaths occurred between the ages of 16 and 45, with a mean age of death of 37 (12). Cardiac dysfunction was the most common cause of death (59.0% of all cases). A further 3.3% of deaths were the result of probable cardiac causes (severe cardiomyopathy and arrythmia). 27.9% of deaths were unrelated to cardiac dysfunction (12); the causes were pneumonia (10%), sepsis (1.6%), renal failure (1.6%), breast cancer (1.6%), accidental drowning (1.6%), suicide (1.6%), and other (not specified, 9.8%). The remaining 10% of deaths had an unknown cause. The median age at death was lower for patients who died from cardiac complications compared with those who died from other causes (26 years versus 41 years) (12).

Diagnosis of FA typically occurs during childhood or adolescence (9, 13), and is based on clinical suspicion of symptoms confirmed by genetic testing for GAA expansion in the *FXN* gene (6). Signs generally appear between 5 and 20 years of age (13), with estimated mean age of onset ranging from 10–15 years (9); however, as age of onset is recorded retrospectively, these estimates may be subject to recall bias. A few individuals have presented earlier than 5 years, and retrospective identification of symptoms earlier in life is common (13), with onset of FA reported in infants as young as 1 year old (9). In typical FA, onset is prior to 25 years of age (10), although atypical and late onset cases can occur. Atypical FA is rare and includes FA with retained reflexes (particularly knee jerks), which occurs in 9% of cases (10). Late onset FA presents after 25 years of age and occurs in 14% of patients, while very late onset FA is characterised by onset over 40 years and is very rare (10). Patients with late or very late onset FA have fewer GAA repeats, less severe functional disability, and slower disease progression (14). On the contrary, a greater number of GAA repeats is associated with earlier symptom onset (5, 15).

The discovery of the causal mutation for FA in 1996 (16) led to a decrease in the time from symptom onset to diagnosis from 4 years to 2 years on average(17). However, time to diagnosis is still typically longer in patients with non-neurological presentation (6.7 years) or with late onset (3 years) (17).

FA-specific genetic test is now required for a conclusive diagnosis (6). Testing options include single-gene testing or a multi-gene panel (18). Single-gene testing is targeted at identifying abnormal GAA expansion in intron 1 of FXN; however, if only one expanded allele is detected (circa 4% of cases), sequence analysis of FXN will also be performed (13, 18). Multi-gene testing, in which other genes of interest are assessed in addition to FXN, is not recommended as a first-line strategy in typical cases but may be helpful for atypical presentations (18). Currently, next-generation sequencing strategies cannot identify expanded repeats and

are therefore not suitable for diagnosing most individuals with FA in Norway (13, 18). Whole exome sequencing (WES) is instead a validated and used method in Sweden and Denmark (19).

1.2.1 Measuring Neurological Progression of FA

Historically, three scales have been used to measure the neurological progression of FA: ICARS (International Cooperative Ataxia Rating Scale), SARA (Scale for Assessment and Rating of Ataxia), and Friedreich Ataxia Rating Scale (FARS) (20). To date, two scales have evolved as the cornerstones: mFARS and SARA. Both scales are now generally accepted and currently used in 2 large natural history studies in Europe and the United States, the EFACTS (21) and FA-COMS (22), respectively. While SARA provides a fast assessment of different impairments in cerebellar ataxias, mFARS is specifically developed for FA to reflect the affected neural substrates on a granular level (23).

FARS was developed to evaluate the functional and neurological deficit of FA with greater weight given to gait and stance (24). The initial neurological assessment was composed of five-subscale assessments measuring bulbar function, upper limb coordination, lower limb coordination, peripheral nervous system, and upright stability. mFARS was developed in collaboration with Friedreich's Ataxia Research Alliance (FARA) and U.S. Food and Drug Administration (FDA) to define a sensitive, clinically meaningful endpoint for use as a primary outcome measure in clinical trials. mFARS is revised by omitting items that do not directly assess functional abilities. The omission of the peripheral nervous system subscore and 2 items of the bulbar subscore resulted in better reliability and validity, as the peripheral nervous system and atrophy of face and tongue do not progress similarly as the remaining items.

The main advantage of mFARS is its excellent interrater reliability (25, 26). mFARS further correlates with functional disease stage, activities of daily living, disease duration, age of onset and repeat length, demonstrating high validity as a clinical measure of the progressive course of FA. One of the major drawbacks is the complexity of the scale and the time it takes to complete the assessment. Therefore, a commonly used substitution for mFARS in clinical setting is the Scale for the Assessment and Rating of Ataxia (SARA). SARA is a compact scale designed for rapid assessment, but it may be more limited in complex studies. It includes most of the same components as mFARS and shows high correlation with mFARS (23, 24).

The mFARS scale consists of 4 subscales that focus on specific areas of the body: bulbar function, upper limb coordination, lower limb coordination, and upright stability. A total of 18 assessments are scored within the range 0-2 to 0-5. Increments of 0.5 may be used if the examiner feels an item falls between 2 defined severities. Scoring is based on a composite score of all these subscales with a maximum score of 93 points, with increasing number indicating a higher disease severity or worsening of neurological function (24). FA patients are typically scored between 25-30 at diagnosis, and 60-70 when ambulation is lost, which is a critical milestone in the disease (27).

The FACOMS natural history study indicates that patient mFARS composite scores will typically increase ~2 points per year. On a population level, age is the best predictor of mFARS progression rate, with younger disease onset age predicting faster progression (22).

1.3 Current clinical pathway

The diagnostic pathway of FA patients in Norway may vary in length due the heterogeneous symptom expression and age of onset, complicating the diagnostic procedure. FA patients are typically referred from GPs to paediatricians at local hospitals, which may further elicit a referral to a neurologist. Following clinical examination, laboratory tests and MR-scanning to exclude differential diagnoses, a genetic test confirms the diagnosis. To date, 4 hospitals in Norway are conducting genetic testing of *FXN* using repeat primed-PCR, fragment analyses and Southern Blot (Oslo University Hospital, Haukeland University Hospital, University Hospital of Northern Norway and Telemark Hospital), which is a well-organized and efficient procedure (28).

Currently, no treatment altering the progressive disease course is available for FA in Norway (29-31), or in any other Nordic country relevant for this assessment (Sweden and Denmark). In addition, in Norway, no county specific treatment guidelines for the management of the disease are available.

The current clinical practice focuses on the management of symptoms, comorbidities and supportive care, as indicated in the international guidelines applied; European Reference Network – Rare Neurological Diseases (ERN-RND) and UK Ataxia Group (6, 13, 32-34). In line with these guidelines, FA patients are typically monitored by a neurologist, cardiologist, and a multidisciplinary team at least annually, in addition to receiving rehabilitation services in the municipalities. For Sweden and Danmark, this is further confirmed by Socialstyrelsen(35) and Sundhed.dk(36).As FA progresses, affected individuals experience worsening gait and limb ataxia, motor weakness, reflex and sensory loss, impairments in speech and swallowing, hearing loss, reduced clarity of vision, and bladder dysfunction (9), leading to loss of independency and premature death. There are no direct treatments for weakness and ataxia (13), with management approaches focusing on prostheses, walking aids, wheelchairs, and physiotherapy (32). Some neurological features can be managed through selective pharmacological therapies, such as: spasticity (baclofen, tizanidine, botulinum toxin); neuropathic pain (gabapentin, pregabalin), and urinary urgency (anticholinergic agents such as oxybutynin) (13).

Non-neurological features of FA can include cardiac complications, diabetes mellitus, and skeletal abnormalities (including scoliosis and foot abnormalities) (9). There are no FA-specific medications to prevent or treat cardiac disease progression, and cardiomyopathy is therefore typically managed according to general cardiology guidelines (13), including antiarrhythmic agents, anti-cardiac failure medication, anticoagulants, and pacemaker insertion (18). Diabetes mellitus in individuals with FA may be treated with diet changes and, if necessary, oral hypoglycaemic medications or insulin (9, 18). Management of scoliosis in FA is similar to the general population, based on physical therapy and bracing to stabilise the spine during growth; severe cases may require surgical intervention (13) (37). Depression is common in people with FA (38). FA patients thus require frequent monitoring for depression and/or other mental health issues and be offered counselling and antidepressant medication (39).

A multidisciplinary approach to treatment is essential to manage FA symptoms and comorbidities (18, 32), including specialist therapists such as physiotherapist, speech therapists and occupational therapists needed to help patients navigate everyday life (29, 31).

1.4 Description of the intervention, anticipated place in the clinical pathway, and subsequent displacement of current treatment

Omaveloxolone have received marketing authorisation valid throughout EU in February 2024 (37) and is the first treatment available FA patients aged 16 years and older.

As described in Section 1.2, FA is characterised by a deficiency in the mitochondrial protein FXN, and suppressed Nrf2 activity (5, 6). Nrf2 dysfunction is associated with mitochondrial dysfunction, oxidative stress, and neuroinflammation (40). *In vitro* activation of Nrf2 by omaveloxolone has been shown to increase Nrf2 levels (41), which, *in vivo*, may result in improved mitochondrial function, reduced oxidative stress, and suppression of neuroinflammation (41).

The recommended dosage of omaveloxolone is 150 mg (3 capsules) taken orally once daily. It is indicated from the age of 16 years until intolerable toxicity or death, meaning its place in the treatment pathway is not restricted to a certain treatment line (37). Omaveloxolone is expected to be used alongside the current standard of care (SoC) rather than replacing it (29-31). Therefore, the relevant comparator is the current SoC alone as described in Section 1.3.

2 Clinical evidence

The systematic literature reviews (SLRs) conducted to select the key efficacy and safety evidence is summarised in Section 2.1. The relevant studies identified are described in Section 2.2. The complete SLR reports are attached to Appendix B: SLR reports.

2.1 Information retrieval

To identify all relevant studies for the STA in question, a series of SLRs were conducted on efficacy, safety, economic and humanistic burden, and the health economic evidence of pharmacologic treatment for FA.

2.1.1 Clinical efficacy and safety literature

2.1.1.1 Methods

The objective of the SLR described here was to collect the evidence on clinical efficacy and safety of pharmacological treatments for FA.

The methods applied followed the standards set forth in the Cochrane Handbook for Systematic Reviews of Interventions (42) as well as the standards required by the key Health Technology Assessment (HTA) bodies, such as the National Institute for Health and Care Excellence (NICE) (43), and the Gemeinsamer Budesausschuss (G-BA)/Institute for Quality and Efficiency in Health Care). In addition, the report followed the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (43). A copy of the protocols describing the methods in further detail is provided in the supplied SLR report that is supplied to the assessors.

The following electronic literature databases were used to conduct systematic literature search: MEDLINE and MEDLINE In-Process, Embase, CDSR, CENTRAL, DARA; NHS EED. To strengthen the evidence collected in this SLR, grey literature searches on conference proceedings and clinical trial registers were also conducted. Details on the conducting of the search and search strings can be found in the supplied SLR report.

Studies were screened against predetermined population, interventions and comparisons, outcomes, and study design (PICOs) criteria to establish which studies were eligible for inclusion in the SLRs. Publications were excluded if they did not meet the selection criteria outlined in Table 4 or were published in a language other than English or German.

The screening followed a standard systematic two-step approach. In the first pass, each title and abstract were reviewed by two independent reviewers to determine its eligibility for inclusion in the SLR. Disagreements were resolved by a third reviewer, as necessary. No study was excluded at the title and abstract level solely because it provided insufficient information. For abstracts that were deemed relevant during title and abstract screening, the corresponding full-text articles were retrieved for further screening. In the second pass of screening, each full-text paper was reviewed by two independent reviewers. Disagreements were resolved by a third reviewer, as necessary. For each excluded study at full-text screening, a specific reason for the exclusion was selected.

After the completion of the study selection process, a list of records included/excluded was summarized in the SLR report, and the flow of study selection was documented according to the PRISMA diagram (44).

Table 4: PICOS eligibility criteria for the clinical efficacy and safety SLR

Criterion	Explanation
Population	• Patients diagnosed with FA, including: ○ Patients with FA categorized with pes cavus (i.e., with pes cavus and without pes cavus) ○ Patients with FA diagnosed with cardiomyopathy and cardiac failure

	• Mixed populations of patients with FA or other neurodegenerative disorder with results reported separately for the population of interest
Interventions	• Systemic agents recommended or currently under investigation for the treatment of FA
Comparators	• Head-to-head comparison of any systemic agent, placebo, or best supportive care • None (for single-arm trials)
Outcomes	**Efficacy**: • Validated measures of ataxia severity, including: • FA Rating Scale (FARS) • Modified Friedrich's Ataxia Rating Scale (mFARS) • Brief Ataxia Rating Scale (BARS) • International Cooperative Ataxia Rating Scale (ICARS) • Modified ICARS (MICARS) • Scale for the Assessment and Rating of Ataxia (SARA) • Barthel Index • Berg Balance Scale • Survival/disease progression • Performance measures • Peak work during maximal exercise testing • 9-hole peg test (9-HPT) • Timed 25-foot walk (T25-FW) • Low-contrast letter acuity **Safety:** • All-cause mortality • Treatment-related/emergent adverse events (AEs) • Serious AEs (SAEs) • Discontinuation due to any cause • Discontinuation due to AEs • Elevated liver enzymes AEs • Frequency of falls [a]
Study Design	• RCT (phase 2 or 3) • Single-arm trials • Non-randomized controlled trials • Observational (non-interventional) controlled studies
Limits	
Period	• Full-text publications: None
	• Conference abstract: past 2 years (2021-2023)
Geography	• Any
Language	• English • German

Abbreviations: FA = Friedreich's ataxia; SLR = systematic literature review; RCT = Randomized controlled trial.

Notes: a) Originally planned to be captured as efficacy outcome; updated to align with trial's reporting, which categorizes the frequency of falls as an AE.

The risk of bias (RoB) assessment of controlled clinical trials included in the clinical efficacy and safety SLR was conducted using the Cochrane Risk of Bias Assessment Tool 2.0 (RoB 2.0) (45). The tool assesses how well each study evaluated the intervention effect on a particular outcome considering the following five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The risk of bias in each domain was rated as low, some concerns, or high risk of bias; then, an overall risk of bias judgement (i.e., low, some concerns, high) was awarded following the algorithm guidance of the RoB 2.0 tool.

The efficacy outcomes of key interest in FA treatment were considered for the RoB assessment. Therefore, the assessment was performed based on the following performance measures, as available according to the respective order of relevance: FARS/mFARS, ICARS, and SARA.

The overall risk of bias for single-arm trials was not formally assessed, as they lack randomization and allocation concealment. These characteristics put the design at an overall risk of bias.

2.1.1.2 Results

A total of 63 records were included in SLR 1 (54 from the original search and 9 from the SLR update #1). Of these, 44 records reporting on 33 unique studies that evaluated pharmacological therapies of interest were prioritized for data extraction. Of the 33 unique trials eligible for data extraction, three were open-label extension (IONIA-E, MICONO-E, and MOXIe extension) and one was a re-randomization of an open-label extension trial (PROTI). Therefore, twenty-nine studies (19 RCTs and 10 single-arm trials) were potentially eligible for quantitative synthesis. The studies evaluated 16 different treatments for FRDA, with idebenone, interferon gamma (IFN-γ 1b), omaveloxolone, recombinant human erythropoietin (rHuEPO), and vatiquinone, being evaluated in two or more studies. Ten studies were conducted in the United States (US), 12 in Europe (Austria, n=2; France, n=1; Germany, n=1; Italy, n=4; Spain, n=3; UK, n=1), and seven were multinational. The follow-up duration varied from 2 weeks to 72 weeks, with one study reporting a longer follow-up (5 years). Four studies exclusively enrolled pediatric patients (i.e., patients up to 19 years; mean age ranged from 12 to 15 years), and seven studies reported on a mixed age population including children, adolescents, and adults (mean age ranged from 11 to 50 years). In the remaining 18 studies, the mean age ranged from 24 to 49 years. The Friedrich Ataxia Rating Scale (FARS) and modified FARS (mFARS) scores were used across studies to assess neurologic function among patients with FRDA. The severity of ataxia was assessed using the International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA) scales. Overall, the RoB across studies was acceptable, with over 80% if the studies judged at low risk or some concerns of bias.

2.1.1.2.1 Efficacy

2.1.1.2.1.1 FARS (0 to 125; higher scores indicate a higher severity/worse function)

FARS was evaluated in eight studies assessing seven different treatments: A0001, carbamylated erythropoietin [CEPO], deferiprone, idebenone, IFN-γ 1b, methylprednisolone, and rHuEPO. The timepoint for reporting FARS ranged from 4 to 26 weeks. The mean change from baseline for total FARS scores ranged from -6.1 at 26 weeks with A0001 0.75 g BID to +6.2 at 26 weeks with Deferiprone 40 mg. Treatment with rHuEPO and IFN-γ 1b resulted in a statistically significant decrease from baseline in FARS scores at 26 and 12 weeks, respectively. On the other hand, treatment with methylprednisolone did not show any significant improvement in FARS. Compared with placebo, A0001 improved FARS scores at four weeks, while deferiprone 40 mg worsened FARS scores at 26 weeks.

2.1.1.2.1.2 mFARS (0 to 93; higher scores indicate a higher severity/worse function)

mFARS was evaluated in six studies assessing five different treatments: IFN-γ 1b, methylprednisolone, RT001, luvadaxistat, and omaveloxolone. The timepoint for reporting FARS ranged from 12 to 48 weeks. The mean change from baseline in mFARS scores ranged from -3 at 12 weeks with placebo to +2.2 at 38 weeks with RT001. Compared with placebo, omaveloxolone 150 mg showed a statistically significant improvement in mFARS scores at 48 weeks.

2.1.1.2.1.3 Other Efficacy Outcomes

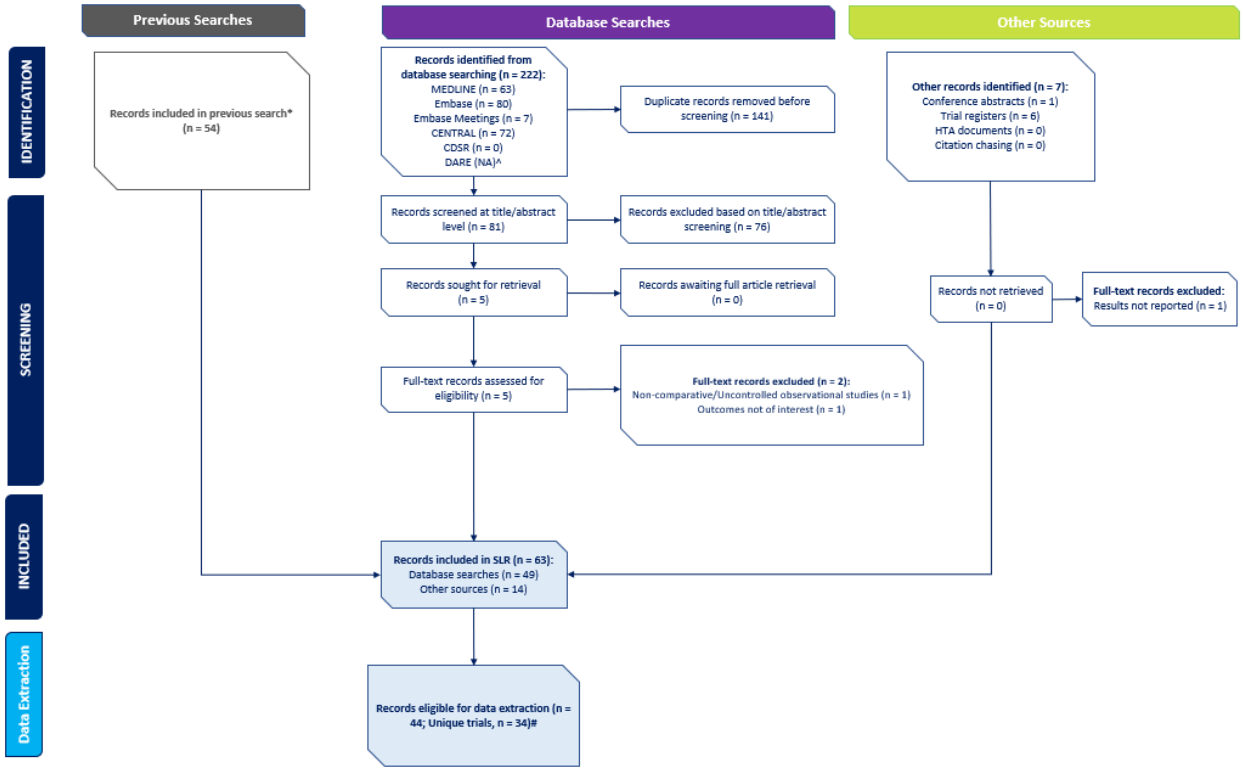
Overall, the results showed mixed findings in terms of the impact of different treatments on the various neurological and performance outcomes in patients with FRDA with some studies reporting statistically significant improvements in ataxia scores, while others did not show any meaningful difference. In the Di Prospero 2007 trial, patients receiving high dose idebenone had a statistically significant improvement in ICARS scores compared to placebo after 24 weeks of treatment. In the FRIEMAX trial, rHuEPO was associated with significantly lower SARA scores at week 48 compared to placebo. Additionally, omaveloxolone 150 mg

showed statistically significant improvement in FARS-ADL scores compared to placebo after 48 weeks of treatment in the MOXIe trial.

2.1.1.2.2 Safety

Safety outcomes were reported in 24 studies with assessment timepoints ranging from 2 to 52 weeks. The occurrence of treatment-emergent adverse events and treatment-related adverse events ranged from 0% to 96% across the different treatment arms, with 100% of patients treated with IFN-ɣ 1b, omaveloxolone, and placebo in the MOXIe – Part 2 study experiencing them. The occurrence of serious adverse events was reported in 16 studies, with higher than 10% of patients treated with idebenone and omaveloxolone experiencing them. In one study, treatment with deferiprone 60 mg/Kg/day was terminated prematurely because of worsening of ataxia in at least two patients.

Figure 1: PRISMA diagram of the clinical and efficacy SLR



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; SLR = Systematic literature review.

*Notes: *Corresponds to eligible records identified from previous systematic literature reviews conducted on June 5, 2023*

^The Database of Abstracts of Review of Effects (DARE) was discontinued in 2015; therefore, no updated search was needed

#Records eligible for extraction excluded observational studies, pooled analyses, and studies reporting data for vitamins/supplements/complementary medicine.

Source: Systematic Literature Reviews to Support HTA Submissions for Omaveloxolone in the Treatment of Friedreich Ataxia (Technical Report)

2.1.2 Health-related quality-of-life, utility, and economic literature

2.1.2.1 Methods

The following electronic literature databases were used to conduct systematic literature searches: MEDLINE and MEDLINE In-Process, Embase, CDSR, PsycINFO, CENTRAL, DARE, NHS EED, and EconLit. To strengthen the evidence collected in this SLR, grey literature searches on post-appraisal reports from several HTA bodies were also conducted. Details on the conducting of the search and search strings can be found in the supplied SLR report.

Table 5: Conducted electronic searches for three systematic literature reviews

Source (via OvidSP)	SLR 2: HRQoL and Utilities	SLR 3: Economic Burden	SLR 4: Economic Evaluations
MEDLINE and MEDLINE In-Process	✓	✓	✓
Embase	✓	✓	✓
CDSR	✓	✓	✓
CENTRAL	✓		
PsycINFO	✓		
DARE[a]	✓	✓	✓
NHS EED[a]		✓	✓
EconLit	✓	✓	✓

Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Review of Effects; HRQoL = healthcare-related quality of life; NHS EED = National Health Service Economic Evaluation Database

[a]The DARE and NHS EED were discontinued in 2015; therefore, only the archived databases (until 2015) were searched.

Studies were screened against predetermined population, interventions and comparisons, outcomes, and study design (PICOS) criteria to establish which studies were eligible for inclusion in the SLRs. Publications were excluded if they did not meet the selection criteria outlined in Table 1 or were published in a language other than English or German.

The screening followed a standard systematic two-step approach. In the first pass, each title and abstract were reviewed by two independent reviewers to determine its eligibility for inclusion in the SLR. Disagreements were resolved by a third reviewer, as necessary. No study was excluded at the title and abstract level solely because it provided insufficient information. For abstracts that were deemed relevant during title and abstract screening, the corresponding full-text articles were retrieved for further screening. In the second pass of screening, each full-text paper was reviewed by two independent reviewers. Disagreements were resolved by a third reviewer, as necessary. For each excluded study at full-text screening, a specific reason for the exclusion was selected.

After the completion of the study selection process, a list of records included/excluded was summarized in the SLR report and the flow of study selection was documented according to the PRISMA diagram (44).

Table 6: PICOS eligibility criteria for humanistic, economic, and economic evaluation literature reviews

Criteria	HRQoL and Utilities	Costs and HCRU	Economic Evaluations

Population	• Patients diagnosed with FA, including:
	  ○ Patients with FA categorized with pes cavus (i.e., with pes cavus and without pes cavus)
	  ○ Patients with FA diagnosed with cardiomyopathy and cardiac failure.
	• Mixed populations of patients with FA or other neurodegenerative disorder with results reported separately for the population of interest		

Interventions	Any interventions (or none required)	Any interventions (or none required)	Systemic agents recommended or currently under investigation for the treatment of FA*
Comparators	Any interventions (or none required)	Any interventions (or none required)	Systemic agents recommended or currently under investigation for the treatment of FA*

Outcomes	• HRQoL or utility weights assessed or mapped using the following instruments:
	  ○ SF-36
	  ○ SF-12
	  ○ PedsQL
	  ○ FSS
	  ○ EQ-5D
	• Direct utility or disutility weights assessed using standard gamble or time trade-off methods
		• Total costs (direct + indirect)
		• Direct costs
		• Indirect costs (i.e., productivity losses; absenteeism, presenteeism, WPAI score)
		• HCRU (i.e., healthcare visits, ED visits, hospitalizations, LOS)
			• Effectiveness measures LY/QALYs/DALYs
			• CERs/ICERs and NMB
			• Cost utility
			• Full economic evaluations (CEAs, CUAs, CBAs, CMA)
			• Budget impact analyses (total incremental budget impact)

Study Design	• Observational studies • Clinical trials[b]	Observational studies	Cost-effectiveness, cost-utility, cost-benefit, cost-minimization or cost-consequence analyses, budget impact models (BIMs)
Limits			
Period	• Full-text publications: None • Conference abstract: past two years (2021–2023)		
Geography	Any		
Language	• English • German		

Abbreviations: FA = Friedreich's ataxia; FSS = functional status scale; HCRU = healthcare resource utilization; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; PedsQL = paediatric Quality of Life; SF-12 = 12-item Short Form Health Survey; SF-36 = 36-item Short Form Health Survey

Notes: a) Originally planned to be captured as efficacy outcome; updated to align with trial's reporting, which categorizes the frequency of falls as an AE.

2.1.2.2 Results

2.1.2.2.1 Health related quality of life results

A total of 35 records (30 from the original search and 5 from SLR update #1) reporting on 33 unique studies were included in SLR 2. Three studies analyzed utilities and 31 analyzed HRQoL.

Eleven studies were conducted in the US, four in Italy, three in Australia, one in Canada, two in Spain, and one in the UK; the rest were multinational and included Europe, North America, and Australia. The studies enrolled patients between 2003 and 2022, in both children and adults. In 17 studies, the treatment for FRDA was reported. The most common treatments were idebenone and omaveloxolone.

2.1.2.2.1.1 Activities of Daily Living (ADL)

A total of 17 studies measured ADLs in FRDA. Among studies that assessed the impact of therapies, many either did not evaluate statistical differences or did not result in a significant change in ADL when compared to baseline or placebo. However, in one study, a statistically significant decline in ADL scores was observed in patients treated with deferiprone 40 mg compared with placebo. Other treatments resulted in minimal or no improvement.

2.1.2.2.1.2 36-item Short Form Health Survey (SF-36)

SF-36 was reported in 14 studies: Nine studies reported the mental and physical component summary scores (MCS and PCS). PCS scores varied from 15.8 to 39.2, while mean MCS scores ranged from 46 to 64.8.

