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.

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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.

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# 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<br>Adverse events<br>Health-related quality of life |
| HE | QALYs<br>Costs<br>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**<br>NCT-number<br>primary reference | **Study design** | **Treated study population** | **Intervention** | **Key endpoints** |
|---|---|---|---|---|
| MOXIe part 1<br>NCT02255435<br>Lynch et al 2019 [9] | - Dose-finding<br>- International<br>- Randomized<br>- Double-blind<br>- Placebo-controlled | - Genetically confirmed FA<br>16 – 40 years old<br>mFARS 10-80 | Omaveloxolone<br>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<br>Main study<br>NCT02255435<br>Lynch et al 2021 [10] | - International<br>- Randomized<br>- Double-blind<br>- Placebo-controlled | - Genetically confirmed FA<br>- 16–40 years old<br>- mFARS 10-80<br>- Severe *pes cavus* limited to 20 % of patients | Omaveloxolone<br>150 mg daily | - Change in mFARS at week 48 (primary endpoint) |
| MOXIe OLE<br>NCT02255435<br>Lynch et al 2023 [11] | - Open-label<br>- Extension study<br>- International | Patients from MOXIe part 1 (n=57) and part 2 (n=92) | Omaveloxolone<br>150 mg daily | - Safety/tolerability<br>- Efficacy: mFARS, ADL, 9-HTP, T25-FW (explorative endpoints) |
| FA-COMS<br>NCT03090789 | - Natural history study<br>- International | - Individuals with clinical diagnosis or genetic confirmed FA | No intervention | - FARS, mFARS |

| | | | | |
|---|---|---|---|---|
| | | - 4-80 years old<br>- Estimated n=2.000 (~1.000 by today) | | |
| EFACTS<br>NCT02069509<br>Reetz et al 2015 [12] | - Natural history study<br>- European | -Genetically confirmed FA<br>-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).

