Omaveloxolone (Friedreich's ataxia)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Omaveloxolon (Friedreich-Ataxie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Medical and scientific advice

- Hans-Peter Vogel

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Bart-Jan Schuman.

IQWiG thanks the respondent and the patient organization 'Friedreich-Ataxie Förderverein' for participating in the written exchange and for their support. The respondent and the 'Friedreich-Ataxie Förderverein' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

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I List of abbreviations

Abbreviation	Meaning
9-HPT	9-Hole Peg Test
ACT	appropriate comparator therapy
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BSC	best supportive care
CI	confidence interval
eGFR	estimated glomerular filtration rate
FA-ADL	Friedreich's Ataxia-Activities of Daily Living
FA-COMS	Friedreich's Ataxia Clinical Outcome Measures Study
FARSn	Friedreich's Ataxia Rating Scale neurological examination
GAA	guanine-adenine-adenine
GAA1	shorter GAA allele in the frataxin gene
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycated haemoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MD	mean difference
mFARS	modified Friedreich's Ataxia Rating Scale
MMRM	mixed-effects model with repeated measures
NYHA	New York Heart Association
OLE	open label extension
PGIC	Patient Global Impression of Change
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form 36
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SmPC	summary of product characteristics
SOC	System Organ Class

Abbreviation	Meaning
T25-FW	Timed 25-Foot Walk
ULN	upper limit of normal

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug omaveloxolone. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 1 July 2025.

Research question

The aim of this report is to assess the added benefit of omaveloxolone in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients ≥ 16 years with Friedreich's ataxia.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of omaveloxolone

Therapeutic indication	**ACT**[a]
Patients ≥ 16 years with Friedreich's ataxia	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Further comments from the G-BA:
- Treatments listed in the German Remedies Catalogue (e.g. voice, speech and language therapy, physiotherapy) can help to alleviate symptoms.
- A comparison with placebo alone does not correspond to the ACT.
- BSC is assumed to be offered in both arms of a study.
- Symptomatic treatment as part of BSC can also include pharmacological therapy.
- In the therapeutic indication in question, patients in both study arms are assumed to receive appropriate treatment for existing or newly emerging symptoms and accompanying diseases. These include, among others, diabetes mellitus (treated with insulin, for example), cardiomyopathies (treated with beta receptor blockers, ACE inhibitors and AT-2 receptor antagonists, for example) and scoliosis (treated by surgical correction if necessary).

ACE: angiotensin converting enzyme; AT-2: angiotensin-2; BSC: best supportive care; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used to derive the added benefit.

Study pool and study design

The study MOXIe Part 2 was used for the benefit assessment of omaveloxolone.

MOXIe Part 2 is a randomized, double-blind, multicentre study comparing omaveloxolone with placebo. The study had a total randomized treatment phase of 48 weeks.

The study included patients with genetically confirmed Friedreich's ataxia who were at least 16 years and no more than 40 years old at the time of inclusion and had a score of at least 20 points and no more than 80 points on the modified Friedreich's Ataxia Rating Scale (mFARS) (with a maximum of 99 points). The patients were not allowed to have changed their exercise regimen within 30 days before the start of the study and had to be willing to remain on the same exercise regimen during the study period. In addition, they had to be able to complete a maximal exercise test (cycle ergometry using a recumbent exercise bike). In addition, the patients had to be able to swallow capsules. Patients with uncontrolled diabetes mellitus were excluded. Patients with clinically significant cardiac disease were also excluded from participation in the study, although the participation of patients with mild to moderate cardiomyopathy associated with Friedreich's ataxia was allowed. Patients with clinically significant liver disease were also excluded. The use of anti-spasticity agents was not permitted in MOXIe Part 2.

Despite some restrictions regarding the permitted concomitant medication, the implementation of the ACT BSC in the MOXIe Part 2 study was considered sufficient.

In MOXIe Part 2, 103 patients were enrolled and randomly assigned to omaveloxolone (N = 51) or placebo (N = 52). The allocation was stratified by pes cavus status (yes/no); no more than 20% of patients were allowed to have a positive pes cavus status.

Treatment with omaveloxolone in the intervention arm was largely in compliance with the summary of product characteristics (SmPC).

The primary outcome was the change in the mFARS score at Week 48. Secondary outcomes included outcomes in the categories morbidity, health-related quality and adverse events (AEs).

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes for MOXIe Part 2 was rated as low.

The results on all-cause mortality, walking ability and discontinuation due to AEs had a low risk of bias. The certainty of results for the outcome of discontinuation due to AEs was limited despite the low risk of bias of the results.

All other results had a high risk of bias due to incomplete observations for potentially informative reasons.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome all-cause mortality. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Functionality

For the outcome functionality, a statistically significant difference between the treatment arms was shown when considering the difference in changes at Week 48. The standardized mean difference (SMD) was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD was not completely below the irrelevance threshold of -0.2. It could therefore not be inferred that the effect was relevant; an added benefit is therefore not proven.

Fine motor skills of the upper limbs

For the outcome fine motor skills of the upper limbs, there was no statistically significant difference between the treatment arms when considering both the non-dominant hand and the dominant hand. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome fine motor skills of the upper limbs; an added benefit is therefore not proven.

Walking ability

There was no statistically significant difference between the treatment arms for the outcome walking ability. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome walking ability; an added benefit is therefore not proven.

Health status

For the outcome health status, a statistically significant difference between the treatment arms was shown when considering the difference in changes at Week 48. The SMD was considered to check the relevance of the result. The 95% CI of the SMD was not completely below the irrelevance threshold of –0.2. It could therefore not be inferred that the effect was relevant; an added benefit is therefore not proven.

Frequency of falls

There was no statistically significant difference between the treatment arms for the outcome frequency of falls. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome frequency of falls; an added benefit is therefore not proven.

Limitation in activities of daily living

No statistically significant difference between the treatment arms was shown for the outcome limitation in activities of daily living. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome limitation in activities of daily living; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded using the Physical Component Summary and the Mental Component Summary of the Short Form 36 (SF-36). There were no statistically significant differences between the treatment arms for either sum score (recording a deterioration of ≥ 9.4 points in the Physical Component Summary and of ≥ 9.6 points in the Mental Component Summary, each corresponding to 15% of the scale range). There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome health-related quality of life; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

There was no statistically significant difference between the treatment arms for the outcome SAEs. For the outcome SAEs, there is no hint of greater or lesser harm of omaveloxolone in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events (AEs)

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs. For the outcome discontinuation due to AEs, there is no hint of greater or lesser harm of omaveloxolone in comparison with BSC; greater or lesser harm is therefore not proven.

Gastrointestinal disorders (System Organ Class [SOC], AEs)

A statistically significant difference to the disadvantage of omaveloxolone versus BSC was shown for the outcome gastrointestinal disorders (AEs). For the outcome gastrointestinal disorders (AEs), there is a hint of greater harm of omaveloxolone versus BSC.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug omaveloxolone versus the ACT is assessed as follows:

Overall, there was a negative effect in the non-serious/non-severe side effects category for the outcome gastrointestinal disorders (AEs). This negative effect of omaveloxolone in an outcome in the category of non-serious/non-severe side effects was not considered sufficient to derive lesser benefit of omaveloxolone compared with the ACT. In summary, there is no hint of an added benefit of omaveloxolone versus BSC for patients with Friedreich's ataxia aged 16 years and older.

Table 3 presents a summary of the probability and extent of the added benefit of omaveloxolone.

