National Institute for Health and Care Excellence

Health Technology Evaluation

Omaveloxolone for treating Friedreich's ataxia in people 16 years and over ID6423

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Biogen Idec	Biogen considers it highly appropriate for omaveloxolone to be referred to the National Institute for Health and Care Excellence (NICE) for appraisal at this time. However, Biogen proposes that a highly specialised technology (HST) evaluation is the most appropriate route. Friedreich's ataxia (FA) is rare, there are no approved treatment options currently available in the UK and the disease severely limits life expectancy and impairs quality of life. Therefore, Biogen believes that omaveloxolone for FA strongly fulfils Criteria 1, 3 and 4 for evaluation via the HST programme. Although there is uncertainty over Criterion 2 (the number of people in England eligible for treatment), in light of the high unmet need, lack of available treatment options and potential ramifications for people with FA and their caregivers if omaveloxolone was routed for evaluation via a single technology assessment (STA), Biogen requests that NICE applies discretion in its decision and reconsiders routing omaveloxolone to the HST evaluation route (further detail is provided in our response to the HST Criteria Company Proforma [ID6423]).	NICE's prioritisation board has decided that this topic will be evaluated as a single technology appraisal (STA). The board concluded that criterion 2, that there should be no more than 300 people in England eligible for the technology in its licensed indication, and no more than 500 across all its

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			indications, was not met.
	ABN Neurogenetics Advisory Group	We agree that this single technology appraisal is appropriate – this is the first proposed disease modifying treatment for FRDA	NICE's prioritisation board has decided that this topic will be evaluated as a single technology appraisal (STA). The board concluded that criterion 2, that there should be no more than 300 people in England eligible for the technology in its licensed indication, and no more than 500 across all its indications, was not met.
	Genetic Alliance UK	None	No changes to scope needed.
	Neurology Clinical Reference Group	Entirely appropriate	Thank you for your comment.
	Ataxia UK	We very much support the evaluation of this topic. There is currently no approved disease modifying treatment for people with Friedreich's ataxia in the UK, and this is a complex highly debilitating progressive condition. The drug to be evaluated has already been granted approval by the EMA in Feb 2024 and by the FDA in Feb 2023. The proposed route of single technology	NICE's prioritisation board has decided that this topic will be evaluated as a single technology appraisal

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		appraisal may be appropriate, however, given the rare nature of Friedreich's ataxia and the high unmet need, consideration should be given to the highly specialised technology appraisal route.	(STA). The board concluded that criterion 2, that there should be no more than 300 people in England eligible for the technology in its licensed indication, and no more than 500 across all its indications, was not met.
Wording	Biogen Idec	Biogen agrees with the wording of the remit in the draft scope and that it accurately reflects any considerations around clinical and cost-effectiveness regarding the intended licensing and marketing authorisation for omaveloxolone.	Thank you for your comment.
	ABN Neurogenetics Advisory Group	The wording of the draft remit in the draft scope is appropriate	Thank you for your comment.
	Genetic Alliance UK	None	No changes to scope needed.
	Neurology Clinical Reference Group	Yes [wording appropriate]	Thank you for your comment.
	Ataxia UK	Yes, we agree the wording is appropriate. The wording does not however reflect the devastating nature of this degenerative condition nor the fact there are no disease-modifying treatments.	Thank you for your comments. We have expanded the background section to

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			include further symptoms.
Timing issues	Biogen Idec	There is a high degree of urgency for NICE to undertake a technology appraisal in FA. The need for people with FA to have rapid access to effective treatments was recognised by the Food and Drug Administration (FDA) in the United States (US), who granted omaveloxolone fast track and priority review, alongside rare paediatric disease and orphan drug designations.[1, 2] Omaveloxolone also received an orphan drug designation from the European Medicines Agency (EMA) in 2018.[3] People with FA, caregivers, patient organisation representatives and clinicians have expressed a need for a treatment that can improve neurological function and slow disease progression as soon as possible. The majority of people with FA continue to deteriorate significantly with current clinical management, which underpins the urgency of this unmet need. FA is a rare, genetic, neurodegenerative movement disorder, that causes progressive and irreversible neurological and non-neurological symptoms, leading to continuous loss of functionality and ultimately incapacitation and early death.[4, 5] Disease manifestations include problems with walking, speech, swallowing, hearing and vision, as well as cardiomyopathy and skeletal abnormalities.[4, 5] The median age at onset of FA is 10–15 years,[6] with total loss of ambulation and confinement to a wheelchair typically occurring at the age of 25–30 years.[4, 6] People with FA often experience cardiac symptoms in the later stages of their condition,[5-7] and cardiac complications are a leading cause of death.[8, 9] The average life expectancy of people with FA is just 39 years.[10] Currently, there are no treatments licensed in the UK that target the underlying mechanism of disease and that can slow disease progression for people with FA. Treatment of people with FA is currently symptomatic, as described in the section below; people with FA receive complex care from a multidisciplinary team (such as physiotherapy, speech therapy, psychological and other specialist support) as well as a range of pharmacological	Thank you for your comments. This topic has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.