2.1.2.2.1.3 Pediatric Quality of Life (PedsQL)

PedsQL was reported in three studies. Patients who needed a mobility device had a lower mean PedsQL score than those who did not, indicating worst HRQoL. Patients who received idebenone for 1 year did not show clear improvements in mean PedsQL score, i.e., no meaningful improvement in HRQoL

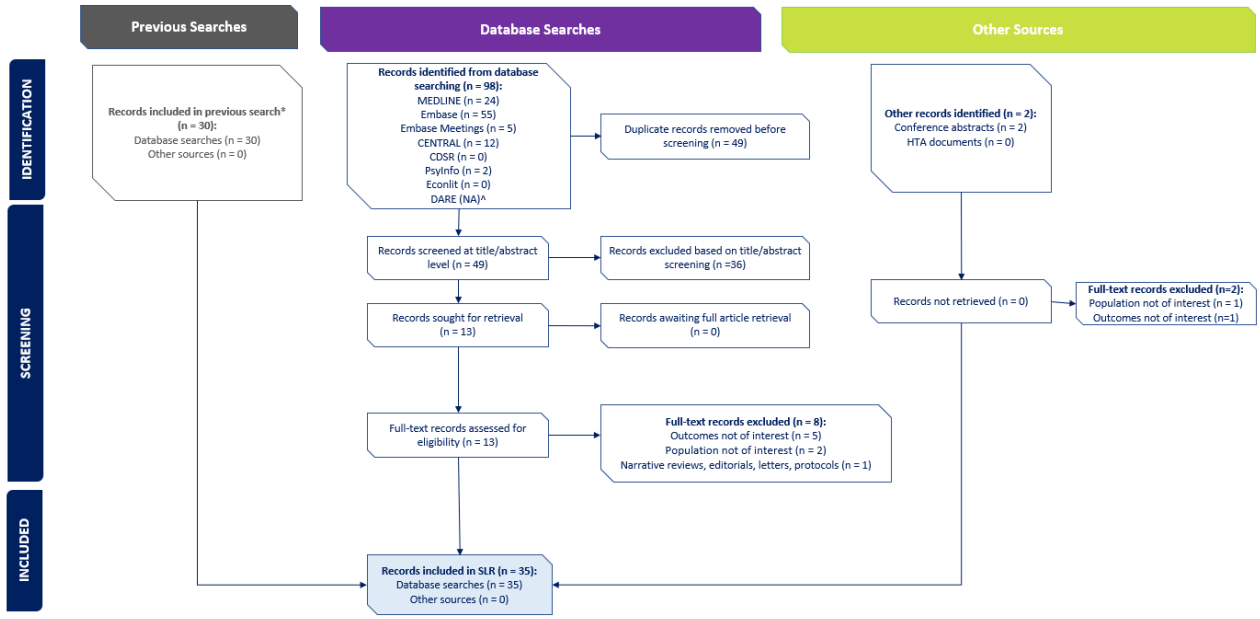
2.1.2.2.1.4 National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25)

HRQoL using NEI-VFQ-25 was described in one study. In this study, patients with FRDA were compared with a published control group from another study. Patients were shown to have a significantly lower visual function than the control group.

2.1.2.2.1.5 Utilities

Utility values were reported in four studies. The standard EQ-5D scores ranged from 0.57 to 0.67 at baseline and declined over time to 0.51 to 0.62 after 4 years. The annual progression rates in EQ-5D impairment were significant in the overall cohort and in the subgroup with early symptom onset. One study measured EQ-5D using a VAS and reported values ranging from 57.7 to 64.4 pre- and post-treatment with EPO or placebo.

Figure 2: PRISMA diagram of humanistic systematic literature review



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; FA = Friedreich's ataxia; HTA = health technology assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review

*Notes: *Includes eligible records identified from previous systematic literature review conducted on June 5, 2023*

^The Database of Abstracts of Review of Effects (DARE) was discontinued in 2015; therefore, no updated search was needed

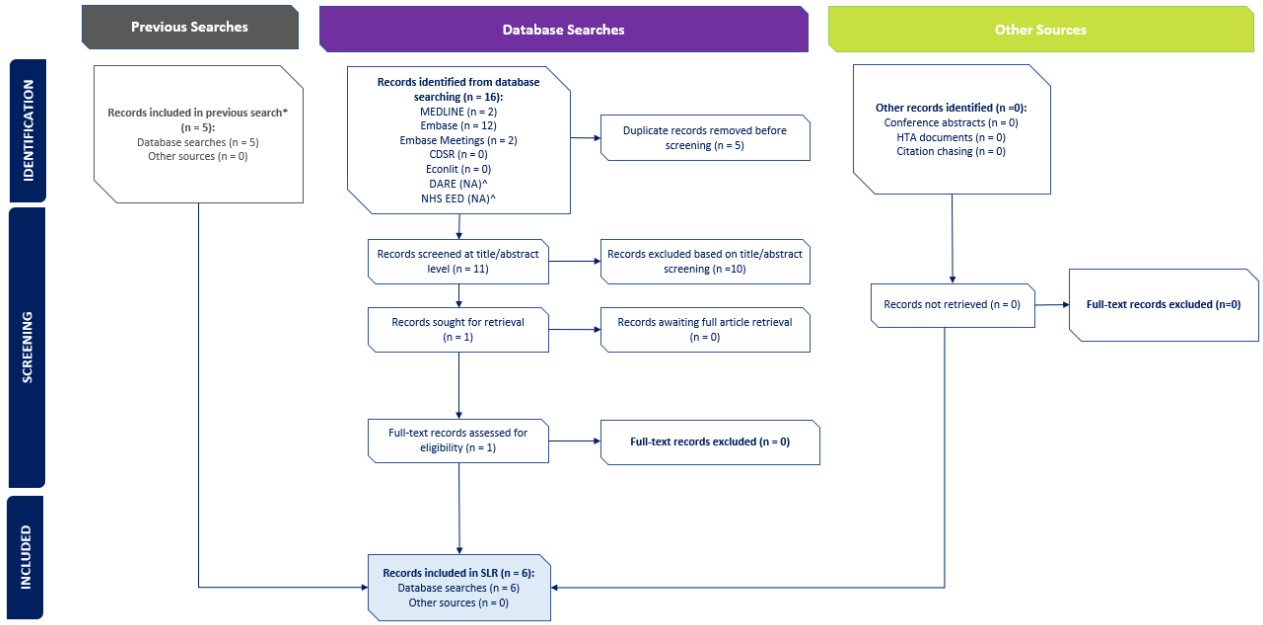
Source: Systematic Literature Reviews to Support HTA Submissions for Omaveloxolone in the Treatment of Friedreich Ataxia (Technical Report)

2.1.2.2.2 Economic burden results

A total of six studies (5 from the original search and 1 from the update) were included in SLR 3. These studies were conducted in the US, Canada, Spain, Germany, Ireland, and the UK, with cost years spanning from 1983 to 2016. Four studies reported healthcare resource utilization (HCRU) data among patients with FRDA, revealing a high burden of frequent consultations, inpatient stays, prescription and nonprescription drugs, diagnostic tests, and hospitalizations. Five studies reported cost data among patients with FRDA, but with heterogeneous methods and results, making it difficult to compare between studies. For instance, in Ireland, the total direct costs of FRDA were estimated to be €33,087 per person per year, whereas mean healthcare costs for patients with FRDA in the US and Canada were USD $12,850 and CAD $34,683, respectively. In the UK, the total annual direct medical costs were £242,314 (nationwide). The total annual indirect costs in the

UK, including work loss and caregiver support, amounted to £14,821 per person. In Ireland, the average annual indirect costs were €45,408 per person, encompassing productivity loss and caregiver assistance. Home modification costs were reported in two studies, with a total cost of €7,252 and €15,820 per person.

Figure 3: PRISMA diagram of economic burden systematic literature review



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; FA = Friedrich's ataxia; HCRU = Healthcare Resource Utilization; HTA = Health Technology Assessment; NHS EED = National Health Service Economic Evaluation Database; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review

*Notes: *Includes eligible records identified from previous systematic literature review conducted on June 5, 2023*

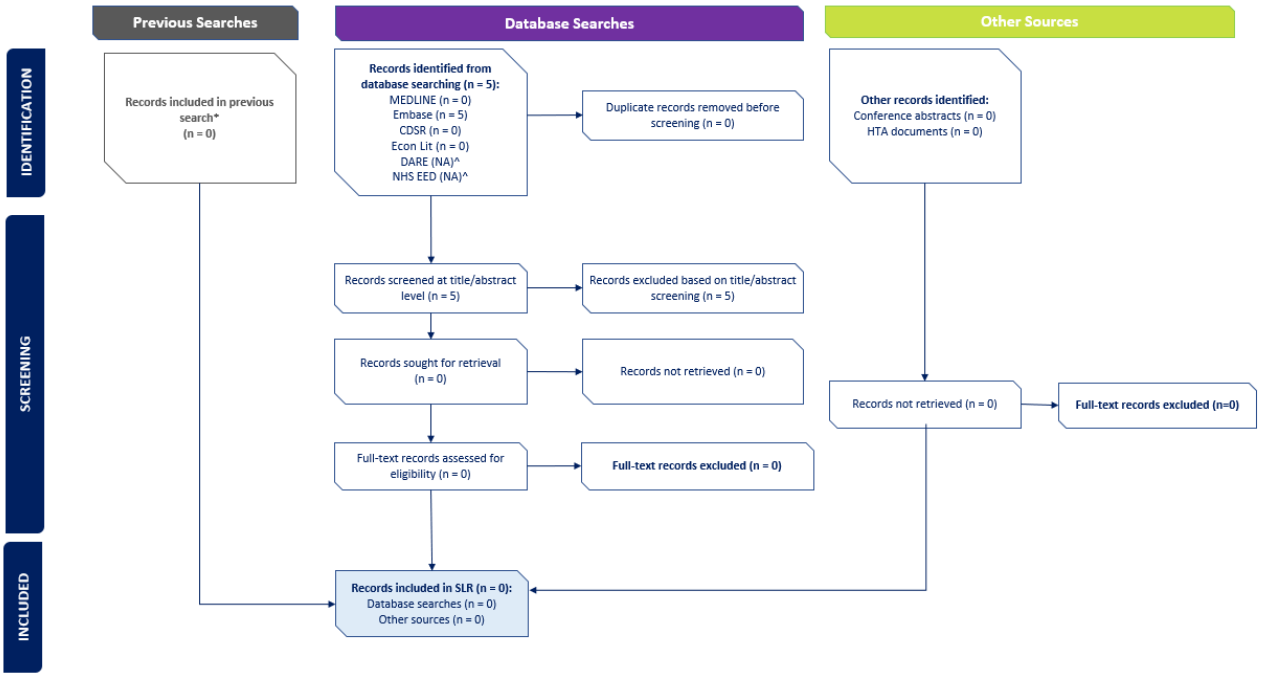
^The Database of Abstracts of Review of Effects (DARE) and the National Health Service Economic Evaluation Database (NHS EED) were discontinued in 2015; therefore, no updated searches were needed

Source: Systematic Literature Reviews to Support HTA Submissions for Omaveloxolone in the Treatment of Friedreich Ataxia (Technical Report)

2.1.2.2.3 Economic evaluations results

A total of 28 unique records (23 from the original search and 5 from the update) were retrieved from the database searches and screened for eligibility. None of the records met the inclusion criteria of this SLR.

Figure 4: PRISMA diagram of economic evaluations systematic literature review



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; HTA = health technology assessment; NHS EED = National Health Service Economic Evaluation Database; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review

*Notes: *No eligible records were identified from previous systematic literature review conducted on June 5, 2023*

^The Database of Abstracts of Review of Effects (DARE) and the National Health Service Economic Evaluation Database (NHS EED) were discontinued in 2015; therefore, no updated search was needed.

Source: Systematic Literature Reviews to Support HTA Submissions for Omaveloxolone in the Treatment of Friedreich Ataxia (Technical Report)

2.1.3 Conclusions from literature reviews

The SLR on efficacy outcomes showed that the current treatments for FA are suboptimal, highlighting the urgent unmet need for the development of efficacious and safe treatments for this indication. Omaveloxolone has emerged as a promising candidate for the treatment of FA, as it has shown sustained long-term benefit and favourable safety profile. Despite the limited data availability, studies assessing the HRQoL outcomes, costs and HCRU implications of FA impact have shown the increased economic and humanistic burden associated with the disease. More research using real-world data is warranted to draw meaningful insights into the economic burden and the HRQoL utilities among FA patients and their caregivers.

2.2 Clinical efficacy evidence

2.2.1 Summary of identified studies relevant for establishing relative efficacy

The pivotal studies supporting the efficacy of omaveloxolone evaluated in the health economic model includes the MOXIe part 1, 2 and their open label extension (OLE) and are summarised as required by the template for this submission in Table 7. The study design and the analyses conducted are described in Section 2.2.3.

Table 7: Summary of clinical studies relevant for establishing relative efficacy.

MOXIe part 1 (46, 47)	
Study ID (NCT number)	NCT02255435
Study design	Phase 2: International, randomized, placebo-controlled, dose-ranging trial.

Study location(s)	United States, Australia, Austria, Brazil, Italy, United Kingdom
Population important inclusion and exclusion criteria, stratification factors, n	Inclusion criteria: Genetically confirmed Friedreich's ataxia, ≥ 16 and ≤ 40 years of age, Modified Friedreich's Ataxia Rating Scale (mFARS) score ≥ 10 and ≤ 80, and ability to complete maximal exercise testing. Exclusion criteria: Uncontrolled diabetes, increased B-type natriuretic peptide, history of clinically significant cardiac disease.
Intervention	Omaveloxolone capsules at 2.5 - 300 mg or placebo once daily.
Comparator	Eligible patients (n=69) were randomized (3:1) to omaveloxolone capsules (various doses) or placebo for 12 weeks.
Primary endpoint	Primary endpoint: Neuromuscular abilities measured as change from baseline in peak work (in Watts/kg) during exercise testing at week 12 using a stationary bicycle.
Important secondary endpoint(s)	Key secondary endpoint: Neurological abilities assessed by change in mFARS at Week 12. Exploratory endpoints: Performance measures (the timed 25-foot walk test, nine-hole peg test, low contrast vision, assessed at baseline and 12 weeks). Health related quality of life (SF-36 Health Survey Update, assessed at baseline and Week 12). Pharmacodynamic parameters: protein and enzyme (AST, GGT, CK, and ferritin) levels in serum samples, and assessment of platelet metabolism. Pharmacokinetic measures: Omav plasma concentration levels. Safety parameters: weight, BMI, vital sign measurements, physical examinations, laboratory test results, concomitant medications, adverse events, and serious adverse events
Observation time	Participants from this study were offered to continue in MOXIe open label extension study.
Data cuts primary analysis and later planned analyses	Current data cut: 13.06.2017 Final analysis: 29.09.2020
Was the study part of the EMA MA approval process relevant for this STA?	☒ check if yes
MOXIe part 2 (46, 48)	
Study ID (NCT number)	NCT02255435
Study design	Phase 2: International, double-blind, placebo-controlled, randomized, registrational trial.
Study location(s)	United States, Europe, and Australia
Population important inclusion and exclusion criteria, stratification factors, n	Inclusion criteria: Genetically confirmed Friedreich's ataxia, ≥ 16 and ≤ 40 years of age, mFARS score ≥ 20 and ≤ 80, and ability to complete maximal exercise testing. Patients with severe pes cavus were included in the study but limited to 20% of subjects enrolled. Exclusion criteria: Uncontrolled diabetes, clinically significant cardiac disease, active infections, significant laboratory abnormalities, or interfering medical conditions.
Intervention	Omaveloxolone capsules, 150 mg, once daily.
Comparator	Eligible patients were randomized (1:1) to omaveloxolone capsules 150 mg (n=51) or placebo (n=52) for 48 weeks. Randomization was stratified by pes cavus status (with / without pes cavus) based on findings from MOXIe Part 1.
Primary endpoint	Primary endpoint: Change in mFARS at Week 48.

Important secondary endpoint(s)	Secondary endpoints: Patient Global Impression of Change [PGIC], Clinician Global Impression of Change [CGIC], 9-hole peg test [9-HPT], Timed 25-foot walk test [T25-FW], Frequency of falls, Peak work during maximal exercise testing, SF-36, Activities of Daily Living [FA-ADL] score. Other endpoints: Vital signs, electrocardiograms, and the frequency and severity of adverse events.
Observation time	Participants from this study were offered to continue in MOXIe open label extension study.
Data cuts **primary analysis and later planned analyses**	Current data cut: 31.19.2019 Final analysis: 05.11.2020
Was the study part of the EMA MA approval process relevant for this STA?	☒ check if yes
MOXIe, Open Label Extension Study (46, 49)	
Study ID (NCT number)	NCT02255435
Study design	Phase 2: Open-label extension study for patients with FA who completed MOXIe Part 1 or Part 2.
Study location(s)	United States, Austria, United Kingdom, Italy, and Australia[c]
Population **important inclusion and exclusion criteria, stratification factors, n**	The study includes all patients following completion of Study 1, Part 1 (n=57) and Part 2 (n=92), regardless of randomized treatment, after a 4-week drug washout period.
Intervention	Omaveloxolone capsules, 150 mg, once daily.
Comparator	Open label with no comparator group. 2 groups: Omaveloxolone-omaveloxolone: those who were randomized to omaveloxolone in MOXIe part 2 and then continued with omaveloxolone in the open-label extension. Placebo-omaveloxolone: those originally randomized to placebo in part 2 who then initiated treatment with omaveloxolone in the open-label extension.
Primary endpoint	Safety/tolerability: Results from physical examinations, laboratory results, vital sign measurements, weights, AEs, SAEs, concomitant medications, pregnancy tests. Sustained efficacy: mFARS, ADL, 9-HTP, T25-FW Delayed start analysis: To evaluate the persistence of omaveloxolone treatment effect by comparing the difference in mFARS scores at the end of the 48-week placebo-controlled period with the difference after 72 weeks (up to 144 weeks) in the open-label extension.
Important secondary endpoint(s)	
Observation time	Study continuation until commercially availability of omaveloxolone. A delayed start analysis after 72 weeks (up to 144 weeks) is published.
Data cuts **primary analysis and later planned analyses**	17.08.2021 interim clinical study report 24.03.22 data cut used for the propensity score matching analysis
Was the study part of the EMA MA approval process relevant for this STA?	☒ check if yes

[c] RTA 408: Post hoc propensity-matched analysis of study 408-C-1402 extension and natural history; section 2.2

Abbreviations: AST = Aspartate aminotransferase; BMI = Body max index; CK= Creatine kinase; EMA = European Medicines Agency; FA = Friedreich's ataxia; GGT = Gamma-glutamyl trasferase; MA = Marketing authorisation; ID = Identification number; mFARS = Modified FA rating scale; STA = Single technology assessment.

2.2.2 Summary of relevant supportive studies.

2.2.2.1 FA-COMS

The ongoing FA-COMS study (NCT03090789) is the largest, global, multicentre, prospective natural history study in FA. The study began enrolling patients in 2003 and is ongoing and currently enrolling, with more than 1,000 patients enrolled to date. The time period of FA-COMS overlaps with MOXIe trial Part 2; the first patient enrolled in the Part 2 pivotal portion of the study in October 2017 and the last Part 2 patient visit was completed by October 2019, when the OLE phase was still ongoing.

Patients are evaluated annually on clinical measures, including FARS and mFARS, other neurologic outcomes, and quality-of-life assessments. All sites received training on the protocol and collection of FARS and other assessments, as well as data entry into standardized case report forms. Principal investigators meet every 3 to 6 months to review the overall conduct of the study, data analysis, results and findings, publications, and study-related issues (49)[d].

Table 8: Summary of relevant supportive studies.

FA-COMS (22)		
Study ID (NCT number)	NCT03090789	
Study design	A global, multicentre, longitudinal, prospective, observational, natural history study of ≥1,250 patients with FA	
Study location(s)	United States and Australia[e]	
Population **important inclusion and exclusion criteria, stratification factors, n**	Individuals with either a clinical diagnosis or genetic confirmation of FA. Exclusion criteria: Signs or symptoms of severe cardiomyopathy (such as congestive heart failure)	
Intervention	-	
Comparator	-	
Primary endpoint	FARS	
Important secondary endpoint(s)	SF-36	
Observation time	ClinicalTrials.gov date "first posted" 27.03.2017	
Data cuts **primary analysis and later planned analyses**	24.03.2021[f]	
Was the study part of the EMA MA approval process relevant for this STA?		☒ check if yes

Abbreviations: EMA = European Medicines Agency; FA = Friedreich's ataxia; FARS: Friedreich's Ataxia Rating Scale; MA = Marketing authorisation; SF-36 = 36-item Short Form Health Survey; STA = single technology assessment.

2.2.2.2 EFACTS

The EFACTS patient registry is a multi-centre, multi-national observational study including patients with genetically confirmed FA seen annually at 16 clinical centres in several European countries.

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[d] *RTA 408: Post hoc propensity-matched analysis of study 408-C-1402 extension and natural history; section 2.2*

[e] *RTA 408: Post hoc propensity-matched analysis of study 408-C-1402 extension and natural history; section 2.2*

[f] *RTA 408: Post hoc propensity-matched analysis of study 408-C-1402 extension and natural history; section 3.2*

Table 9: Summary of relevant supportive studies.

EFACTS (21)	
Study ID (NCT number)	NCT02069509
Study design	A multi-national, prospective, observational, natural history study of ≥1,200 patients with FA
Study location(s)	Europe (Austria, Belgium, Czechia, France, Germany, Greece, Ireland, Italy, Spain and the UK).
Population important inclusion and exclusion criteria, stratification factors, n	Individuals with genetic confirmation of FA. For control group, genetically confirmed absence of FA. Exclusion criteria: Signs or symptoms of severe cardiomyopathy (such as congestive heart failure)
Intervention	-
Comparator	-
Primary endpoint	Disease progression by clinical examination (SARA)
Important secondary endpoint(s)	ADL, EQ-5D
Observation time	ClinicalTrials.gov date "first posted" 24.02.2014
Data cuts primary analysis and later planned analyses	N.R
Was the study part of the EMA MA approval process relevant for this STA?	☐ check if yes

Abbreviations: EMA = European Medicines Agency; FA = Friedreich's ataxia; FARS: Friedreich's Ataxia Rating Scale; MA = Marketing authorisation; N.R = Not reported; SF-36 = 36-item Short Form Health Survey; STA = single technology assessment.

2.2.3 Clinical study design and analysis

2.2.3.1 MOXIe part 1 and 2

MOXIe Part 1 was a 12-week, dose-ranging study designed to determine the safety, pharmacodynamics, and potential benefits of omaveloxolone in 69 patients with FA (50). The study concluded that a 160 mg dose of omaveloxolone was optimal for safety, efficacy, and pharmacokinetics. Omaveloxolone is available as 2.5, 10, or 50 mg capsules, and a dose of 150 mg was therefore selected for further investigation in Part 2 because it was expected to provide a similar pharmacologic response to 160 mg while also reducing the number of capsules patients are required to take each day (47).

MOXIe Part 2 was a multicentre, double-blind, placebo-controlled, randomised, parallel-group Phase 2 trial conducted at 11 clinical sites across Australia, Europe, and the United States (51). Eligible participants aged 16–40 years with genetically confirmed FA were assigned in a 1:1 ratio to receive either 150 mg omaveloxolone daily (n=51) or placebo (n=52) for 48 weeks. A follow-up safety visit was conducted at Week 52 (4 weeks after the final dose). The primary outcome was the change from baseline in mFARS at Week 48 and key secondary outcomes included fall frequency, patient, and clinician assessment of improvement (PGIC, CGIC), activities of daily living (ADL) and SF-36 Health Survey Update.

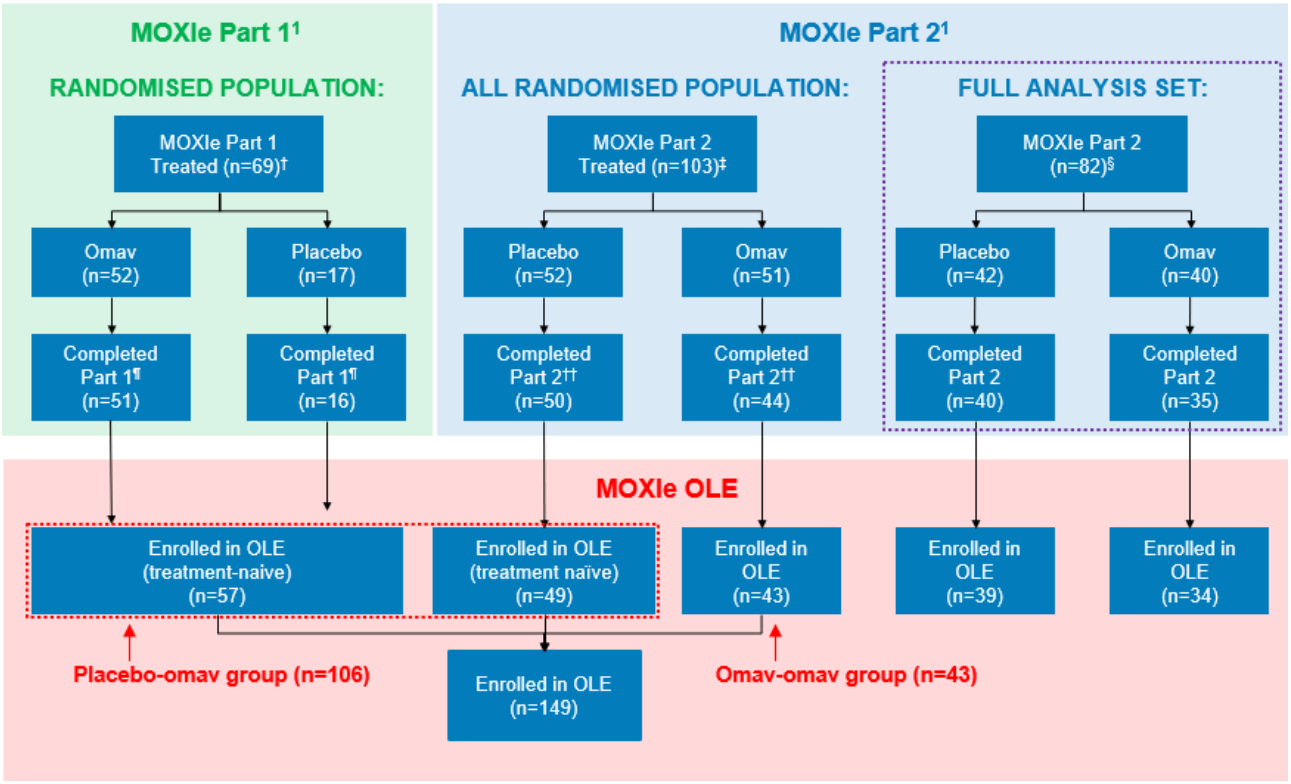
Mixed models repeated measures (MMRM) was used to analyse the change from baseline mFARS compared to placebo at week 48 collected in Part 2. The MMRM used site and baseline mFARS as covariates, and the following fixed factors: treatment group, time, the interaction between treatment and time, and the interaction between baseline and time. The analysis used post-baseline mFARS values collected through 48 weeks (6 repeated measurements at weeks 4, 12, 18, 24, 36, and 48) as the response.

An unstructured covariance matrix was assumed to model the within-subjected variance–covariance errors and values for missing data were not imputed in the primary analysis of efficacy.

2.2.3.2 MOXIe OLE

The MOXIe OLE assessed the long-term (144 weeks) safety and tolerability of omaveloxolone in patients completing the Part 1 and 2 studies (no patient enrolled in Part 1 participated in Part 2). All patients received omaveloxolone 150 mg/daily (n=149). As patients from MOXIe Part 1 had only received the study drug for 12 weeks and had been off treatment for at least 12 months prior to enrolling in the OLE, these patients were considered treatment-naïve at enrolment in the OLE.

Figure 5 MOXIe part 1 and 2, and OLE trial patient flow.



Abbreviations: OLE = Open label extension

Notes: †All 69 patients enrolled in the study and who received at least one dose of study drug. ‡All patients who received at least one dose of randomised study drug. §All patients enrolled without pes cavus who had at least one post-baseline measurement (whether they received study drug). ¶Completed 12 weeks of treatment. ††Completed Week 48 on treatment and had a Week 52 visit. Continuation/termination of OLE at database lock on 17th August 2021

Source: Lynch (2019)(50), Reata Pharmaceuticals (2021)(52)

2.2.3.3 Delayed-start analysis.

To assess whether omaveloxolone had a persistent effect on FA disease course, a post hoc 'delayed-start' analysis was conducted across MOXIe Part 2 and the MOXIe OLE. For both the MOXIe part 2 and the OLE, the main outcome was change in mFARS from baseline. The key outcome of the delayed-start analysis was the difference in this outcome between treatment groups in the 'delayed-start period' (OLE week 72) versus the 'placebo-controlled period' (MOXIe part 2 week 48). The difference between the omaveloxolone-omaveloxolone and the placebo-omaveloxolone cohort is based on results from patients that were randomised to receive placebo in MOXIe part 2 and then received omaveloxolone in the OLE (n=106), versus those randomised to receive omaveloxolone in MOXIe part 2 and then continued receiving omaveloxolone in the MOXIe OLE (n=43).

The persistence of a separation between treatment groups is assessed by comparing the difference between groups at the end of the 'placebo-controlled period', with the difference between groups in the 'delayed-start period'. In symptomatic treatment, it is expected that after the delayed-start, there will be no difference between the early start and the delayed start group. However, with a disease-modifying treatment, it is expected that there will be a difference in outcomes after the delayed-start due to a persistent treatment effect.

An MMRM model was fit using all available data from both MOXIe part 2 and the OLE through to OLE week 144 for the non-inferiority analysis. This MMRM model included treatment, time, and the interaction of treatment and time as fixed factors, as well as baseline mFARS, study site, and the interaction of baseline mFARS and time as covariates. The difference in mFARS between treatment groups was estimated using the MMRM estimates the end of the MOXIe part 2 and the OLE.