Table 3: Omaveloxolone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients ≥ 16 years with Friedreich's ataxia	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Further comments from the G-BA:
- Treatments listed in the German Remedies Catalogue (e.g. voice, speech and language therapy, physiotherapy) can help to alleviate symptoms.
- A comparison with placebo alone does not correspond to the ACT.
- BSC is assumed to be offered in both arms of a study.
- Symptomatic treatment as part of BSC can also include pharmacological therapy.
- In the therapeutic indication in question, patients in both study arms are assumed to receive appropriate treatment for existing or newly emerging symptoms and accompanying diseases. These include, among others, diabetes mellitus (treated with insulin, for example), cardiomyopathies (treated with beta receptor blockers, ACE inhibitors and AT-2 receptor antagonists, for example) and scoliosis (treated by surgical correction if necessary).

ACE: angiotensin converting enzyme; AT-2: angiotensin-2; BSC: best supportive care; G-BA: Federal Joint Committee

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA’s assessment conducted in the context of the market launch in 2024, where the G-BA had determined a non-quantifiable added benefit of omaveloxolone. However, in the G-BA’s assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 2 Research question

The aim of this report is to assess the added benefit of omaveloxolone in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients ≥ 16 years with Friedreich's ataxia.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of omaveloxolone

Therapeutic indication	**ACT**[a]
Patients ≥ 16 years with Friedreich's ataxia	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Further comments from the G-BA:
- Treatments listed in the German Remedies Catalogue (e.g. voice, speech and language therapy, physiotherapy) can help to alleviate symptoms.
- A comparison with placebo alone does not correspond to the ACT.
- BSC is assumed to be offered in both arms of a study.
- Symptomatic treatment as part of BSC can also include pharmacological therapy.
- In the therapeutic indication in question, patients in both study arms are assumed to receive appropriate treatment for existing or newly emerging symptoms and accompanying diseases. These include, among others, diabetes mellitus (treated with insulin, for example), cardiomyopathies (treated with beta receptor blockers, ACE inhibitors and AT-2 receptor antagonists, for example) and scoliosis (treated by surgical correction if necessary).

ACE: angiotensin converting enzyme; AT-2: angiotensin-2; BSC: best supportive care; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

In Module 4 A and B, however, the company presented separate analyses relating to 2 research questions:

- Module 4 A: treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older who can no longer walk independently
- Module 4 B: treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older who can still walk independently

For this purpose, patients who were no longer able to walk independently were defined as those scoring > 2 points in item E7 'gait' of the upright stability subscale of the modified Friedreich's Ataxia Rating Scale (mFARS). Patients who were still able to walk independently were defined as those scoring ≤ 2 points. The division of the research question by the company

was assessed as not appropriate and this benefit assessment was therefore based on the research question of the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used to derive the added benefit. This concurred with the company’s inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study lists on omaveloxolone (status: 16 April 2025)
- Bibliographical literature search on omaveloxolone (last search on 16 April 2025)
- Search of trial registries/trial results databases for studies on omaveloxolone (last search on 16 April 2025)
- Search on the G-BA website for omaveloxolone (last search on 16 April 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on omaveloxolone (last search on 9 July 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: omaveloxolone vs. BSC

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
408-C-1402 (MOXIe[d])	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7-9]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

ACT: appropriate comparator therapy; BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: omaveloxolone vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MOXIe (Part 2[b])	RCT, double-blind, parallel[c]	Patients aged ≥ 16 and ≤ 40 years with FA ▪ mFARS score ≥ 20 and ≤ 80[d]	omaveloxolone (N = 51) placebo (N = 52)	Screening: 60 days Treatment: 48 weeks Observation: up to 4 weeks after the end of treatment[e]	11 centres in Australia, Austria, Italy, United Kingdom and United States Part 2: 10/2017–10/2019	Primary: change in mFARS score at Week 48 Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Part 1 (dose-ranging study) is not relevant for this benefit assessment
c. Stratified by pes cavus status (yes/no); no more than 20% of patients were allowed to have a positive pes cavus status.
d. Mean of the measurements at Screening and Day 1; the 2 values had to be within 4.5 points of each other. In the study, the mFARS was calculated from the FARSn by excluding the peripheral nervous system subscale (see Figure 1). This allows values from 0 to 99 to be achieved, with lower values meaning better symptoms.
e. After the randomized treatment phase, patients could receive omaveloxolone in a single-arm extension phase. This phase is still ongoing.

AE: adverse event; FA: Friedreich's ataxia; FARSn: Friedreich's Ataxia Rating Scale neurological examination; mFARS: modified Friedreich's Ataxia Rating Scale; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, direct comparison: omaveloxolone vs. placebo

Study	Intervention	Comparison
MOXIe Part 2	omaveloxolone 150 mg/day, orally	placebo, orally
	Dose modification: ▪ Dose reductions were not allowed ▪ Interruption of therapy for up to 21 days in case of toxicity	
	Disallowed prior and concomitant treatment ▪ Within 30 days before the start of treatment and during the study: anticoagulants (exception: < 81 mg acetylsalicylic acid) ▪ Within 14 days before the start of treatment and during the study: antioxidants (exception: vitamin E in the recommended daily dose), anti-spasticity agents ▪ Within 7 days before the start of treatment and during the study: herbal preparations, sensitive substrates for cytochrome P450 2C8 or 3A4, moderate or strong inhibitors or inducers of cytochrome P450 3A4, p-glycoprotein substrates **Allowed concomitant treatment** ▪ Antibiotics, pain medication ▪ Therapy of accompanying diseases with stable dosage ▪ Exercise regimen without any changes[a]	

a. Patients were not allowed to have changed their exercise regimen within 30 days before the start of treatment and had to be willing to remain on the same exercise regimen during the study period.

FA: Friedreich's ataxia; RCT: randomized controlled trial

Study design

MOXIe Part 2 is a randomized, double-blind, multicentre study comparing omaveloxolone with placebo. The study had a total randomized treatment phase of 48 weeks.

The study included patients with genetically confirmed Friedreich's ataxia who were at least 16 years and no more than 40 years old at the time of inclusion and had a score of at least 20 points and no more than 80 points on the mFARS calculated according to the protocol. In the study, the mFARS was calculated from the Friedreich's Ataxia Rating Scale neurological examination (FARSn) by excluding the peripheral nervous system subscale (see Figure 1). This allows values from 0 to 99 to be achieved, with lower values meaning better symptoms. The patients were not allowed to have changed their exercise regimen within 30 days before the start of the study and had to be willing to remain on the same exercise regimen during the study period. In addition, they had to be able to complete a maximal exercise test (cycle ergometry using a recumbent exercise bike). Only patients with adequate kidney function (defined as an estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2)were enrolled. Patients had to have a left ventricular ejection fraction of ≥ 40%. In addition, the patients had to be able to swallow capsules. Patients with uncontrolled diabetes mellitus (glycated haemoglobin [HbA1c] > 11.0%) were excluded. Patients with clinically significant cardiac disease (including New York Heart Association [NYHA] class > 2, brain natriuretic

peptides [BNP] > 200 pg/mL) were also excluded from participation in the study, although the participation of patients with mild to moderate cardiomyopathy associated with Friedreich's ataxia was allowed. Patients with clinically significant liver disease (including an increase in aspartate aminotransferase [AST] or alanine aminotransferase [ALT] of more than 1.5 times the upper limit of normal [ULN]) were also excluded. Patients who had taken anti-spasticity agents within 14 days before the first day of treatment were also excluded from the study. The use of anti-spasticity agents was not permitted in MOXIe Part 2.