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		treatments to manage a wide range of symptoms and complications.[7] Current clinical management does not halt or slow the progression of FA. Early initiation of effective treatment is therefore crucial to slow progression of FA, in order to mitigate irreversible neurological and non-neurological manifestations that substantially limit patients' life expectancy.[4, 7, 10] In summary, there is an urgent and significant unmet need for a treatment that can improve neurological outcomes and slow disease progression in people with FA. Omaveloxolone is the first and only therapy to target the underling mechanism of disease and with the potential to slow FA progression, as demonstrated by significant changes in the modified Friedreich's ataxia rating scale (mFARS) versus placebo in the pivotal MOXIe trial.[11-13]	
	ABN Neurogenetics Advisory Group	Omaveloxolone was licensed by the FDA in Feb 2023. In this period while the efficacy is being evaluated FRDA patients will be deteriorating and potentially losing the opportunity to benefit from this drug. We regard this as an urgent situation for our patients	Thank you for your comments. This topic has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.
	Genetic Alliance UK	None	No changes to scope needed.
	Neurology Clinical Reference Group	Moderate [urgency]	Thank you for your comments. This topic has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.
	Ataxia UK	Friedreich's ataxia is a progressive condition with a high impact on the quality of life of individuals with the condition and their families. Omaveloxolone has	Thank you for your comments. This topic

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		been shown in trials to slow progression of the condition, and this is supported in practice by the clinical experiences of using the drug in the US over more than one year, so there is much urgency for the evaluation to take place. The patient community is very frustrated by the lack of access to this treatment in the UK, especially when the drug has become available in other countries	has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.
Additional comments on the draft remit	Biogen Idec	No further comments	Thank you for your comment.
	ABN Neurogenetics Advisory Group	None	No changes to scope needed.
	Genetic Alliance UK	None	No changes to scope needed.
	Neurology Clinical Reference Group	None	No changes to scope needed.
	Ataxia UK	None	No changes to scope needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Biogen Idec	Biogen does not agree with the estimated prevalence of FA reported in the draft scope. The higher bound of the prevalence range stated in the draft scope (1:20,000–54,000) originates from an EMA pan-European estimate that deviates markedly from other published prevalence estimates. There is a high	We have updated the estimates of prevalence and population to reflect the figures in Vankan et al.

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		level of variation in population estimates for FA across Europe.[14] For instance, the prevalence of FA in Spain and France is estimated to be 1:20–25,000 and 1:43,000, respectively, whereas the prevalence in Sweden is estimated to be 1:420,000.[14] As a result, the European-wide EMA prevalence estimate is not an appropriate source for determining the prevalence of FA in the UK. Furthermore, Dürr et al., 1996 is not a primary source of epidemiological data. We recommend therefore that the wording of the background section is updated to reflect the most widely used UK prevalence estimate from Vankan et al. of 1:54,000, and references 3 and 4 are removed.[14] While Biogen agrees that the estimates for the number of people with FA in the UK are uncertain, the upper range in the draft scope (3,400) is an overestimation. Biogen estimates that there are approximately 800–1,000 people with FA in the UK care system, which is in line with Ataxia UK's current estimates (please see the HST criteria checklist Criterion 2 for further information). Prevalence estimates from Vankan et al. (with estimates for Scotland, Northern Ireland and Wales removed) would yield ~997 patients, for a total population in England of 57.1 million (and a population prevalence of 1:57,266, as described in Criterion 1 of the HST Criteria Company Proforma [ID6423]).[14, 15] As per the intended indication, [redacted] would not be eligible to receive omaveloxolone, which would substantially reduce the total number of eligible patients, although data are not available to confirm this figure. With respect to nomenclature, the background section does not currently refer to FA as a rare disease. Genomics England's definition of a rare condition is one that affects less than 1:2,000 of the general population, and the prevalence of FA is estimated to be lower than NICE's definition of a 'very rare' disease (1:50,000; see Criterion 1 of the HST Criteria Company Proforma [ID6423] for further details).[16] Biogen requests that the introductory text is amended to reflect the rarity of FA in the scope.	We have added that it is a rare disease.