2.2.4 Summary of relevant ongoing studies

Omaveloxolone is currently being evaluated in a paediatric population in a phase 1 study This trial is not relevant for this STA but was included for completeness and transparency. In addition, an international phase 3 trial in the paediatric population is planned to start between July-September 2024

Table 10: Summary of relevant ongoing studies

A Study of Omaveloxolone in Children With Friedreich's Ataxia (53)	
Study ID (NCT number)	NCT06054893
Study design	Open-label, phase 1 study to evaluate the pharmacokinetics, safety, and tolerability of a single-dose of omaveloxolone in children. Non-randomized, sequential assignment.
Study location(s)	USA (Children's Hospital of Philadelphia)
Population ***important inclusion and exclusion criteria, stratification factors, n***	Children of ≥2 to <16 years of age with FA (20 participants, still recruiting)
Intervention	Omaveloxolone
Comparator	None
Primary endpoint	• Apparent clearance (CL/F) of omaveloxolone • Maximum concentration (Cmax) of omaveloxolone • Volume of distribution (V/F) of omaveloxolone • Area under the plasma concentration-time curve from 0 to extrapolated infinity of omaveloxolone • Area under the plasma concentration-time curve from 0 to t_{last} of omaveloxolone • Area under the plasma concentration-time curve from 0 to 24 hours of omaveloxolone
Key secondary endpoints	N/A
Primary data cut	
Estimated completion date	February 1st, 2024
Relevance of this study for the decision problem	Potential indication expansion

Abbreviations: FA: Friedreich's Ataxia, CL/F: apparent clearance, Cmax: maximum concentration, V/F: volume of distribution

Sources: Clinical trial.gov (53)

2.3 Clinical evidence synthesis

2.3.1 Background

In MOXIe Part 2, omaveloxolone delayed disease progression with a significant difference in mFARS scores at 48 weeks (51) and had a persistent effect on disease course over 144 weeks in patients from MOXIe Part 2, who went on to participate in the MOXIe OLE trial, highlighting the importance of early treatment (51, 54, 55). Accruing data in the MOXIe OLE trial provided longer-term follow-up for disease progression in patients receiving omaveloxolone and ensures a comprehensive use of all available data relating to the efficacy of omaveloxolone; however, there is no long-term placebo arm for comparison. The ICH E10 (56, 57) and the

NICE Decision Support Unit (57) discuss considerations in the choice of an appropriate external control and methods for replicating randomisation in an external control. Based on this guidance, the MOXIe OLE trial data were formally compared to natural history external controls using propensity matching to provide longer term efficacy data in support of the statistically significant benefit demonstrated by the MOXIe part 2 trial.

Propensity score matching is used to replicate randomisation by identifying control individuals which are similar to the treated individuals based on propensity score. It allows for comparison of the outcomes between individuals who differ in treatment effect but are very similar in other characteristics. The methodology is elaborately described by the decision support unit of NICE in a technical support document (57).

2.3.2 Objective

Following ICH E10 and NICE DSU guidance, to ensure a comprehensive use of all available data relating to the efficacy of omaveloxolone, a 1:1 propensity score matched analysis was performed. This allows comparing the progression of mFARS in treated patients from the MOXIe trials with the natural progression of mFARS in untreated patients derived from the FA-COMS database, over 3 years.

The objective was to evaluate the efficacy of omaveloxolone in the MOXIe OLE trial using the FA-COMS as external comparator. The primary efficacy endpoint was the change from baseline in mFARS score at year 3. The secondary endpoints were the changes from baseline in mFARS at year 1 and 2.

2.3.3 Methods

2.3.3.1 Data and comparability

The MOXIe OLE was conducted in 11 sites in 5 countries, including United States, Austria, United Kingdom, Italy, and Austria. Of these, 8 sites, accounting for 84% of patients enrolled in MOXIe OLE were active sites for the FA-COMS study. Given the significant overlap between study sites, the SoC is expected to be similar for patients in both studies. Furthermore a few investigators from both FA-COMS and MOXIe trials took part in the development of international FA SoC guidelines (39). The time period for FA-COMS also overlaps with the MOXIe trials.

Further supporting the comparability of studies, key enrolment criteria in both studies ensured inclusion of a similar cohort, namely males and females, approximately 16 to 40 years of age with genetically confirmed FA. Although mFARS was not an enrolment criterion for either the MOXIe OLE trial or the FA-COMS, the propensity-matched scoring included baseline mFARS as a parameter for identifying the external control cohort. The key inclusion criteria of the two studies are compared in Table 11.

Table 11: Key inclusion and exclusion criteria in MOXIe OLE and FA-COMS studies

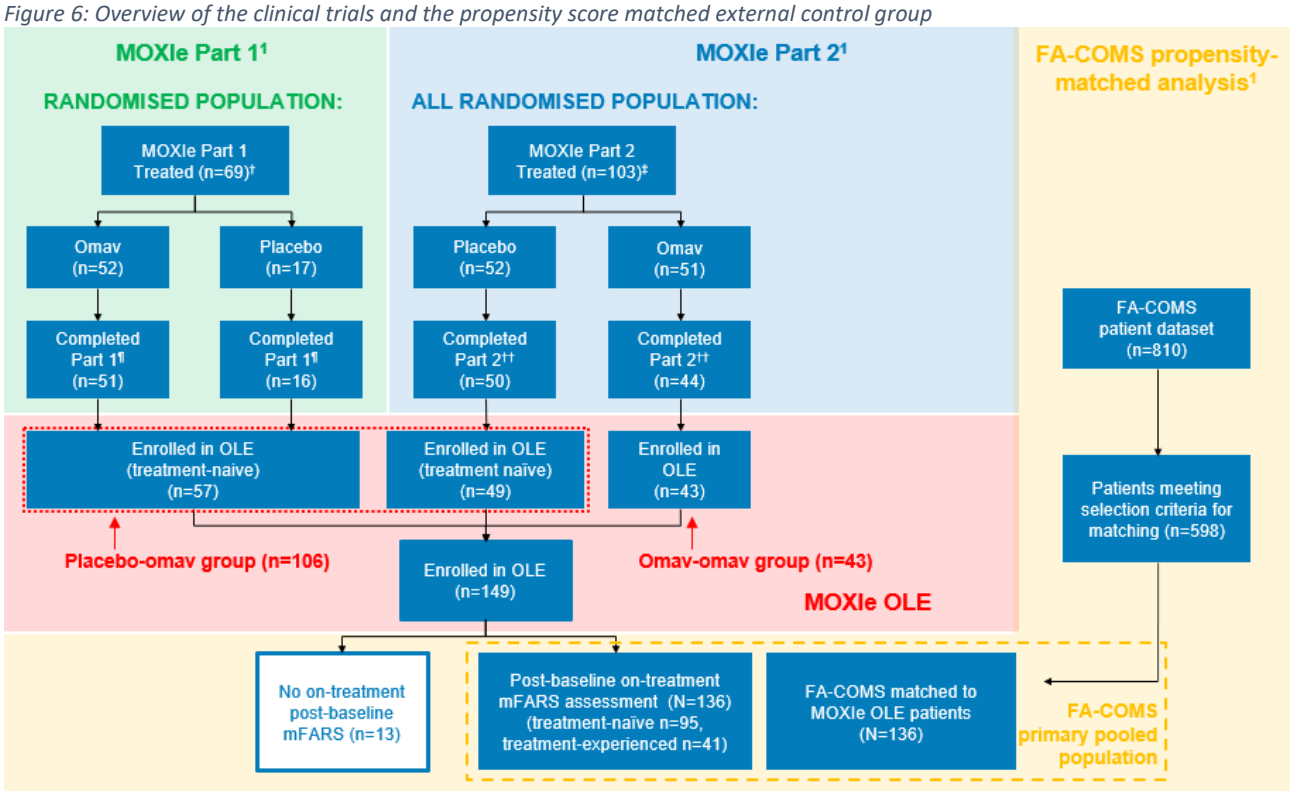
	MOXIe OLE	FA-COMS
Inclusion criteria	• Male or female who completed treatment in MOXIe Part 1 or 2 which enrolled patients ≥16 years of age and ≤40 years of age. • Genetically confirmed FA	• Male and female children and adults of any age, includes cohort patients ≥16 years of age and ≤40 years of age. • Genetically confirmed diagnosis of FA
Exclusion criteria	• History of clinically significant left-sided heart disease and/or clinically significant cardiac disease • Uncontrolled diabetes (HbA1c >11.0%) • B-type natriuretic peptide value >200 pg/mL	

	• Cognitive impairment that may preclude ability to comply with study procedures	

Abbreviations: FA = Friedreich ataxia; HbA1c = glycated hemoglobin; mL = milliliters; pg = picogram.

Source: Report Post hoc propensity-matched analysis of study 408-C-1402 Extension and Natural History (49)

Figure 6: Overview of the clinical trials and the propensity score matched external control group



Abbreviations: FA-COMS = Friedreich's Ataxia Clinical Outcome Measures; mFARS= modified Friedreich Ataxia Rating Scale; OLE = open-label extension; omav= omaveloxolone.

Notes: †All 69 patients enrolled in the study and who received at least one dose of study drug. ‡All patients who received at least one dose of randomised study drug. §All patients enrolled without pes cavus who had at least one post-baseline measurement (whether or not they received study drug). ¶Completed 12 weeks of treatment. ††Completed Week 48 on treatment and had a Week 52 visit.

2.3.3.2 **Statistical analysis**

For this analysis, data from the 24 March 2022 interim database lock for the MOXIe OLE were used. The FA-COMS dataset, which contains de-identified patient level data from 810 patients who consented to have their data shared outside of the core FA-COMS study, was current as of 24 March 2021.

The study populations were derived from the full MOXIe OLE dataset (n=149) and the full FA-COMS dataset (n=810), as displayed in

Figure 6. For inclusion in the study patients must have had i) baseline mFARS, ii) at least one post-baseline mFARS within 3 years after baseline, and iii) values for all propensity score model covariates (i.e., sex, baseline mFARS score, age at baseline, age of FA onset, and baseline gait score).

Table 12: Alignment between MOXIe OLE and FA-COMS

Aspect	
Definition of endpoints	mFARS was collected in both studies
Statistical analysis (including estimand, how intercurrent events and missing data were addressed)	A post hoc comparative analysis was conducted using propensity score matched patients from FA-COMS as untreated external control groups. Specifically, patients from FA-COMS were matched to MOXIe OLE trial patients using propensity scores based on multiple covariates: sex, baseline age, age of FA onset, baseline mFARS score, and baseline gait score. Selection of these covariates was based on clinical relevance (i.e., factors considered prognostic for FA progression) and availability in both studies. The change in mFARS from baseline at year 3 for MOXIe OLE patients compared to the matched FA-COMS patients was analysed as primary efficacy endpoint using MMRM analysis.
Duration of follow-up	3 years (in line with MOXIe OLE)
Which countries are covered	*MOXIe:* United States, Austria, United Kingdom, Italy, Australia *FA-COMS:* United States, Australia, New Zealand, Canada, India

Abbreviations: mFARS: modified Friedreich's Ataxia Scale, FA-COMS: Friedreich's Ataxia Clinical Outcome Measures, OLE: open label extension, MMRM: mixed model repeated measures

Source: Report Post hoc propensity-matched analysis of study 408-C-1402 Extension and Natural History (49)

2.3.3.3 Propensity score matching

Propensity score matching aims to mimic some of the characteristics of a randomized study, allowing to estimate longer term efficacy than the placebo control period, leveraging data from the treated population in MOXIe OLE trial and the FA-COMS database as control, as described in section 2.3.1. The observed covariates used for determining propensity scores are controlled for in patients having the same propensity score. Differences between the MOXIe trial and FA-COMS groups should therefore be accounted for and are likely not a result of the observed covariates. Computation of the propensity score was coupled with diagnostics to assess the adequacy of matching techniques that were used at the analysis stage. The matching was carried out as optimal 1:1 matching without replacement.

Several assumptions were made when creating the analysis populations for the proposed design and propensity score computation. The first assumption is the 'strongly ignorable treatment assignment' (58) meaning that the treatment assignment must be independent of the change from baseline in mFARS score over time given the covariates used in the analysis. There is a positive probability of being in the omaveloxolone or the FA-COMS population, meaning the propensity score estimated from the logistic regression model must be strictly greater than 0 and less than 1 (also described as the assumption of positivity). The second assumption is the stable-unit treatment value assumption (59), meaning that the outcomes of one individual are not affected by the group assignment of another. These assumptions were met in this analysis approach using propensity scores.

2.3.3.4 Computation of propensity score

The propensity score was estimated using logistic regression with covariates. The criteria for determining model fit were different from those of a standard logistic regression analysis, as the goal of a propensity score analysis is to create balance in key covariates across the MOXIe OLE trial patients and the FA-COMS patients,

and not to estimate a treatment effect. Omission of covariates that are potentially related to the outcome could increase the bias, arguing for a strategy of including more, rather than fewer, covariates in the model.

Factors established as prognostic and available in both studies were selected as covariates for the logistic regression model used for determining propensity scores. Some factors, such as GAA1 repeat, have been determined to be prognostic but were not available for all patients. Notably, the presence of pes cavus was not a matching criterion for the FA-COMS external cohort as it was not systematically evaluated in the same manner as Study 1402 Extension or available for all patients. The covariates included in the logistic regression model to calculate propensity scores are summarized in Table 13. Further details on the methods of the propensity score matching is supplied in the publication (see Appendix C: Publication of propensity matched analysis).

Table 13: Covariates included or considered in the propensity score analysis

Logistic regression covariate	Rationale for inclusion	Number (%) of FA-COMS patients with data (n=810)	Number (%) of MOXIe OLE trial patients with data (n=149)
Age	Age is the primary determinant of phenotypic severity (20)	807 (99.6%)	149 (100%)
Age of FA onset	Surrogate for relative rate of progression and GAA repeat length(20)	801 (98.9%)	149 (100%)
Sex	Sexual dimorphisms inconsistently observed in ataxia studies (Klockgether, Lüdtke et al. 1998, Friedman, Farmer et al. 2010)	810 (100%)	149 (100%)
Gait score at baseline	Allows matching of patients at the same level of function (60)	790 (97.5%)	149 (100%)
mFARS score at baseline	Allows matching of patients at the same level of function(60)	789 (97.4%)	149 (100%)
Other covariates considered but not included			
GAA1 repeat length	Not included	745 (92.0%)	131 (87.9%)
Pes caves	Not included	432 (53.3%)	149 (100%)

[a]The definition of pes cavus between the 2 studies was not consistent. Pes cavus was based on clinical judgment in FA-COMS; however, MOXIe OLE trial 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.

Abbreviations: FA: Friedreich's Ataxia, FA-COMS: Friedreich Ataxia Clinical Outcome Measures, OLE: open label extension, mFARS: modified Friedreich's Ataxia Scale; GAA= Guanosine-adenosine- adenosine

Source: Report Post hoc propensity-matched analysis of study 408-C-1402 Extension and Natural History (49)

The change from baseline in mFARS scores was assessed over 3 years in all patients from the OLE and according to treatment history (omaveloxolone-omaveloxolone and placebo-omaveloxolone groups). Each analysis population was based on a new propensity score match.

Sensitivity analysis was performed based on a subset of the FA-COMs population having baseline mFARS and age within the range observed in MOXIe OLE (mFARS 8 to 74 and age 16 to 40).

The propensity score is a linear combination of the covariates requiring that patients have a similar propensity score rather than a caliper match on a full group of covariates. Computation of the propensity score was coupled with diagnostics to assess the adequacy of matching techniques used as described in Table 14.

Table 14: Diagnostic measures to assess the adequacy of matching techniques

Aspect	Diagnostic	Source
Standardized difference of the means of the propensity score	A B-value of less than 0.5 indicating a good match	Rubin (2006) (61)
Standardized difference of the means of each covariate	A B-value of less than 0.5 indicating a good match	
Ratio of the variances of the propensity score	A B-value between 0.8 and 1.25 indicating a good match. Values ranging from 0.5 to 2 are listed in Stuart (2010) and in the software documentation (SAS) as acceptable.	Rubin (2006), Stuart (2010) (61, 62)
Covariate-specific Diagnostics	A B-value between 0.8 and 1.25 indicating a good match. Values ranging from 0.5 to 2 are listed in Stuart (2010) and in the software documentation (SAS) as acceptable.	

Source: Report Post hoc propensity-matched analysis of study 408-C-1402 Extension and Natural History (49)

2.3.4 Results

2.3.4.1 Propensity score matching

The results of the diagnostic assessments for the propensity score matching for the three populations in the MOXIe OLE trial: the omaveloxolone-omaveloxolone group, the placebo-omaveloxolone group, and the pooled group. Diagnostics for these three populations are the propensity score matching are displayed in the Table 15 below. For the propensity score model used in this analysis, the standardized difference of the means of propensity score was well below the 0.5 boundary (described in Section 2.3.3) for all three populations. The same was true for the standardized difference of the means of each covariate. Additionally, the ratio of the variances of the propensity score was close to 1, greater than 0.8, and less than 1.25 for all 3 populations. The ratio of the variances of the residuals for most covariates met the criteria for an acceptable match. The ratio of the variances of the residuals for age and age of FA onset covariates fall below 0.5 in these populations. This is due to the variability in these covariates; as shown in Table 15 for the pooled population, there is higher variability in these covariates in the matched FA-COMS patients compared to MOXIe OLE trial patients. Taken together, the diagnostic results demonstrate that the propensity score matching was good for all three populations.

Table 15: Resulting diagnostics after propensity score matching of FA-COMS and MOXIe OLE trial

Diagnostic	Criteria for good or acceptable match	Pooled (match 1)	Placebo-omaveloxolone (match 2)	Omaveloxolone-omaveloxolone (match 3)
Standardized Difference of the Means of the Propensity Score	<0.5	0.0055	0.0090	0.0012
Standardized difference of the means of covariates				
Sex	<0.5	0	0	0
Baseline gait	<0.5	0.0672	0.0802	0.0325
Baseline mFARS	<0.5	0.0826	0.1103	0.0828

Age	<0.5	0.0375	0.0902	0.1357
Age at FA onset	<0.5	0.0292	0.0645	0.0424
Ratio of the variances of the propensity score	Close to 1; >0.8 and <1.25	1.0243	1.0411	0.9974
Ratio of the variances of the residuals for covariates				
Sex	0.5 to 2	0.9999	1.0044	0.9993
Baseline gait	0.5 to 2	0.5751	0.5022	0.5599
Baseline mFARS	0.5 to 2	0.6068	0.4986	0.5479
Age	0.5 to 2	0.3428	0.3305	0.2005
Age at FA onset	0.5 to 2	0.3194	0.2852	0.4325

[a]Criteria for a "good" match shown for standardized difference of the means of the propensity score, standardized difference of the means of the propensity score for each covariate, and ratio of the variances of the propensity score. Criteria for an "acceptable" match shown for the ratio of the variances of the residuals for each covariate.

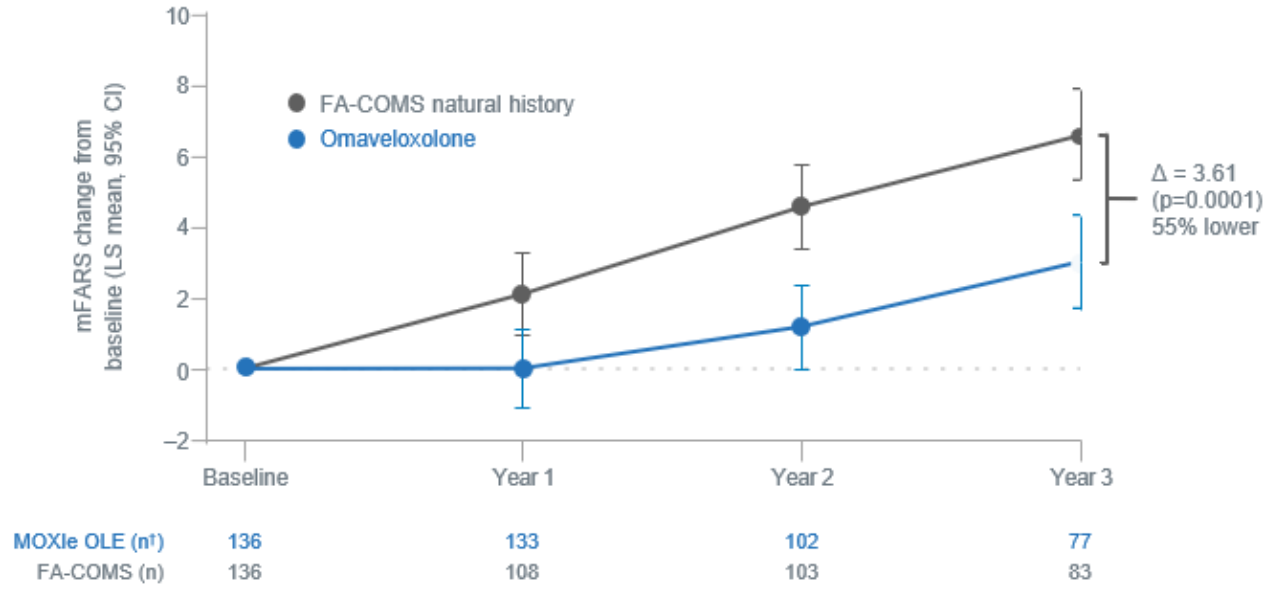
Abbreviations: FA = Friedreich's Ataxia; mFARS = modified Friedreich's Ataxia Scale.

Source: Report Post hoc propensity-matched analysis of study 408-C-1402 Extension and Natural History (49)

2.3.4.2 Endpoints

At Year 3, the mFARS score had increased by 6.6 points in the FA-COMS group compared with 3.0 points in the overall MOXIe OLE group, a difference of 3.61 points (p=0.0001) (Figure 7). These data suggest that patients receiving omaveloxolone had a 55% reduction in the extent of disease progression compared with patients with FA receiving standard of care only (63).

Figure 7: Post hoc propensity-matched analysis of mFARS score between patients in the natural history FA-COMS study and MOXIe OLE



Abbreviations: CI = confidence interval; FA-COMS = Friedreich Ataxia Clinical Outcome Measures; LS = least squares; mFARS = modified Friedreich Ataxia Rating Scale; OLE = open-label extension.
Source: Lynch (2022) (63)

In addition to the overall MOXIe OLE population, propensity score matching was performed according to treatment history from MOXIe Part 1 and Part 2 (placebo-omaveloxolone or omaveloxolone-omaveloxolone). Patients treated with omaveloxolone showed consistently lower disease progression compared with the FA-

COMS cohort at Year 3, regardless of whether they received placebo or omaveloxolone earlier in MOXIe. This was demonstrated by a significant difference in mFARS change from baseline to Year 3 for MOXIe OLE versus FA-COMS patients (–4.09 for the placebo-omaveloxolone group and –3.76 for the omaveloxolone-omaveloxolone group) (Table 16).

Table 16: mFARS change from baseline by treatment history in MOXIe OLE

	mFARS LS mean change from baseline to Year 3		Difference (MOXIe OLE vs FA-COMS) at Year 3	P-value
	MOXIe OLE	**FA-COMS**	**-**	
Placebo-omaveloxolone (n=95)	3.206 (0.7586)	7.293 (0.7194)	–4.087 (1.0453)	<0.01
Omaveloxolone-omaveloxolone (n=41)	2.377 (1.3263)	6.141 (0.7586)	–3.764 (1.8173)	0.04

Abbreviations: FA-COMS = Friedreich Ataxia Clinical Outcome Measures; LS = least squares; mFARS = modified Friedreich Ataxia Rating Scale; OLE = open-label extension.

Source: Lynch (2022) (63)

The annual cumulative change in mFARS for patients from the natural history study compared with those receiving omaveloxolone is also presented for each of three populations (pooled population, omaveloxolone-omaveloxolone and placebo-omaveloxolone) (Table 17).

Table 17: Cumulative change in mFARS for each population in the propensity score matched analysis

Time	Cumulative change					
	Pooled population		**Omaveloxolone-omaveloxolone**		**Placebo-omaveloxolone**	
	Omaveloxolone	**Placebo**	**Omaveloxolone**	**Placebo**	**Omaveloxolone**	**Placebo**
Year 1	0.015	2.113	-0.431*	2.322	1.054	2.479
Year 2	1.179	4.584	1.175	4.23	1.099	3.565
Year 3	3.004	6.611	3.206	7.293	2.377	6.141

Abbreviations: mFARS = modified Friedreich Ataxia Rating Scale

*Notes: *Negative change in mFARS is assumed to be a statistical artefact and is assumed to be equal to maintenance of mFARS score (annual change of 0)*

Source: Propensity-matched analysis (64)

2.3.5 Discussion

Both the propensity score-matched analysis of MOXIe extension and FA-COMS data, and the delayed-start analysis suggest a clinically meaningful slowing of FA progression with omaveloxolone over 3 years. The supportive data from the OLE and PSM are accepted by EMA, and considered suitable and well-designed (37). The PSM is strengthened by the fact that FA-COMS is considered to be a well-known international cohort for FA. Internal validity is strengthened by rigorous matching on key covariates, minimizing bias between groups. However, external validity may be limited due to the specific selection criteria of both studies, potentially not reflecting the broader FA population.

The assumption of exchangeability is not directly testable but supported by comparable baseline characteristics and standard of care between groups. Limitations include the absence of GAA1 repeat length and pes cavus as covariates in the propensity score model due to data availability and assessment differences. Additionally, the potential placebo effect in this non-placebo-controlled study cannot be fully accounted for.

Despite these limitations, the consistency of results across multiple sensitivity analyses and the comparability to the MOXIe Part 2 placebo-controlled trial strengthens the evidence for the potential benefit of omaveloxolone for the treatment of FA.

3 Health economic analysis – methods and PICO

3.1 Decision problem

The objective of the health economic analysis conducted was to assess the cost-utility of omaveloxolone for the treatment of FA in patients aged 16 and older in the Norwegian clinical setting. As mentioned in Section 1.4, omaveloxolone is expected to be used alongside the SoC rather than replace it. Therefore, the analysis assesses omaveloxolone plus SoC as intervention and SoC alone as comparator.

3.2 Model structure and applicability

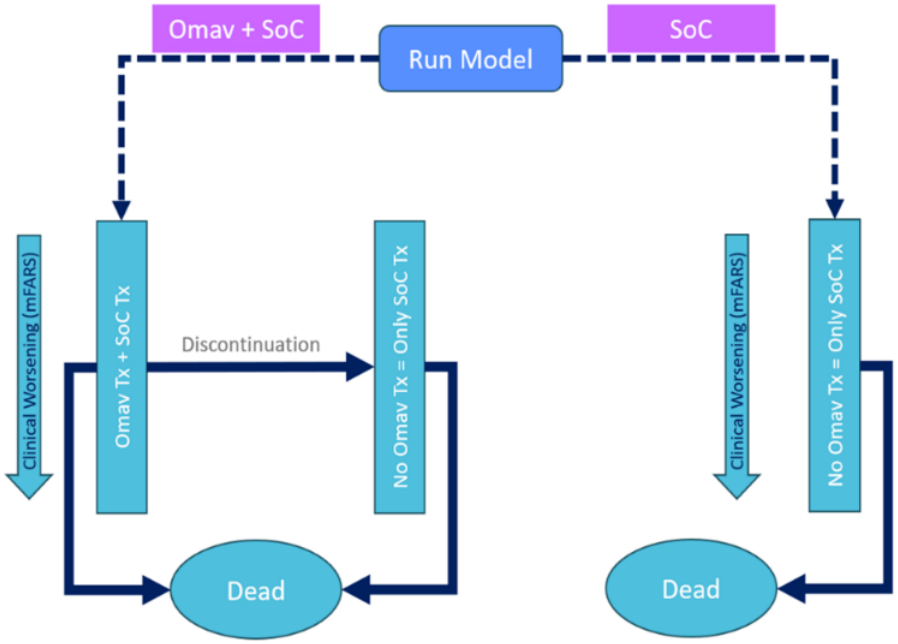
The model was developed using Microsoft Excel (Office 365) and programmed using standard Excel functions wherever possible. Visual basic was used sparingly and was limited to running sensitivity analyses and for navigation purposes. A description of the model's instruction (i.e. color coding, user sheets available and navigation) are included in the "Intro" sheet.

This submission focuses on a Norwegian base case. Nevertheless, country specific inputs in the model are automatically updated to Swedish and Danish changing country selection in the model "Settings" sheet. Country specific inputs and references are included in the model in the JNHB datastore sheet.

3.2.1 Model Structure

The model used for this analysis is a regression-based model using key populations' characteristics (age of onset, baseline age, percent male/female, baseline mFARS score, and baseline gait score) to predict the patients' mFARS score over time for both intervention and comparator. The natural progression of FA by mFARS is estimated independently of treatment status. The progression of FA by mFARS is reduced by a rate ratio which is estimated from the propensity matched analysis of MOXIe OLE and FA-COMS.The mFARS score is determined for both treatments' arms and age of onset subgroups. Time in the model is used to inform survival, costs, and utilities for each group at each model cycle (one year). The results of each subgroup are aggregated to estimate cost and QALY for the overall FA population. The structure of the model is schematised in Figure 8.

Figure 8: Regression-based model structure



Abbreviations: mFARS = modified Friedreich's Ataxia Rating Scale; Omav = omaveloxolone; SoC = standard of care, Tx = treatment

The mFARS progression over time for SoC patients is informed by natural history data from the FA-COMS database (see section 2.2.2). The mFARS progression for patients on omaveloxolone plus SoC is calculated by applying a treatment effect on the mFARS trajectory for SoC patients estimated using data from the propensity-matched analysis (64) (see Section 2.3).

Death can occur at any time in the model, and survival is calculated at the end of each model cycle as a function of age or mFARS and applied as the mortality risk for the next model cycle. Patients on omaveloxolone plus SoC are subject to both mortality and treatment discontinuation risks, and mortality risk is applied before treatment discontinuation risk.