Despite some restrictions regarding the permitted concomitant medication, the implementation of the ACT BSC in the MOXIe Part 2 study was considered sufficient.

According to the German S1 guideline on ataxias in adulthood (2023), treatment of Friedreich's ataxia should include treatment of cardiomyopathy according to general cardiological standards and treatment of diabetes mellitus [10], if these are present. The guideline also includes recommendations for exercise therapy.

The treatment of cardiomyopathy was sufficiently ensured in the MOXIe Part 2 study. Patients were to remain on their individual exercise regimen during the entire study period. However, with regard to the treatment of spasticity, it can be assumed that the concomitant treatment with baclofen in 3 patients in the intervention arm represented a protocol deviation. However, the importance of anti-spasticity agents in the treatment of Friedreich's ataxia was not elaborated upon in the treatment recommendations of the German guideline for Friedreich's ataxia. In addition, a current clinical guidance for the management of Friedreich's ataxia assessed non-pharmacological treatments for spasticity as notably more valuable [11], so that this deviation regarding concomitant treatment was considered negligible. Patients with Friedreich's ataxia were expected to have received intensive medical care, including treatment optimization, even before inclusion in the study. In view of the study duration and the slow progression of the disease, it was assumed that maintaining the individual exercise regimen and the concomitant medication did not cause a relevant bias in the study results.

In MOXIe Part 2, 103 patients were enrolled and randomly assigned to omaveloxolone (N = 51) or placebo (N = 52). The allocation was stratified by pes cavus status (yes/no); no more than 20% of patients were allowed to have a positive pes cavus status. The pes cavus status was determined using the beam of a flashlight. If the beam could be seen on the medial side of the foot when shone from the lateral side, pes cavus was present. If a participant had pes cavus on one foot, the pes cavus status was categorized as positive [7,8]. The primary analysis of the study was based on patients with negative pes cavus status.

Treatment with omaveloxolone in the intervention arm was largely in compliance with the summary of product characteristics (SmPC) [12].

The primary outcome was the change in the mFARS score at Week 48. Secondary outcomes included outcomes in the categories morbidity, health-related quality and adverse events (AEs).

Primary analysis population with negative pes cavus status

The primary analysis of the efficacy was to be based solely on patients with negative pes cavus status. According to the company, severe pes cavus would bias the results of the mFARS, especially in the subscales of lower limb coordination and upright stability. However, the therapeutic indication of this benefit assessment also includes patients with positive pes cavus status. Thus, the results of the entire intention-to-treat population of the study were relevant and were used for the benefit assessment.

Further investigations

The MOXIe Part 2 study is an RCT that was used for this benefit assessment.

With the dossier, the company also presented further investigations as supportive evidence for the primary outcome mFARS with a maximum score of 99 points. The supportive evidence included an early-start versus delayed-start analysis and a non-randomized comparison without a common comparator versus the Friedreich's Ataxia Clinical Outcome Measures (FA-COMS) population [13]. The early-start versus delayed-start analysis and the non-randomized comparison included patients from the single-arm MOXIe open-label extension (OLE) phase. Inclusion in the MOXIe OLE required prior participation in MOXIe Part 1 or Part 2. Patients in these studies were not allowed to have any major protocol deviations which, in the assessment of the investigator, made them unsuitable for participation. Of the 172 patients from MOXIe Part 1 and Part 2, 149 were included in the MOXIe OLE. As a result of inclusion in the study, 43 patients continued to receive omaveloxolone and 106 patients switched from placebo to omaveloxolone. The investigators and patients who transitioned from MOXIe Part 2 to MOXIe OLE remained blinded to the treatment in MOXIe Part 2. In Module 4, the company stated that 33 patients were excluded from the transition to MOXIe OLE, but mathematically, the figure should have been 23 patients. The company did not provide any reasons for the exclusion of these patients.

Early start vs. delayed start analysis

Patients in the intervention arm of MOXIe Part 2 who continued treatment with omaveloxolone until the end of treatment in MOXIe OLE were eligible for inclusion in the early-start group. Patients in the placebo arm of MOXIe Part 2 who participated in MOXIe OLE and started treatment with omaveloxolone were eligible for inclusion in the delayed-start group.

The company additionally presented an analysis of the change in the mFARS score from baseline to Week 144 and a responder analysis on the proportion of patients "with average or faster disease progression" (≥ 1.9 points/year), corresponding to least 7 points on the mFARS for an observation period of 196 weeks (48 weeks of treatment in MOXIe Part 2, 4 weeks of follow-up, 144 weeks of treatment in MOXIe OLE). All analyses of the company were based on the definition of mFARS with a maximum of 99 points specified in the study protocol. In addition, the company presented supplementary analyses on walking ability and descriptive presentations on mortality and AEs.

The analyses of early-start versus delayed-start were not suitable to answer the research question of this benefit assessment and were not used for this benefit assessment. The analyses of the RCT MOXIe Part 2 were used, from which results on mortality, walking ability, AEs and mFARS in the validated version with 93 points were available (see also Section I 4.1).

Non-randomized comparison

The company performed a propensity score matching analysis for the non-randomized comparison without a common comparator. The comparison was made between MOXIe OLE patients and FA-COMS patients. To include patients in the study population for the propensity score matching analyses, an mFARS score at baseline and at least one post-baseline mFARS score within 3 years of baseline had to be available. In addition, data had to be available for all covariates of the propensity score matching analysis (sex, baseline mFARS score, age at baseline, age at onset of disease, baseline gait score). This applied to a total of 136 patients from the MOXIe OLE and 598 patients from the FA-COMS study, of which 136 patients were selected for comparison as part of propensity score matching. The company presented analyses comparing both groups with regard to the change in the mFARS score with a maximum of 99 points at Year 1, 2 and 3 versus baseline.

The non-randomized comparison was not used for this benefit assessment due to methodological limitations. No systematic search was presented for the identification of confounders. Instead, the consideration of confounders was based on the availability of data in both comparator arms. For example, pes cavus status was not considered as a confounder, as it was not systematically recorded in FA-COMS in the same way as in the MOXIe study programme. The guanine-adenine-adenine (GAA) repeat length in the shorter GAA allele in the frataxin gene (GAA1) was also not considered because the corresponding data were not available. However, it is known that the GAA1 repeat length in particular is associated with the severity of the disease [14].

The analyses of the RCT MOXIe Part 2 were used, from which results on mFARS in the published version with 93 points were available (see also Section I 4.1).