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		Biogen requests further text updates to accurately reflect aspects of FA. For instance, in addition to the role of frataxin protein deficiency in cell death, frataxin deficiency also results in mitochondrial dysfunction, iron overload and oxidative stress, and defective antioxidant responses, which in turn leads to progressive neurodegeneration.[17] Oxidative stress is exacerbated by impaired activity of the transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), a crucial regulator of cellular antioxidant pathways.[4, 17, 18] Nrf2 is a master transcription factor that regulates the expression of genes involved in mitochondrial metabolism, redox balance, and inflammation.[19-21] Nrf2 function is suppressed in a number of mitochondrial disorders, including Parkinson's disease and FA.[20] Biogen would therefore request that the following sentence is revised as bolded: "A lack of frataxin in people with Friedreich's ataxia results in insufficient energy production, oxidative stress and iron accumulation in cell mitochondria (where energy is produced), as well as impaired activity of the regulatory protein Nrf2, leading to mitochondrial dysfunction and progressive neurodegeneration."	We have added some detail on the biological effects of the condition at a cellular level.
		Finally, the reference used to support the average age of death in people with FA was published in 1996. A more recent study of survival and mortality in FA was published by Indelicato et al., 2023, which reports a mean age of death of 39 years, and therefore Biogen would suggest this is cited in the background information.[10]	We have updated the average age of death to reflect the more recent evidence.
		In 'The Voice of the Patient' summary report from a meeting led by four leading patient advocacy groups (Friedreich's Ataxia Research Alliance, Muscular Dystrophy Association, National Ataxia Foundation and Cure FA Foundation) and the FDA, 145 people with FA and their caregivers expressed that while a cure for FA is needed, if this was not available, slowing or stopping of disease progression would be very important.[22] Currently available treatments cannot slow the progression of FA. Biogen therefore requests that the phrase 'no curative treatments' be replaced with 'no treatments that can slow disease progression', to reflect the significant unmet need in FA.	We have changed no curative treatment to no treatments that can slow progression.

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	ABN Neurogenetics Advisory Group	Adequate	Thank you for your comment.
	Genetic Alliance UK	None	No changes to scope needed.
	Neurology Clinical Reference Group	Good	Thank you for your comment.
	Ataxia UK	We would like to highlight a number of clarifications and additional information to be included in this section: The section provides a good description of Friedreich's ataxia, however it lacks detail on some of the symptoms people can experience and thus may not emphasise enough the seriousness, severity and high impact on quality of life. For example, swallowing problems, hearing and eyesight issues, urinary and bowel issues and orthopaedic issues such as scoliosis are not included. These are described in this reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5862303/ Prevalence – Exact data is lacking for the UK. But the figures quoted for likely numbers (1,300-3,400 in the UK) we believe are an overestimate. Estimates from European studies suggest 1:20,000 to 1:50,000. The 2013 paper (your ref 5) suggests 1:54:000 for the UK i.e.: 1,055 for England. To note those figures include children as well as adults. Ataxia UK's database has 805 people with Friedreich's ataxia in the UK. Taking all this information together a more realistic estimate for the total number of Friedreich's ataxia patients in England would be around 1,300, so the number of adults would be lower. The paper quoted for mortality is quite old and there is a more recent paper from the EFACTS European natural history study that reports an average life	Thank you for your comments. We have added a further description of symptoms. We have updated the prevalence and population figures.

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		expectancy of 39 and in this cohort the range is 13-73. The reference for this is *Indelicato, E; Reetz, K; Maier, S et al. Predictors of Survival in Friedreich's Ataxia: A Prospective Cohort Study. Movement Disorders. 2024;39(3):510-518.* Although there are no NICE guidelines, Ataxia UK worked with ataxia specialists to create Ataxia guidelines for the UK (these include guidance on Friedreich's ataxia). See Ataxia UK website and this publication: (https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1013-9) In the description of the current treatments, it is important to note that there are no disease modifying treatments for Friedreich's ataxia, and nothing to slow or stop the progression of the condition. The only treatments available are for symptomatic relief of some associated symptoms (such as spasticity). Importantly there are only symptomatic relief treatments for some and not all symptoms. There are no treatments for symptomatic relief of the ataxia, which is what impacts patients the most. We feel the current draft does not reflect the current situation and gives the over-optimistic impression that there are many treatment options for patients.	
Population	Biogen Idec	The population is defined appropriately and is in line with the anticipated MA for omaveloxolone.	Thank you for your comment.
	ABN Neurogenetics Advisory Group	Yes [appropriately defined]	Thank you for your comment.
	Genetic Alliance UK	None	No changes to scope needed.
	Neurology Clinical	Appropriate	Thank you for your comment.