A life-time time horizon is used in the analysis. Each of the age of onset subgroups has a different follow up time depending on their starting age in the model, which is based on the mean age of diagnosis of each subgroup in the incident population (baseline visit within 3 years of diagnosis) in FA-COMS Database. Specifically, the cohorts with an age of onset younger than 7 years as well as the one with age of onset from 8 to 14 years are followed in the model from age 16 up to 100 years; the cohort with an age of onset of 15 to 24 years is followed in the model from age 25.3 years up to 100 years; and the cohort with an age of onset of after 24 years is followed in the model from age 48.2 years up to 100 years.

Different cost categories are included in the economic analysis (described in detail in Section 3.7). The user can easily include or exclude different cost categories in the excel model from the setting sheet.

In the analysis base case, direct medical costs (treatment acquisition, disease management, AE, comorbidities), and direct non-medical costs (education, transportation and caregivers' costs) are included. Administration costs are not accounted for as omaveloxolone is an oral treatment. Similarly, no additional patients time cost is expected to be incurred by patients treated with omaveloxolone compared to patients treated with SoC. Disease management and comorbidity related resource use were estimated including recurring and one-off resources (see section 3.7). Specifically, costs related to recurring resource use were estimated by mapping mFARS score to ADL score and assigning associated costs at each cycle. Costs related to one-off resource use were estimated by mapping mFARS to ADL, comparing ADL to specified ADL thresholds between consecutive model cycles and then

assigning appropriate costs. Treatment cost was assigned to patients receiving omaveloxolone while on treatment.

Scenario analyses were conducted including indirect costs (patients' productivity losses), caregivers health related quality of life, or excluding non-medical resource use.

Utilities values by mFARS categories were derived from a linear regression between mFARS (cross-walked from SARA) and EQ-5D, based on data from EFACTS and assigned to each model cycle based on patients mFARS score. The utility regression is described in detail in Section 3.6.4. Disutilities associated with adverse events are also applied.

The impact of including caregivers' health related quality of life was tested in the scenario analysis.

Table 18: Model overview

Topic	Description
Population	Patients with FA, tracked in the model by prognostic factor of age of onset. Age of onset subgroups (starting age is 16 years or older)(60): • Age of onset less than or equal to 7 years old • Age of onset between or equal to 8 to 14 years old • Age of onset between or equal to 15 to 24 years old • Age of onset over 24 years old Results of model aggregated for overall FA population
Clinical aspects	• Combination of linear mFARS progression (by treatment status and age of onset subgroup) and naturally extended logistic extrapolation with asymptote at mFARS of 93. • Comorbidity (i.e., cardiomyopathy, scoliosis, diabetes) prevalence (by age) • Mortality included using HR by mFARS category applied to overall FA population mortality. • Adverse event rates (by treatment status)
Treatment effect	Observed treatment effect (for the first 3 years on treatment) is captured by a ratio of the change in mFARS for omaveloxolone vs SoC
Resource use and costs	• Omaveloxolone acquisition costs • Medical resource use costs, • Adverse event costs, • Comorbidity costs, • Non-medical resource use costs (transportation, education and professional and informal caregivers support) Patient productivity losses is included in a scenario analysis, as well as the exclusion of non-medical costs.
Utilities	• Patient utility by mFARS • Disutility associate with adverse events • Caregiver disutility by patient mFARS (excluded in the base case)

Abbreviations: FA = Friedreich's Ataxia; FA-COMS = Friedreich Ataxia Clinical Outcome Measures; HR = Hazard ratio; mFARS = Modified Friedreich Ataxia Rating Scale; SoC = standard of care.

3.2.2 Perspective and formalities

In Table 19 below, the perspective and main settings of the health economic model are described.

Table 19: Perspective and formalities applied in the health economic analysis.

Topic	Description
Model type	Regression-based model, based on mFARS progression from the FA-COMS study for SoC and a rate ratio reducing mFARS progression from the MOXIe trials for omaveloxolone plus SoC
Cycle length	One year. In line with annual visits in FA-COMS.
Half cycle correction	Yes
Discount rates	In line with DMP guidelines for the Norwegian base case presented 4% for costs and utilities in year 0-39 3% for costs and utilities in year 40-79 2% for costs and utilities in year 80+ In the excel file, discount is automatically updated to Swedish (3%) and Danish (3.5%) standard when changing country in the setting sheet.
Utility age adjustment	Yes
Perspective	Limited societal perspective
Time horizon	Lifetime

Abbreviations: FA-COMS = Friedreich Ataxia Clinical Outcome Measures Study; mFARS = Modified Friedreich Ataxia Rating Scale; DMP = Direktoratet for medisinske produkter; SoC = standard of care.

3.2.3 Applicability of the model to the decision problem

No previous health economic evaluation has been published for patients with FA. The regression model was considered the best structure to estimate the treatment effect as measured in the MOXIe trial, allowing for continuous representation of change in mFARS over time, which would be limited with a health state model approach. Other limitations considered in using a health state model were the lack of consensus on significant threshold defining health states and the limited number of health states transitions observed in RCTs.

The structure of the current model is simple and transparent, limiting the need of supportive data from the literature. Furthermore, it was considered pivotal to allow leveraging the over 13 years of patient-level data on the natural history for patients with FA publicly available from the FA-COMS registry, considered a unique source of evidence for a rare disease such FA.

3.2.4 Model requirements.

The model requirements of DMP have been met.

3.3 Population

3.3.1 Norwegian clinical practice

The targeted patient population concerns all patients of 16 years and older who have been diagnosed with FA. As there is no current treatment available for these patients, the current prevalent population is eligible for treatment with omaveloxolone (see Section 5.1). The age of onset plays a role in the severity and progression of FA, but there is no distinction within the indication and eligibility.

As FA is a rare disease, there is limited availability of published data on FA patients in Norway.

A cross-sectional study conducted in 2014 identified 29 genetically confirmed FA patients, investigated molecularly with genotype characterization including size determination of GAA repeat expansions and frataxin measurements (65). Among these, the reported mean age of onset was 9.6 and the mean disease duration was 15.2. Non-neurological comorbidities as scoliosis, hear involvement and diabetes were reported by 85%, 7% and 48% of the patients, respectively. Disease neurological severity, assessed with the Scale for the Assessment and Rating of Ataxia (SARA) score, was on average 21.6 (65).

Table 20: Clinical characteristics of included FA patients in Norway at time of study

Characteristic	Mean (SD) or %
Gender (Female)	48%
Age at onset (years)	9.6 (5.7)
Duration of the disease (years)	15.2 (11.6)
SARA score [a]	21.6 (9.6)
Presenting symptom	Unsteady: 93% Cardiomyopathy: 7%
Disability stage [b]	4.4 (1.5)
Extensor plantar response	Bilateral: 59 % unilateral: 15 % Equivocal: 7 % normal: 19 %
Reduced vibratory sense	93%
Dysphagia	93%
Dysarthria	89%
Scoliosis	85%
Diabetes	7%
Depression	33%
Heart involvement	48%
FXN pg/mcg	0.198 (0.214)
GAA repeats, allele 1	615 (161.8)
GAA repeats, allele 2	759 (160.6)

Abbreviations: GAA= Guanosine-adenosine- adenosine; FXN = Frataxin; SARA = Scale for the Assessment and Rating of Ataxia; SD = Standard Deviation

Notes: a) SARA: ataxia assessment form composed of eight items that sum to a total score of 0: no ataxia, to 40: most severe ataxia. b) Disability stage 1-7: 1:(no disability), 1:(no functional handicap but signs at examination, 2:(mild, able to run, walking unlimited), 3:(moderate, unable to run, limited walking without aid), 4:(severe, walking with one stick), 5:(walking with two sticks), 6:(unable to walk, requiring wheelchair), 7:(confined to bed)

Source: Wedding 2015 (65)

3.3.2 Clinical documentation

The propensity score-matched analysis included the MOXIe OLE complete randomised population (pooled population) which had i) baseline mFARS, ii) at least one post-baseline mFARS within 3 years after baseline, and iii) values for all propensity score model covariates and the matched FA-COMS population. The baseline characteristics of MOXIe OLE, and both the unmatched and matched FA-COMS populations are described in Table 21.

P-values for the difference between MOXIe OLE and matched FA-COMS was obtained by two-sample t-test for age, age at FA onset, mFARS, gait, height, weight, BMI, systolic and diastolic blood pressure, heart rate, ADL Total Score, GAA1 and GAA2 repeat length and by Chi-Square test for sex, ethnicity, and race. The non-matched FA-COMS demographics and baseline characteristics were not compared for significant differences. Slight differences observed in GAA1 and GAA2 (the longer of the two FXN GAA intron 1 repeats) repeat length, although significant, were not clinically meaningful based on ceiling effects of the GAA1 length (66-68). In the propensity-matched study of Lynch et al. (2023), more information can be found on the sensitivity analysis performed on the sensitivity subgroups from FA-COMS.

Table 21: Demographics and baseline characteristics of the pooled population in the MOXIe extension, the propensity-matched population from FA-COMS, and the non-matched population of FA-COMS

Characteristic	Statistic	Matched FA-COMS	MOXIe OLE*	Non-Matched FA-COMS
Ethnicity (n [%])	n	136	136	455
	Hispanic or Latino	6 (4.4%)	6 (4.4%)	12 (2.6%)
	Not Hispanic or Latino	129 (94.9%)	130 (95.6%)	432 (94.9%)
	Not reported	1 (0.7%)	0	11 (2.4%)
	p-value	-	0.99	N/A
Race (n [%])	n	130	136	428
	White	125 (96.2%)	133 (97.8%)	412 (96.3%)
	Non-White	5 (3.8%)	3 (2.2%)	16 (3.7%)
	p-value	-	0.43	N/A
Height (cm)	n	89	136	276
	Mean (SD)	165.1 (14.7)	169.3 (10.4)	156.7 (19.2)
	p-value	-	0.020	N/A
Weight (kg)	n	95	136	299
	Mean (SD)	61.0 (20.7)	69.1 (16.7)	52.4 (21.4)
	p-value	-	0.0018	N/A
BMI (kg/m2)	n	89	136	270
	Mean (SD)	22.0 (5.7)	24.0 (5.2)	20.2 (5.4)

	p-value	-	0.0069	N/A
Systolic Blood Pressure (mmHg)	n	82	136	252
	Mean (SD)	121.4 (15.0)	121.1 (13.5)	118.8 (14.2)
	p-value	-	0.90	N/A
Diastolic Blood Pressure (mmHg)	n	82	136	252
	Mean (SD)	73.2 (10.5)	75.3 (8.7)	69.5 (9.1)
	p-value	-	0.15	N/A
Heart Rate (beats/min)	n	82	136	250
	Mean (SD)	85.2 (15.4)	79.8 (12.6)	86.2 (14.7)
	p-value	-	0.0089	N/A
ADL Total Score	n	124	136	432
	Mean (SD)	11.8 (5.9)	12.5 (4.9)	11.6 (7.0)
	p-value	-	0.28	N/A
GAA1 Repeat Length	n	129	119	439
	Mean (SD)	590 (246)	721 (270)	664 (225)
	≥ 675, n (%)	54 (41.9%)	66 (55.5%)	233 (53.1%)
	p-value	-	<0.0001	N/A
GAA2 Repeat Length	n	121	116	426
	Mean (SD)	863 (232)	728 (297)	942 (209)
	p-value	-	0.0001	N/A
Age (years)	n	136	136	462
	Mean (SD)	26.2 (13.7)	26.6 (7.3)	22.4 (13.8)
	Min, max	6, 64	16, 41	5, 73
	p value	–	0.76	N/A
Age at FA onset	n	136	136	462
	Mean (SD)	15.2 (10.5)	15.5 (5.3)	12.3 (8.6)
	p value	–	0.81	N/A
Sex (n [%])	n	136	136	462
	Female	70 (51.5%)	70 (51.5%)	234 (50.6%)
	Male	66 (48.5%)	66 (48.5%)	228 (49.4%)
	p value	–	1	N/A
mFARS	n	136	136	462
	Mean (SD)	41.0 (16.1)	42.2 (12.6)	44.8 (18.1)
	Min, max	5.3, 77.0	8.2, 73.5	2.0, 91.0
	p value	–	0.50	N/A

Gait (assessment #7 in FARS section E [upright stability])	n	136	136	462
	Mean (SD)	2.7 (1.69)	2.8 (1.36)	2.3 (1.69)
	p value	–	0.58	N/A

Abbreviations: ADL = Activity of daily living; BIM Body max index; FA = Friedreich's Ataxia; FARS = Friedreich Ataxia Rating Scale; GAA= Guanosine-adenosine- adenosine; mFARS = Modified Friedreich Ataxia Rating Scale; N/A =Not applicable; OLE = Open label extension; SD = Standard Deviation.

*Notes: *MOXIe OLE data reflect the pooled population (both omaveloxolone-omaveloxolone and placebo-omaveloxolone arms)*

Source: Lynch (2022) (63)

3.3.3 Health economic model

Age of onset is specified in the model as it was identified by expert clinicians to be an important prognostic factor (1, 14) determining patient rate of disease progression as well as comorbidities such as cardiomyopathy (69, 70). This is supported by recently published analysis based on 1,115 FA patients from FA-COMS, indicating that early-onset patients (0–7 years) declined about 50% faster than those with typical onset (8–14 years) and twice as fast as intermediate-onset patients (15–24 years) (60).

The population baseline characteristics in the economic model (Table 22) were informed by the FA-COMS database (71). This data contained hundreds of patients who had their initial mFARS score recorded many years after age of onset. Given the emergence of a disease-modifying treatment option in FA coupled with the likely guidelines and evolution of disease knowledge, such a gap between clinical outcomes assessment and diagnosis is unlikely. Therefore, the baseline characteristics of patients with an mFARS score recorded within 3 years of diagnosis in FA-COMS were considered the most appropriate for inclusion. Further, baseline characteristics were used to ensure compatibility between FA-COMS and MOXIe given these same characteristics were used in the propensity-matched analysis (64) used to estimate treatment effect in the economic model.

The model is flexible to start at any age; however, in the base case, the model assumes that patients with age of onset less than 7 years old and between 8 and 14 years old start treatment at age 16 years, to align with the indication of omaveloxolone (72, 73) while older patients groups enter in the model in alignment with their baseline age.

Table 22: Characteristics of the modelled population

Age of onset subgroup	≤ 7 years old	8 - 14 years old	15 - 24 years old	> 24 years old
Baseline age	10.6 years old	14.9 years old	25.3 years old	48.2 years old
% male	52.1%	51.8%	53.2%	57.7%
Baseline Gait score	1.50	1.48	1.47	1.56
Baseline mFARS	39.0	34.7	28.6	26.8
Age of entering model	16.0 years old	16.0 years old	25.3 years old	48.2 years old
Proportion in model	34%	40%	18%	8%

Abbreviations: mFARS = Modified Friedreich Ataxia Rating Scale.

Source: Internal analysis of FA-COMS database (71)

3.3.4 Summary

Table 23 compares the population characteristics for MOXIe OLE and the FA-COMS included in the model to the ones available for the Norwegian population reported by Wedding et al, 2015 (65). The observed age of onset was somewhat lower for the Norwegian population compared to both MOXIe OLE and FA-COMS, while in the model the age of onsets defines the models' subgroups. Nevertheless, the age of onset in the economic model was defined by the mean age at baseline in the analysis of the incident population in FA-COMS, which included patients with baseline visit within 3 years of diagnosis. The difference in GAA1 repeated length was lower between the Norwegian and the MOXIe populations than the one measured between the MOXIe OLE and the matched FA-COMS populations, therefore not expected to be clinically significant.

Table 23: Summary and comparison of patient population relevant for the decision problem

Patient characteristics	**Expected in Norwegian clinical practice - (Wedding et al, 2015)**(65)	**Clinical documentation - Matched FA-COMs population** (63)	**Economic model**			
Age at FA onset	9.6	15.2	≤ 7 years old	8 - 14 years old	15 - 24 years old	> 24 years old
Age (years)*	-	26.2	16.0	16.0	25.3	48.2
% male	52%	51.5%	52.1%	51.8%	53.2%	57.7%
Baseline mFARS	-	41.0	39.0	34.7	28.6	26.8
GAA1 repeated length	615	721	-	-	-	-

Abbreviations: FA = Friedreich's Ataxia; GAA= Guanosine-adenosine- adenosine; mFARS = Modified Friedreich Ataxia Rating Scale.

*Notes: * In the economic model reflect the starting age*

Source: Wedding 2015 (65), internal analysis of FA-COMS database (71)

3.4 Intervention

3.4.1 Norwegian clinical practice

The expected use in the Norwegian setting is in line with the therapeutic indication described in the SmPC. Omaveloxolone is indicated for the treatment of FA in patients aged 16 years and older. Omaveloxolone should be initiated and supervised by physicians with experience in the treatment of patients with FA. The recommended dose is 150 mg omaveloxolone (oral use, 3 hard capsules of 50 mg each) once daily.

3.4.2 Clinical documentation

Omaveloxolone is available as 2.5, 10, or 50 mg capsules. The recommended dose (150 mg daily) is in line with the dosage used in MOXIe Part 2.

In Part 2, mean duration of treatment in was 9.9 months for omaveloxolone and 10.7 for placebo. Mean compliance was 89.7% for the placebo group and 86.9% for the omaveloxolone group (48). The treatment duration data was taken from MOXIe part 2 instead of the OLE trials as there were some

challenges in the follow-up in the OLE (i.e., at some timepoints numbers were low because of COVID restrictions), the best available estimate for compliance was therefore in MOXIe part 2.

In the OLE, mean duration of treatment was 42.4 months for omaveloxolone-omaveloxolone and 38.1 for placebo-omaveloxolone, while compliance was 86.6% for the placebo-omaveloxolone group, 89.4% for the omaveloxolone-omaveloxolone group, and 87.4% for the pooled population.

3.4.3 Health economic model

The intervention used in the model is aligned with the SmPC and clinical documentation. Patients with diagnosed FA of 16 years and older receive 150 mg of omaveloxolone daily. The compliance of omaveloxolone was 86.9% in the MOXIe Part 2, which is implemented in the economic model. There is no reason to believe that the therapeutic indication and/or intervention would be different in the Norwegian setting.

Treatment discontinuation was also investigated in MOXIe part 2 and OLE (74, 75) and it is describe in detail in Section 3.4.3.

3.4.4 Summary

The dosing and posology described in the SmPC is expected to be the same in Norwegian clinical practice and is thus implemented similarly into the health economic model.

Table 24: Summary and comparison of use of the intervention relevant for the decision problem.

Characteristics of the intervention	Expected in Norwegian clinical practice	Clinical documentation MOXIe Part 2 and OLE	Health economic model MOXIe Part 2 and OLE
Posology	150 mg/day (SmPC)	150 mg/day	150 mg/day
Duration of treatment	-	MOXIe part 2: 0.82 years (0.26)[7] OLE: 2.60 years (0.524)	9.05 years
Premedication/co-medication	N/A	N/A	N/A
Subsequent treatment	N/A	N/A	N/A

Abbreviations: N/A 0 Not applicable; OLE = Open label extension; SmPC = Summary of product characteristics.

Notes: Duration of treatment in health economic model resulting from discontinuation and death

Source: SmPC Skyclarys (37), MOXIe part 2 CSR (48), MOXIe OLE and FA-COMS study (64)

3.5 Comparator(s)

3.5.1 Norwegian clinical practice

Currently, there are no EMA approved therapies for FA. The most recent consensus clinical management guidelines for FA recommend symptomatic treatment only (33, 34, 37). Norwegian sources confirm no listed treatment for FA, and only mention symptom-oriented strategies and treatment of comorbidities such as diabetes mellitus (29-31). Other pharmacological (i.e. antioxidants) and non-pharmacological therapies are assumed to be covered by the medical health care resource use and equal in both treatment arms.

3.5.2 Clinical documentation

Not applicable

3.5.3 Health economic model

Not applicable

3.5.4 Summary

There is no current treatment for FA approved by EMA or available in Norway. The health economic model includes cost of SoC in the comparator arm as for the omaveloxolone arm. Background and concomitant medication costs were not included in the analysis as these are not expected to differ between treatment arms and will not influence disease progression.

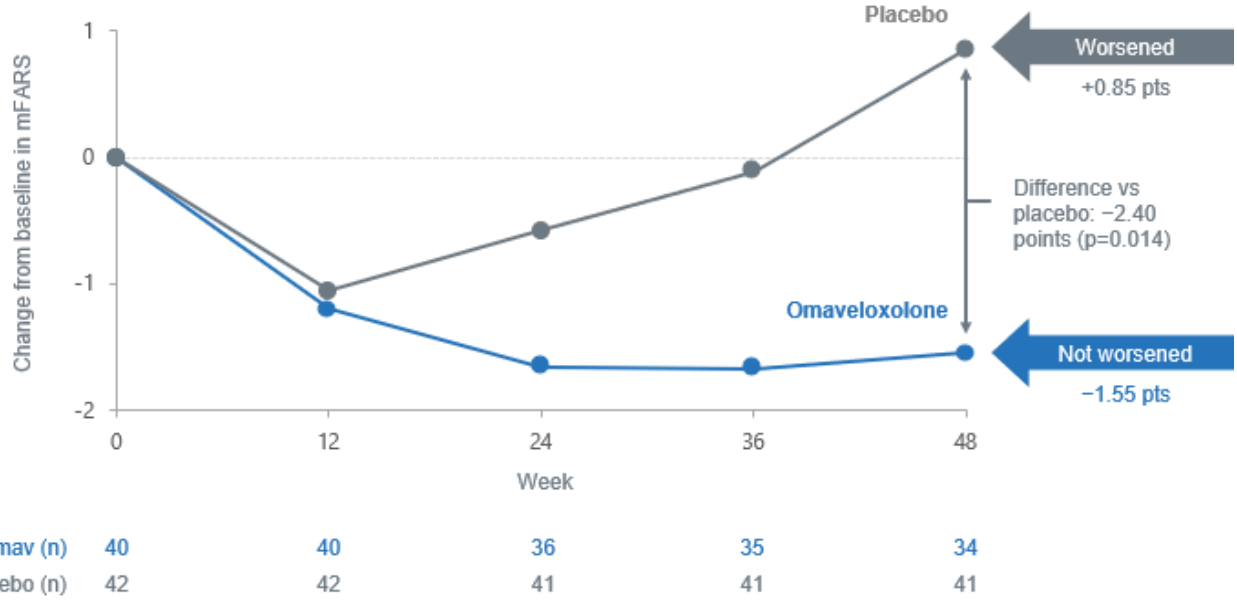
3.6 Clinical outcomes and model inputs

3.6.1 Main outcomes of the pivotal trials

3.6.1.1 MOXIe Part 2

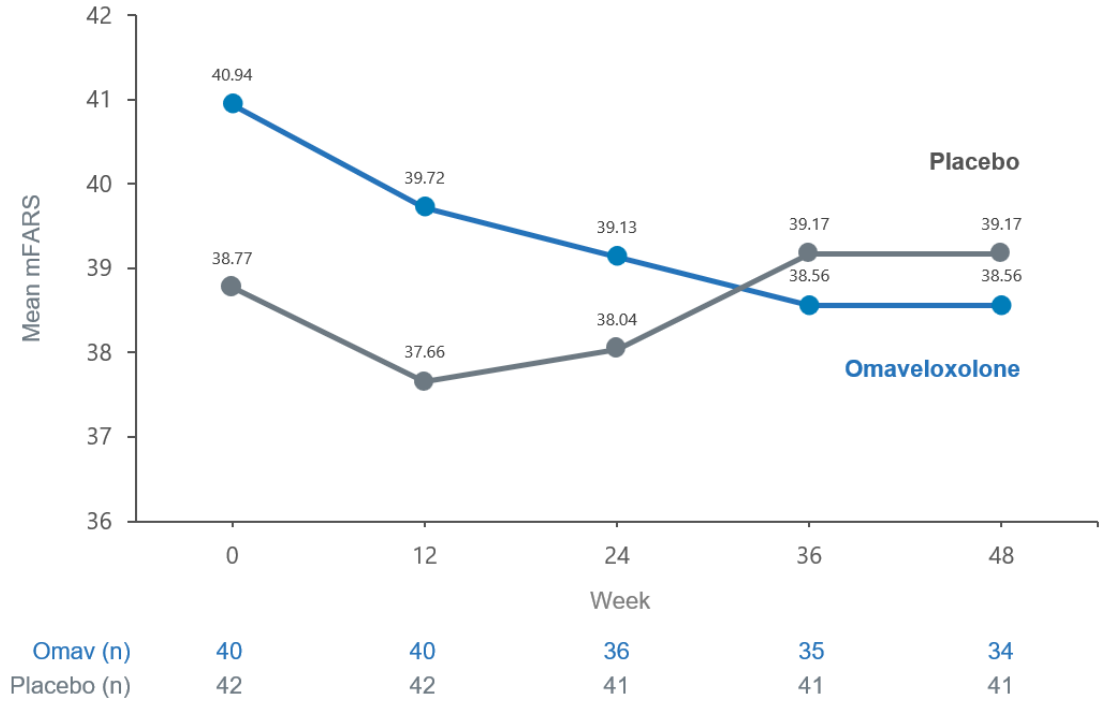
In MOXIe Part 2, omaveloxolone treatment delayed the progression of FA, as shown by a mean reduction in mFARS of 1.55 (95% CI –2.93, –0.18) from baseline to Week 48 (Figure 9). In contrast, although there was a slight potential placebo effect in the first 12 weeks, patients in the placebo group experienced a mean mFARS score increase of 0.85 (95% CI –0.43, 2.13) from baseline to Week 48. The mean difference between treatment arms was –2.40 (95% CI –4.31, –0.5) in favour of omaveloxolone (p=0.014) (51). Figure 10 presents the mean mFARS score by each timepoint in the trial. In the omaveloxolone arm, the mean mFARS score decreased (improved) from 40.94 at baseline to 38.56 at Week 48. In the placebo arm, the mean mFARS score increased (worsened) from 38.77 at baseline to 39.17 at Week 48 (76).

Figure 9: Mean change from baseline in mFARS score over 48 weeks in MOXIe Part 2



Abbreviations: FAS = full analysis set; mFARS = modified Friedreich Ataxia Rating Scale.
Note: The FAS was used for primary analysis of efficacy and was limited to patients without pes cavus who had at least one postbaseline measurement.
Source: Lynch (2021) (51)

Figure 10: Mean mFARS score over 48 weeks in MOXIe Part 2



Abbreviations: FAS = full analysis set; mFARS = modified Friedreich Ataxia Rating Scale.
Note: The FAS was used for primary analysis of efficacy and was limited to patients without pes cavus who had at least one postbaseline measurement.
Source: MOXIe Part 2 CSR (76)

Table 25 shows the change in each of the mFARS components among patients in MOXIe Part 2, as well as the difference between omaveloxolone and placebo. Patients receiving omaveloxolone showed improvement across all mFARS components versus placebo, with a beneficial trend in all components and a significant improvement in upper limb coordination and a numerical improvement in upright stability being the key drivers of effect (76).

Table 25: Mean mFARS component scores and change from baseline to Week 48 (FAS)

mFARS component	LS mean (95% CI) at week 48		LS mean difference (95% CI), omaveloxolone vs placebo	P value
	Omaveloxolone (n=40)	**Placebo (n=42)**		
Bulbar	–0.19 (–0.34, –0.04)	–0.02 (–0.16, 0.11)	–0.17 (–0.37, 0.04)	0.11
Upper limb coordination	–1.15 (–2.03, –0.26)	0.14 (–0.68, 0.97)	–1.29 (–2.51, –0.06)	0.04
Lower limb coordination	–0.32 (–1.02, 0.38)	–0.11 (–0.76, 0.54)	–0.21 (–1.17, 0.76)	0.67
Upright stability	0.10 (–0.59, 0.79)	0.82 (0.18, 1.46)	–0.72 (–1.67, 0.24)	0.14

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; mFARS, modified Friedreich Ataxia Rating Scale
Source: Reata data on file – MOXIe Part 2 CSR (76)

Patients receiving omaveloxolone in MOXIe Part 2 experienced improvements in activities of daily living, with all secondary outcomes assessed numerically favouring omaveloxolone versus placebo (51).

Omaveloxolone improved FA-ADL scores compared with baseline and reached nominal statistical significance versus placebo at Week 48 (–0.17 vs 1.14; p=0.04) (Table 26) (51). Mean PGIC and CGIC scores at Week 48 numerically improved (decreased) among patients receiving omaveloxolone (3.90 and 3.93, respectively), although there was no significant difference compared with placebo (Table 26). The PGIC and CGIC scores correlated positively with changes in mFARS (Pearson correlation for mFARS versus PGIC r=0.47; p<0.0001; CGIC r=0.44; p<0.0001) (51).