Characteristics of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: omaveloxolone vs. placebo (multipage table)

Study **Characteristic** **Category**	**omaveloxolone** **N[a] = 51**	**Placebo** **N[a] = 52**
MOXIe		
Age [years], mean (SD)	23 (6)	24 (8)
Age category [years], n (%)		
< 18	9 (18)	15 (29)
≥ 18	42 (82)	37 (71)
Sex [F/M], %	61/39	33/67
Family origin, n (%)		
White	50 (98)	50 (96)
Other	1 (2)	2 (4)
Region, n (%)		
United States	36 (71[b])	35 (67[b])
Non-USA	15 (29[b])	17 (33[b])
Pes cavus, n (%)		
No	41 (80[b])	42 (81[b])
Yes	10 (20[b])	10 (19[b])
mFARS[c], mean (SD)	40.8 (10.1)	37.9 (10.8)
Age at disease onset [years], mean (SD)	14.8 (5.7)	15.3 (5.3)
Time since disease onset [years], mean (SD)	4.7 (3.8)	4.4 (4.4)
Average time in which an exercise regimen was conducted [hours/week], mean (SD)	5.8 (4.5)	5.1 (4.3)
GAA1 repeat length, mean (SD)	737 (207)[d]	676 (268)[d]
GAA2 repeat length, mean (SD)	782 (311)[e]	762 (316)[e]
GAA1 repeat length ≥ 675, n (%)	26 (51)[d]	21 (40)[d]
Walking ability, n (%)		
Ambulatory	46 (90)	49 (94)
Non-ambulatory	5 (10)	3 (6)
History of cardiomyopathy, n (%)	25 (49)	15 (29)
History of areflexia, n (%)	47 (92)	51 (98)
History of foot surgery, n (%)	4 (8)	2 (4)
History of sensory neuropathy, n (%)	26 (51)	26 (50)
History of difficulty swallowing, n (%)	12 (24)	17 (33)
History of scoliosis, n (%)	39 (76)	37 (71)
History of scoliosis surgery, n (%)	16 (31)	10 (19)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: omaveloxolone vs. placebo (multipage table)

Study **Characteristic** **Category**	**omaveloxolone** **N[a] = 51**	**Placebo** **N[a] = 52**
Treatment discontinuation, n (%)[f]	7 (13.7)	2 (3.8)
Study discontinuation, n (%)[g]	6 (11.8)	1 (1.9)

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. In the study, the mFARS was calculated from the FARSn by excluding the peripheral nervous system subscale (see Figure 1). This allows values from 0 to 99 to be achieved, with lower values meaning better symptoms.
d. Data for N = 41 patients in the omaveloxolone arm and N = 43 in the placebo arm
e. Data for N = 40 patients in the omaveloxolone arm and N = 42 in the placebo arm
f. Reasons for treatment discontinuation in the intervention vs. comparator arm were the following (percentages based on the number of randomized patients): AEs 4 vs. 2 (8% vs. 4%), withdrawal of consent 3 vs. 0 (6% vs. 0%).
g. Reasons for study discontinuation in the intervention vs. comparator arm were the following (percentages based on the number of randomized patients): withdrawal of consent 4 vs. 1 (8% vs. 2%), administrative reasons 2 vs. 0 (4% vs. 0%).

AE: adverse event; F: female; GAA: guanine-adenine-adenine; GAA1: shorter GAA allele in the frataxin gene; M: male; mFARS: modified Friedreich's Ataxia Rating Scale; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the patients were largely balanced between both treatment arms of MOXIe Part 2. Existing differences were considered to be random and could be explained by a comparatively small number of patients. The average patient age was 23 years in the intervention arm and 24 years in the comparator arm, with a lower proportion of patients under the age of 18 in the intervention arm (18% versus 29%). The proportion of women was higher in the intervention arm than in the comparator arm (61% versus 33%). There were more patients with a GAA1 repeat length ≥ 675 in the intervention arm (51%) than in the comparator arm (40%). The proportion of patients with cardiomyopathy (mild to moderate cardiomyopathies according to the inclusion criteria) was also higher in the intervention arm than in the comparator arm (49% vs. 29%). The majority of patients were enrolled in the United States (71% versus 67%) and were of white family origin (98% versus 96%). According to the diagnostic criterion used in the study (see Section I 3.2), 20% of the patients in the intervention arm had pes cavus and 19% in the comparator arm, whereby the proportion of patients with pes cavus in the study was limited to 20% according to the protocol. The mean score in the mFARS (with a maximum score of 99 points) was 40.8 points in the intervention arm and 37.9 points in the comparator arm. Most patients in both study arms were able to walk (90% versus 94%).

Treatment was discontinued more frequently in the intervention arm than in the comparator arm (13.7% versus 3.8%). The most common reason for treatment discontinuation was due to

AEs. The study was discontinued more frequently in the intervention arm than in the comparator arm (11.8% versus 1.9%). The most common reason for study discontinuation was withdrawal of consent.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: omaveloxolone vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MOXIe Part 2	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low.

Transferability of the study results to the German health care context

The company stated that MOXIe Part 2 was conducted in several European centres, for example in Austria and Italy. It added that the included patient population consisted of a substantial proportion of Caucasian patients (control arm: 93.8%; omaveloxolone arm: 100%). It concluded that study data were overall transferable to the German health care context.

The company pointed out that the treatment options for Friedreich's ataxia are limited and that no effective drug specifically approved for Friedreich's ataxia has been available to date. According to the company, the treatment of Friedreich's ataxia recommended by the current guidelines in Germany is therefore based on a multidisciplinary approach aimed at alleviating symptoms such as unsteady gait or pain and maintaining the patients' independence for as long as possible. It added that the treatment of accompanying diseases such as cardiomyopathy or depression, physiotherapy and occupational therapy to alleviate ataxic symptoms, and the use of mobility aids, such as walking sticks, walking aids or wheelchairs, play a central role here.

The company stated that the recommendations of the German S1 guideline on the treatment of ataxias in adulthood of the Association of the Scientific Medical Societies include, among other things, the treatment of the cardiomyopathy commonly observed in patients with Friedreich's ataxia in accordance with general cardiological standards [10]. The company

explained that according to the guideline, regular cardiological examinations are necessary to detect changes in cardiac function at an early stage and that for this purpose, the cardiac function of the patients was regularly checked as part of the MOXIe study programme. The company pointed out that the German Medical Association's 2023 National Care Guideline on chronic heart failure recommends, for example, individualized treatment based on the New York Heart Association's step-by-step scheme [15]. The company stated that patients received adequate, individualized treatment as part of the MOXIe study programme, and that patients in both study arms were treated with the ACE (angiotensin converting enzyme) inhibitor lisinopril or beta-blockers (e.g. metoprolol); other drugs used included class 1c antiarrhythmics, histamine H2 receptor antagonists or ivabradine. Thus, according to the company, the German health care context for the treatment of cardiomyopathy was adequately represented in the MOXIe study programme.

The company pointed out that the German guideline recommends physiotherapy and/or occupational therapy to alleviate ataxic symptoms, such as unsteady gait, coordination problems and muscle weakness, in order to establish an individualized exercise regimen for the patients [10], and that in the MOXIe study programme, this was represented by the fact that all patients were to continue their individual exercise regimen throughout the entire study period. The company emphasized that baclofen, which is recommended in the German guideline for the treatment of spasticity, was also a concomitant medication in the study.

The company stated that pain in patients with Friedreich's ataxia required targeted pain therapy and emphasized that patients in both study arms of the MOXIe study programme were treated with the painkiller paracetamol or propionic acid derivatives such as ibuprofen, and that other painkillers, such as opioids or the anticonvulsant drug gabapentin, were also used in both study arms.

The company stated that depression is common in patients with Friedreich's ataxia and that, as part of the MOXIe study programme, patients in both study arms were treated with selective serotonin reuptake inhibitors established in Germany for the treatment of depression (e.g. sertraline, escitalopram). According to the company, other antidepressants and antipsychotics taken by the patients during the study included tricyclic antidepressants (e.g. amitriptyline), monoamine oxidase inhibitors (e.g. bupropion, trazodone) or risperidone.