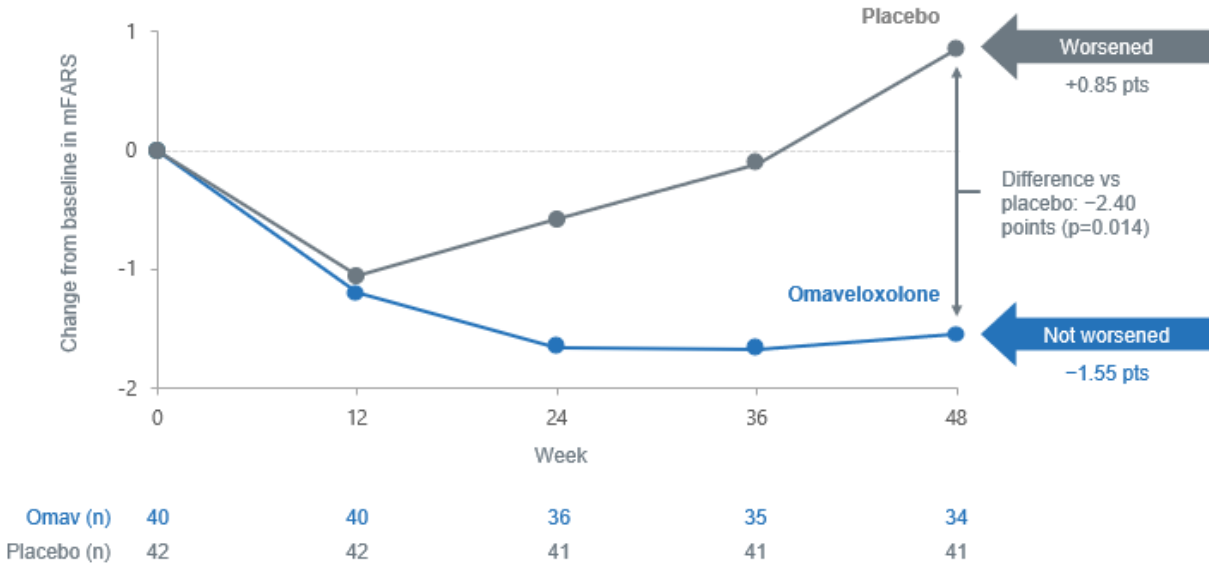


**Figure 1 Mean change from baseline in mFARS score over 48 weeks (FAS population)**

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

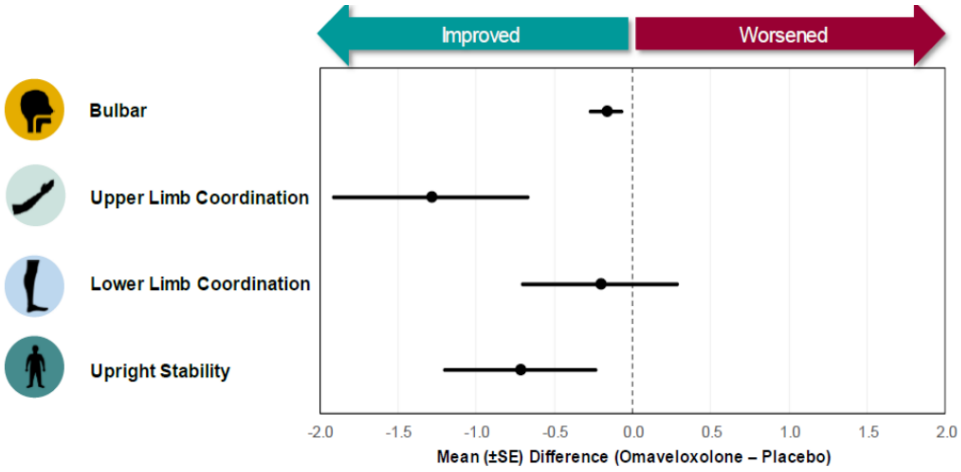


**Figure 2 Analysis of changes in mFARS subscales at week 48 from MOXIe part 2 (FAS population)**

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

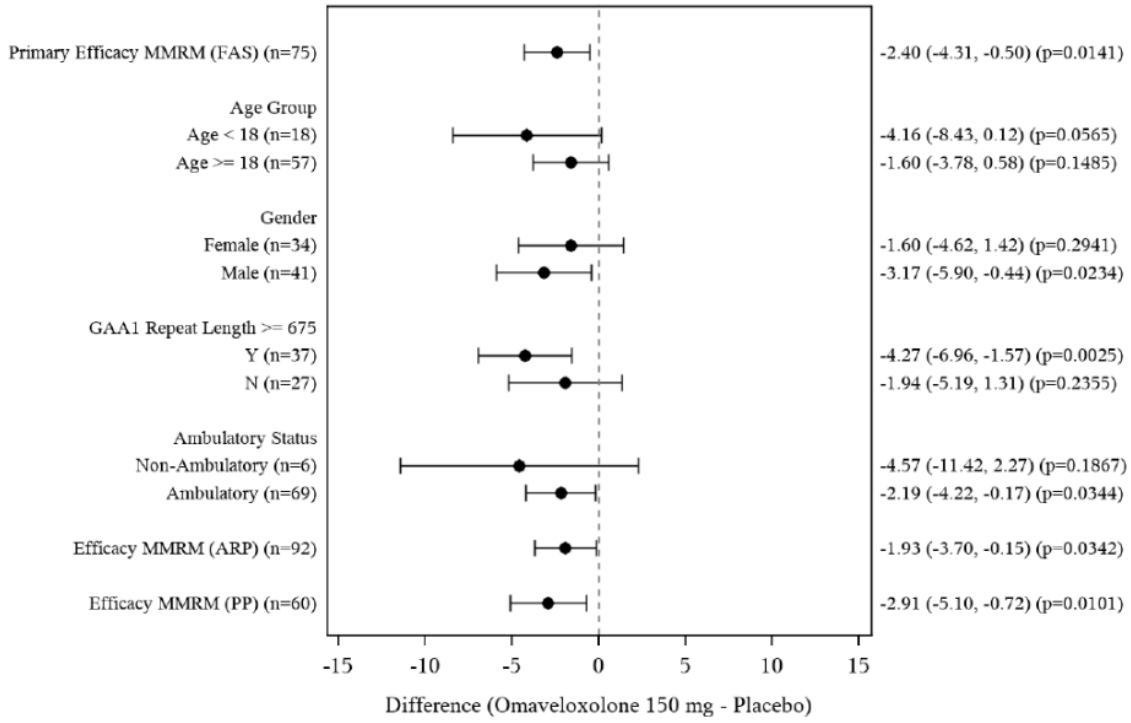


**Figure 3 Change in mFARS at week 48 in pre-specified subgroups**
ARP, all randomized population, FAS, full analysis set, MMRM, mixed model for repeated measures, PP, per protocol. LS (Least Squares) differences estimated from a MMRM analysis using visit 4, 12, 24, 36 and 48.

### 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.<br>Of these 810 had consented to share data outside FA-COMS |
| **Endpoint** | mFARS (key endpoint)<br>Assessed every 24 weeks | mFARS was collected<br>Assessed yearly |
| **Duration of follow-up** | 3 years<br>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.<br>• Genetically confirmed FA | • Male and female children and adults 4-80 years old<br>• Genetically confirmed FA |
| **Exclusion criteria** | • History of clinically significant left-sided heart disease and/or clinically significant cardiac disease<br>• Uncontrolled diabetes (HbA1c >11.0%)<br>• B-type natriuretic peptide value >200 pg/mL<br>• 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.