Table 26: Secondary endpoints and post hoc analyses of FAS patients who improved or worsened in primary and secondary measures at Week 48 of MOXIe Part 2 (FAS)

Outcome	Change from baseline to Week 48[†]		LS mean difference, omaveloxolone vs placebo	P value
	Omaveloxolone (n=40)	Placebo (n=42)		
PGIC	3.90	4.33	–0.43	0.13
CGIC	3.93	4.06	–0.13	0.52
9-HPT, 1/s	–0.0014	–0.0001	–0.0013	0.18
T25-FW, 1/s	–0.0169	–0.0226	0.0058	0.46
Frequency of falls (over 48 weeks), median	3.0	8.5	0.30	0.30
Peak work, W/kg	0.03	0.09	–0.06	0.22
FA-ADL	–0.17	1.14	–1.30	0.04

Abbreviations: 9-HPT = 9-hole peg test; CGIC = Clinician Global Impression of Change; FA-ADL = Friedreich Ataxia Activities of Daily Living; FAS = full analysis set; LS = least squares; PGIC = Patient Global Impression of Change; T25-FW = timed 25-foot walk test.

Notes: [†]Mean changes for PGIC and CGIC responses and p values were analysed using an analysis of covariance, with treatment group and site as fixed factors and Week 48 values as the outcome with multiple imputation for missing Week 48 values based on the treatment group to which the subject was assigned. Mean changes and p values for 9-HPT, T25-FW, peak work, and FA-ADL were estimated using a mixed-model repeated measures analysis

Source: Lynch 2021 (51)

The FA-ADL includes nine parameters that cover multiple aspects of FA, including speech, personal hygiene, walking, and bladder function. In MOXIe Part 2, all nine parameters numerically favoured omaveloxolone versus placebo (Table 27) (51, 76), suggesting that the treatment can have a positive effect on different aspects of patients' lives, with the potential to benefit their overall QoL.

Table 27: Change from baseline to Week 48 in FA-ADL parameters in MOXIe Part 2 (FAS)

FA-ADL	Omaveloxolone (n=40)	Placebo (n=42)
Speech	–0.014	0.085
Swallowing	–0.097	0.122
Cutting food and handling utensils	–0.083	–0.037
Dressing	–0.014	0.073
Personal hygiene	–0.083	0.183
Falling	0.014	0.122
Walking	0.000	0.183
Quality of sitting position	–0.083	0.195
Bladder function	0.139	0.256

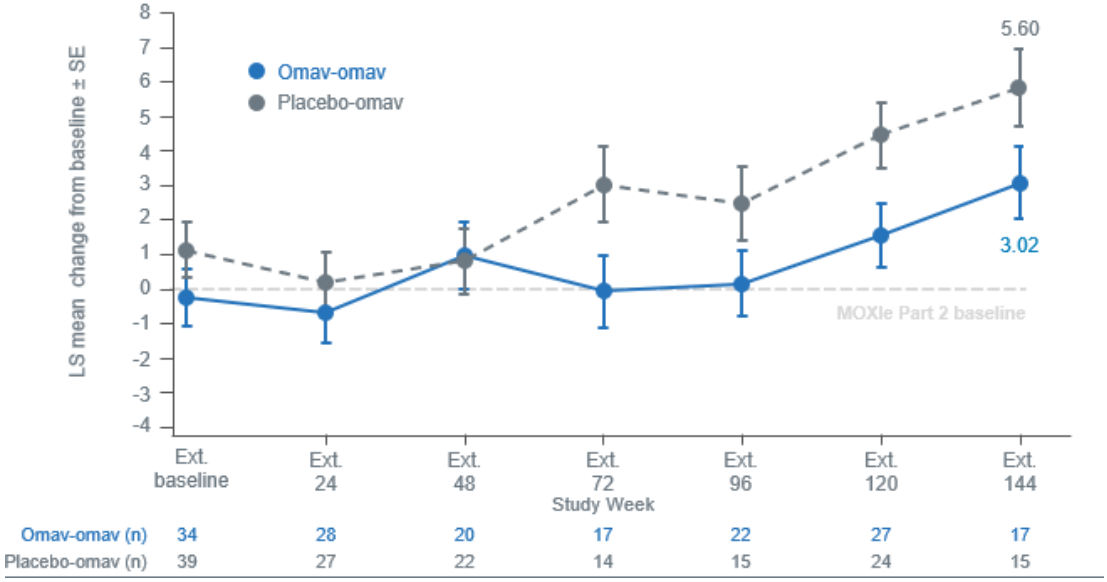
Abbreviations: FA-ADL = Friedreich ataxia – Activities of Daily Living; FAS = full analysis set.
Source: MOXIe Part 2 CSR (76)[8]

3.6.1.2 Long term efficacy and delayed treatment start

To assess whether omaveloxolone had a persistent effect on FA disease course, a post hoc "delayed start" analysis was conducted across MOXIe Part 2 and the OLE. A key outcome was the change from baseline in mFARS between the cohort of subjects who received omaveloxolone treatment during both MOXIe Part 2 and the OLE (these subjects were considered "early starters "of omaveloxolone and are hereafter termed the omaveloxolone-omaveloxolone cohort) and those subjects who received placebo during MOXIe Part 2 followed by omaveloxolone in the OLE (considered "delayed starters" of omaveloxolone and hereafter termed the placebo-omaveloxolone cohort).

The post hoc analysis showed that the positive effect of omaveloxolone on mFARS persisted over 144 weeks of the MOXIe OLE, as demonstrated by the numerical difference between the omaveloxolone-omaveloxolone and placebo-omaveloxolone groups across almost all timepoints assessed (Figure 11). At Week 48 of MOXIe Part 2, there was a 2.17-point difference in mFARS between the treatment groups in favour of the omaveloxolone group ($p<0.05$). At Week 72 of the OLE, the difference between the treatment groups was 2.91 in favour of the omaveloxolone-omaveloxolone group ($p<0.05$) (55). This separation persisted across the OLE, except for Week 48 where the curves temporarily converged. However, it should be noted that many Week-48 clinic visits (for mFARS assessment) were missed because they were scheduled at the peak of the COVID-19 pandemic in Spring to Autumn 2020. Missing mFARS assessments at Week 48 could potentially explain, at least partially, the convergence of the two curves at this timepoint.

Figure 11: Change from baseline in mFARS from baseline (end of MOXIe Part 2) and Week 144 in MOXIe OLE



Abbreviations: LS = least squares; mFARS = modified Friedreich Ataxia Rating Scale; OLE = open-label extension; Omav = omaveloxolone.
Note: For subjects in the placebo-omaveloxolone arm, the analysis included data from all visits from MOXIe Part 2 baseline to OLE Week 144. At the time of database lock, there were 23 subjects who had not yet reached Week 144.
Source: MOXIe OLE delayed start report (55)

The delayed start analysis also highlighted the importance of initiating omaveloxolone treatment at an early stage in the FA treatment pathway; subjects in the placebo-omaveloxolone cohort did not recover the benefits (lower mFARS score) observed in the omaveloxolone-omaveloxolone cohort who

[8] *RTA 408 CSR: A phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of Friedreich's Ataxia: part 2; Table 14.2.32.1*

started treatment 1 year earlier (55). At Week 72 of the delayed start analysis, there was a 2.91 separation between the groups' mFARS scores (Figure 11). Thereafter, the trajectories of each curve tracked in parallel, with the difference between the groups being –2.19, –2.74, and –2.58 at OLE Weeks 96, 120, and 144, respectively (Figure 11), suggesting that the difference in mFARS scored between each patient cohort would persist.

3.6.1.3 FA-COMS comparison

The results of the propensity score matched analysis are described in Section 2.3.4 as indicated by this dossier template.

3.6.2 Relative efficacy

The model captures the progression of FA by estimating mFARS scores over time based on baseline characteristics and age of onset. Other clinical inputs considered in the model include treatment effect and discontinuation (for patients receiving omaveloxolone), mortality, prevalence of comorbidities in the FA population.

3.6.2.1 Natural disease progression

3.6.2.1.1 Study outcome

Natural disease progression is informed by the change in mFARS over time as key outcome of the MOXIe trials and FA-COMS.

3.6.2.1.2 Modelling of study outcome (intervention and comparator)

The change of mFARS for patients on the SoC arm is estimated using a multivariate linear model that predicts mFARS scores developed based on 13 years of observed data from FA-COMS (71) and extrapolated over the model time horizon.

3.6.2.1.2.1 Up to 13 years

The multivariate linear model allows unique mFARS trajectories to be captured for each age of onset subgroup for the observation period. The FA-COMS analysis population was assumed to be representative of the Norwegian population (see Section 3.3). The analysis population included all patients with complete data on mFARS for at least one visit, mFARS score at baseline, gait score at baseline, age of onset, and gender, which are the variable used as covariates in the propensity score matched analysis.

A linear and non-linear logistic model were explored. The linear model (Figure 12) more closely matches the observed data from FA-COMS than the non-linear fit (Figure 13), as demonstrated by better goodness-of-fit statistics presented in Table 28. Therefore, the multivariate linear model was used in the base case to estimate SoC mFARS progression from the baseline age of each cohort to 13 years later (Table 29).

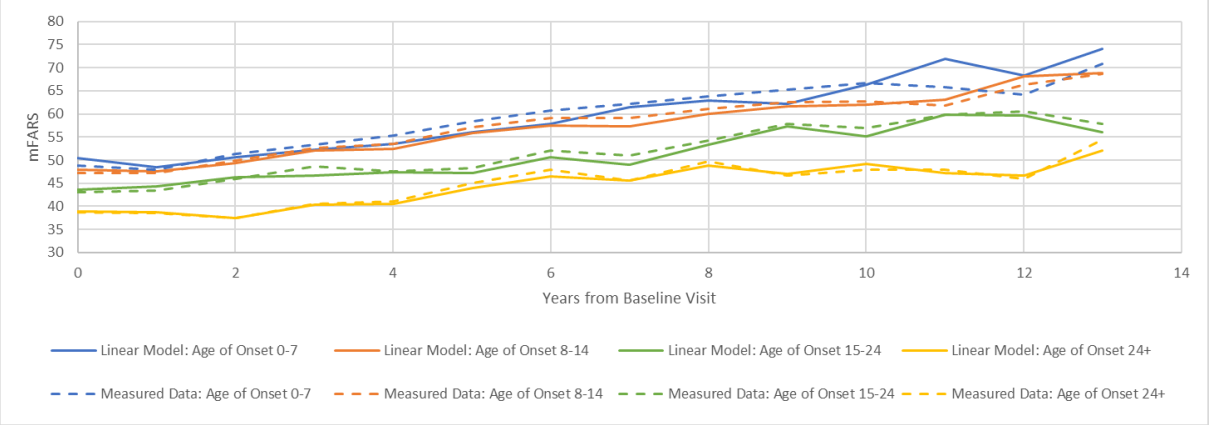
Table 28: Linear and non-linear model fit to natural mFARS progression

Goodness-of-fit measure	Linear model	Non-linear logistic model
AIC	21,047.08	22,948.48
BIC	21,132.57	23,041.54

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; FA-COMS = Friedreich's Ataxia Clinical Outcome Measures Study; mFARS = modified Friedreich's Ataxia Rating Scale

Source: Internal analysis of FA-COMS database (71)

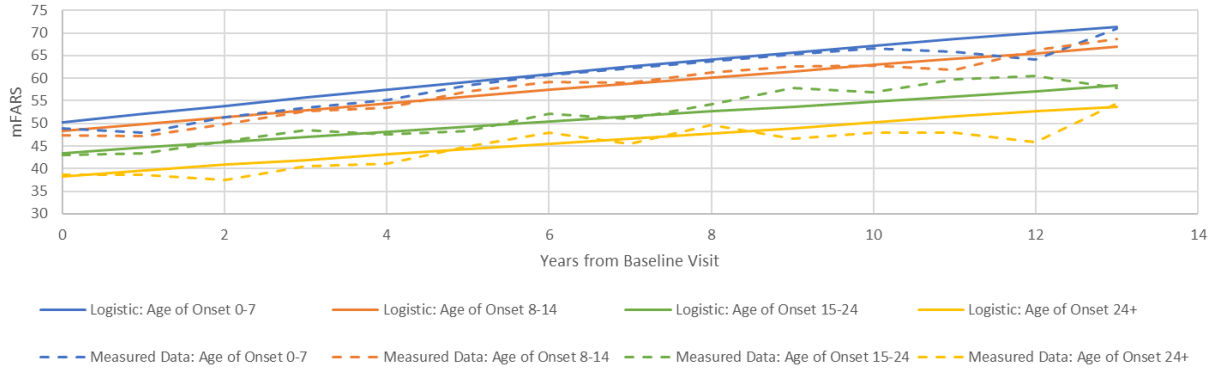
Figure 12: Average mFARS Progression (Observed and Predicted) by Age of Onset Subgroup From FA-COMS (Linear Fit; Base Case)



Abbreviations: FA-COMS = Friedreich's Ataxia Clinical Outcome Measures Study; mFARS = modified Friedreich's Ataxia Rating Scale.

Source: Internal analysis of FA-COMS database FA-COMS database(71)

Figure 13: Average mFARS Progression (Observed and Predicted) by Age of Onset Subgroup from FA-COMS (Logistic Fit)



Abbreviations: FA-COMS = Friedreich's Ataxia Clinical Outcome Measures Study; mFARS = modified Friedreich's Ataxia Rating Scale

Source: Internal analysis of FA-COMS database FA-COMS database(71)

Table 29: Multivariate Linear Model of natural mFARS progression

Parameter	Beta Coefficient	SE*	p-value*	Lower 95% CI*	Upper 95% CI*
% Male	0.69	0.39	0.0799	-0.08	1.47
Baseline Gait Score	0.43	0.24	0.0675	-0.03	0.89
Baseline mFARS	0.85	0.023	<0.0001	0.80	0.89
Age of Onset Category: 8–14 years old	6.30	0.72	<0.0001	4.88	7.71
Age of Onset Category: 15–24 years old	5.58	0.74	<0.0001	4.13	7.02
Age of Onset Category: > 24 years old	4.74	0.82	<0.0001	3.12	6.35
Age of Onset Category: ≤ 7 years old	7.49	0.80	<0.0001	5.92	9.06
Time (Years) Since Baseline: ≤ 7 years old**	1.66	0.054	<0.0001	1.56	1.77

Time (Years) Since Baseline: 8–14 years old**	1.44	0.043	<0.0001	1.36	1.53
Time (Years) Since Baseline: 15–24 years old**	1.04	0.057	<0.0001	0.93	1.15
Time (Years) Since Baseline: > 24 years old**	1.10	0.076	<0.0001	0.95	1.25

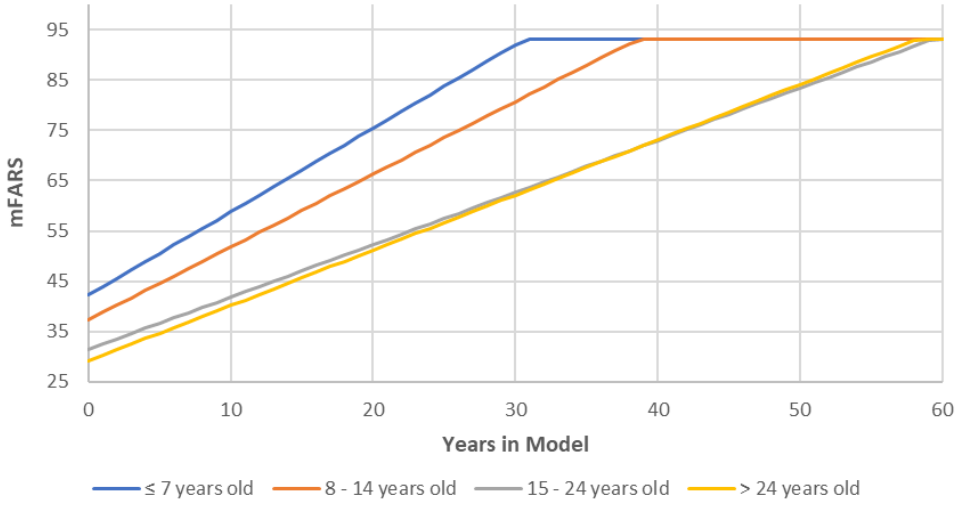
Abbreviations: mFARS = modified Friedreich's Ataxia Rating Scale; SE = Standard error. *SE values are not directly used in CEM, **beta coefficients

Source: Internal analysis of FA-COMS database FA-COMS database(71)

3.6.2.1.2.2 From 13-year and after

Two extrapolations beyond the 13-year observation period were considered. The first method assumed that the linear trajectory continued beyond the observation period until it reached its cap at an mFARS score of 93, the maximum possible mFARS score (Figure 14). This first method employed a simple, transparent assumption to avoid overcomplicating the model where data cannot support any extrapolation method.

Figure 14: Modelled SoC mFARS Trajectory (With Linear Extrapolation) for Each Age of Onset Subgroup (Alternative scenario)

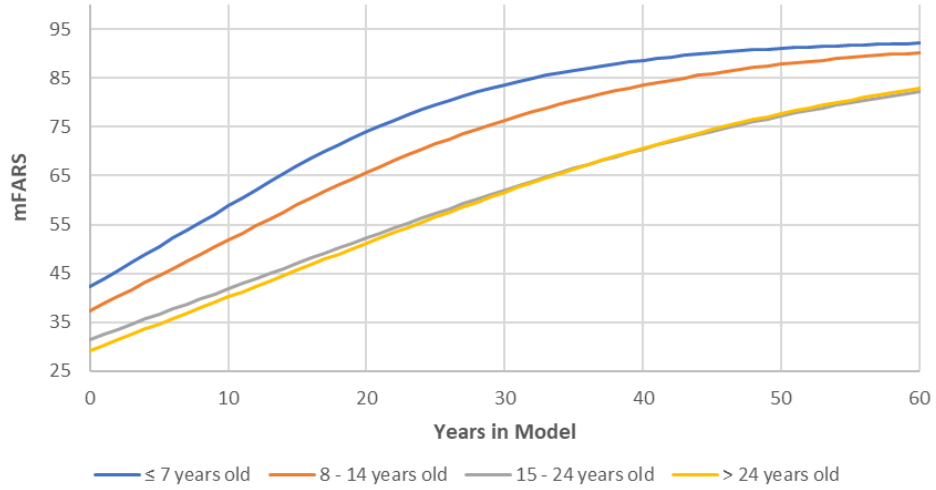


Abbreviations: mFARS = modified Friedreich's Ataxia Rating Scale, SoC = standard of Care.

Source: Internal analysis of FA-COMS database FA-COMS database(71)

The second method employed a naturally extended logistic extrapolation with an asymptote at mFARS of 93 and was implemented to account for the expected slowing of progression at worsening disease stages (Figure 15), as confirmed by clinical experts (4). The logistic extension was used in the base case because it reflected a more clinically plausible trajectory as confirmed by clinical experts (4)

Figure 15: Modelled SoC mFARS Trajectory (With Logistic Extrapolation) for Each Age of Onset Subgroup (Base Case)



Abbreviations: mFARS = modified Friedreich's Ataxia Rating Scale, SoC = standard of Care.

Source: Internal analysis of FA-COMS database FA-COMS database(71)

3.6.2.2 Treatment effect

3.6.2.2.1 Study outcome

The MOXIe Part 2 trial resulted in a mean difference in change of mFARS from baseline of -2.40 points for omaveloxolone compared to placebo at 48 weeks (reported in Section 3.6.1.1)

The delayed-start analysis conducted on the MOXIe Part 2 and OLE data indicated the benefit of starting omaveloxolone at an early stage, as subject in the placebo-omaveloxolone cohort had lower mFARS compared to the omaveloxolone-omaveloxolone cohort who started treatment 1 year earlier. At Week 72, there was a 2.91 separation between the groups' mFARS scores. Thereafter, the trajectories of each curve tracked in parallel, with the difference between the groups being –2.19, –2.74, and –2.58 at OLE Weeks 96, 120, and 144, respectively (reported in Section 3.6.1.2).

The propensity score-matched analysis conducted using the pooled MOXIe OLE population and the matched FA-COMS suggested a mean mFARS difference of 3.61 points at year 3 (reported in section 2.3.4). The base case uses data from the pooled population, as a higher patient count greatly improves the robustness of the results. This approach was validated by a clinical expert (4).

3.6.2.2.2 Modelling of study outcome (intervention and comparator)

The model was designed to compare treatment with omaveloxolone and SoC, to SoC over the lifetime of the patient; however, the MOXIe studies only directly compare mFARS progression with these options for 48 weeks.

Therefore, the treatment effect over the model time horizon was derived from the propensity-matched analysis (64), which compared patients receiving omaveloxolone and SoC in the MOXIe extension studies to patients from FA-COMS. FA-COMS was also used to estimate mFARS progression on SoC in the model (section 3.6.2.1.2).

The propensity-matched analysis allowed for the use of the 3-year follow-up data from the single-arm MOXIe extension study (instead of only one year of placebo-controlled data from the MOXIe, part 2 clinical trial) by creating a synthetic control arm from FA-COMS patients for the calculation of the long-term treatment effect of omaveloxolone and SoC compared with SoC.

The results from this analysis were presented as an annual cumulative change in mFARS for patients from the natural history study compared with those receiving omaveloxolone. The complete results are reported in Table 17.

Because a higher patient count greatly improves the robustness of results, the base case uses data from the pooled population; this approach was also confirmed with clinical experts.(4)

Treatment effect from the observed data in the MOXIe extension study was used to estimate both treatment effect over years 1 to 3 (i.e., the period of observed data) as well as to extrapolate the treatment effect for years 4+ (after observed data) over the model time horizon. Because the study itself was based on small sample sizes with fewer patients considered in the study each year, instead of using the cumulative change in mFARS over time to estimate treatment effect, the effect of omaveloxolone was estimated based on a rate ratio to consider the cumulative change in mFARS over multiple years.

Because of low patient count in the MOXIe trial extension (n=136), a rate ratio was not estimated for each age of onset subgroup; one rate ratio was assumed the same for all subgroups.

The rate ratio was defined as the change in mFARS for patients on omaveloxolone and SoC divided by the change in mFARS for patients on SoC:

$$RR = \frac{(\Delta mFARS)_{\text{omav}}}{(\Delta mFARS)_{\text{SoC}}}$$

The calculations and the resulting rate ratio are shown in Table 30.

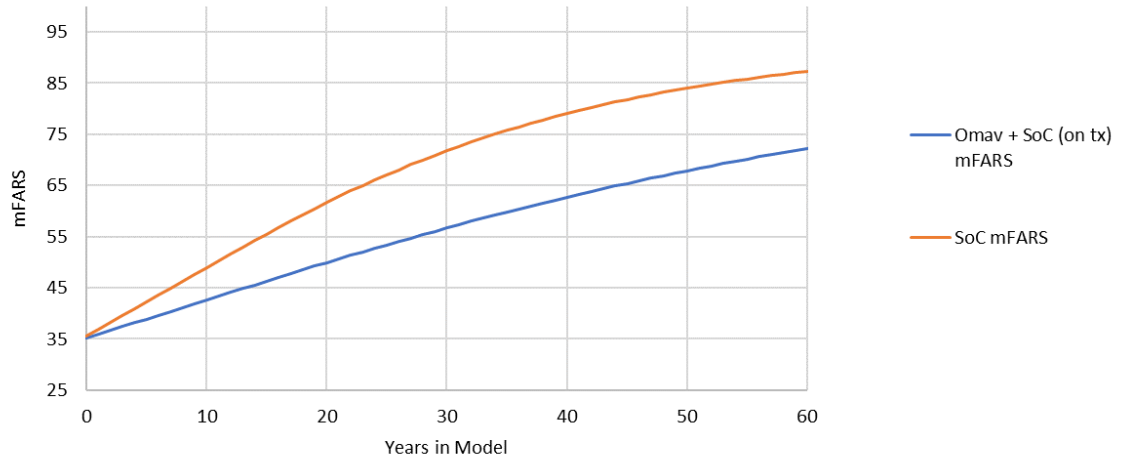
Table 30: Rate ratios used to estimate treatment effect

	Omaveloxolone	Placebo
Cumulative change resulted from propensity score matched analysis	3.004	6.611
Rate ratio	3.004/6.611 = 0.454	

Source: Lynch (2024) (64)

The resulting progression for patients on omaveloxolone plus SoC in the base case (assuming a logistic extrapolation and a short-term treatment effect defined by the average treatment effect over 3 years of observation) is shown in Figure 16.

Figure 16: mFARS Progression for Patients on omaveloxolone plus SoC compared to SoC



Abbreviations: mFARS = modified Friedreich's Ataxia Rating Scale, SoC = standard of Care-

Source: Health economic model of omaveloxolone in FA in Norway

3.6.2.3 Discontinuation

3.6.2.3.1 Study outcome

Omaveloxolone treatment discontinuation was investigated in MOXIe part 2 and the OLE (74, 75).

In MOXIe part 2, 13.7% of patients discontinued treatment at year 1 (7/51 patients) (64). The time to treatment discontinuation curves were generated for the MOXIe OLE omaveloxolone-omaveloxolone arm and used to calculate the exponential risk for treatment discontinuation in the first year and Years 2 to 4 (Table 31). In the OLE, 13% of patients receiving omaveloxolone discontinued treatment during year 1, while 5.6% of patients discontinued annually in the subsequent years (year 1 to 4) (Table 31).

Table 31: Time to discontinuation values in MOXIe OLE at year 1 and year 4

Parameter	Value
TTD curve at year 1 (Month 12)	87.0%
TTD curve at year 4 (Month 40)	76.1%

Abbreviations: TTD = Time to discontinuation.

Source: Internal Evidera analysis of MOXIe open-label extension[33]

3.6.2.3.2 Modelling of study outcome (intervention and comparator)

The time to treatment discontinuation curves were generated for the MOXIe OLE placebo-omaveloxolone arm and used to calculate the exponential risk for treatment discontinuation in the first year and Years 2 to 4. Data from the OLE was preferred as clinical trial information was considered the best source for treatment discontinuation rates of omaveloxolone.

The user can specify the duration for which the 5.6% annual risk is applicable. After the specified time, it is assumed that patients no longer will discontinue treatment (except for death).

The base case assumes that patients may discontinue treatment at any time (i.e., the duration for which the 5.6% annual risk is applicable, is indefinite).

Patients who discontinue treatment with omaveloxolone are conservatively assumed to receive no further treatment effect immediately after discontinuation, such that the annual change in mFARS of patients on omaveloxolone + SoC is the same as that of patients on SoC. There is no data to inform treatment effect after discontinuing treatment, thus a conservative assumption of immediately reverting to SoC progression was assumed.

Table 32: Estimated annual discontinuation rates

Parameter	Value
Exponential annual risk of discontinuation (Year 1)	1- (87.0%) = 13.0%
Exponential annual risk of discontinuation (Year 2-4)	1-EXP(LN(76.1%/87.0%)/((40-12)/12)) = 5.6%

Source: Health economic model of omaveloxolone in FA in Norway. Discontinuation risk were calculated from the treatment-naïve cohort in the MOXIe open-label extension study

3.6.2.4 Mortality

3.6.2.4.1 Study outcome

No deaths were recorded in either MOXIe Part 2 or OLE.

3.6.2.4.2 Modelling of study outcome (intervention and comparator)

Previously published literature on mortality was sparse (none of the resulting literature from the clinical SLR reported death as an outcome), and while data from FA-COMS included data for mortality, it was incomplete and unreliable, based on data testing and discussions with experts (71, 77).

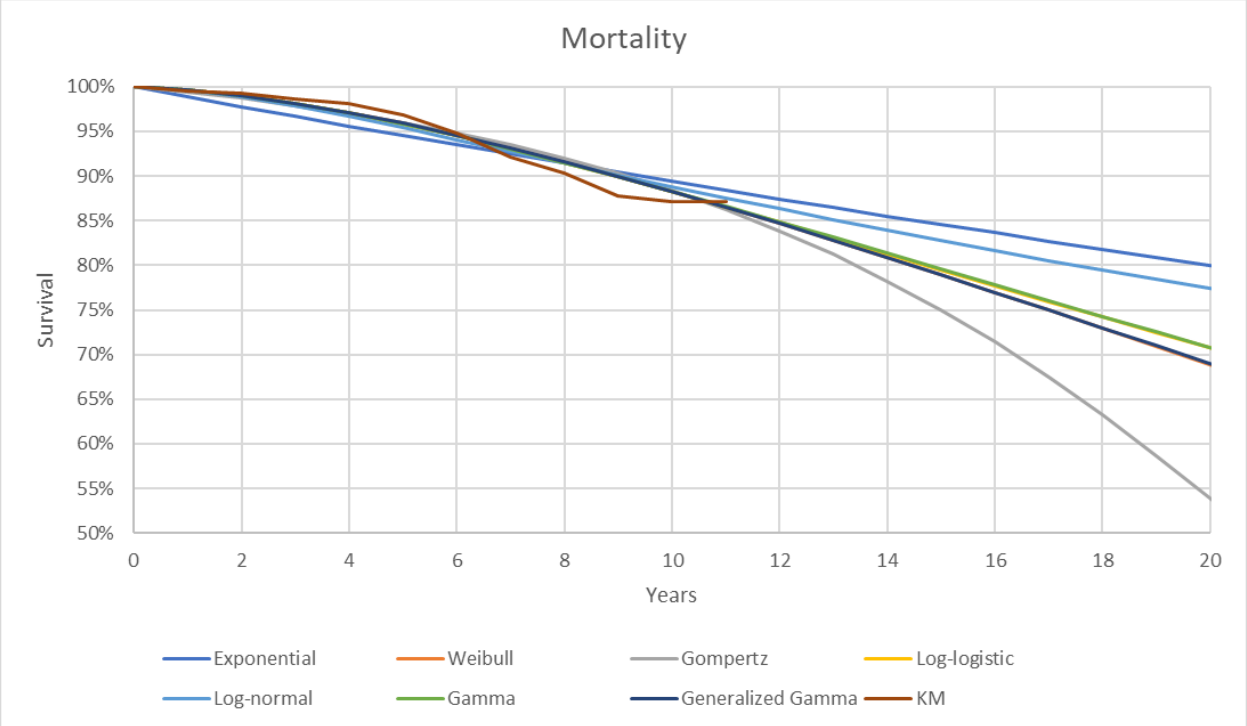
Mortality in the health economic model is estimated based on data reported in Indelicato et al. (2023) (78), an investigation of FA mortality based on 12 years of observed patient-level data from the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) (78) as well as analyses of FA-COMS.(79)

This method approximated hazard ratio (HR) values by mFARS score and applied them to a derived overall survival (OS) curve for the full FA population to generate OS curves by mFARS score. As patients change mFARS category, their risk is assumed to be that of the new OS curve at the current timepoint. Disease specific mortality risk is always bounded below the general population mortality informed by Norwegian life tables from Statistics Norway (80).