Finally, the company concluded that the results of MOXIe Part 2 were transferable to the German health care context, particularly in view of the rare nature of Friedreich's ataxia, the guideline-compliant supportive treatment of concomitant symptoms and the demographic characteristics of the patients.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Functionality, recorded with the mFARS
  - Fine motor skills of the upper limbs, recorded with the 9-Hole Peg Test (9-HPT)
  - Walking ability, recorded with the Timed 25-Foot Walk (T25-FW)
  - Health status, recorded using the Patient Global Impression of Change (PGIC)
  - Frequency of falls
  - Limitation in activities of daily living, recorded with the Friedreich's Ataxia-Activities of Daily Living (FA-ADL)
- Health-related quality of life
  - recorded with the Short Form 36 (SF-36)
- Side effects
  - Serious AEs (SAEs)
  - Discontinuation due to AEs
  - Gastrointestinal disorders (System Organ Class [SOC], AEs)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A and Module 4 B).

Table 10 shows for which outcomes data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: omaveloxolone vs. placebo

Study	Outcomes										
	All-cause mortality[a]	Functionality (mFARS)[b]	Fine motor skills of the upper limbs (9-HPT)[c]	Walking ability (T25-FW)	Health status (PGIC)	Frequency of falls	Limitation in activities of daily living (FA-ADL)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AE)
MOXIe Part 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

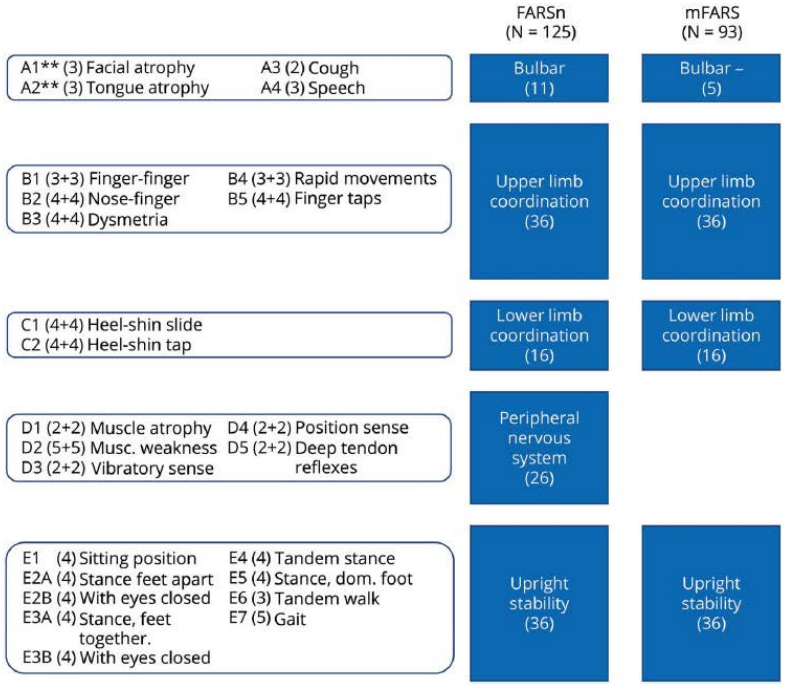
a. The results on all-cause mortality are based on the information on fatal AEs.
b. The functionality was recorded with the mFARS in the version with a total score of 93 points, see the following text section for reasons.
c. The fine motor skills of the upper limbs were assessed with the 9-HPT, testing both hands (non-dominant hand and dominant hand).

9-HPT: 9-Hole Peg Test; AE: adverse event; FA-ADL: Friedreich's Ataxia-Activities of Daily Living; mFARS: modified Friedreich's Ataxia Rating Scale; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36; SOC: System Organ Class; T25-FW: Timed 25-Foot Walk

Notes on outcomes

Functionality

The company presented analyses on the functionality recorded with the FARSn. The FARSn is a functional test that measures functionality for patients in a total score and in 5 subscales: bulbar function, upper limb coordination, lower limb coordination, peripheral nervous system and upright stability [16]. The mFARS is based on the FARSn, see also Figure 1.



Maximum score/subscale/item scores are shown in brackets. Items in subscales B, C, and D are conducted separately on lateral sides; ** items A1 and A2 are excluded in the mFARS examination. FARS = Friedreich Ataxia Rating Scale; mFARS = modified FARS.

Figure 1: Measurement model of the neurological examination of the FARSn and the mFARS
From Rummey 2019 [16]

The FARSn allows a minimum total score of 0 points and a maximum total score of 125 points, with a higher score indicating greater physical impairment. As shown in Figure 1, the mFARS is a reduction of the FARSn with the aim of representing functionality only. For this purpose, the subscale on the peripheral nervous system and 2 items (A1: facial atrophy and A2: tongue atrophy) from the subscale on bulbar function are excluded. This leads to an improved informative value of the measurement instrument [16].

The maximum total score of the published mFARS is 93 points, i.e. the sum of the scores of the 4 subscales and deduction of the items facial atrophy and tongue atrophy. However, in MOXIe Part 2, the mean change at Week 48 with a maximum mFARS total score of 99 points was defined as the primary outcome. Although only the 4 subscales of the mFARS were recorded, in contrast to the analysis of the mFARS with a maximum of 93 points, the 2 items facial atrophy and tongue atrophy were included in the analyses defined in the MOXIe study protocol, resulting in a maximum of 99 points. The company did not justify this type of analysis.

With the dossier, the company presented post hoc analyses based on the published analysis of the mFARS with a maximum of 93 points. In addition to operationalization via the mean change at Week 48, a responder analysis was conducted based on the proportion of patients "with average or faster disease progression" (≥ 1.9 points/year). The company justified the

selection of the response criterion by stating that the average annual progression in patients with Friedreich's ataxia is 1.9 points on the mFARS. It took the study duration of 48 weeks as approximately 1 year. The average annual progression did not correspond to the requirements for response criteria described in IQWiG's *General Methods* [1]. As explained in IQWiG's *General Methods*, for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified and exactly 15% of the scale range in post-hoc analyses. The response criterion of 1.9 points was not predefined and was notably below 15% of the scale range (14 points).

Functionality is a patient-relevant outcome. The analyses of the mean change in published mFARS (maximum 93 points) at Week 48 were used for this assessment.

Fine motor skills of the upper limbs

With the dossier, the company presented analyses on the outcome fine motor skills of the upper limbs recorded with the 9-HPT for both hands (non-dominant hand and dominant hand). The time required to conduct the test was recorded; both the dominant and non-dominant hands were tested individually in 2 consecutive trials, and the results of both hands in both trials were averaged individually. For the average time per hand, the reciprocal values (1/average time) were calculated for the analysis in order to enable a normal distribution of the data, according to the company. Fine motor function of the upper limbs is a patient-relevant outcome. The analyses for both hands were used for this assessment.

Walking ability

In the dossier, the company presented an analysis on the outcome walking ability, recorded with the T25-FW. It presented an analysis of the change in the reciprocal time values (1/average time to enable a normal distribution of the data, according to the company) at Week 48 compared with baseline. Only ambulatory patients were included in the analysis. As a restoration of walking ability is not to be expected in Friedreich's ataxia (even with treatment using omaveloxolone), it was appropriate not to assess changes in walking ability in patients who were unable to walk at baseline. Walking ability is a patient-relevant outcome. The analysis was used for this assessment.

Health status

With the dossier, the company presented analyses on the outcome of health status, recorded using the PGIC. As part of the PGIC, patients assess the change in their health status since the start of treatment. To do this, they complete the statement "Since the start of the study treatment, my health status is ..." with one of 7 options: very much improved (1 point), much improved (2 points), minimally improved (3 points), unchanged (4 points), minimally worse (5 points), much worse (6 points) and very much worse (7 points).