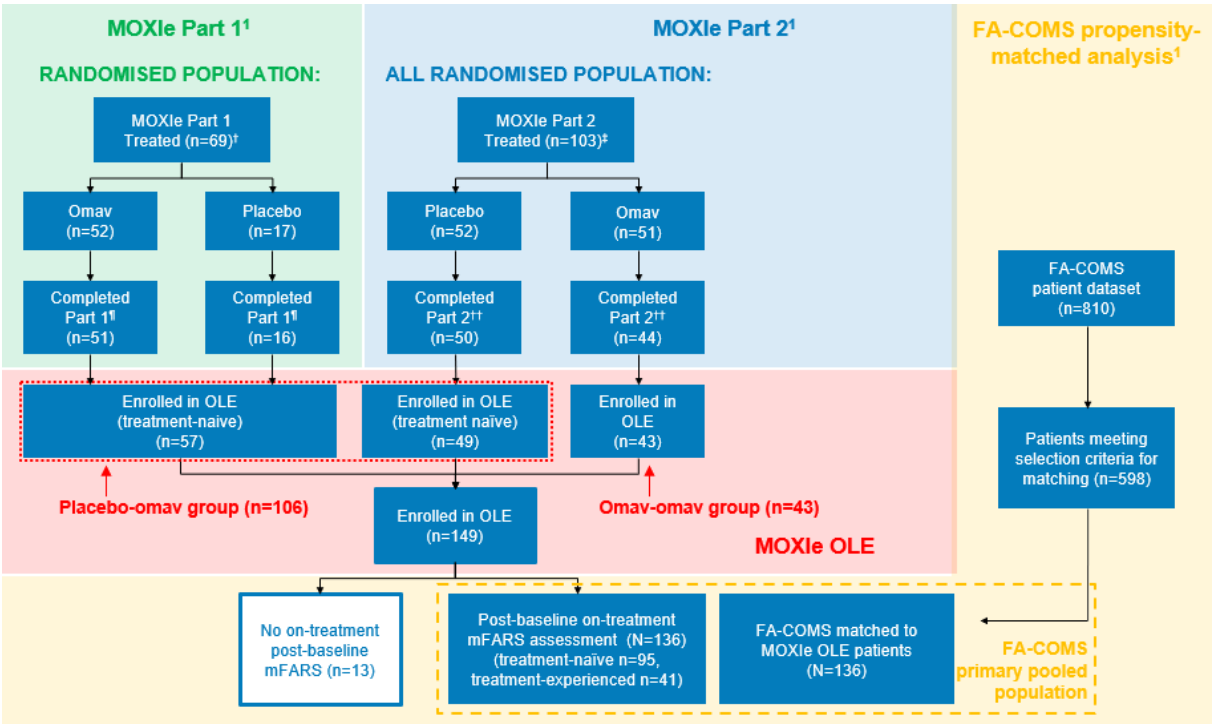


**Figure 4. Overview of MOXIe populations and external control group FA-COMS (from submission dossier)**

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).