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	Reference Group		
	Ataxia UK	Yes [appropriate]	Thank you for your comment.
Subgroups	Biogen Idec	Biogen considers the suggested subgroup detailed in the draft scope to be inappropriate. Omaveloxolone would provide the only treatment option available to people with FA that has the potential to slow disease progression, as demonstrated by significant changes in mFARS versus placebo in the pivotal MOXIe trial.[11, 12] and should therefore be considered for all [redacted]. As noted in the "Timing issues" section of Comment 1, there is a significant and urgent unmet need across the whole population of people with FA. As a rare disease, the population of FA is small; there is no available evidence to assess clinical outcomes and cost-effectiveness for the suggested subgroup, and more broadly it is not appropriate to further reduce the population size and increase uncertainty through investigation of subgroups.	We have removed the suggested subgroups.
	ABN Neurogenetics Advisory Group	It has been suggested that there may be differential benefit in patients with and without pes cavus which should be considered in addition to early and late onset.	Following scoping consultation, we have removed subgroups.
	Genetic Alliance UK	We do not see any rationale for creating subgroups of the FA population.	We have removed the suggested subgroups.
	Neurology Clinical Reference Group	None	No changes to the scope needed.

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	Ataxia UK	No, we do not believe there are any useful subgroups to be evaluated separately. We will specifically address the proposed subgroup of late versus early disease onset. Although there are in theory people diagnosed within these two categories (before or after the age of 25), there is a continuum with age of onset, with individuals having a wide range of disease onset. In addition, it would be difficult to ascertain the exact point of disease onset at an individual level as it would rely on when individuals were diagnosed or seen by a neurologist, whether clinicians recorded the symptoms, issues round misdiagnoses, when patients came forward with symptoms etc. We also think that the condition is too rare to consider subgroups for the evaluation of the drug. We are not aware of any subgroups that would benefit more from the drug than others. Indeed, because the drug has disease-modifying properties one would expect from a scientific perspective that all patients should benefit.	Thank you for your comments. We have removed the suggested subgroups.
Comparators	Biogen Idec	Biogen does not agree with the distinction in the draft scope of established clinical management and best supportive care (BSC) as two separate comparators. Clinical management of FA varies widely across the UK, and distinguishing between established clinical management and BSC is not clinically appropriate, nor would it be possible to make this distinction with available clinical and economic evidence. Biogen agrees that there are no relevant pharmacological treatments to be included as comparators to omaveloxolone for people with FA, and therefore the comparator in this submission should be BSC, which captures the standard of care currently used to treat FA. The appropriate comparison is omaveloxolone with BSC versus placebo with BSC (BSC alone). In the absence of treatments that can slow progression, the medications listed in the draft scope under “current clinical management” are relevant and common components of real-world clinical practice in England and Wales.	Thank you for your comments. We have amended the comparators to refer to best supportive care.

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	ABN Neurogenetics Advisory Group	Biogen considers the outcome measures listed in the draft scope to be appropriate and relevant to people with FA. Biogen would expect that disease progression is also listed as a key outcome for consideration in the appraisal. As noted in the "Background information" section of Comment 2, disease progression is a highly relevant measure to people with FA.	Thank you for your comments. We have added further outcomes that indicate disease progression.
	Genetic Alliance UK	We are informed by our member Ataxia UK that there are currently no condition modifying treatments available for FA. The treatments here are medical and interventional versions of 'best supportive care', and should not be seen as a set of individual alternatives to omaveloxolone.	Thank you for your comments. We have amended the comparators to refer to best supportive care.
	Neurology Clinical Reference Group	The only possible disease modifying comparator is Coenzyme Q10 which does not seem to be mentioned	Thank you for your comment. Following consultation with clinical experts, the comparator has been changed to best supportive care alone.
	Ataxia UK	It should be made clear that there are no comparator drugs for Friedreich's ataxia. The drugs listed should be considered under 'standard of care' for symptomatic relief of associated symptoms and not affecting the underlying condition. And the comparison should be 'Omaveloxolone (with Standard of care)' versus 'Standard of care alone'. Within standard of care, treatment of other associated symptoms such as depression, and the use of occupational therapy, for example, should be added.	Thank you for your comments. We have amended the comparators to refer to best supportive care.
Outcomes	Biogen Idec	Biogen considers the outcome measures listed in the draft scope to be appropriate and relevant to people with FA. Biogen would expect that disease progression is also listed as a key outcome for consideration in the appraisal. As noted in the "Background information" section of Comment 2, disease progression is a highly relevant measure to people with FA.	Thank you for your comments. We have added disease progression as an outcome.