The company's primary analysis considered the PGIC score at Week 48. In the dossier, the company additionally provided responder analyses of the proportion of patients with a 'clinically relevant improvement' in the PGIC (< 4 points) and of the proportion of patients with an unchanged or improved health status (≤ 4 points), as well as the proportion of patients with a deterioration in health status (> 4 points) at Week 48. Only a descriptive analysis of the proportion of patients with at least 'much' improvement in the PGIC of < 3 points was predefined as a responder analysis. As an improvement due to treatment is not generally expected in patients with Friedreich's ataxia and no responder analysis was predefined for the proportion of patients with deterioration, the primary analysis of the PGIC score at Week 48 was used.

Frequency of falls

In the dossier, the company presented an analysis on the outcome of frequency of falls. The data was recorded by the patients using a falls diary in paper format, which was given to the patients at screening. Patients were instructed to record any instances of falls between screening and the end of treatment, including the date and time of each fall, the preceding activity prior to the fall, the perceived cause of the fall, and if an injury was sustained after the fall. The analysis was based on the total number of falls from the start to the end of treatment, with incidence rates calculated. Frequency of falls is a patient-relevant outcome. The analysis was used for this assessment.

Limitation in activities of daily living

In the dossier, the company presented an analysis on the outcome of limitation in activities of daily living, recorded with the FA-ADL. The FA-ADL is a patient-reported disease-specific questionnaire for recording limitations in activities of daily living. The questionnaire contains 9 items on speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, and bladder function. The scale for the individual items ranges from 0 to 4, with a low value (0) meaning no limitation and a high value (4) meaning loss of function or full dependence on assistance. The total score is determined by adding up the individual items so that the total scale covers the range from 0 (no limitation) to 36 points (maximum limitation). If some of the questionnaire items were not answered, the entire FA-ADL was categorized as missing. The company's analysis took into account the change in the FA-ADL total score at Week 48.

The FA-ADL was assessed to be a sufficiently validated instrument. The limitation in activities of daily living is a patient-relevant outcome. The analysis was used for this assessment.

Methods

The standardized mean difference (SMD) was used to assess the clinical relevance of a mean difference (MD). The company presented calculations for this, which it referred to as

Hedges' g. However, it did not sufficiently describe how the calculation was conducted. In particular, it did not explain how the estimation of the standard deviation pooled across the treatment groups, which is included in the original Hedges' g, was replaced. The results were therefore verified by means of calculations conducted by the Institute. This was done using the estimated MD and the associated standard error (from the mixed-effects model with repeated measures [MMRM] or the analysis of covariance [ANCOVA]) as well as various assumptions regarding the number of people included in the analyses. There were minor deviations from the company's calculations. However, as there was no difference in the assessment of clinical relevance, the company's calculations are presented in this assessment.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: omaveloxolone vs. placebo

Study		Outcomes										
	Study level	All-cause mortality[a]	Functionality (mFARS)[b]	Fine motor skills of the upper limbs (9-HPT)[c]	Walking ability (T25-FW)	Health status (PGIC)	Frequency of falls	Limitation in activities of daily living (FA-ADL)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AE)
MOXIe Part 2	L	L	H[d]	H[d]	L	H[d]	H[d]	H[d]	H[d]	H[d]	L[e]	H[d]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The functionality was recorded with the mFARS in the version with a total score of 93 points, see Section I 4.1 for reasons.
c. The fine motor skills of the upper limbs were assessed with the 9-HPT, testing both hands (non-dominant hand and dominant hand).
d. Incomplete observations for potentially informative reasons.
e. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.

9-HPT: 9-Hole Peg Test; AE: adverse event; FA-ADL: Friedreich's Ataxia-Activities of Daily Living; H: high; L: low; mFARS: modified Friedreich's Ataxia Rating Scale; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36; SOC: System Organ Class; T25-FW: Timed 25-Foot Walk

The results on all-cause mortality, walking ability and discontinuation due to AEs had a low risk of bias.

All other results had a high risk of bias due to incomplete observations for potentially informative reasons. For this assessment, the numbers of patients with values at the various time points of recording were used, where available. According to the company, data on the frequency of falls were available for 51 versus 52 patients until at least Week 36. However, of the 6 versus 1 patients with study discontinuation (12% versus 2%), at least 1 patient discontinued the study before Week 12, which contradicted the statement that data were available on all patients until at least Week 36. There was no complete overview of when the observation (or the study) ended for each patient. No data on the number of patients under observation at the various data collection points were available for the outcomes in the side effects category. In combination with the different proportions of patients with treatment discontinuation (7 versus 2, i.e. 14% versus 4%) or study discontinuation (6 versus 1, i.e. 12% versus 2%) between the arms and the potentially informative reasons for this, this resulted in a high risk of bias for the results on SAEs and gastrointestinal disorders (AEs).

Certainty of results for discontinuations due to AEs

The certainty of results for the outcome of discontinuation due to AEs was limited despite the low risk of bias of the results. Premature treatment discontinuation for reasons other than AEs was a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

I 4.3 Results

Table 12, Table 13 and Table 14 summarize the results on the comparison of omaveloxolone with placebo in patients with Friedreich's ataxia aged 16 years and older. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 12: Results (mortality, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: omaveloxolone vs. placebo

Study Outcome category Outcome	omaveloxolone N	omaveloxolone Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	omaveloxolone vs. placebo RR [95% CI][a]; p-value[b]
MOXIe Part 2					
Mortality					
All-cause mortality[c]	51	0 (0)	52	0 (0)	–
Health-related quality of life					
SF-36					
Physical Component Summary (PCS, deterioration[d])	44	3 (7)	51	4 (8)	0.89 [0.21; 3.71]; 0.880
Mental Component Summary (MCS, deterioration[e])	44	3 (7)	51	3 (6)	1.16 [0.25; 5.42]; 0.914
Side effects					
AEs (supplementary information)	51	51 (100)	52	52 (100)	–
SAEs	51	5 (10)	52	3 (6)	1.70 [0.43; 6.74]; 0.531
Discontinuation due to AEs	51	4 (8)	52	2 (4)	2.04 [0.39; 10.65]; 0.530
Gastrointestinal disorders (SOC, AE)	51	34 (67)	52	21 (40)	1.65 [1.13; 2.42]; 0.010

a. RR, CI: Cochran-Mantel-Haenszel, adjusted for pes cavus status. For SAEs and discontinuation due to AEs: no information on the model.
b. p-value: Institute's calculation (unconditional exact test, CSZ method according to [17]).
c. The results on all-cause mortality are based on the data on fatal AEs.
d. A score decrease by ≥ 9.4 points from baseline to Week 52 is considered a clinically relevant deterioration (scale range: 0 to 100). No responder analyses are available on the subscales.
e. A score decrease by ≥ 9.6 points from baseline to Week 52 is considered a clinically relevant deterioration (scale range: 0 to 100). No responder analyses are available on the subscales.