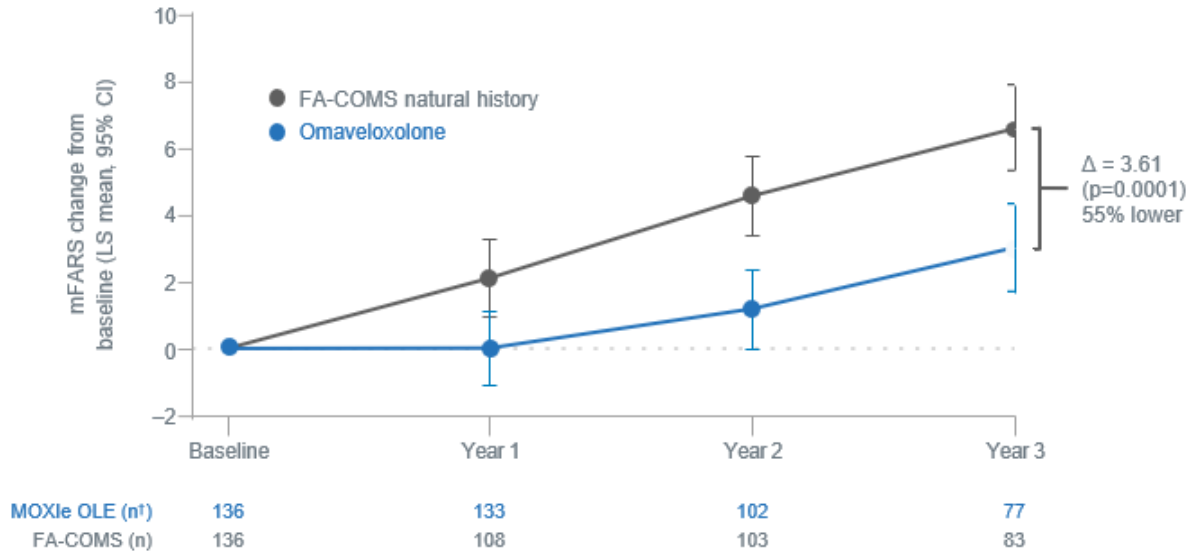


**Figure 5. PS-analysis: LS (least squares) mean change in mFARS from baseline over time (primary pooled population)**

**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.

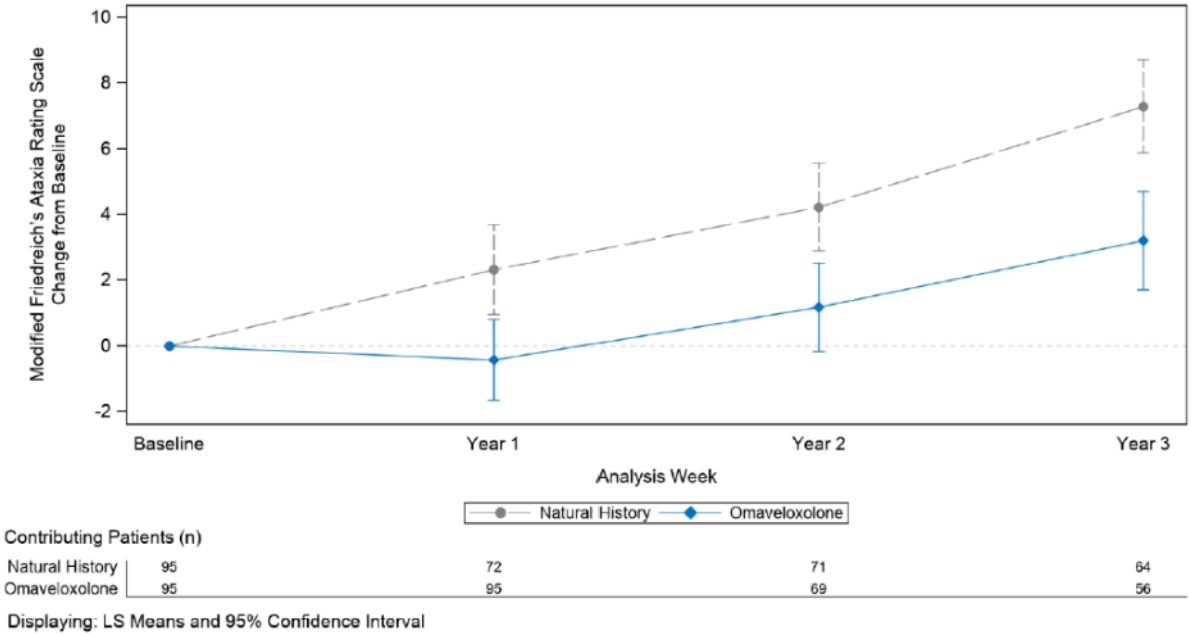


**Figure 6. PS analysis: LS mean change in mFARS over time (placebo-omav population)**

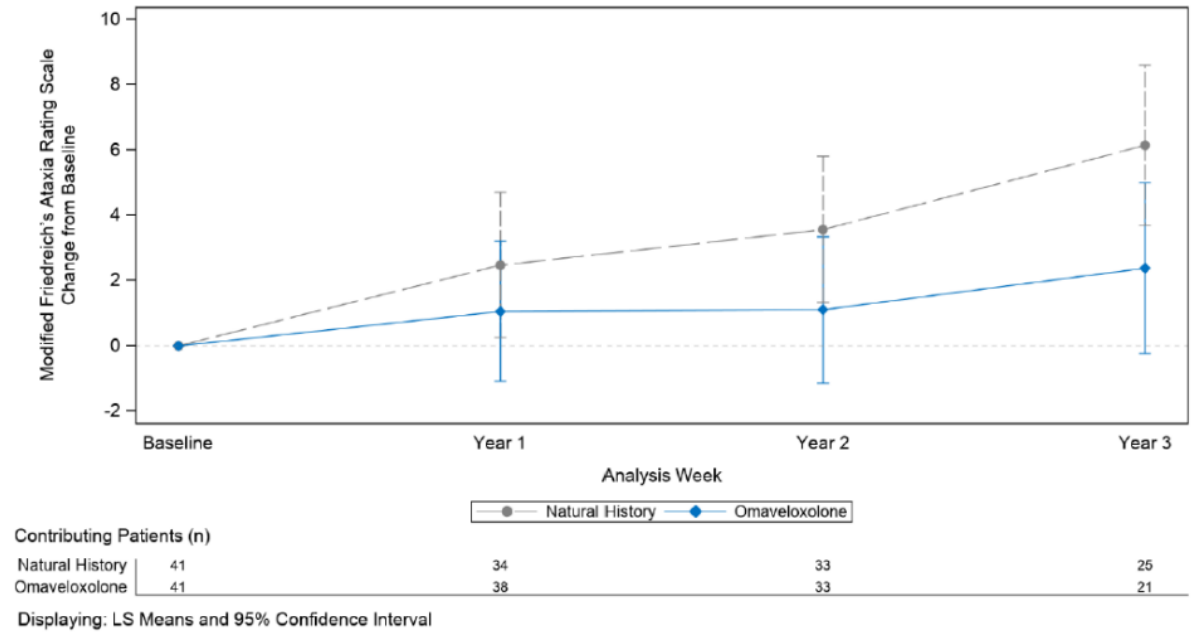


**Figure 7. PS analysis: LS mean change in mFARS over time for patients with no prior omaveloxolone use (omav-omav population) (patients that had received prior omaveloxolone in MOXIe part 2)**