An OS curve for the full FA population was generated combining published Kaplan-Meier (KM) survival curves based on prognostic factors from Indelicato et al. (2023)(78).

The KM curve for the overall FA population was then fitted with various distributions to provide a long-term mortality prediction for the entire population. The KM curves with all the fitted distributions are presented in Figure 17 and the parameters and AIC/BIC goodness of fit metrics are presented in Table 33.

Figure 17: Overall survival Kaplan-Meier and fitted distributions for overall FA population in Indelicato et al. (2023)(78)



Abbreviation: KM = Kaplan–Meier.

Source: Analyses of Indelicato et al. (2023)(78)

Table 33 OS Distribution Parameters and AIC/BIC Metrics

Parameter	AIC	BIC	α	β	γ
Exponential [rate (log)]	485.491	489.857	-4.494		
Weibull [scale (log), shape (log)]	477.530	486.263	-5.703	0.454	

Gompertz [rate (log), shape]	479.420	488.153	-5.170	0.139	
Log-logistic [scale (log), shape (log)]	477.394	486.126	3.539	0.488	
Log-normal [meanlog, sdlog (log)]	482.253	490.986	4.113	0.397	
Gamma [scale (log), shape (log)]	477.690	486.423	-3.196	0.510	
Generalised Gamma [mu, sigma(log), Q)]	479.530	492.629	3.626	-0.446	0.991

Abbreviations: AIC = Akaike information criteria, BIC = Bayesian information criteria

Source: Analyses of Indelicato et al. (2023)(78)

The goodness-of-fit statistics (AIC/BIC) did not differ greatly between the distributions, and visually none of the distributions closely resembled the shape of the KM curve, so there was no distribution that was clearly the best visual fit to the KM curve. Based on the AIC/BIC metrics, log-logistic was the best fitting distribution. However, given that as patients progress, they move from one mortality curve to another based on disability stage, clinically implausible scenarios (i.e., lower mortality hazard for a worse disease stage) could arise due to the mathematical property of the rise and decline of hazard over time in the log-logistic distribution. Therefore, the exponential distribution was chosen as the base case to model mortality.

The use of an exponential distribution assumes mortality risk is constant and does not evolve over time. This is a strong assumption, however, a recent publication on mortality in a FA population suggests that this assumption may be supported since age was found not to be a strong driver of mortality, rather age at onset, disability stage, and comorbidities were the leading drivers.(78)

The use og the log-logistic distribution was tested in the scenario analysis, together with the gamma distribution, in which the mortality hazards increase over time.

Subsequently, HR values by mFARS category (increments of 10) were estimated. This step linked the survival derived from Indelicato et al. (2023)(78) to mFARS scoring from FA-COMs for use in the model:

- Indelicato et al. (2023)(78) reported HR of OS based on disability score (i.e., a value of 2.01 for a unit increase in baseline disability score [based on median of 5]), which is defined similarly to ataxia disease staging, the latter a parameter in the FA-COMS database.
- Due to the similarity between the definitions of disability stage and disease ataxia staging, it was possible to crosswalk the two scoring systems and have HR by baseline disease ataxia stage, which would allow the link to use this data in the present model. The HR values associated with the disability stage (and disease ataxia stage) are detailed in Table 34.
- Then, an internal analysis of FA-COMS was performed to generate a distribution of disease ataxia stage by mFARS categories (categories are defined in increments of 10 points).
- The distribution of disease ataxia stage by mFARS category was used to create a weighted average of the reported HR values by disability stage to generate the HR values by mFARS category which are presented in Table 35.

Table 34: Mortality HR for Disability Stage and Disease Ataxia Staging

Parameter	AIC	BIC
1 (no functional handicap, but signs at the examination)	0 (Normal)	2.01^(1-5)=0.061
2 (mild, able to run, walk unlimited)	1 (Minimal signs detected by physician; can run jump without loss of balance. No disability.)	2.01^(2-5)=0.123
3 (moderate, unable to run, limited walking without aid)	2 (Symptoms present, but still mild. Cannot run or jump without loss of balance. Capable of independent life, but ADL restricted. Minimal disability.)	2.01^(3-5)=0.248

4 (severe walking with one stick)	3 (Symptoms overt, significant. Regular/periodic holding onto wall or furniture or use of a cane for stability and walking. Mild disability.)	2.01^(4-5)=0.498
5 (walking with two sticks)	4 (Requires a walker, Canadian crutches, two canes, or other aids. Can perform some ADL. Moderate disability.)	2.01^(5-5)=1
6 (unable to walk, requiring wheelchair)	5 (Confined but can navigate wheelchair. Can perform some ADL that do not require standing or walking. Severe disability.)	2.01^(6-5)=2.01
7 (confined to bed)	6 (Confined to wheelchair or bed with total dependency for all ADL. Total disability.)	2.01^(7-5)=4.04

Abbreviations: AIC = Akaike information criteria BIC = Bayesian information criteria ADL = activities of daily living; HR = hazard ratio.

Note: HR is estimated using the difference between the reference disability stage of 5 and the given stage.

Source: Disability stage definitions (Indelicato et al. 2023)(78), Disease ataxia stage definitions (Delatycki 2009)(81), HR for unit increase in disability stage (Indelicato et al. 2023)(78)

Table 35: Mortality HR by mFARS category

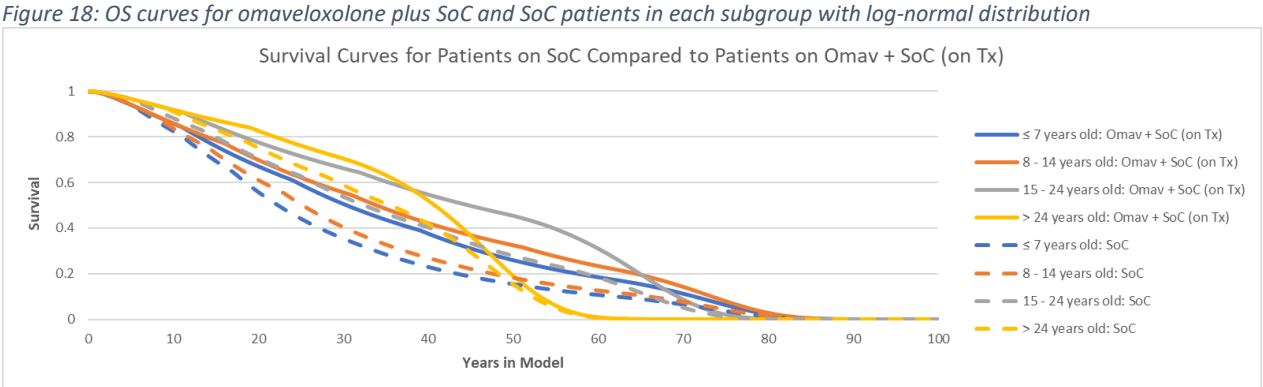
mFARS Category	HR
0–10	0.130
10–20	0.214
20–30	0.291
30–40	0.411
40–50	0.711
50–60	1.283
60–70	1.847
70-80	2.594
80–90	3.690
90+	3.965

Abbreviations: HR = hazard ratio; mFARS = modified Friedreich's Ataxia Rating Scale

Source: Calculated using disease ataxia stage distribution by mFARS (internal Evidera analysis of FA-COMS database(79)) and calculated HR for disease ataxia stage (HR for unit increase reported in Indelicato et al. [2023](78))

The OS curves for the omaveloxolone and SoC arms are presented in Figure 18. Patients who discontinue omaveloxolone are assumed to have the same mortality risk as patients on SoC alone.

Figure 18: OS curves for omaveloxolone plus SoC and SoC patients in each subgroup with log-normal distribution



Abbreviations: mFARS = modified Friedreich's Ataxia Rating Scale; Omav = omaveloxolone; OS = overall survival; SoC = standard of care; Tx = treatment

A limitation of this approach is that EFACTS population includes only adult patients, but a large portion of patients developed FA before age 18. The median age of onset of the population is 13 years old (IQR 8–18 years old) but the median age at inclusion in the study is 31 years old (IQR 22–43 years old). This results in the study population being highly progressed, as demonstrated with the median disability stage of 5 (IQR 3–6).

By relating mortality risk to disease severity, this mortality approach assumes an indirect treatment effect on mortality. No direct treatment effect on mortality is assumed due to the lack of evidence from MOXIe that omaveloxolone affects mortality.

3.6.2.5 Relevant supportive outcomes not used in the health economic model

Not applicable.

3.6.3 Safety

3.6.3.1 Clinical documentation

Overall, omaveloxolone was well tolerated in MOXIe Part 2 and the OLE. In Part 2, all patients in both treatment arms experienced at least one AE, with most AEs being mild to moderate in intensity. The most common AEs that occurred more frequently with omaveloxolone versus placebo were headache, nausea, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), fatigue, diarrhoea, and abdominal pain (Table 36) (51). Only a small number of patients permanently discontinued study treatment due to AEs (four patients [7.8%] in the omaveloxolone group and two patients [3.8%] in the placebo group).

In the OLE, AEs were reported by >90% of patients; the most frequent AEs in the omaveloxolone-omaveloxolone group were upper respiratory infection, nausea, and abdominal pain, while in the placebo-omaveloxolone group increased ALT, headache, and nausea were the most common (Table 36) (54).

Serious AEs occurred in <10% of patients receiving omaveloxolone in Part 2 or the OLE. No deaths were reported during the study

Table 36: Adverse events in MOXIe Part 2 and OLE

Adverse event, n (%)	**MOXIe Part 2** (51, 76)		**MOXIe OLE** (54)	
Summary of AEs	**Omaveloxolone (n=51)**	**Placebo (n=52)**	**Omaveloxolone-omaveloxolone (n=43)**	**Placebo-omaveloxolone (n=106)**
≥1 AE	51 (100)	52 (100)	39 (90.7)	103 (97.2)
≥1 SAE	5 (9.8)	3 (5.8)	4 (9.3)	6 (5.7)
Discontinuation due to AE	4 (7.8)	2 (3.8)	1 (2.3)	8 (7.5)
AEs occurring in >20% of patients in any treatment arm of Part 2 or OLE				
Contusion	17 (33.3)	19 (37.3)	2 (4.7)	12 (11.3)
Headache	19 (37.3)	13 (25.0)	5 (11.6)	19 (17.9)
Upper respiratory tract infection	14 (28)	15 (29)	9 (20.9)	15 (14.2)

Excoriation	13 (25.5)	12 (23.1)	2 (4.7)	15 (14.2)
Nausea	17 (33.3)	7 (13.5)	7 (16.3)	17 (16.0)
ALT increased	19 (37.3)	1 (1.9)	4 (9.3)	24 (22.6)
Fatigue	11 (21.6)	7 (13.5)	5 (11.6)	12 (11.3)
Diarrhoea	10 (19.6)	5 (9.6)	3 (7.0)	13 (12.3)
Abdominal pain	11 (21.6)	3 (5.8)	7 (16.3)	9 (8.5)
AST increased	11 (21.6)	1 (1.9)	1 (2.3)	9 (8.5)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; OLE = open-label extension; SAE = serious adverse event.

Elevated ALT and AST were observed at a higher frequency in the omaveloxolone group than in the placebo group. However, these increases were transient and reversible, with the peak effect occurring at 12 weeks before levels normalised with continued treatment. The increases were not associated with elevated total bilirubin, Hy's law criteria, clinical symptoms, or other signs of liver injury (51).

These findings align with a study of another Nrf2 activator, bardoxolone methyl, in which elevated ALT and AST was observed in the absence of other indicators of liver damage, peaked within 4 weeks of treatment initiation, and trended back towards baseline over 48 weeks (82). The study suggested that increases in ALT and AST were the result of the transcriptional effects of the drug on Nrf2 (including Nrf2-mediated increases in mitochondrial metabolism) and indicated a form of drug tolerance or adaptation instead of liver toxicity. Therefore, the ALT and AST increases observed with omaveloxolone treatment may be related to the pharmacological activity of the drug and may reflect improvements in mitochondrial metabolism, rather than liver injury (82).

3.6.3.2 Health economic model

The model included adverse events from the clinical trial that were emphasised during discussions with clinicians (2). As confirmed with these clinicians, the model assumes that all adverse events will occur within the first year of treatment (i.e., the first model cycle). The rates of adverse events used in the model, shown in Table 37, correspond to the selected moderate and severe events rates reported in the MOXIe Part 2[9]. The costs and disutility values associated with adverse events are present in Sections 3.7.3 and 3.6.5, respectively.

Table 37: Adverse events incorporated in the health economic model

Adverse event	**Incidence (from MOXIe part 2 CSR (83))**	
	Omaveloxolone	**SoC**
Nausea	5.9%	0.0%
Diarrhea	2.0%	1.9%
Oropharyngeal pain	2.0%	0.0%
Influenza	7.9%	0.0%

Abbreviations: CSR = Clinical study report; SoC = standard of care.

Source: MOXIe part 2 CSR (83)

[9] RTA 408 CSR: A phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of Friedreich's Ataxia: part 2; 14.3.5.1

3.6.4 Health-related quality of life (HRQoL)

3.6.4.1 Clinical documentation

This section describes the HRQoL outcomes measured during the clinical development program. The MOXIe part 2 trial included the change in the 36-item short form health survey (SF-36) and the change in the FA activities of daily living (ADL) score as two exploratory objectives of MOXIe Part 2.

3.6.4.1.1 SF-36

The SF-36 total score is a 0-100 scale assessed by investigating 8 health concepts (limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions.

In the MOXIe part 2, SF-36 was assessed at day 1, week 24 and 48. The mental component scale (MCS) and the physical component scale (PCS) of the SF-36 manual were summarized at baseline and Week 48, along with the change from baseline by treatment. An MMRM was fit with change from baseline as the outcome and baseline MCS/PCS, treatment group, visit, treatment group–by-visit interaction, and baseline MCS/PCS by visit interaction as covariates. The comparison of omaveloxolone with placebo was estimated using the difference in adjusted means and 95% CI for the difference in changes from baseline to Week 24 and baseline to Week 48

The mean change in SF-36 scores at week 48 was small and similar between the 2 treatment groups, mean (SD)= 68.9 (21.6) and 68.7 (19.6)[10] for omaveloxolone and placebo, respectively. No treatment-related trends were observed, and there were no statistically significant differences between treatment groups[11].

3.6.4.1.2 ADL score

ADL assesses 9 items (speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, bladder function) with items scores from 0-5 resulting in a possible total score from 0 to 36 where higher scores reflect a worse ability.

ADL was assessed at day 1, week 24, 36 and 48 using an MMRM with the change from baseline as the outcome and baseline ADL, treatment group, visit, treatment group–by-visit interaction, and baseline ADL by visit interaction as covariates.

ADL scores at Week 48 were improved from baseline with omaveloxolone (lower scores suggests improved function) and reached statistical significance relative to placebo: LS mean difference (SE) -1.30 (0.62), p = 0.04. This change was driven by significant worsening from baseline for patients who received placebo, whereas patients who received omaveloxolone did not worsen. Moreover, all 9 sections of the ADL (e.g., speech, swallowing, dressing) were numerically improved with omaveloxolone[12]. Thus, concurrent with the neurological improvements evidenced by improved mFARS scores, omaveloxolone patients also experienced functional improvements.

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[10] RTA 408 CSR: A phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of Friedreich's Ataxia: part 2; 14.3.34.1

[11] RTA 408 CSR: A phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of Friedreich's Ataxia: part 2; 14.2.35.1

[12] RTA 408 CSR: A phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of Friedreich's Ataxia: part 2; 14.2.32.1

Table 38: SF-36 and ADL scores results – MOXIe Part 2 CSR (Table 14.2.34.1 and 14.2.32.1)(48)

	SF-36		ADL	
	Omaveloxolone (n=40)	**Placebo (n=42)**	**Omaveloxolone (n=40)**	**Placebo (n=42)**
Baseline **n** **Mean (SD)**	40 70.550 (22.1637)	42 68.952 (20.5722)	40 10.738 (4.7663)	42 9.869 (4.8339)
Week 24 **n** **Mean (SD)**	36 75.250 (23.1447)	41 71.415 (20.5183)	36 10.361 (4.4811)	41 10.476 (5.0274)
Week 36 **n** **Mean (SD)**	-	-	36 11.028 (4.7689)	41 10.598 (4.8026)
Week 48 **n** **Mean (SD)**	36 68.917 (21.5637)	41 68.683 (19.6156)	36 10.556 (4.7174)	41 11.073 (4.9982)
LS mean change from baseline **n** **Mean (SD or SE)**	36 -2.694 (23.0414)	41 0.488 (21.9774)	36 -0.17(±0.450) (p = 0.71)	41 1.14 (± 0.421) (p = 0.009)
LS mean difference between treatment groups **Mean (SE)**	Not reported		-1.30 (± 0.629) (p = 0.04)	

Abbreviations ADL = Activities of daily leaving: LS = Least square; SD = Standard deviation; SE = Standard error; SF-36 = 36-item short form health survey; n = number.

Source: MOXIE Part 2 CSR (48)

ADL was collected also in the OLE. Baseline values for the mean total ADL score were similar in both prior treatment groups (12.698 in the placebo-omaveloxolone group and 12.000 in the omaveloxolone-omaveloxolone group). Changes from baseline in total ADL score for the placebo-omaveloxolone group at Week 24 and Week 48 were 0.244 and 0.390, respectively. Changes from baseline in total ADL score for the omaveloxolone-omaveloxolone group at Week 24 and Week 48 were -0.068 and 0.212, respectively.

3.6.4.2 Health economic model

In the economic analysis, patient utility for each age of onset grouping by mFARS score associated with that group at a given model cycle. Two methods are included in the analysis for the utility's estimation:

- EQ-5D data from the EFACTs database, a European based multi-national observational study. This was used in the base case as EQ-5D data was available (preferred instrument of all the agencies relevant for this submission), in addition to refer to a cohort of European patients, arguably easily comparable to the Nordic population.
- SF-36 data from FA-COMS database. This was included in the sensitivity analysis, to align the source of utility data to the one informing natural history of FA progression in the economic model

3.6.4.2.1 EQ-5D from EFACTS

A linear regression was conducted on 5 years of data from patients in EFACTS that reported population averages of EQ-5D values and SARA scores, published by Reetz et al. (2021) (84). The SARA scores were cross walked to mFARS scores using the algorithm published by Rummey et al. (2022) (23), which was based on an FA population. The regression parameters are detailed in Table 39.

This linear regression uses EQ-5D directly from the EFACTS study. The main drawback to this analysis results from the limited data available as only 5 data points were reported annually over 5 years. Although the intercept in this linear regression is greater than one, the utility values generated in the model analysis are always less than one due to the initial mFARS of each patient subgroup. Nonetheless, a precautionary measure that limits the utility values to less than one is present in the CEM utility calculations.

Table 39: Utility regression parameters

Parameter	Value	SE
Intercept	1.252	0.179
Slope	-0.012	0.003
Mean age of source population	33.7 years old	-
R-squared	0.834	0.014
F-statistic	11.118	
Degrees of freedom	3	
Regression of sum of squares	0.003	
Residual sum of squares	0.000	

Abbreviation: SE = standard error

Source: Internal Evidera analysis of Reetz et al. (2021).(84)

Note: The linear analysis of Reetz et al (2021) has a Pearson's R^2 value of 0.8344.

3.6.4.2.2 SF-36 from FA_COMS mapped into EQ-5D

A regression analysis was performed using FA-COMS(79) patient-level SF-36 data (transformed to EQ-5D-3L using a published mapping algorithm using a generalised least squares model (85)) and mFARS for the same visits predict EQ-5D from mFARS to predict patient utility from mFARS. The compliance rates of SF-36 in FA-COMS are reported in section 6.6 in the Appendix of this submission. Questionnaires with any missing data were excluded from the analyses without imputation. The Generalised Least Squares (GLS) model parameters of the regression analysis of EQ-5D and mFARS are displayed in Table 40

Table 40: Regression of EQ-5D on mFARS using GLS model

Predictors	Estimates	Confidence interval	p-value
Intercept	0.8632827	0.836, 0.890	<0.001
mFARS (slope)	-0.0043211	-0.004, -0.005	<0.001
Median age of source population		**20 years old**	
Random Effects			
Observations	2101		
Marginal R2/Conditional R2	0.222/0.656		

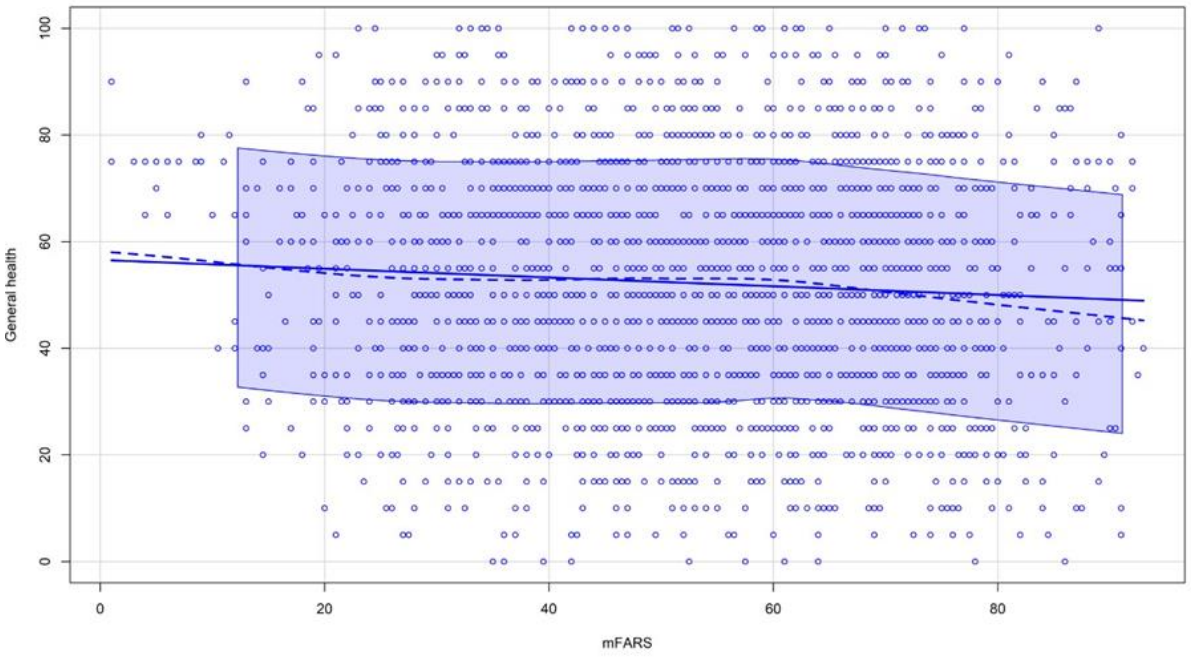
Abbreviation: GLS = Generalised Least Squares; mFARS = modified Friedreich's Ataxia Scale.

Source: Internal Evidera analysis of FA-COMS database(79)

A regression to predict EQ-5D from mFARS was implemented in the model base case to predict patient utility for each age of onset subgroup. FA-COMS reported patient-level SF-36 data and mFARS for the same visits, which were used to generate a regression model through a multi-step process:

1. The total SF-36 data, which did not show strong sensitivity to change in mFARS, as shown in Figure 19, and corroborated by literature (86) was converted to EQ-5D data using a published mapping algorithm, using a generalised least squares model (85).
2. Run linear regression analysis on mFARS and converted EQ-5D data, with underlying data from FA-COMS. Additionally, a less smoothed curve was generated which supported the linear regression approach given the linear pattern except at the lowest and highest mFARS scores as shown in Figure 20.

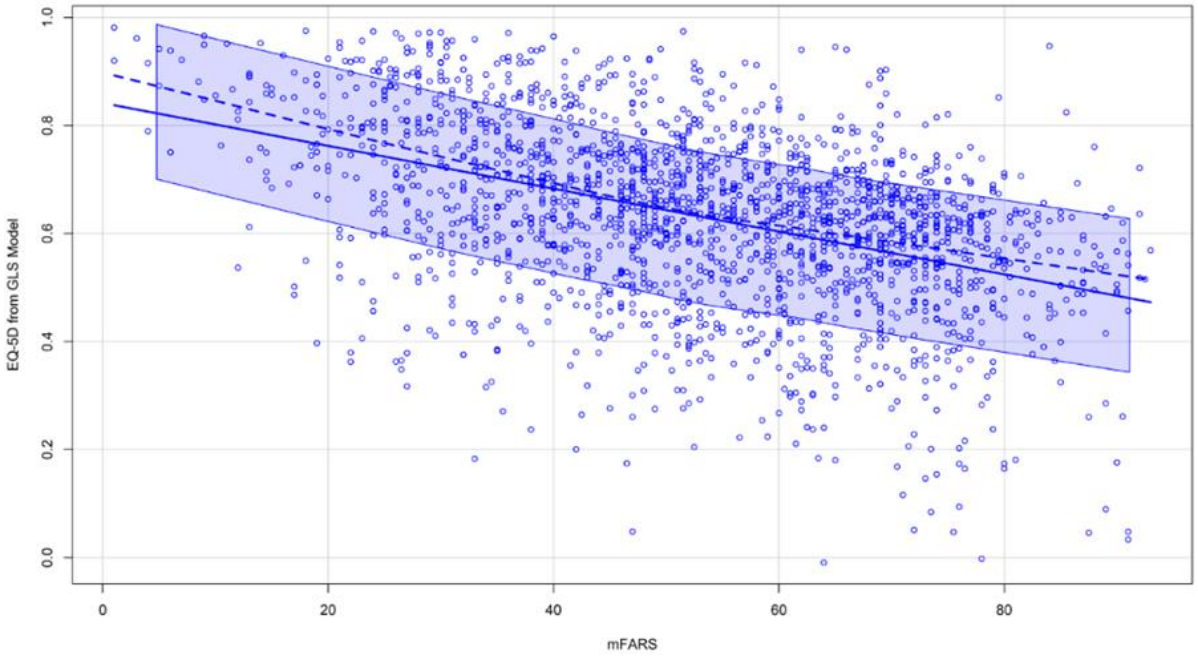
Figure 19: Total SF-36 correlation analysis with mFARS



Abbreviations: mFARS = modified Friedreich's Ataxia Rating Scale

Source: Internal analysis of FA-COMS database (71)

Figure 20: Converted EQ-5D correlation analysis with mFARS (FA-COMS)



Abbreviations: FA-COMS = Friedreich's Ataxia Clinical Outcome Measures Study; mFARS = modified Friedreich's Ataxia Rating Scale

Source: Internal analysis of FA-COMS database using GLS mapping algorithm (71, 79, 85)

3.6.4.2.3 General Norwegian population utility

The Norwegian general population utility for men and women 16 years and over by age is informed by the model as presented by the most recently available DMP estimates (87).

The model assumes that patient utility changes with patient age as demonstrated by the general population utility. The model uses the average age in the utility source, the current age of the patient in the model for each age of onset subgroup) and the baseline gender distribution for each age of onset subgroup (assumed constant over the model time horizon) to adjust patient utility by age.

$$Utility\ Adjustment\ Factor_{Age_{cur}} = \frac{\left(Utility_{Male,Age_{cur}} * \%_{Male} + Utility_{Female,Age_{cur}} * \%_{Female}\right)}{\left(Utility_{Male,Age_{ref}} * \%_{Male} + Utility_{Female,Age_{ref}} * \%_{Female}\right)}$$

3.6.4.2.4 Caregiver disutility

The model can further consider caregiver disutility. Due to the rarity of the disease, there is a lack of data on caregiver disutility for patients with FA in literature. Caregivers' health related quality of life is not included in the base case analysis but are explored in one of the scenario tested in the scenario analysis.

The model allows for the consideration of FA caregiver quality-of-life impacts by assuming caregiver disutility for non-ambulatory FA patients to be similar to those caring for non-ambulatory patients with Duchenne muscular dystrophy (DMD) as reported in a cross-sectional multinational study of more than 700 caregivers for patients with DMD (88). The value used was reported in a system literature review that took the reported values and determined the caregiver disutility associated with ambulatory compared with non-ambulatory patients was -0.11 per year.(89) FA patients without caregivers or

those who have caregivers but are ambulatory do not contribute to these quality-adjusted life year (QALY) losses. The model assumes that any non-ambulatory patient will require some caregiving (details on the proportion of patients requiring caregiving are presented in Section 3.7.4.1-healthcare resource use). The proportion of patients for each category of mFARS (10 point increments) with a score of 4 on either ADL Walking or ADL Falling scales (i.e., non-ambulatory patients) was multiplied by the reported value from Landfeldt to approximate an average caregiver disutility value for all FA patients in each category of mFARS, as shown in Table 41. These calculated disutility values are applied to each model cycle when caregiver disutility was included in model settings.