AE: adverse event; CI: Confidence interval; CSZ: convexity, symmetry, z-score; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients (for the outcomes on health-related quality of life: number of patients at Week 48); PGIC: Patient Global Impression of Change; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36; SOC: System Organ Class

Table 13: Results (morbidity, continuous) – RCT, direct comparison: omaveloxolone vs. placebo (multipage table)

Study Outcome category	omaveloxolone			Placebo			omaveloxolone vs. placebo
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Mean change at Week 48 mean[b] [95% CI]**	**N[a]**	**Values at baseline mean (SD)**	**Mean change at Week 48 Mean[b] [95% CI]**	**MD [95% CI]; p-value[b]**
MOXIe Part 2							
Morbidity							
Functionality (mFARS)[c]	50	40.67 (10.16)	−1.01 [−2.28; 0.27]	52	37.81 (10.78)	0.82 [−0.38; 2.01]	−1.82 [−3.59; −0.06]; 0.043 SMD: −0.42 [−0.84; −0.01]
Bulbar function[d]	50	0.73 (0.50)	−0.08 [−0.18; 0.03]	52	0.63 (0.63)	−0.03 [−0.13; 0.07]	−0.05 [−0.19; 0.10]
Upper limb coordination[e]	50	10.75 (3.71)	−0.72 [−1.51; 0.07]	52	9.90 (3.53)	0.11 [−0.62; 0.84]	−0.83 [−1.91; 0.25]
Lower limb coordination[f]	50	6.29 (2.58)	−0.13 [−0.73; 0.48]	52	6.25 (2.29)	−0.30 [−0.86; 0.26]	0.17 [−0.66; 1.00]
Upright stability[g]	50	22.89 (6.53)	−0.11 [−0.88; 0.67]	52	21.02 (7.13)	0.94 [0.22; 1.67]	−1.05 [−2.12; 0.02]
Fine motor skills of the upper limbs (9-HPT)[h]							
Non-dominant hand, [1/s]	45	0.0205 (0.0080)	−0.0010 [−0.0022; 0.0001]	51	0.0204 (0.0070)	−0.0002 [−0.0013; 0.0008]	−0.0008 [−0.0024; 0.0007] 0.298
Dominant hand, [1/s]	45	0.0229 (0.0077)	−0.0002 [−0.0011; 0.0008]	50	0.0227 (0.0076)	−0.0007 [−0.0016; 0.0002]	0.0005 [−0.0008; 0.0018] 0.422
Walking ability (T25-FW)[i], [1/s]	39[j]	0.13 (0.07)	−0.02 [−0.03; −0.01]	44[j]	0.14 (0.06)	−0.02 [−0.03; −0.01]	0.00 [−0.01; 0.02] 0.504
Health status (PGIC)[k]	50	–	3.91 [3.44; 4.38]	52	–	4.47 [4.02; 4.92]	−0.56 [−1.06; −0.06] 0.028[l] SMD: −0.45 [−0.86; −0.04]
Limitation in activities of daily living (FA-ADL)[m]	45	11.03 (4.49)	0.28 [−0.56; 1.12]	51	9.85 (4.72)	1.05 [0.27; 1.84]	−0.78 [−1.93; 0.38] 0.187

Table 13: Results (morbidity, continuous) – RCT, direct comparison: omaveloxolone vs. placebo (multipage table)

Study Outcome category	omaveloxolone			Placebo			omaveloxolone vs. placebo
Outcome	N[a]	Values at baseline mean (SD)	Mean change at Week 48 mean[b] [95% CI]	N[a]	Values at baseline mean (SD)	Mean change at Week 48 Mean[b] [95% CI]	MD [95% CI]; p-value[b]
a. Minimum number of patients taken into account in the effect estimation; baseline values are based on all 51 vs. 52 randomized patients. b. Mean and CI (per treatment group) as well as MD, CI and p-value (group comparison): MMRM; adjusted for study centre, pes cavus status, baseline value, treatment group, time, interaction term between treatment group and time and interaction term between baseline value and time. The effect represents the difference in changes (from baseline) between the treatment groups at Week 48. c. The functionality was recorded with the mFARS in the version with a total score of 93 points, see Section I 4.1 for reasons. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 0 to 93). d. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 0 to 5). e. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 0 to 36). f. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 0 to 16). g. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 0 to 36). h. The fine motor skills of the upper limbs were assessed with the 9-HPT, testing both hands (non-dominant hand and dominant hand). Higher values mean better symptoms. i. Higher values mean better symptoms. j. Minimum number of patients included in the effect estimation. Only 46 vs. 49 patients were able to walk at baseline. Of these, values were available for 45 vs. 47 patients at baseline. k. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 1 to 7). l. Mean and CI (per treatment group), MD, associated CI and p-value (group comparison): ANCOVA with multiple imputation of 6 vs. 1 patients using treatment, study centre, pes cavus status and post-baseline values of health status; adjusted for study centre, pes cavus status, baseline value and treatment group. Effect represents the difference in values at Week 48 between the treatment groups. Lower values mean better symptoms; negative effects mean an advantage for the intervention. m. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 0 to 36). 9-HPT: 9-Hole Peg Test; ANCOVA: analysis of covariance; CI: confidence interval; FA-ADL: Friedreich's Ataxia-Activities of Daily Living; MD: mean difference; mFARS: modified Friedreich's Ataxia Rating Scale; MMRM: mixed-effects model with repeated measures; N: minimum number of patients included in the effect estimation; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; T25-FW: Timed 25-Foot Walk						

Table 14: Results (morbidity, number of events per time) – RCT, direct comparison: omaveloxolone vs. placebo

Study Outcome Subscale	omaveloxolone		Placebo		omaveloxolone vs. placebo
	N	Adjusted incidence rate [95% CI][a] n_E/N (SD)	N	Adjusted incidence rate [95% CI][a] n_E/N (SD)	Rate ratio [95% CI]; p-value[a]
MOXIe Part 2					
Morbidity					
Frequency of falls	51[b]	0.04 [0.03; 0.05]; 11.24 (18.98)	52[b]	0.05 [0.03; 0.06]; 15.00 (23.67)	0.82 [0.50; 1.34]; 0.425

a. Rates per day and CI (per treatment group) as well as rate ratio, CI and p-value (group comparison): Poisson model with natural logarithm of time in the study (in days) as offset variable; adjusted for pes cavus status.
b. On the one hand, it was stated that data on the frequency of falls until at least Week 36 were available for 51 versus 52 patients. On the other hand, of the 6 vs. 1 patients with study discontinuation, at least 1 patient discontinued the study before Week 12, which contradicts the statement that data were available on all patients throughout the study.

CI: confidence interval; n_E: number of events (sum of events across all patients); N: number of analysed patients; RCT: randomized controlled trial

Based on the available information, no more than indications, for example of an added benefit, can be determined for the outcomes of all-cause mortality and walking ability, and no more than hints for the outcomes of functionality, fine motor skills of the upper limbs, health status, frequency of falls, limitations in activities of daily living, health-related quality of life, SAEs and gastrointestinal disorders (AEs) due to the high risk of bias, and for the outcome of discontinuation due to AEs due to competing events for the outcome to be assessed.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome all-cause mortality. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Functionality

For the outcome functionality, recorded with the mFARS in the version with a total score of 93 points, a statistically significant difference between the treatment arms was shown when considering the difference in changes at Week 48. The SMD was considered to check the

relevance of the result. The 95% confidence interval (CI) of the SMD was not completely below the irrelevance threshold of –0.2. It could therefore not be inferred that the effect was relevant; an added benefit is therefore not proven.

Fine motor skills of the upper limbs

For the outcome fine motor skills of the upper limbs, recorded with the 9-HPT, there was no statistically significant difference between the treatment arms when considering both the non-dominant hand and the dominant hand. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome fine motor skills of the upper limbs; an added benefit is therefore not proven.

Walking ability

No statistically significant difference between the treatment arms was shown for the outcome walking ability, recorded using the T25-FW. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome walking ability; an added benefit is therefore not proven.