### 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.

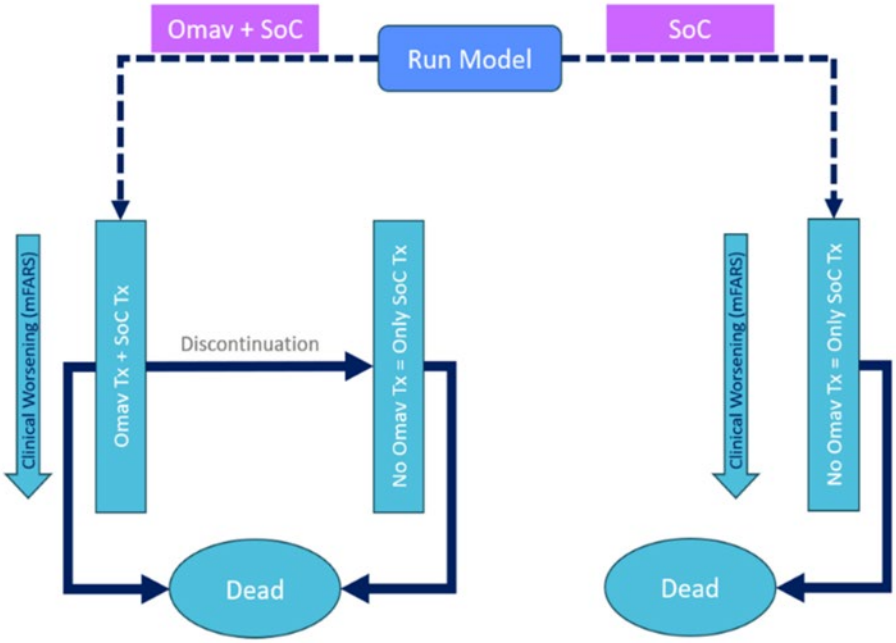


**Figure 8. Structure of the company's regression-based model**

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.