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	ABN Neurogenetics Advisory Group	In addition to the domains listed we would suggest consideration of objective and validated measures of disease progression, such as the SARA score.	Thank you for your comment. NICE scopes do not specify particular scales or instruments to avoid excluding clinical trials that use scales or instruments not specified in the scope.
	Genetic Alliance UK	None	No changes to the scope needed.
	Neurology Clinical Reference Group	Yes [appropriate]	No changes to the scope needed.
	Ataxia UK	Although it may be included within 'neurological symptoms' we think it is important to include symptoms such as upper limb coordination, fatigue and speech. In addition to mobility, these symptoms have the greatest impact on the quality of life of people with Friedreich's ataxia. Disease progression is also an important outcome. Slowing or stopping progression is extremely important to people with Friedreich's ataxia at all stages of the condition.	Thank you for your comments. We have added disease progression and further outcomes after consultation with clinical experts.
Equality	Biogen Idec	Biogen supports access to treatment for all people with FA regardless of their age, disease severity and socioeconomic background. We are aware that care of people with FA in the UK is currently mainly provided by three specialist ataxia centres, located in London (National Hospital for Neurology and Neurosurgery), Sheffield (Royal Hallamshire Hospital) and Oxford (John Radcliffe Hospital).[23] Biogen are aware of patients who are required to travel long distances at considerable cost, in order to access specialist care. For instance, patients in Wales are many hours away	Thank you for your comment. Equalities issues will be considered as part of the evaluation. No change to scope needed.

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		from any of the specialist centres. Variable access to treatment centres is therefore a potential driver of health inequalities in FA. Equality of access is a key consideration for Biogen and we are committed to supporting the availability of omaveloxolone to all eligible patients in England and Wales. Furthermore, the stated intent for NICE to route this evaluation through the STA programme, rather than the more appropriate HST programme, could have implications for equity and equality for individuals with FA. Routing via the STA programme does not fully consider the urgent, unmet need that can be addressed by omaveloxolone in the FA patient population and does not fully account for the very rare nature of FA as recognised by the FDA and EMA's orphan designations.[2, 3] An STA routing for omaveloxolone could therefore result in unjustifiable delays in access for this patient population. Biogen has concerns that routing a product for a rare condition – with a significant unmet need and severity – through the STA programme, would result in inequality in the potential for its access.	The committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS (including use of other available treatments, diagnostics, or best supportive care). The extent of unmet health need is reflected within the severity definition.
	ABN Neurogenetics Advisory Group	If Omaveloxolone is licensed for use in the UK, but not NICE approved, patients who are able to afford to purchase it will start treatment, while those who cannot afford the drug will not receive it. This will create a "2-tier" management approach, and will discriminate against poorer, disadvantaged and vulnerable subjects with FRDA- who already lose out on supportive therapies. Patients are desperate to try something, and some have even resorted to flying to the US to embark on treatment (something that only the very privileged can afford to do).	Thank you for your comment. Equalities issues will be considered as part of the evaluation. No change to scope needed.
	Genetic Alliance UK	None	No changes to the scope needed.

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	Neurology Clinical Reference Group	None	No changes to the scope needed.
	Ataxia UK	None	No changes to the scope needed.
Other considerations	Biogen Idec	Not applicable	No changes to the scope needed.
	ABN Neurogenetics Advisory Group	Consideration of equitable provision of genetic testing and identification of eligible patients. Consideration of recommendations for further research and licensing for the paediatric FRDA population	Thank you for your comments. These will be for discussion by the technology appraisals committee. No changes to the scope needed.
	Genetic Alliance UK	None	No changes to the scope needed.
	Neurology Clinical Reference Group	None	No changes to the scope needed.
	Ataxia UK	In addition to using evidence from the trial, there is growing real world evidence for the use of omaveloxolone, mostly from the US where the drug has been available for over one year. In countries such as France data is also being collected as part of their early access criteria. We are aware that there is data from the global natural history study (FA-GCC) related to experiences of clinical use of omaveloxolone.	Thank you for your comments. Any available real-world evidence submitted to NICE will be considered by the technology appraisals committee.
Questions for consultation	Biogen Idec	How is Friedreich's ataxia currently diagnosed in the NHS? Biogen's current understanding is that FA is typically diagnosed during childhood or adolescence,[6, 7] based on clinical suspicion of symptoms with	Thank you for your comments.

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		confirmation by genetic testing for expansion of the GAA repeat in the *FXN* gene.[5] The typical presenting symptoms of FA are gait ataxia and balance and coordination disturbances.[6, 24] Other suggestive clinical findings include musculoskeletal features (e.g. scoliosis), hypertrophic non-obstructive cardiomyopathy, optic atrophy and/or deafness and endocrinological features (e.g. glucose intolerance).[25] A genetic test is required for a conclusive diagnosis of FA.[5] Testing options include single-gene testing or a multi-gene panel.[25] Single-gene testing is targeted at identifying abnormal GAA expansion in intron 1 of *FXN*; however, if only one expanded allele is detected (~4% of cases), sequence analysis of *FXN* will also be performed.[7, 25] In the UK, *FXN* is tested via multi-gene panels included in the National Genomic Test Directory;[26] as such, Biogen considers that genetic testing in FA is routinely used currently to identify the majority of people living with the condition. How is Friedreich's ataxia currently treated in the NHS? Are there existing clinical guidelines? What is established clinical management without omaveloxolone for this condition? The UK patient advocacy group Ataxia UK published guidelines on the clinical management of progressive ataxias, including FA, in 2019.[27] More recent guidelines from a global perspective were published in 2022 and were endorsed by Friedreich's Ataxia Research Alliance (FARA).[28] Of note, the UK guidelines consider data from proxy conditions (e.g. multiple sclerosis) if condition-specific information is not available. In addition, in 2023, the National Neurosciences Advisory Group (NNAG), with the support of NHS England, published guidance on the optimal clinical management of adults with movement disorders, including progressive ataxias such as FA.[29] In England and Wales, people with FA are treated by a multidisciplinary team (MDT), due to the complex and multisystemic nature of the disease. A	Thank you for your comments.