The model also includes an adjustment to avoid the caregiver QALY trap, where a longer survival would result in increased caregiver QALY losses.(90) Instead, the total patient population eligible for caregiver QALY losses is limited by the survival of SoC. Therefore, even if more patients are alive on omaveloxolone plus SoC than on SoC at a specific timepoint, the proportion of patients that the caregiver disutility is applied to is the same for both treatment arms (the proportion of patients still alive on SoC).

This methodology for approximating caregiver disutility has limitations. First, this method assumes an equivalency between the caregiving demands for DMD patients and FA patients, which although are both progressive neuro-muscular disorders, have different disease characteristics. It also assumes a single caregiver through course of the disease, though this is likely to increase after progression. Additionally, this method assumes that patient loss of ambulation is the only cause of caregiver disutility. The use of a single milestone to capture caregiver utility is likely oversimplifying the disease, which progressively worsens multiple aspects of a patient's everyday functioning, all of which can impact patient and caregiver quality of life. However, clinicians confirm that ambulation status has the largest impact on patient wellbeing (and by extension caregiver wellbeing),(3) with one clinician stating that their objective in treating FA patients is to keep them mobile.(3) Therefore, the model uses the aforementioned approach based on patient ambulation status.

Table 41: Caregivers disutility calculations

mFARS	Proportion of non-ambulatory (%)	Disutility
mFARS: 0–10	0.00%	0
mFARS: 10–20	0.00%	0
mFARS: 20–30	0.00%	0
mFARS: 30–40	0.51%	-0.000556492
mFARS: 40–50	7.20%	-0.007923729
mFARS: 50–60	32.04%	-0.035247678
mFARS: 60–70	75.16%	-0.082671875
mFARS: 70–80	91.30%	-0.100434783
mFARS: 80–90	97.39%	-0.107130435
mFARS: 90+	100.00%	-0.11

Abbreviation: mFARS = modified Friedreich's Ataxia Rating Scale.

Source: Proportion non-ambulatory patients (Internal Evidera analysis of FA-COMS database(79)); caregiver disutility (Pennington 2020 (89)) multiplied by proportion of non-ambulatory patients

3.6.5 Adverse event disutility

For each adverse event, the model considers the disutility and duration associated with each event and uses that to calculate the QALY loss for each event. The disutility values and durations associated with each AE, detailed in Table 42, were based on values used in National Institute for Health and Care

Excellence submissions in similar neuromuscular disease areas (TA767 (91), TA706 (92), TA533(93)). Based on these references, only influenza's disutility is effectively included in the model.

Table 42: Disutilities and duration of adverse events in the health economic model

AE	Disutility	Duration	QALY loss per episode	Source
Nausea	0	11 days	0	Assumption from TA767 (91) for non-serious nausea AEs
Diarrhoea	0	20 days	0	Assumption from TA767 (91) for non-serious diarrhoea AEs
Oropharyngeal pain	0	20 days	0	Disutility: Assumption in TA706 (92) for oropharyngeal pain Duration: TA533 (93) for nasopharyngitis
Influenza	-0.08	1 day	-0.000219	Assumption from TA533 (93) for influenza-like illness

Abbreviations: AE = Adverse event; QALY = Quality-adjusted life year, TA = Technology appraisal

3.7 Resource use, costs, and model inputs

In the section, the cost and resource use for the Norwegian model are described. The unit cost for Sweden and Denmark are shown together with their references in Section 6.7 (Appendix G).

3.7.1 Medicine acquisition costs of intervention and comparator(s)

The EMA defined dose is 150 mg of omaveloxolone daily, which entails three tablets every day. Due the formulation as a tablet, set dose, and expected duration of one pack of 30 days, no drug wastage is assumed (37). The relative dose intensity in the model is 86.91%, in line with the data from MOXIe part 2, and reflects for example non-adherence and down titration observed in case of serious AEs (76).

Table 43: Medicine acquisition costs

	Product number	Strength	Pack size	Maximum AUP excluding VAT, pr. pack
Omaveloxolone (Skyclarys)	102493	50 mg	90 tablets	280,022 NOK

Abbreviations: AUP = Pharmacy retail price = VAT, value added tax.

Source: Skyclarys EPAR (37)

3.7.1.1 Other relevant medicine acquisitions costs

This health economic model does not consider other medicine acquisition costs as there are no current treatments available for FA. Symptomatic treatments by specialists are captured in the mFARS-dependent healthcare resource use. Comorbidities are costed through increased healthcare resource use.

3.7.2 Health state and event costs

This health economic model is regression-based and categorises patients by mFARS score. The FA-COMS and MOXIe trials did not capture healthcare resource use or costs, which prevents direct costing. Furthermore, no clear estimates were identified in the literature, especially on how health care resource use varies with increasing mFARS. Therefore, expert opinion was used to inform the resource use of patients based on changes in ADL score throughout the subcategories. This metric is more suitable than mFARS as it captures changes in disease severity that can be linked to changes in resource use.

Clinicians were asked to define the resource use for 'baseline' patients (i.e., patients with a score of 0–1 in the relevant ADL subcategories) and then specify the number of additional medical yearly visits or one-time resource uses that patients would accrue for an increase in the relevant ADL score. To avoid double counting, some ADL subcategories, such as walking and falling, were combined if relevant according to clinicians. Next, mFARS scores were categorised by increments of 10, from 0-10 to 90+ (93 is the worst and highest mFARS score). Based on patient counts from FA-COMS, distributions of ADL scores per category (0-1, 2, 3, 4) were estimated within each mFARS category. This results in a distribution of the ADL scores in each subcategory (walking/falling, dressing/hygiene/feeding, swallowing/speech, bladder function, sitting position) within each mFARS category. The input from clinicians on resource use based on ADL score is supplied as appendix to the submission (see Appendix D: KOL input on HCRU based on ADL scores).

To estimate the incidence of patients entering each mFARS category, the difference in these proportions in subsequent mFARS category was taken, when applicable, and used to calculate one-time resource use costs. Resources associated with recurring use (e.g., neurologist visits) have the

annual resource use frequency specified based on the mFARS score. Therefore, the patients are assumed to accumulate recurring resource costs every year specific to their mFARS score. Resources that are required only once (e.g., wheelchair) are assumed to accumulate costs associated with additional units of the resource required only when the patient enters a new mFARS category.

The resource use by ADL score obtained from clinicians was weighted using the proportions by mFARS score in each model cycle. Healthcare resource use encompasses two parts: healthcare professional (HCP) visits, and home modifications, aids, medical devices.

3.7.2.1 Healthcare professional visits

Most of these resources were reported by Giunti et al. (94), in their cross-sectional observational study in patients with FA, estimating direct medical and non-medical costs, productivity loss, and non-recurring costs and resource use burden in the UK. This model uses clinical opinion to inform the use of these resources. Resource use (Table 44) and costs (Table 46) were separated by annually recurring and one-time costs. Additional resource use for comorbidities is also included in Table 45, as the ADL subscore used to calculate resource use by mFARS do not capture the impact of important comorbidities on FA patients.

3.7.2.2 Home modifications, aids, and medical devices

Costs for home modifications, aids, and medical devices are also included in the model as these costs are within the scope of the limited societal perspective that is relevant for Norway, as suggested by the JNHB guidelines. The resources are informed by the observational study of Giunti et al. (94). The resource use in FA patients was also elicited by clinical opinion and estimated as described above. Unit costs of these resources are also displayed in Table 46. These costs were estimated from the UK NHS price from Giunti et al, which was then inflated to 2023 GBP and then converted to 2023 NOK (94). The calculated increase in resource use for increase in mFARS category is presented in Table 45. The included comorbidities were assumed to not have an impact on home modifications, aids, and medical devices.

Table 44: Healthcare resource costs and use by mFARS category and comorbidity per year

Visits per year	mFARS: 0-10	mFARS: 10-20	mFARS: 20-30	mFARS: 30-40	mFARS: 40-50	mFARS: 50-60	mFARS: 60-70	mFARS: 70-80	mFARS: 80-90	mFARS: 90+	Cardiomyopathy	Scoliosis	Diabetes
Neurologist	2.05	2.18	2.58	3.03	3.88	4.80	5.72	7.23	8.49	10.00	2.00	2.00	0.00
Cardiologist	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	3.00	0.00	0.00
Primary Care Physician	1.00	1.00	1.06	1.13	1.17	1.29	1.48	1.82	2.12	3.30	0.00	0.00	3.00
Orthopaedic Specialist	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	3.00	0.00
Psychiatrist	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Occupational Therapist	2.09	2.99	3.93	4.83	5.76	6.80	8.28	9.47	9.85	9.65	0.00	0.00	0.00
Dietician	1.00	1.00	1.04	1.06	1.07	1.11	1.18	1.38	1.67	2.65	0.00	0.00	12.00
Nurse Practitioner	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Physiotherapist	8.00	11.20	13.12	14.83	15.29	14.14	11.51	10.78	10.54	10.17	0.00	8.00	0.00
Speech therapist	2.09	3.78	4.82	5.26	5.90	7.21	8.91	10.86	12.24	12.83	0.00	0.00	0.00
Palliative care physician	0.00	0.00	0.01	0.03	0.16	0.70	1.69	2.52	3.84	5.48	2.00	0.00	0.00
Home health nurse	0.00	0.00	0.05	0.14	0.41	1.60	3.79	6.24	10.21	16.35	4.00	0.00	0.00
Endocrinologist	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.00
Hospitalisations	0.00	0.05	0.28	0.57	1.03	1.78	2.66	3.41	3.90	5.65	2.00	1.00	0.00

Abbreviations: mFARS = modified Friedreich's Ataxia Scale.

Source: Internal analysis

Table 45: Home modifications, aids, and medical devices by mFARS category

	mFARS: 0-10	mFARS: 10-20	mFARS: 20-30	mFARS: 30-40	mFARS: 40-50	mFARS: 50-60	mFARS: 60-70	mFARS: 70-80	mFARS: 80-90	mFARS: 90+
Cane/Walker	0.00	0.05	0.10	0.17	0.30	0.29	0.08	0.01	0.00	0.00
Wheelchair	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Adaptive bath/shower	1.05	0.05	0.29	0.26	0.39	0.44	0.66	0.82	0.73	0.35
Changes to home flooring	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Door widening	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Electric bed	1.00	0.00	0.05	0.03	0.09	0.22	0.33	0.21	0.04	0.03
Handrail and grabrail	0.05	0.10	0.34	0.41	0.66	0.74	0.84	0.75	0.72	0.33
Hoists	0.00	0.00	0.08	0.04	0.23	0.56	1.02	0.91	0.75	0.37
Ramps	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Specialized mattress	0.00	0.00	0.05	0.03	0.16	0.47	0.82	0.54	0.52	0.35
Stair lift	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Stair rail	0.00	0.40	0.33	0.38	0.40	0.33	0.09	0.01	0.00	0.00
Extensive home improvement	1.00	0.05	0.15	0.20	0.46	0.75	0.84	0.38	0.11	0.06
Feeding tube	0.00	0.00	0.00	0.01	0.00	0.00	0.01	0.03	0.08	0.39
Catheter	0.00	0.00	0.02	0.06	0.09	0.14	0.26	0.31	0.21	0.39

Abbreviations: mFARS = modified Friedreich's Ataxia Scale.

Source: Internal analysis

Table 46: Unit costs for healthcare resource use in health economic model

Healthcare resource	Unit costs (NOK)	Source
Neurologist	3,657	Norwegian DRG 2024 (95) (901O Poliklinisk konsultasjon vedr andre sykdommer i nervesystemet): weight 0,070
Cardiologist	2,978	Norwegian DRG 2024 (95) (905C Pol konsultasjon vedr angina pectoris og iskemisk hjertesykdom, unntatt AMI): weight 0,057
Primary Care Physician	621	Direktoratet for medisinske produkter (2024) (96) Legebesøk - Spesialist i allmennmedisin 2019. Price inflated to latest value available for CIP (May 2024)
Orthopaedic Specialist	2,665	Norwegian DRG 2024 (95)](808Y Ortopedisk bandasjering): weight 0,051
Psychiatrist	599	Norwegian DRG 2024 (95) (TD32A Polikliniske konsultasjoner - Andre depressive tilstander - Voksne): weight 0,163 [Enhetsrefusjon i 2024 for TSB/PHV=3675]
Occupational Therapist	559	Direktoratet for medisinske produkter (2024) (96) Sykepleier 2019 Price inflated to latest value available for CIP (May 2024)
Dietician	559	Direktoratet for medisinske produkter (2024) (96) Sykepleier 2019 Price inflated to latest value available for CIP (May 2024)
Nurse Practitioner	598	Direktoratet for medisinske produkter (2024) (96) Specialsykepleier 2019 Price inflated to latest value available for CIP (May 2024)
Physiotherapist	261	Norwegian DRG 2024 (95) (992O Fysisk treningsterapi som ledd i spesialisthelsetjenester til pasienter med somatiske lidelser): weight 0,163 [Enhetsrefusjon i 2024 for TSB/PHV=3675]
Speech therapist	598	Direktoratet for medisinske produkter (2024) (96) Sykepleier 2019 Price inflated to latest value available for CIP (May 2024)
Palliative care physician	621	Direktoratet for medisinske produkter (2024) (96) Legebesøk - Spesialist i allmennmedisin 2019. Price inflated to latest value available for CIP (May 2024)
Home health nurse	559	Direktoratet for medisinske produkter (2024) (96) Sykepleier 2019 Price inflated to latest value available for CIP (May 2024)
Endocrinologist	3,030	Norwegian DRG 2024 (95) (910O Poliklinisk konsultasjon vedr andre endokrine/ernærings-/ stoffskiftesykdommer): weight 0,058
Hospitalisations	21,402	Direktoratet for medisinske produkter (2024) (96) Liggedøgn - Generelt, gjennomsnitt. 2017 Price inflated to latest value available for CIP (May 2024)
Cane/Walker	1,550	Giunti, Greenfield et al. (2013) (94), Table 8; Inflated to 2024 NOK
Wheelchair	31,009	
Adaptive bath/shower	74,451	Giunti, Greenfield et al. (2013) (94), Table 6; Inflated to 2024 NOK
Changes to home flooring	22,641	
Door widening	27,718	
Electric bed	25,499	
Handrail and grabrail	3,713	
Hoists	24,425	
Ramps	37,189	

Specialized mattress	9,094	
Stair lift	17,362	
Stair rail	943	
Extensive home improvement	48,1051	
Feeding tube	598	Assumed as a nurse practitioner visit
Catheter	598	Assumed as a nurse practitioner visit

Source: Costs were derived from Norwegian DRG costs (95), DMP unit costs (96), or inflated and exchanged to 2024 NOK from observational study of FA patients (94)

3.7.3 Adverse events costs

Adverse events were based on Norwegian DRG costs from 2024.

Table 47: Costs of adverse events included in the model

Adverse event	Costs (NOK)	Source
Nausea	2,717	Norwegian DRG 2024 (95) (917A - Pol kons vedr lymfom, leukemi, myelomatose og visse andre benmargssykdommer): weight 0,052
Diarrhea	3,240	Norwegian DRG 2024 (95) (916O - Poliklinisk konsultasjon vedr sykdommer ved bloddannelse eller i immunsystemet): weight 0,62
Oropharyngeal pain	2,299	Norwegian DRG 2024 (95) (901E - Annen poliklinisk konsultasjon vedr smerterelaterte tilstander): weight 0,044
Influenza	3,239	Norwegian DRG 2024 (95) (916O - Poliklinisk konsultasjon vedr sykdommer ved bloddannelse eller i immunsystemet): weight 0,062

Abbreviations: DRG = Diagnosis-related group.

Source: Norwegian DRG costs (95)

3.7.4 Miscellaneous costs

The model allows for the inclusion indirect and non-medical resource use. Though not included in the base-case of the health economic analysis, this section describes their estimation to facilitate exploration of scenarios where these costs are included.

3.7.4.1 Caregiver cost

Due to the nature of the disease, patients with FA may require significant caregiver support. To capture costs associated with caregiver support, the model considers the proportion of patients in need of caregiving as well as the average number of hours required for caregiving based on disease severity.

The average number of caregiving hours required for patients with FA by disease severity is based on clinician feedback. Clinicians provided estimations based on ADL scores, which were then converted to mFARS ranges.

Patients with a maximum ADL score of 2 (i.e., indicative of mild severity of disease) in at least one ADL category are assumed to require 6 caregiver hours a week, patients with a maximum score of 3 (i.e., indicative of moderate severity of disease) in at least one ADL category are assumed to require 3 caregiver hours 7 days a week (i.e., 21 caregiver hours per week), and patients with a maximum score

of 4 (i.e., indicative of more severe disease) in at least one ADL category require constant 24/7 caregiver attention (i.e., 168 caregiver hours per week).

The proportion of patients requiring a caregiver was assumed to be any patients with an ADL score of 2 or higher, as estimated using data from FA-COMS. To estimate the average number of caregiver hours per week, a distribution of maximum ADL score by mFARS score category (defined in increments of 10) was calculated using data from FA-COMs database and multiplied by the hours indicated by the clinician (*Table 48*). This model assumes that caregiver hours are divided into hours coming from either informal caregiving or professional caregiving.

3.7.4.1.1 Professional Caregiver Support Costs

Professional caregiver support provides medical support to patients at their home and is considered a direct non-medical expense. It is assumed that 14% of caregiver hours required by patients is performed by professional caregivers, based on a patient survey from Giunti et al. (94). The average professional caregiver was taken from the Norwegian unit cost database from the DMP as Spesialsykeplejer. (96). The calculated average number of professional caregiver hours required by the FA population is an average of all patients, including those without caregivers, and is displayed in Table 48.

Table 48: Resource use and costs of professional and informal caregiver based on mFARS category

	mFARS Ranges									
	0–10	**10–20**	**20–30**	**30–40**	**40–50**	**50–60**	**60–70**	**70–80**	**80–90**	**90+**
Proportion of patients requiring caregiving	18%	58%	76%	92%	98%	100%	100%	100%	100%	100%
Average caregiver hours per week*	6.0 hrs	7.1 hrs	11.0 hrs	14.7 hrs	29.3 hrs	69.7 hrs	133.3 hrs	158.4 hrs	166.7 hrs	168.0 hrs

Abbreviation: hrs = hours; mFARS = modified Friedreich's Ataxia Rating Scale.

**Average number of caregiver hours required per patient across patients requiring caregiver*

Source: FA-COMS Database, KOL feedback

3.7.4.1.2 Informal caregiver costs

Informal caregiver costs account for the time spent caring for an individual by a family member where the individual had to take time off work. It is assumed that 86% of caregiver hours required by patients is performed by informal caregivers, based on the patient survey from Giunti et al. (94). Additional costs parameters used to calculate caregiver time costs are presented in Table 49.

Table 49: Informal caregiver costs estimation

Parameters	**Value**	**Source**
Proportion of caregivers taking time off work	22%	Giunti et al. (2013) (94)
Average hourly caregiver wage	272 NOK	Direktoratet for medisinske produkter (2024) (96) Pasient og pårørende fritid 2017 Price inflated to May of 2024

Abbreviation: GBP = British pound sterling; NOK = Norwegian Krone.

3.7.4.2 Other direct non-medical costs

Other non-medical patient costs include transportation and education support, which is defined as additional help in school applicable to patients 18 years old or younger and reported in Giunti et al. (2013) (94). The model ignores respite care costs despite being reported in Giunti et al. (2013) since they were minimal, and it was unclear how to avoid double counting costs with other caregiving cost categories.

The model also includes transportation costs, a cost not reported by Giunti et al. (2013). Annual costs of transportation is based on the average transportation cost included in the DMP Enhetskostnads database, multiplied by the average number of physician visits per year based on patient mFARS score (which was the total number of direct medical visits) as detailed in Table 29.

Table 50: Education support and transportation costs in the model

Direct non-medical costs	Costs (NOK)	Source
Education support (annual)	2,841	Cost and Payer Coverage Source: Giunti 2013 (94), cohort costs and payer coverage reported in Table 9 for 75 patient cohort; Costs exchanged to NOK in 2009, and inflated to 2024. Note: only applied to patients younger than 18 years old.
Travel costs to/from each appointment	1,719	Source: DMP, Enhetskostnader: Pasientreise (2024)[726*2 and inflated from 20920 to May 2024] (96)
Number of Appointments per year by mFARS score		
mFARS 0–10	18.2	Summation of all the medical visits (excluding home health nurse which would travel to the patient) specified in Table
mFARS 10–20	24.2	
mFARS 20–30	28.9	
mFARS 30–40	32.7	
mFARS 40–50	36.3	
mFARS 50–60	39.8	
mFARS 60–70	43.4	
mFARS 70–80	49.5	
mFARS 80–90	54.7	
mFARS 90+	61.7	

Abbreviation: mFARS = modified Friedreich's Ataxia Rating Scale.

3.7.4.3 Indirect costs

Productivity losses calculations are implemented in the economic model, but not included in the base case as recommended by DMP. The inclusion is explored in the scenario analysis and available for other countries to be included (i.e. Sweden). Employment rate specific for FA patients, as well as the average hours worked per week was reported by Giunti et al (13% and 23.6 respectively).

Table 51: Patients productivity loss – general population data

Variable	Value	Source
% employment	96%	Labour force survey (unemployment in % of labor force 4%) SSB (97)
Average hours worked per week	34.2	09303: Employed persons (LFS), by contractual working hours, contents, year and sex - SSB (97)

Average hourly wage	272	Direktoratet for medisinske produkter (2024) (96) Netto lønn - Per time (2024)

4 Health economic analysis – Results

An overview of the base case settings and the alternative tested in the scenario analysis are reported in Table 52. The results for base case and all sensitivity analyses are presented in the following sections.

Table 52: Overview of the base case and scenarios conducted

Item	Base case	Alternative scenarios presented in the scenario analysis
Time horizon	Lifetime (up to patients age of 100)	• 40 years (regardless of age of onset subgroup)
Perspective	Cost included in the analysis: • Drug acquisition • Medical and non-medical resource use • Comorbidities • AE • Professional and informal caregivers	• Excluding non-medical resource use and informal caregivers • Including productivity losses • Including caregivers QALY losses
Discount rates	For both costs and outcomes • 4% from 0-39 years • 3% from 40-79 years • 2% after 80 years	• 0% for both cost and outcomes regardless of time horizon • 5% for both cost and outcomes regardless of time horizon
Population baseline characteristics	FA-COMS population with an mFARS recorded within 3 tears of diagnosis	• Full FA-COMS population • MOXIe part 2
mFARS natural history long term extrapolation	Logistic extrapolation (natural extension) with asymptote at 93 mFARS	• Linear extrapolation with flat cap at 93 mFARS
Treatment discontinuation	Annual discontinuation rate of 13% for the first year and 6% thereafter	• Annual discontinuation rate of 13% for the entire time horizon • Annual discontinuation rate of 6% for the entire time horizon
Mortality	FA OS curve extrapolated with an exponential distribution and mFARS specific HR	• Loglogistic distribution • Gamma distribution
Utility	Linear regression based on EFACTS dataset (SARA cross-walked into mFARS and EQ-5D)	• Linear regression based on FA-COMS dataset (mFARS and SF-36 mapped into EQ-5D)

Abbreviations: EFACTS = European Friedreich's Ataxia Consortium for Translational Studies; FA = Friedreich's ataxia; mFARS = modified Friedrich Ataxia Rating Scale; OS = Overall survivals; QALY = Quality-adjusted life year; SARA = Scale for the Assessment and Rating of Ataxia

4.1 Incremental analysis of costs and outcomes

4.1.1 Base case results

The results of the costs utility analysis of omaveloxolone for the treatment of FA in patients aged 16 years and older in the Norwegian clinical setting are shown in Table 53. In the base case, omaveloxolone was associated with higher costs and higher QALY compared to SoC. Acquisition costs accounted for most of the incremental cost followed by comorbidities costs. On the contrary, omaveloxolone was related to lower disease management, non-medical resource and informal caregivers' costs.

Table 53: Summary of discounted results of the incremental cost-effectiveness analysis.

Per patient	Omaveloxolone	Standard-of-care	Difference
Discounted life years			
Total life years	19.18	18.55	0.63
Discounted QALYs			
Total QALYs	**12.07**	**10.62**	**1.45**
QALYs patient	12.07	10.62	1.45
QALYs caregiver	0.00	0.00	0.00
QALYs, adverse events	-0.000017	0.000000	-0.000017
Discounted costs (NOK)			
Total costs	31,154,711	4,977,106	26,177,605
Medicine costs	26,649,127	-	26,649,127
Adverse reactions	527	62	465
Medical resource use costs	1,932,514	2,404,417	-471,903
Comorbidity	1,191,105	1,160,919	30,186
Non-medical resource use costs	1,323,058	1,338,095	-15,037
Informal caregivers	58,380	73,614	-15,234
Incremental results	**Intervention vs. Comparator**		
ICER (NOK per QALY)	**18,092,625**		
ICER (NOK per life year gained)	**41,276,278**		

Abbreviations: ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life year.

4.1.2 Sensitivity and scenario analysis

The sensitivity analysis undertaken include a deterministic sensitivity analysis (DSA), a scenario analysis and a probabilistic sensitivity analysis (PSA).

4.1.2.1 Deterministic sensitivity analysis

All model inputs relevant to the base case were considered in the DSA except time horizon and cost and health outcome discount rates, as these parameters tend to disproportionately impact results and can dwarf the impact of other relevant parameters on model outcomes. These parameters were instead investigated through scenario analyses. Additionally, certain parameters that do not have any uncertainty associated with the input value (e.g., number of tablets per pack) are excluded from the DSA.

The fifteen parameters with the highest impact on the ICER are summarised in Table 54, and in Figure 21 as a tornado diagram.

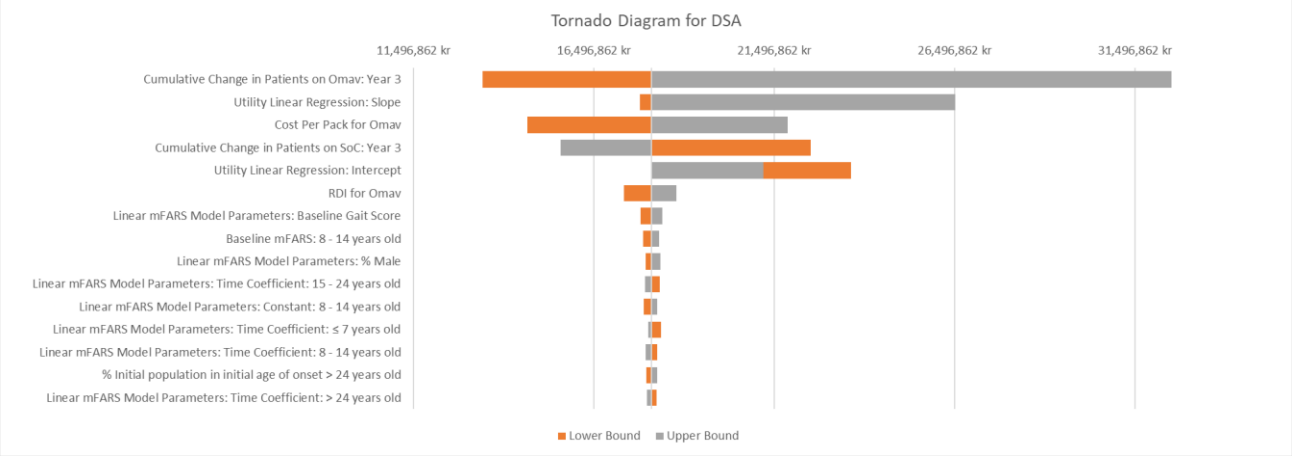
Table 54: Deterministic one-way sensitivity analysis

	Base case value	Lower bound	Upper bound	ICER (lower bound)	ICER (upper bound)
Base case					18,092,625
Cumulative Change in Patients on Omav: Year 3	3.004	1.917	4.490	13,406,573	32,503,674
Utility Linear Regression: Slope	-0.0121	-0.0182	-0.0060	17,769,916	26,512,482
Cost Per Pack for Omav	280,022	227,837	337,507	14,660,149	21,873,753
Cumulative Change in Patients on SoC: Year 3	6.611	5.429	7.974	22,502,818	15,582,216
Utility Linear Regression: Intercept	1.2522	0.9010	1.6034	23,616,502	21,188,232
RDI for Omav	86.9%	83.3%	90.2%	17,323,177	18,781,369
Linear mFARS Model Parameters: Baseline Gait Score	0.848	0.804	0.892	17,788,699	18,401,362
Baseline mFARS: 8 - 14 years old	34.7	32.9	36.5	17,864,349	18,299,064
Linear mFARS Model Parameters: Time Coefficient: 15 - 24 years old	0.431	0.000	0.892	17,930,471	18,339,473
Linear mFARS Model Parameters: % Male	1.039	0.926	1.152	18,323,838	17,914,945
Linear mFARS Model Parameters: Constant: 8 - 14 years old	6.297	4.882	7.713	17,872,180	18,247,971
Linear mFARS Model Parameters: Time Coefficient: ≤ 7 years old	1.661	1.556	1.766	18,366,512	18,012,717
Linear mFARS Model Parameters: Time Coefficient: 8 - 14 years old	1.445	1.360	1.529	18,260,615	17,933,465
% Initial population in initial age of onset > 24 years old	7.5%	5.0%	10.5%	17,953,714	18,259,701
Linear mFARS Model Parameters: Time Coefficient: > 24 years old	1.099	0.949	1.248	18,231,406	17,970,888

Abbreviations: ICER = Incremental cost-effectiveness ratio; mFARS = modified Friedreich's Ataxia Scale; NOK = Norwegian Krone; OS = Overall Survival; SoC = standard of care; RDI = relative dose intensity.