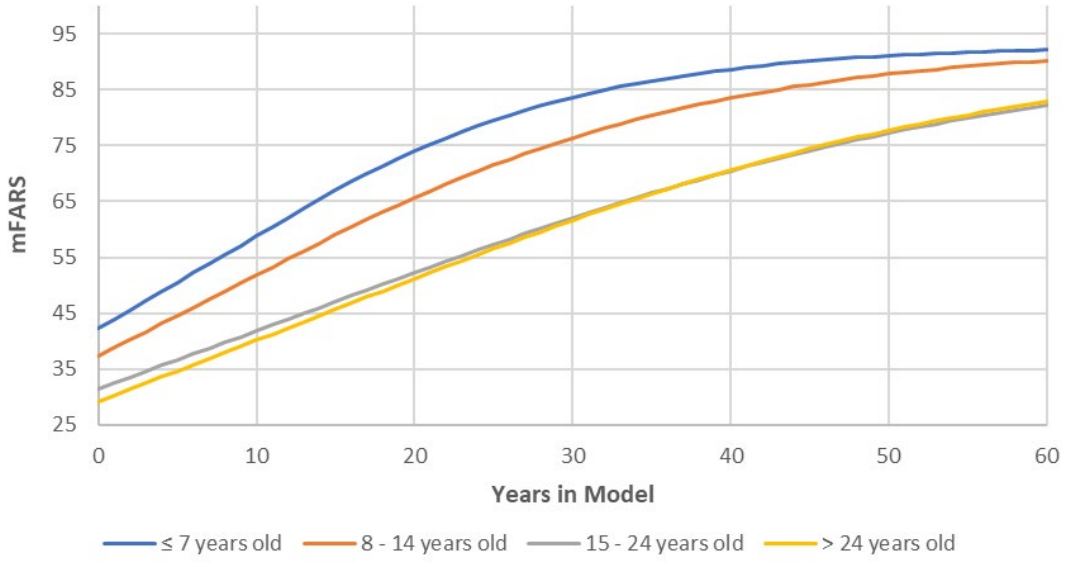


**Figure 9. Modelled SoC mFARS Trajectory (With Logistic Extrapolation) for Each Age of Onset Subgroup**

### 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 | |

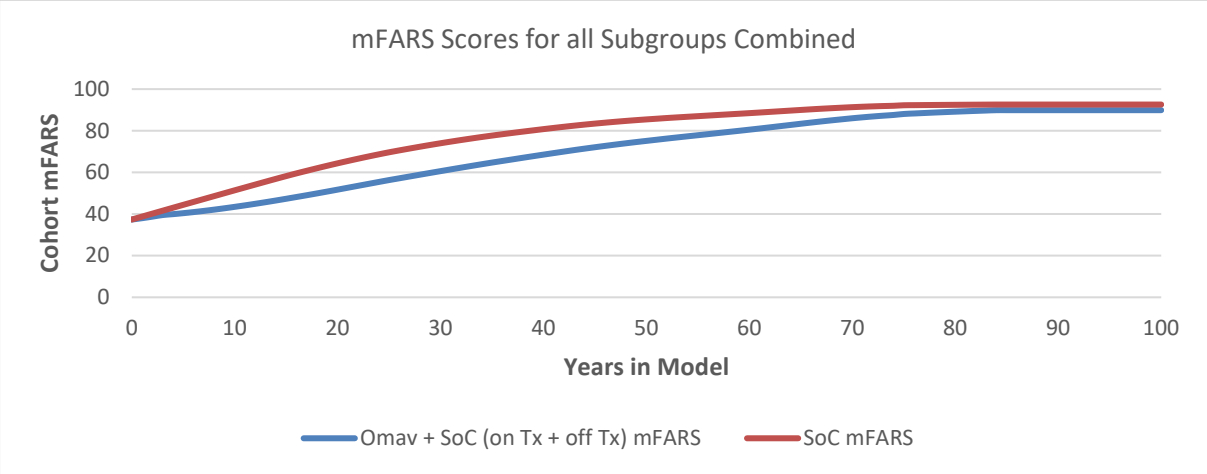


**Figure 10. Modelled mFARS progression for all age sub-groups combined**

### 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.

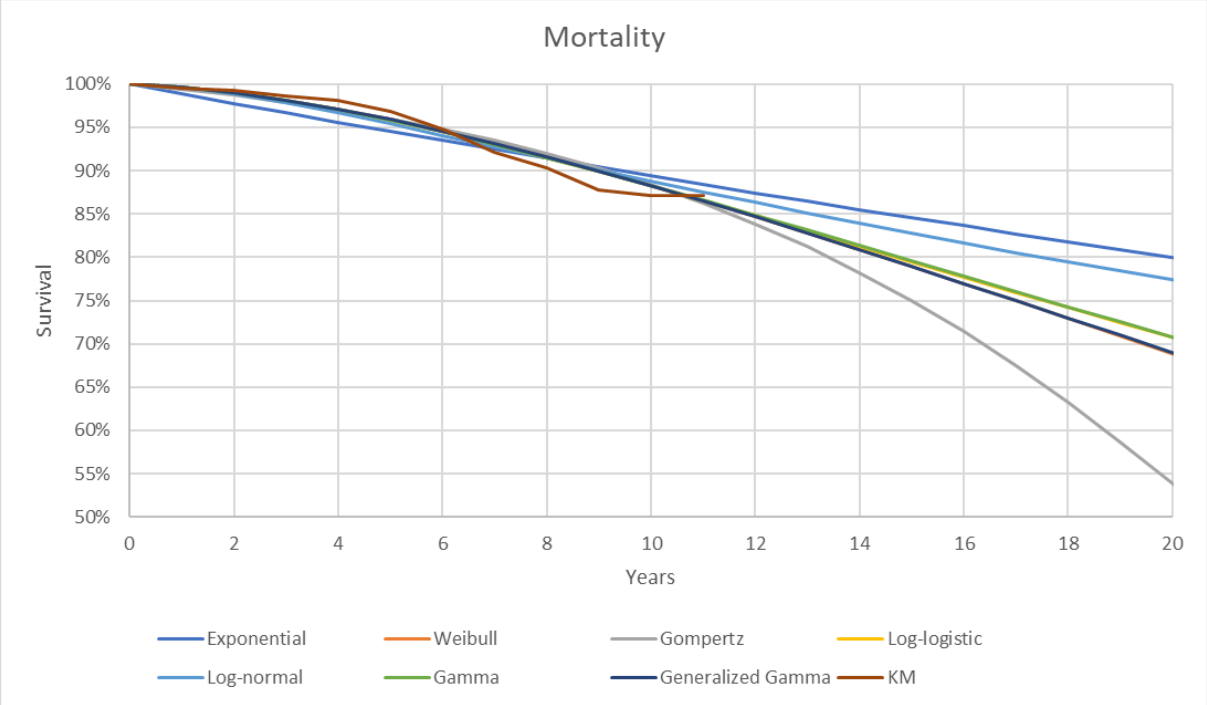


**Figure 11. Overall survival Kaplan-Meier and fitted distributions for overall FA population in Indelicato et al. (2023)**

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.

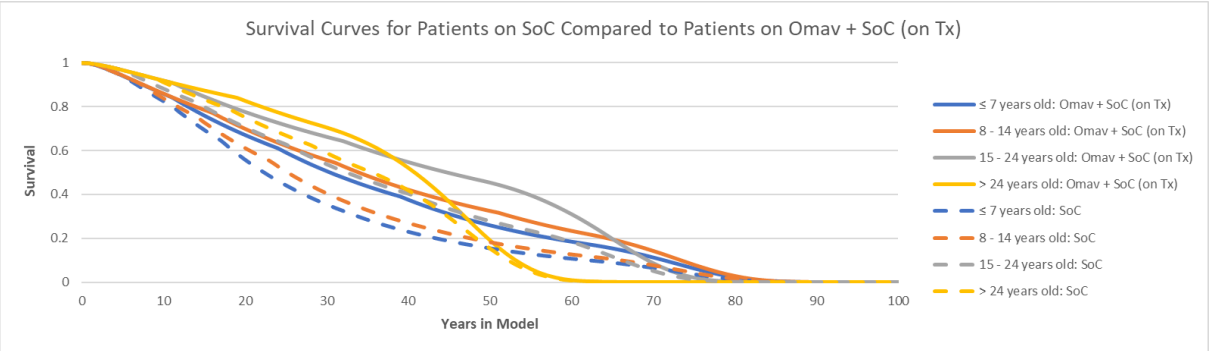


**Figure 12. OS curves for omaveloxolone plus SoC and SoC patients in each subgroup with exponential distribution**

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.