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		neurologist is central to the MDT and FA patient management, alongside physiotherapists and a specialist nurse, with cardiologists, endocrinologists and psychologists involved in care from the time of diagnosis.[3,38] As symptoms develop, other relevant specialties become involved with patient care; this may include speech therapists, urologists, ophthalmologists, occupational therapists and pulmonary specialists.[3,38] People with FA typically have regular appointments with the MDT or general practitioner to monitor progress.[30] In some cases, people with FA receive care in a specialist ataxia centre, however, there are only three specialist centres in England (London, Oxford and Sheffield; see "Equality" section of Comment 2 above). Current treatment of FA is symptomatic, as there are no treatments that can slow the progression of FA. For example, a speech and language therapist may support with two of the most common symptoms of ataxia – dysarthria and dysphagia. An occupational therapist may support with adapting to the gradual loss of mobility and function, to help with activities of daily living. A physiotherapist may help a person with FA maintain their limb function, through exercises and walking aids. Pharmacological interventions can help with symptoms such as muscle spasms, cramps and stiffness, urinary urgency and/or incontinence, eye problems, erectile dysfunction, nerve pain and depression.[30] As discussed in the "Comparators" section of Comment 2, the comparators proposed in the draft scope should be combined into a single "BSC" comparator, comprising of symptomatic and/or supportive care, co-ordinated via a MDT (as described above). Where do you consider omaveloxolone will fit into the existing care pathway for the disease? Omaveloxolone will be used as the first-line treatment for FA, alongside BSC. Would omaveloxolone be used in addition to (as an add on) or in place of current treatments for symptoms of the condition?	See previous responses.

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		Omaveloxolone will be used as the first-line treatment for FA, alongside BSC. How should best supportive care be defined? As discussed in the "Comparators" section above, Biogen does not consider "established clinical management" and "BSC" to be distinct comparators and believes that BSC should be considered the sole comparator in this evaluation. Please see the "Comparators" section for further details on the definition of BSC. BSC typically comprises complex multidisciplinary care to manage the range of symptoms experienced in FA. A neurologist is often central to FA patient management with cardiologists, endocrinologists and psychologists involved in care from the time of diagnosis.[3,38] As symptoms develop, other relevant specialties become involved with patient care; this may include speech therapists, urologists, ophthalmologists, occupational therapists and pulmonary specialists.[3,38] Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom omaveloxolone is expected to be more clinically effective and cost effective or other groups that should be examined separately? This is discussed in the "Subgroups" section of Comment 2 above. Biogen does not consider that there are any subgroups that should be examined separately in the evaluation given the significant unmet need present in the wider FA population. How is severity measured Friedreich's ataxia? How is severity linked to age of onset? Should time of onset Friedreich's ataxia be considered as a separate subgroup? Disease severity is measured through disease progression measures.[6] A variety of rating scales and performance measures have been employed	See previous responses. See previous responses. See previous responses.

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		which assess combinations of different signs and symptoms (neurological and non-neurological) experienced by individuals with FA, including:[6, 31] The International Co-operative Ataxia Rating Scale (ICARS) The Scale for the Assessment and Rating of Ataxia (SARA) The Friedreich Ataxia Rating Scale (FARS) and modified FARS (mFARS) ICARS was the first widely accepted scale; however, its use in FA clinical studies has since diminished.[31] Both SARA and FARS are now generally accepted and used in two large natural history studies in Europe (EFACTS) and the US (FACOMS).[31] Compared to SARA, the FARS provides a more detailed evaluation of overall patient status, which may support the separate evaluation of individual domains.[31] Correlations have been reported between mFARS (which focusses on functional abilities) and walking speed, cadence and stability indexes, in addition to pathophysiological aspects of the disease.[32] The mFARS also has excellent test–retest properties and its validity has been assessed in many observational studies, demonstrating its high correlation with age of onset, and patient reported outcome measures such as the activities of daily living (ADL) scale.[32-35] In a natural history study of adults and children with FA (N=812), FARS score correlated with disease duration, staging and ADL score.[33] FARS and mFARS scores were found to worsen over time at a rate of approximately 2 points per year.[33] Age of onset (which is strongly correlated to age at diagnosis) can predict the development of comorbid conditions such as cardiomyopathy and scoliosis.[36] As discussed in the “Subgroups” section of Comment 2 and the previous question, Biogen does not consider that there are any subgroups that should be examined separately in the evaluation given the small size of the trial population and resulting small sample size of any subgroups, which would introduce further uncertainty. The unmet need in FA is significant across the entire population of people living with this progressive condition, and fast	