Notes: Cumulative change at Year 3 is related to treatment effect and indirectly impacts the rate ratio for Year 3 (and extrapolations beyond Year 3)

Figure 21: Tornado diagram of deterministic sensitivity analysis



Abbreviations: DSA = Deterministic sensitivity analysis; ICER = Incremental cost-effectiveness ratio; mFARS = modified Friedreich's Ataxia Scale; OS = Overall Survival; RDI = Relative dose intensity; SoC = standard of care.

4.1.2.2 Scenario analysis

The following scenarios were included in the sensitivity analysis to explore the outcomes of the model with different settings and assumptions (Table 55).

Changing the source of the utility in the model had the highest impact on the results, increasing the ICER because of the smaller impact on mFARS score on quality of life, almost doubling the ICER. On the contrary, not discounting cost and outcomes, significantly decreases the ICER (-33%).proportionally increasing benefits accrued during the time horizon compared to costs. Increasing the discount rate to 5% have in comparison a smaller impact on the ICER (+14%). Another scenario having a significant impact on the results include varying the baseline patients characterises, altering the natural history of the disease (mFARS progression).

Table 55: Scenario analyses of model to explore model robustness to different settings

Scenario	Incremental cost (NOK)	Incremental benefit (QALYs)	ICER (NOK/QALY)
Base Case	26,177,605	1.447	18,092,625
1. Time horizon 40 years	25,882,251	1.315	19,679,639
2. Discount Rate - 0% for both costs and outcomes	39,903,653	3.300	12,092,662
3. Discount Rate - 5% for both costs and outcomes	24,162,209	1.175	20,560,891
4. Baseline Cohort - Full FA-COMS	24,988,486	1.135	22,023,488
5. Baseline Cohort - MOXIe Part II	25,900,872	1.255	20,634,095
6. mFARS Extrapolation - Linear	26,148,163	1.514	17,267,908
7. OS extrapolation using Loglogistic distribution	25,443,212	1.338	19,012,059
8. OS extrapolation using Gamma distribution	25,372,354	1.311	19,349,786

9. Tx. Discontinuation - One Discontinuation Rate (0.013)	15,924,511	0.888	17,934,528
10. Tx. Discontinuation - One Discontinuation Rate (0.06)	27,145,200	1.497	18,137,808
11. FA-COMS utility analysis	26,177,605	0.742	35,297,561
12. Excluded non-medical and indirect costs	26,207,876	1.447	18,113,547
13. Included productivity losses	26,156,758	1.447	18,078,216
14. Including caregivers QALY	26,177,605	1.701	15,385,188

Abbreviations: NOK = Norwegian Krone; OS = Overall survival; QALY = Quality-adjusted life year; Tx = Treatment.

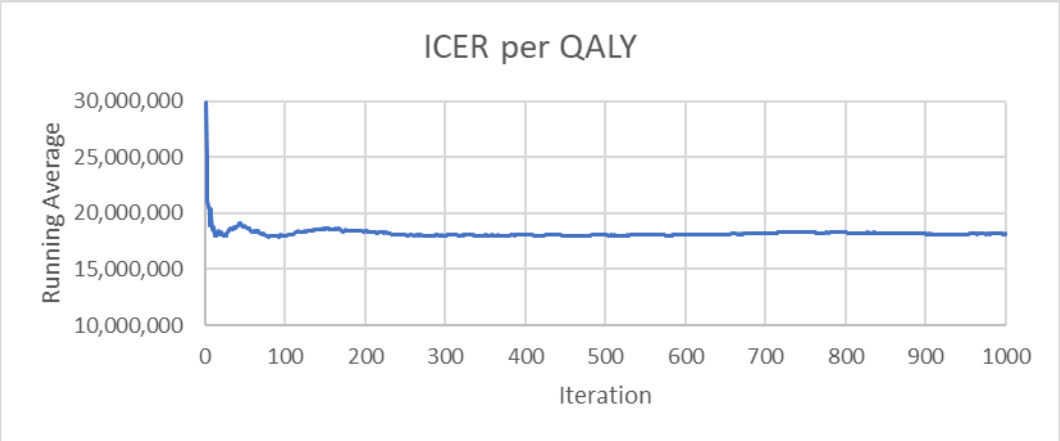
4.1.2.3 Probabilistic sensitivity analysis

In the PSA was conducted to generate probabilistic results from the economic model, varying randomly and simultaneously the variable of the model for 1,000 iterations. The distributions were assigned according to the following rules as per Briggs et al. (2006) (98):

- Proportions and utilities were assumed to have beta distributions (either parameterised with reported SE or from patient counts)
- Ages, time periods, rates, and ratios were assumed to have lognormal distributions.
- Costs are assumed to have a gamma distribution.
- Parameters whose value is correlated with other parameters through a covariance matrix are calculated through either a Dirichlet distribution or a multinormal distribution.
    - Dirichlet distribution was used when the sum of multiple parameters should remain constant (e.g., the age of onset distribution of the initial population).
    - Multinormal distributions were used in all other distributions where parameters were correlated (e.g., patient baseline utility linear regression parameters).
- All other parameters are assumed to have normal distributions.

A convergence plot demonstrated convergence with less than 500 iterations (Figure 22).The convergence for ICER outcomes was estimated by dividing the running average for costs by the running average for LY or QALY, instead of calculating the running average of ICERs for each iteration. The latter method tends to be volatile with weaker convergence than the incremental costs and effects that compose it.

Figure 22: Convergence plot of PSA iterations



Abbreviations: QALY = Quality-adjusted life year.

The mean probabilistic results are presented in the Table 56 below.

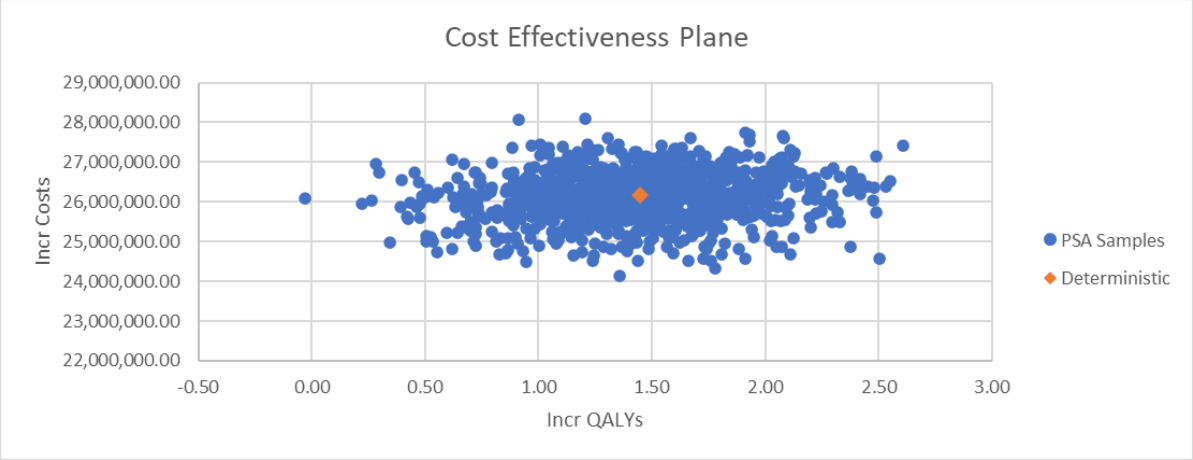
Table 56: Probabilistic results of the health economic analysis

	Deterministic Base Case	Probabilistic mean
Incremental costs	26,177,605	26,146,672
Incremental LYs	0.63	0.61
Incremental QALYs	1.45	1.44
ICER per LY	41,276,278	42,555,607
ICER per QALY	18,092,625	18,146,283

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

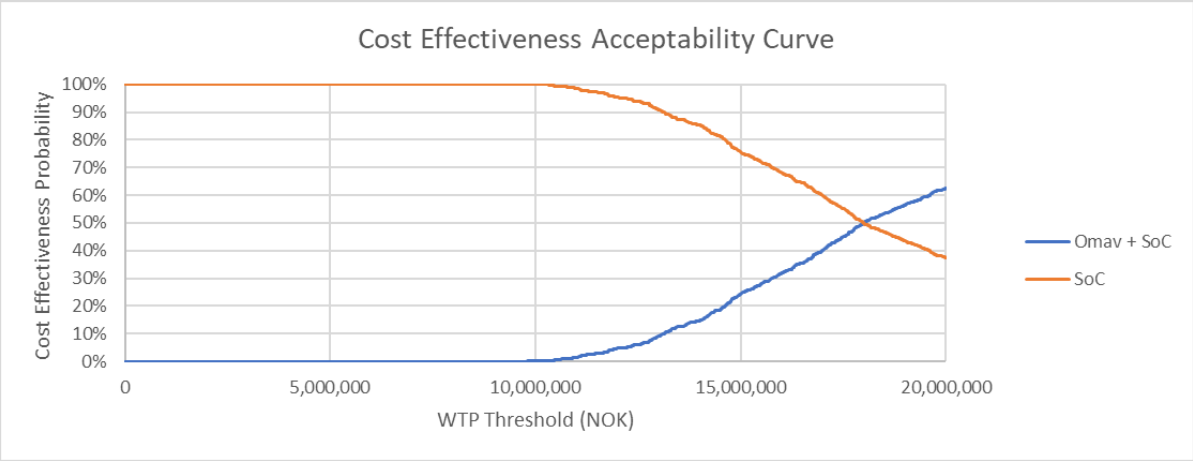
The resulting ICERs of the 1000 iterations were plotted in the cost-effectiveness plane (Figure 23) to visually display the distribution of the results along the axes of incremental costs and incremental QALYs.

Figure 23: Cost-effectiveness plane



Abbreviations: PSA = Probabilistic sensitivity analysis

Figure 24 Cost effectiveness acceptability curve



Abbreviations: WTP = Willingness to pay

4.2 Quantification of severity (DMP)

The absolute shortfall calculations were implemented in the economic model using the DMP template (87). The mean age at treatment initiation in the model was 20 years after weighting of the subgroups by age of onset. The average age of entering the model was multiplied by the proportion of patients in each respective age of onset group. The health state utility value for the best health state in the model was 0.842, calculated as weighted average of baseline utility for each age of onset subgroup. Entering these two variables into the DMP severity calculation sheet, resulted in an absolute shortfall of 35.3 QALYs.

Table 57: Severity calculations

Average age at treatment initiation	A	20
Expected remaining QALYs (undiscounted) for the general population without the disease	$QALYs_A$	**52.8**
Expected remaining QALYs (undiscounted) for those with the disease and without the new treatment (that is, prognosis of patients treated with current standard treatment)	P_A	**17.5**
Number of QALYs lost due to disease (absolute shortfall)	AS	**35.3**

Abbreviations: QALY = Quality adjusted life years

5 Budget impact analysis

5.1 Epidemiology of the disease in Norway

FA is a rare disease (6, 17), with FARA estimating approximately 15,000 people globally living with FA (99). Population estimates for FA are complicated by variation in prevalence across geographical and racial groups (9, 100). FA is the most common form of hereditary ataxia across the US, Europe, the Middle East, South Asia, and North Africa (6, 9, 32), with the disease occurring mainly in Caucasians, rarely in Black sub-Saharan African populations and very rarely in East Asian populations (9, 100).

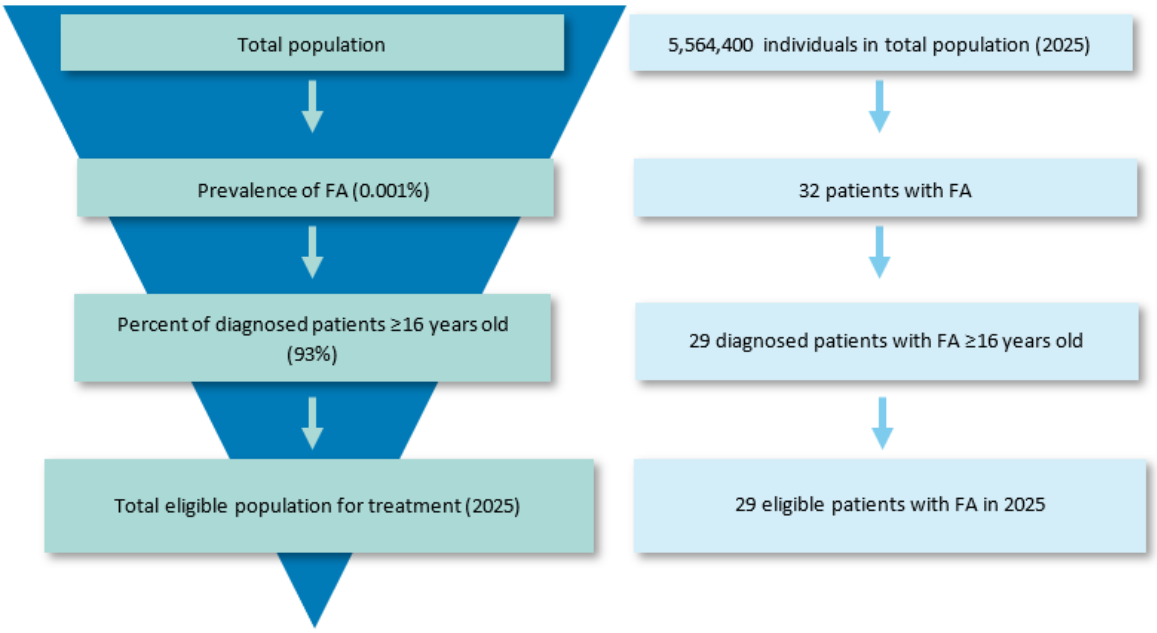
A recent 2022 global systematic review identified studies from Europe, Libya, Brazil, Guam and Canada, with calculated prevalence ranging from 0.00 (Guam) to 4.71 (Northern Spain) per 100,000 (101). Values for Norway ranged between 0.6 to 13.9. Nevertheless, the higher estimates derived from dated studies when genetic diagnostic was not available and should be considered with caution. A cross-sectional study including hospital archives and laboratory searches, and all included patients were investigated clinically and molecularly with genotype characterisation including size determination of GAA repeat expansions and frataxin measurements. Twenty-nine FA patients were identified in Norway, corresponding to a prevalence of 1:176 000.

As FA is a recessive genetic disorder, its incidence and prevalence are not expected to vary significantly over the next years.

5.2 Eligible patient population and market share

The number of patients eligible to receive omaveloxolone was derived as shown in the funnel below (Figure 25). For each year in the model, the prevalence of FA (0.001%) was obtained from published literature, which was then multiplied with the expected number of the Norwegian total population. Lastly, the percentage of patients 16 years of age and older (93%; derived from a Reata Pharmaceuticals health claims analysis(102)) was used to calculate patients who will be eligible to receive omaveloxolone per year, which resulted in 29 patients for 2025.

Figure 25: Eligible patient population



Abbreviations: FA = Friedreich's Ataxia.

Notes: Total population for 2025 estimated based on total population (2024) and population growth available for 2023.

Sources: Total population and annual population growth (103); Prevalence: (65); Proportion of patients older than 16 years (104)

The total Norwegian population in the BIM was assumed to grow yearly based on the annual population growth registered in 2023 (latest available data). The resulting number of patients eligible for treatment for the years 2025-2029 is shown in Table 58.

Table 58: Patients expected to be treated between 2025-2029

Number of patients	2025	2026	2027	2028	2029
Eligible for treatment	29	30	30	31	31
Expected market shares of omaveloxolone	50%	63%	75%	88%	100%
Patients expected to be treated with omaveloxolone	24	26	27	29	31

The uptake assumptions considered early movers and patients hesitant to receiving new treatment. Additionally, these accounted for system readiness: As omaveloxolone will be the first treatment in this therapy area, physicians will likely need to be educated. The uptake is therefore assumed to be 50% in the first year, reaching 100% within the year 5 of the time horizon.

5.3 Budgetary consequences

Undiscounted costs from the CUA were used to calculate the budget impact. The categorisation of costs in regional health authorities' costs and other health care services was done following the costing used in the cost effectiveness model. All home modifications, aids and medical devices were assumed as cost incurred in other health care services. Professional health care visits were categorised based on their unit costs, as shown in Table 59. In the economic model, this categorisation can be modified by the user for both health care professional and home modification resource used.

Table 59: Categorisation of costs by health professionals

Health care prof.	Costed as

Neurologist	Regional health authorities
Cardiologist	Regional health authorities
Primary Care Physician	Other
Orthopedic Specialist	Regional health authorities
Psychiatrist	Regional health authorities
Occupational Therapist	Other
Dietician	Other
Nurse Practitioner	Other
Physiotherapist	Regional health authorities
Speech therapist	Other
Palliative care physician	Other
Home health nurse	Other
Endocrinologist	Regional health authorities
Hospitalizations	Regional health authorities

5.3.1 Consequences for the medicinal budget

The consequence for the medicinal budget reflects the cost of omaveloxolone for the treatment of the FA population in Norway, as the current SoC does not include any pharmacological treatment. The price for omaveloxolone included in the BIM was the AUP price including VAT (NOK 350,027).

Table 60: Consequences for the medicinal budget

	2025	2026	2027	2028	2029
Skyclarys is approved for reimbursement	66,159,141	133,057,970	210,552,403	299,253,581	396,807,701
Skyclarys is NOT approved for reimbursement	0	0	0	0	0
Budget impact of the recommendation	66,159,141	133,057,970	210,552,403	299,253,581	396,807,701

5.3.2 Budgetary consequences for the Regional Health Authorities overall

5.3.2.1 Regional Health Authorities, excluding medicinal products

In this section are included costs assumed to be supported by the regional health authorities as specialist care as visits with a neurologist, cardiologist, orthopaedic specialist, psychiatrist physiotherapist, endocrinologist, and hospitalisation costs.

The budgetary consequences for the regional health authorities excluding medicinal products, results in a higher spending in the first year of the time horizon, and cost saving from year 2 to 5.

Table 61: Consequences for Regional Health Authorities

	2025	2026	2027	2028	2029
Skyclarys is approved for reimbursement	3,253,836	6,598,573	9,998,497	13,351,812	16,693,701
Skyclarys is NOT approved for reimbursement	3,251,573	6,637,232	10,112,387	13,519,656	16,937,880

Budget impact of the recommendation	2,262	-38,658	-113,890	-167,843	-244,179

5.3.2.2 Budgetary consequence not related to the Regional Health Authorities

All cost related to home modifications, aids and medical devices are included as costs not covered by the regional health authorities, as well as visits expected to be place in primary care as primary care physicians' visits, occupational therapists, dieticians, home nurses and palliative care physicians.

The budgetary consequences not related to regional health authorities result in cost savings throughout the model time horizon.

Table 62: Consequences not related to the Regional Health Authorities

	2025	2026	2027	2028	2029
Skyclarys is approved for reimbursement	2,342,172	6,592,987	8,838,211	12,108,509	16,950,959
Skyclarys is NOT approved for reimbursement	2,507,154	8,543,818	10,934,798	13,259,678	20,691,340
Budget impact of the recommendation	-164,982	-1,950,831	-2,096,587	-1,151,168	-3,740,381

5.3.3 Budgetary consequences for the health care sector overall

The budget impact related to the introduction of omaveloxolone is shown (in millions) in Table 63.

Table 63: Budgetary consequences for the health care services (in millions)

	2025	2026	2027	2028	2029
Skyclarys	72	146	229	325	430
Of which: Costs related to medicinal products covered by the Regional Health Authorities	66	133	211	299	397
Of which: Costs related to the Regional Health Authorities, excluding medicinal products	3	7	10	13	17
Of which: Costs not related to the Regional Health Authorities	2	7	9	12	17
Skyclarys is NOT approved for reimbursement	6	15	21	27	38
Of which: Costs related to medicinal products covered by the Regional Health Authorities	0	0	0	0	0
Of which: Costs related to the Regional Health Authorities, excluding medicinal products	3	7	10	14	17
Of which: Costs not related to the Regional Health Authorities	3	9	11	13	21
Budget impact of the recommendation	66	131	208	298	393
Of which: Costs related to medicinal products covered by the Regional Health Authorities	66	133	211	299	397
Of which: Costs related to the Regional Health Authorities, excluding medicinal products	0	0	0	0	0
Of which: Costs not related to the Regional Health Authorities	0	-2	-2	-1	-4

5.3.4 Discussion of budget impact uncertainty

The budget impact is directly connected to the cost effectiveness analysis and therefore the results depend on the settings and assumptions taken (discussed in the next section). In addition, number of patients eligible for treatment and uptake assumptions play a key role in the estimated budget impact. As FA is a rare disease, published data on the prevalence of the disease is limited.

6 Conclusion

Overview

FA is a severe, disabling disease, eventually leading to premature death, for which there is no current treatment in Norway. Currently, omaveloxolone is the only disease-modifying treatment approved in the US and Europe. Omaveloxolone can slow down disease progression as has been demonstrated in the MOXIe clinical trials and is further supported by longer term data in combination with the propensity matched analysis. The cost effectiveness analysis presented in this submission was based on a straightforward and fit for purpose regression-based model.

Clinical evidence

As FA is a rare disease, published literature is sparse and oftentimes when available, it is based on few patients or short follow-up, which can cause uncertainty around the reliability of parameters. Therefore, when possible, data from natural history registries was leveraged either directly from the publicly available patient-level dataset or indirectly as results from published studies informed by FA-COMS data for model inputs. link data from FA-COMS and MOXIe, mFARS was used to track disease progression in the model. Both FA-COMS and MOXIe contained mFARS as measure of disease progression and severity. This allowed the conduction of a propensity-matched analysis (64) to inform treatment effect of omaveloxolone. By propensity matching patients from the MOXIe OLE trial to patients in the FA-COMS database, a relative treatment effect could be estimated by constructing an external control.

Regression-based model

The model considered the baseline characteristics of patients with an mFARS score recorded within 3 years of diagnosis in FA-COMS in the base case. This population was used as the base case as it is representative of the long-term value of omaveloxolone over the lifecycle. However, in scenario analysis, the full FA-COMS population was used to estimate the baseline characteristics in the model to illustrate the cost-effectiveness of omaveloxolone of prevalent patients in the first year's post-reimbursement. Nevertheless, the full FA-COMS population represents a slightly older baseline prevalent population compared to what expected in Norway.

Additionally, using mFARS to track the patient journey allowed for linking of other outcomes in FA-COMS, such as utility and ADL scores, which were used to estimate health-related quality-of-life and healthcare resource use.

Utility was estimated in the base case using EQ-5D data from EFACTS, based on cross-walking SARA to mFARS. An additional scenario was conducted based on cross-walking SF-36 to EQ-5D scores at various mFARS scores. While the approach is scientifically sensible, the data from FA-COMS has clear limitations. Specifically, upon inspection of the data, some outliers seemed unreasonable after discussion with clinical experts. For example, some patients with severe disease had unexpectedly high utility values, which was clinically implausible. However, this may be due to reporting bias or caregiver responses not reflecting patient experiences in severe disease. As a cross-reference, Xiong et al. reported HRQoL in patients with FA as measured by SF-36 and other instruments using data from FA-COMS. The study confirmed worsening HRQoL as the disease progressed similar to the present analysis (86). Further, Xiong et al. found that while HRQoL scales capturing physical functioning, including that

of SF-36, may better reflect disease progression, overall, they may be too insensitive to change to capture the variability of HRQOL in patients with a rare disease such as FA, when basing outcomes on a small sample size (86).

Information on patient mortality was limited and not reported consistently in the publicly available FA-COMS dataset. Thus, the published literature was reviewed, and the results of Indelicato et al. (2022)(78) were leveraged to inform mortality for patients with FA. This study was chosen as it estimated the overall survival by disease severity for up to 12 years using EFACTS, the large European natural history database. To further cross-check the validity of Indelicato et al. (2022), other studies reporting mortality in patients with FA were reviewed (12). Tsou et al. (2011), a retrospective case-control study of 61 deceased and 38 living patients with FA published in 2011 estimated a mean age at death of 36.5 years (12), while older smaller studies reported mean ages at death between 36.6 and 41 years (105-108). Indelicato et al. (2022)(78) was within the range with a mean age at death of 39 years; because the age at onset slightly varied in these studies, this modest variation in the mean age at death was expected.

Based on results of the sensitivity analysis, the most influential model parameter is the cumulative change of mFARS in patients on omaveloxolone. This parameter is used to estimate the treatment effect, as derived from the propensity-matched analysis. It was chosen to represent treatment effect in the model as this data came directly from the propensity-matched analysis, and therefore, contained information that could be used to estimate its uncertainty.

Finally, because FA is a progressive disease, patients rely heavily on caregiver support as the disease worsens. In the base case, conform to HTA recommendations, productivity losses or caregiver HRQoL were not included. Their impact was tested in the scenario analysis as it is believed to be substantial.

Strengths and limitations

A major strength of this analysis is that it directly leverages data from a large natural history study, which allows for linking between mFARS, which defines disease progression and treatment effect, as well as other parameters that inform the model. FA-COMS is well-known and well-used in the published literature, so where data gaps existed, the analysis was able to leverage some additional studies from FA-COMS. With most model inputs based off FA-COMS, there is inherently less uncertainty and fewer assumptions. However, FA is a rare disease and there is a paucity of data for some aspects of the disease, such as mortality. Therefore, there is uncertainty in these parameters, and assumptions from clinical experts were explored where needed.

Notably, an inherent limitation of using mFARS and other measures in FA was well described by Rummey et al. (2022): “Because the mFARS and other measures represent constructs to assess functional progression rather than actual biological change over time, correlations with ADL and QOL measures do not necessarily reflect the situation of individual participants, especially at the limits of the scale, in more advanced patients. Relatively uniform events such as loss of ambulation may be timed slightly differently based on exact results from the mFARS, ADL scores, timed walks, and disability scales. Thus, extrapolating the present population-based research findings to clinical care of a specific individual is imperfect.”

To further strengthen the model and analyses, the overall conceptualization and structure as well as the estimation and use of parameters were externally validated in multiple ways throughout implementation. Specifically, an international ad board with health economic modeling experts (Matt Stevenson and Paul Miller) was undertaken to design the model structure from the perspective of an HTA. Further, three expert clinicians (Dr. Susan Perlman, Dr. David Lynch, Dr. Paolo Giunti) with years of experience in treating patients with FA at all stages of the disease in the US and EU were interviewed throughout the project to gain insight into the disease and how it translates into the model in terms of structure, inputs, and assumptions. They were further used to solicit feedback to define HCRU in terms of ADL.

Implications of health economic analysis

Importantly, a high ICER is commonly reported in rare diseases. This is generally due to limited clinical efficacy available for orphan drugs, given there are fewer number of patients available for a clinical trial, which proves challenging to demonstrate significant clinical differences. Further, rare diseases like FA are complex in nature, with variable clinical courses (e.g., based on age of onset). When using a single outcome, such as mFARS, to define disease progression, clinical benefit may be diminished if there is variability of disease progression in subgroups of an already limited number of patients. Moreover, using standard economic techniques presents a challenge for orphan drugs as there is more uncertainty around parameters and assumptions are required. Finally, orphan drug costs are generally expensive due to high research and development costs as compared to small unit sales volume.

As observed herein, the cost-effectiveness of omaveloxolone is considerably influenced by treatment efficacy, treatment cost, mortality and health-related quality-of-life. While the scientific approaches used for the present evaluation have been rigorously employed, due to the rarity of FA and the paucity of data, assumptions were necessary to inform model structure and parameters in some instances.

At a patient-focused drug development meeting on FA in 2017, patients expressed that while a cure for the disease is needed, a slowing or stopping of disease progression would be most valuable for the treatment of FA. Additionally, patients indicated in a survey that balance/walking, upper limb coordination, manual dexterity, and fatigue were major symptoms of the disease that contributed to the loss of independence in FA. Patients expressed that treatment of individual symptoms could have great impact on improving their quality of life (109)

Omaveloxolone is the only approved treatment to slow disease progression in patients with FA, which provides an important advancement for a previously unserved population which a high unmet need.

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Appendices

6.1 Appendix A: Skyclarys EPAR

ID2024_12 omaveloxolone EPAI

6.2 Appendix B: SLR reports

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6.3 Appendix C: Publication of propensity matched analysis

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6.4 Appendix D: KOL input on HCRU based on ADL scores

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6.5 Appendix E: Market authorisation

ID2024_12 EMA authorisation.pdf

6.6 Appendix F: SF-36 reports from FA-COMS

ID2024_FA_-_COMS_SF36_EQ5D_Analys

6.7 Appendix G: Costs included in model for Denmark and Sweden

ID2024_12_appendixG_costs_HCR