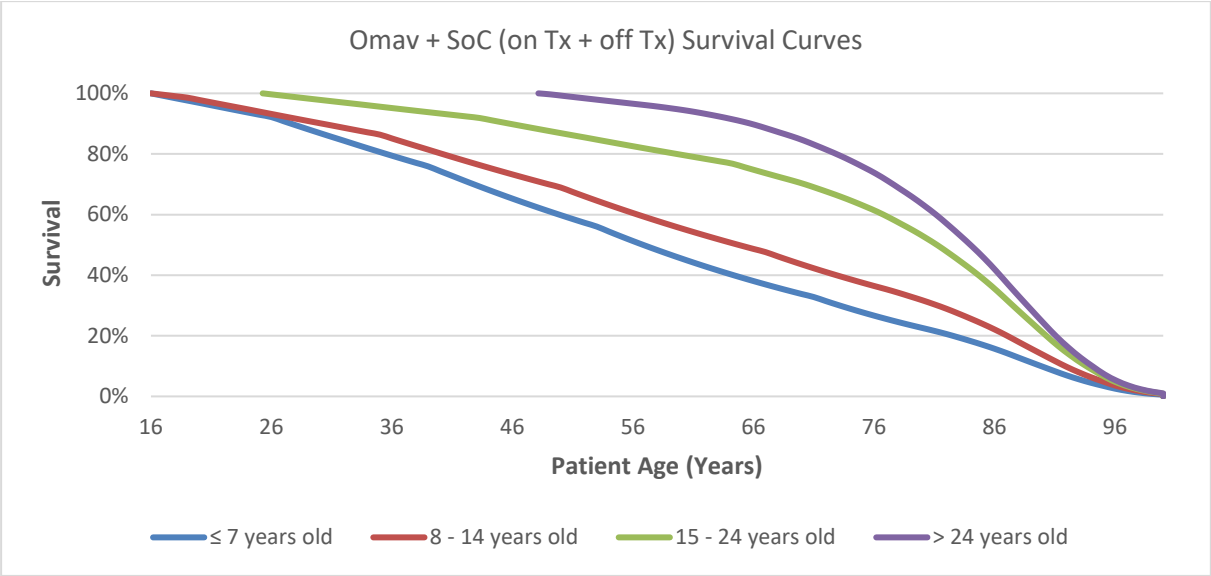


**Figure 13. Estimated survival for patients treated with omaveloxolone + SoC in company's analysis. Survival is based on exponential survival curves, general population mortality, and estimated HR for different mFARS categories**

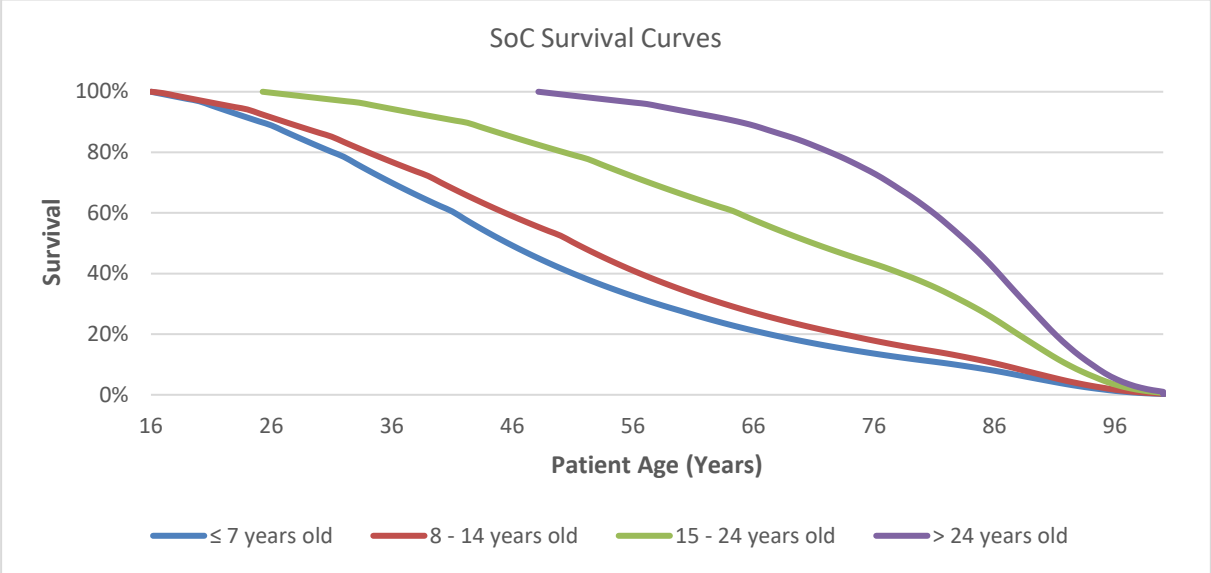


**Figure 14. Estimated survival for patients treated with SoC in company's analysis. Survival is based on exponential survival curves, general population mortality, and estimated HR for different mFARS categories**