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		access to a treatment with the potential to slow disease progression, is urgently needed across the population. How many people in England and Wales aged over 16 have Friedreich's ataxia? Would omaveloxolone be suitable for everyone in this group? As discussed in the "Background information" section of Comment 2, Biogen estimates that there are approximately 800–1,000 people with FA in the UK care system, based on feedback from clinical and patient groups. This include [redacted] who, under the proposed indication, would not be eligible to receive omaveloxolone. Therefore, the anticipated number of eligible patients is expected to be considerably lower than this estimate, though exact numbers are uncertain. Is there data to inform the prevalence of Friedreich's ataxia by region in England? As discussed in the "Background information" section of Comment 2, there is variability in prevalence estimates for FA. Nevertheless, best available regional estimates demonstrate that FA is a rare disease affecting fewer that 1:50,000 in England and Wales (see Criterion 1 of the HST Criteria Company Proforma [ID6423] for further details).[14] Please select from the following, will omaveloxolone be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details) C: Biogen expects that omaveloxolone would be prescribed in secondary care with routine follow-up in secondary care. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.	See previous responses. See previous responses. Thank you for your response.

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		It is expected that both the intervention and comparator (BSC) would be delivered in secondary care. Would omaveloxolone be a candidate for managed access? Biogen would welcome an early discussion about potential service models for implementation. Do you consider that the use of omaveloxolone can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Omaveloxolone slows the progression of FA, and so is expected to accrue health benefits related to mitigating disease progression, many of which are unlikely to be captured in full by the quality-adjusted life year (QALY) calculation. The disability burden in FA is substantial, and increases as the disease progresses, with patients eventually losing all autonomy. In a survey of people with FA, 60% felt that loss of independence was one of the most significant effects of the disease.[22] Patients are also concerned about the impact this dependence has on their family and friends.[22] Patients know their condition will only worsen and that there are no treatments available,[37] which leads to fear for the future; availability of treatments which have the potential to slow disease progression, such as omaveloxolone, would provide a more hopeful outlook to people living with FA. The sensory loss associated with FA may limit patients' ability to work, as described by a teacher with FA: *"I can't filter out the background noise to focus on the topic and I can't hear students at the back of the class."*[37] Only 13% of UK patients with FA are reportedly in paid employment (mean work time of 23.6 hours per week).[38] Sensory loss also affects social interactions and communication, ultimately leading to feelings of isolation: *"The most common word I hear is "huh" thanks to my dysarthria, and I barely hear that due to hearing loss"* and *"Without vision you have nothing – isolation from the*	Thank you for your comments.

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		world is complete".[37] These sensory impairments compound the loss of independence that patients already experience due to their limited mobility.[37] FA is a rare disease and health-related quality of life data (e.g. EQ-5D) are therefore limited; where available, the EQ-5D may also lack specificity for patients with FA. For example, fatigue has been reported to be incompletely captured by the EQ-5D.[39, 40] People with FA report fatigue as a key issue affecting their daily lives with young people with FA often missing school because of fatigue.[22] They have a limited amount of energy during the day, much of which is used to complete simple tasks because activities of daily living require more effort to complete.[22] Due to the rapid progression and irreversible nature of FA, people with FA and their caregivers face a significant mental and emotional burden with a UK neurologist reporting that: "*The impact [of FA] is absolutely enormous…the entire family is affected. It is absolutely catastrophic from a social and psychological perspective for the entire family"*.[37] In the UK, only 29% and 19% of caregivers were in full- or part-time employment, respectively, and 22% of these had to take time off work to care for the person with FA.[38] Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Beyond the effect of omaveloxolone on disease progression, the MOXIe trial demonstrated the positive effect of omaveloxolone on functional outcomes, for example via the Friedreich Ataxia Activities of Daily Living (FA-ADL) measure. Surveys and direct quotes from patients and caregivers can also be used to provide context on the impact of the disease and the treatment benefit of omaveloxolone across clinical, humanistic and economic outcomes. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the	Thank you for your comments.