Health status

For the outcome health status, recorded with the PGIC, a statistically significant difference between the treatment arms was shown when considering the difference in changes at Week 48. The SMD was considered to check the relevance of the result. The 95% CI of the SMD was not completely below the irrelevance threshold of –0.2. It could therefore not be inferred that the effect was relevant; an added benefit is therefore not proven.

Frequency of falls

There was no statistically significant difference between the treatment arms for the outcome frequency of falls. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome frequency of falls; an added benefit is therefore not proven.

Limitation in activities of daily living

No statistically significant difference between the treatment arms was shown for the outcome limitation in activities of daily living, recorded using the FA-ADL. There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome limitation in activities of daily living; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded using the Physical Component Summary and the Mental Component Summary of the SF-36. There were no statistically significant differences between the treatment arms for either sum score (recording a deterioration of ≥ 9.4 points in the Physical Component Summary and of ≥ 9.6 points in the Mental Component Summary,

each corresponding to 15% of the scale range). There is no hint of an added benefit of omaveloxolone in comparison with BSC for the outcome health-related quality of life; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs. For the outcome SAEs, there is no hint of greater or lesser harm of omaveloxolone in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs. For the outcome discontinuation due to AEs, there is no hint of greater or lesser harm of omaveloxolone in comparison with BSC; greater or lesser harm is therefore not proven.

Gastrointestinal disorders (AEs)

A statistically significant difference to the disadvantage of omaveloxolone versus BSC was shown for the outcome gastrointestinal disorders (AEs). For the outcome gastrointestinal disorders (AEs), there is a hint of greater harm of omaveloxolone versus BSC.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for this benefit assessment:

- Age (< 18 years versus ≥ 18 years)
- Sex (male versus female)
- GAA1 repeat length (< 675 versus ≥ 675)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The subgroup analyses presented were incomplete. The company did not conduct any interaction tests for the characteristic age for the following outcomes: fine motor skills of the upper limbs as determined by the 9-HPT (in each case non-dominant and dominant hand),

health status (PGIC), limitation of activities of daily living (FA-ADL) and gastrointestinal tract disorders (AEs). The company did not justify this.

The presented subgroup analyses showed one statistically significant interaction for the characteristic age in the outcome walking ability (p-value for the interaction: 0.043). However, the results per subgroup were not presented by the company. It was therefore not possible to assess the relevance of the interaction. Overall, there was a potential incompleteness of content.

For the outcome gastrointestinal disorders (AEs), the company stated that it had added the interaction between subgroup characteristic and treatment to the model to test homogeneity, without stating which type of model was used, so that these could also be interaction tests regarding the odds ratio or the risk difference. Regardless of the type of model used, given the size of the p-values, it was assumed that there was no statistically significant interaction.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 15).

Table 15: Extent of added benefit at outcome level: omaveloxolone vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier**	**omaveloxolone vs. placebo** **Proportion of events (%) or mean change or adjusted incidence rate** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit not proven / added benefit not proven
Morbidity		
Functionality (mFARS)	Mean: −1.01 vs. 0.82 MD: −1.82 [−3.59; −0.06]; p = 0.043 SMD: −0.42 [−0.84; −0.01][c]	Lesser benefit not proven / added benefit not proven
Fine motor skills of the upper limbs (9-HPT)	Non-dominant hand: Mean: −0.0010 vs. −0.0002 MD: −0.0008 [−0.0024; 0.0007]; p = 0.298 Dominant hand: Mean: −0.0002 vs. −0.0007 MD: 0.0005 [−0.0008; 0.0018]; p = 0.422	Lesser benefit not proven / added benefit not proven
Walking ability (T25-FWT)	Mean: −0.02 vs. −0.02 MD: 0.00 [−0.01; 0.02]; p = 0.504	Lesser benefit not proven / added benefit not proven
Health status (PGIC)	Mean: 3.91 vs. 4.47 MD: −0.56 [−1.06; −0.06]; p = 0.028 SMD: −0.45 [−0.86; −0.04][c]	Lesser benefit not proven / added benefit not proven

Table 15: Extent of added benefit at outcome level: omaveloxolone vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier**	**omaveloxolone vs. placebo** **Proportion of events (%) or mean change or adjusted incidence rate** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Frequency of falls	Adjusted incidence rate: 0.04 vs. 0.05 Rate ratio: 0.82 [0.50; 1.34]; p = 0.425	Lesser benefit not proven / added benefit not proven
Limitation in activities of daily living (FA-ADL)	Mean: 0.28 vs. 1.05 MD: −0.78 [−1.93; 0.38] p = 0.187	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
SF-36		
Physical Component Summary (deterioration)	7% vs. 8% RR: 0.89 [0.21; 3.71]; p = 0.880	Lesser benefit not proven / added benefit not proven
Mental Component Summary (deterioration)	7% vs. 6% RR: 1.16 [0.25; 5.42]; p = 0.914	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	10% vs. 6% RR: 1.70 [0.43; 6.74]; p = 0.531	Greater/lesser harm not proven
Discontinuation due to AEs	8% vs. 4% RR: 2.04 [0.39; 10.65]; p = 0.530	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	67% vs. 40% RR: 1.65 [1.13; 2.42] RR: 0.61 [0.41; 0.89][d] p = 0.010 Probability: hint	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm, extent: minor

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper or lower limit of the confidence interval.
c. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

9-HPT: 9-Hole Peg Test; AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FA-ADL: Friedreich's Ataxia-Activities of Daily Living; mFARS: modified Friedreich's Ataxia Rating Scale; MD: mean difference; PGIC: Patient Global Impression of Change; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36; SMD: standardized mean difference; T25-FW: Timed 25-Foot Walk

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 16: Positive and negative effects from the assessment of omaveloxolone in comparison with BSC

Positive effects	Negative effects
–	Non-serious/non-severe side effects ▪ Gastrointestinal disorders (AEs): hint of greater harm – extent: minor
AE: adverse event; BSC: best supportive care	

Overall, there was a negative effect in the non-serious/non-severe side effects category for the outcome gastrointestinal disorders (AEs). This negative effect of omaveloxolone in an outcome in the category of non-serious/non-severe side effects was not considered sufficient to derive lesser benefit of omaveloxolone compared with the ACT. In summary, there is no hint of an added benefit of omaveloxolone versus BSC for patients with Friedreich's ataxia aged 16 years and older.

The result of the assessment of the added benefit of omaveloxolone in comparison with the ACTs is summarized in Table 17.

Table 17: Omaveloxolone – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients ≥ 16 years with Friedreich's ataxia	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Further comments from the G-BA:
- Treatments listed in the German Remedies Catalogue (e.g. voice, speech and language therapy, physiotherapy) can help to alleviate symptoms.
- A comparison with placebo alone does not correspond to the ACT.
- BSC is assumed to be offered in both arms of a study.
- Symptomatic treatment as part of BSC can also include pharmacological therapy.
- In the therapeutic indication in question, patients in both study arms are assumed to receive appropriate treatment for existing or newly emerging symptoms and accompanying diseases. These include, among others, diabetes mellitus (treated with insulin, for example), cardiomyopathies (treated with beta receptor blockers, ACE inhibitors and AT-2 receptor antagonists, for example) and scoliosis (treated by surgical correction if necessary).

ACE: angiotensin converting enzyme; AT-2: angiotensin-2; BSC: best supportive care; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of an at least minor added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2024, where the G-BA had determined a non-quantifiable added benefit of omaveloxolone. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-86.html.