## 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.

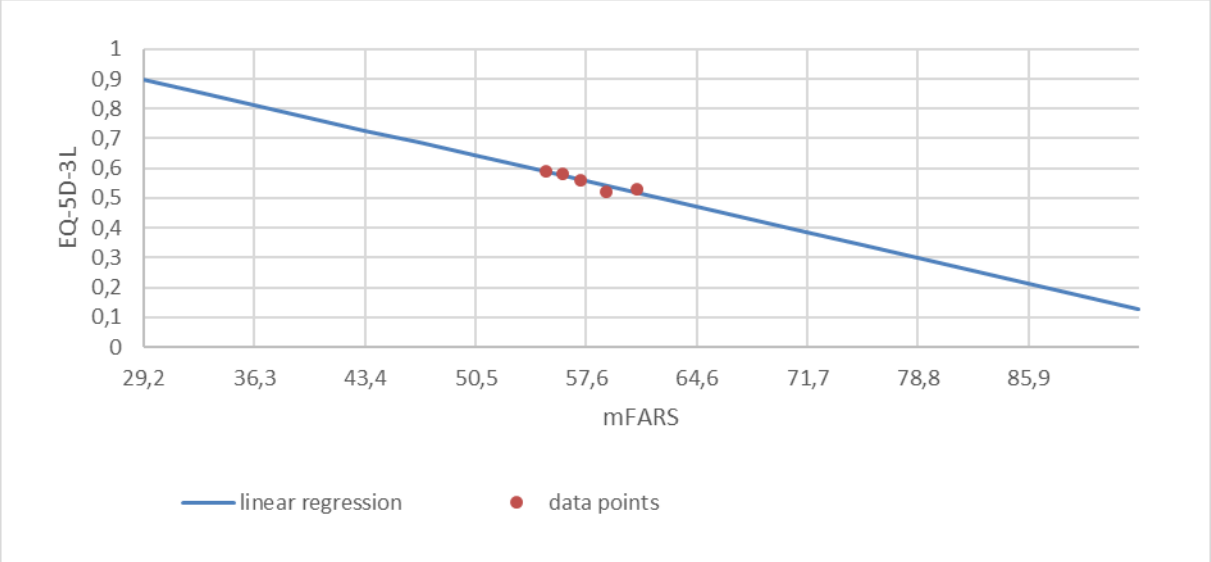


**Figure 15. Estimated relation between EQ-5D-3L and mFARS in the model, based on EFACTS study**

**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.

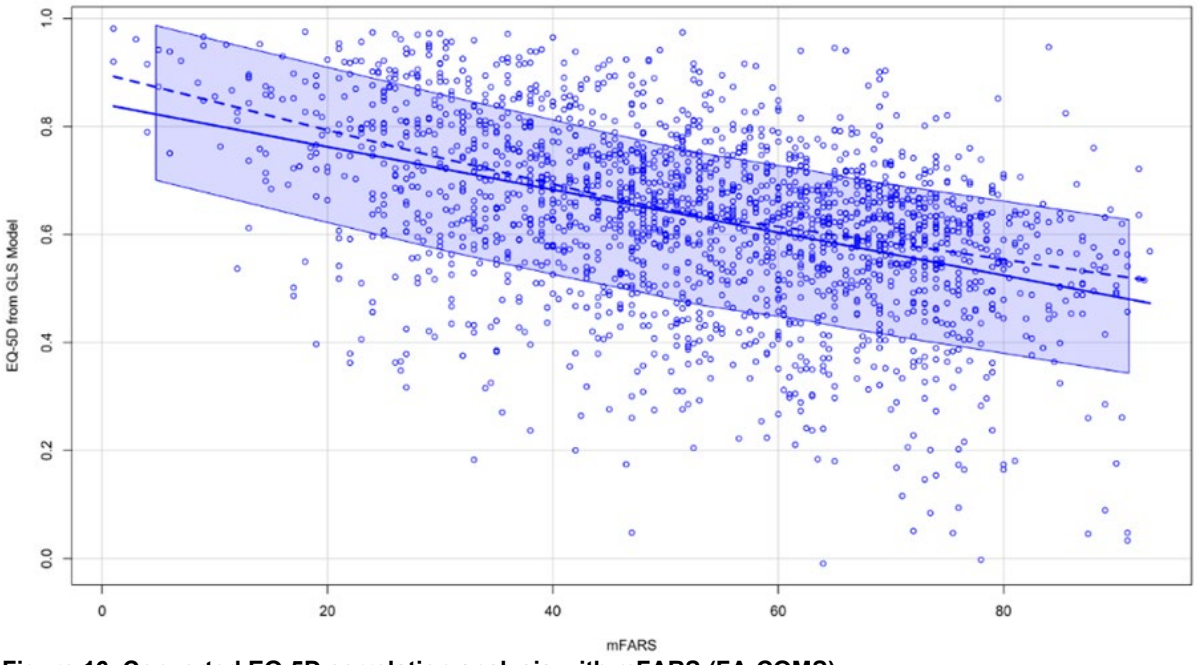


**Figure 16. Converted EQ-5D correlation analysis with mFARS (FA-COMS)**

## 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 |