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		proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which omaveloxolone will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. Please refer to the "Equality" section of Comment 2 above. NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation). Biogen believes that omaveloxolone should be assessed using the HST pathway and requests that NICE applies discretion and reconsiders its decision, in light of the evidence presented in the "Appropriateness of an evaluation and proposed evaluation route" section of Comment 1 above, and in the HST Criteria Checklist submitted alongside this consultation comment form.	See previous responses.
	ABN Neurogenetics Advisory Group	Epidemiology of ataxia – suggest consulting with Dr Mark Wardle/Prof Neil Robertson	Thank you for your comments. Practicalities of

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		Consideration of the practical initiation, maintenance and follow-up of patients prescribed omaveloxolone with appropriate monitoring and supportive care for a complex multi-system neurological disease	administering technologies and monitoring and supportive care are not in the remit of NICE's technology appraisals programme. No changes to the scope needed.
	Genetic Alliance UK	None	No changes to the scope needed.
	Neurology Clinical Reference Group	None	No changes to the scope needed.
	Ataxia UK	1. How is Friedreich's ataxia currently diagnosed in the NHS? In the majority of cases diagnosis is made by neurologists in secondary care, or at Specialist Ataxia Centres. Genetic testing can identify the common genetic mutations (expansion in GAA repeats), although more in-depth analysis may be required for the 4% with point mutations. Diagnosis can take a long time due to lack of awareness of Friedreich's ataxia, leading to referral delays and misdiagnoses. 2. How is Friedreich's ataxia currently treated in the NHS? Are there existing clinical guidelines? What is established clinical management without omaveloxolone for this condition? Ataxia UK, working with clinical experts in the UK has produced Ataxia guidelines for diagnosis and management (and these include Friedreich's ataxia). See Ataxia UK website and this publication: (https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1013-9)	Thank you for your comments.

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		https://www.ataxia.org.uk/healthcare-professionals/resources-for-healthcare-professionals/medical-guidelines/ These guidelines are endorsed by the European reference network for rare neurological diseases. In addition, there are Friedreich's ataxia international guidelines created by a collaboration of specialists on FA around the world (these are included in your scoping document, ref 6). Management for FA (without omaveloxolone) involves symptomatic relief treatments and input from many different healthcare professionals to manage the complex needs. In England there is also an Ataxia care pathway within the 'Optimal clinical pathway for adults with movement disorders' developed by the National neurosciences advisory group (in collaboration with Ataxia UK and clinical experts): https://www.nnag.org.uk/optimal-clinical-pathway-for-movement-disorders. This pathway acknowledges the important role of the three Specialist Ataxia Centres (accredited by Ataxia UK) 3. Where do you consider omaveloxolone will fit into the existing care pathway for the disease? Prescribed in secondary care with routine follow-up in secondary care. 4. Would omaveloxolone be used in addition to (as an add on) or in place of current treatments for symptoms of the condition? As there are no disease modifying treatments to slow or stop progression of FA, omaveloxolone would be the main treatment provided in addition to the standard clinical care provided to patients. 5. How should best supportive care be defined? This is described in the 'Optimal clinical pathway for adults with movement disorders' and Ataxia medical guidelines (see point 2 above)	

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		6. Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom omaveloxolone is expected to be more clinically effective and cost effective or other groups that should be examined separately? No, we do not believe that Omaveloxolone would be more effective in any subgroup. See answer above in subgroups question. 7. How is severity measured Friedreich's ataxia? How is severity linked to age of onset? Should time of onset Friedreich's ataxia be considered as a separate subgroup? Severity of Friedreich's ataxia is commonly measured using rating scales (SARA and mFARS) within trials. In clinical practice rating scales are normally used in Ataxia Specialist Centres, but we think they are unlikely to be used in other non-specialist clinics. See answer above regarding subgroups. 8. How many people in England and Wales aged over 16 have Friedreich's ataxia? Would omaveloxolone be suitable for everyone in this group? In Ataxia UK's database there are 805 people with FA living in the UK. Age data is not registered on all people, therefore the estimate for people aged 16 and over is not as accurate (but is at least 727 individuals). More information on geographical distribution can be provided. Yes, omaveloxolone is suitable for everyone in this group (apart from any with contraindications). 9. Is there data to inform the prevalence of Friedreich's ataxia by region in England?	

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		Ataxia UK has information on the regional distribution of people with Friedreich's ataxia registered with the charity. We are happy to provide this information.	
Additional comments on the draft scope	Biogen Idec	No additional comments	No changes to scope needed.
	ABN Neurogenetics Advisory Group	None	No changes to scope needed.
	Genetic Alliance UK	None	No changes to scope needed.
	Neurology Clinical Reference Group	None	No changes to scope needed.
	Ataxia UK	In the economic analysis we think it would be important to include the impact on carers and family members, as Friedreich's ataxia impacts the lives of many people who provide support to the individuals with the condition. We would also like to mention that as Friedreich's ataxia is a rare disease it is important to refer to the Rare Disease Framework for England.	Thank you for your comments. We have amended to background section to refer to the condition as rare. The committee will consider the impact of the condition on carers.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Sheffield Children's NHS Foundation
UCL/ UCLH