

# NCPE Assessment

## Technical Summary

Omaveloxolone (Skyclarys®)

HTA ID: 24033

15 December 2025

Applicant: Biogen (Idec) Ireland Ltd.

Omaveloxolone for the treatment of  
Friedreich's ataxia in adults and  
adolescents aged 16 years and older



The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of omaveloxolone (Skyclarys®).

Following assessment of the Applicant's submission, the NCPE recommends that omaveloxolone (Skyclarys®) not be considered for reimbursement.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Biogen (Idec) Ireland Ltd.) Health Technology Assessment of omaveloxolone (Skyclarys®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

#### **About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

## Summary

---

In May 2025, Biogen (Idec) Ireland Ltd. submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of omaveloxolone (Skyclarys®) for the treatment of Friedreich's ataxia (FA) in adults and adolescents aged 16 years and older. Biogen (Idec) Ireland Ltd. is seeking reimbursement of omaveloxolone (Skyclarys®) on the High-Tech Drug Arrangement.

Omaveloxolone is expected to work by activating the Nrf2 protein that protects cells against toxic forms of oxygen and blocking the protein NF-KB, which plays an important role in the inflammatory process. By protecting cells and reducing inflammation, omaveloxolone targets the symptoms of FA. Omaveloxolone should be taken at a dose of 150mg (3 x 50mg tablets) once daily (o.d.) and is, potentially, a long-term treatment. The SmPC does not make any recommendation on treatment duration.

FA is a rare, rapidly progressive autosomal recessive disorder, affecting the nervous system, heart and musculoskeletal system, and metabolism. The current standard of care (SOC) for adults and adolescents with FA aged 16 years and older in Ireland is best supportive care (BSC). BSC involves management of the neurological and non-neurological components of FA. Patients are seen by multidisciplinary teams including occupational therapy, physiotherapy, and speech and language therapy, and undergo regular neurological, cardiac, and endocrine review. Omaveloxolone is the first pharmacological therapy licensed for the treatment of FA.

### **1. Comparative effectiveness of omaveloxolone**

The clinical trial programme of omaveloxolone includes MOXie Part 2, a 48-week randomised, placebo-controlled, parallel-group, double-blind phase II study to evaluate the safety and efficacy of omaveloxolone (150mg o.d.) versus placebo in participants with FA. Omaveloxolone or placebo were administered alongside BSC. The primary endpoint in MOXie Part 2 was change from baseline in modified Friedreich's Ataxia Rating Scale (mFARS), an objective 93-point physician-assessed measure of neurological function in FA patients. Higher mFARS scores indicate more severe impairment. At 48 weeks, omaveloxolone demonstrated significant improvement in mFARS compared to placebo. The mFARS of 40

participants on omaveloxolone changed by –1.55 points on average (95% confidence interval [CI] -2.93, -0.18), compared to 0.85 (95% CI –0.43, 2.13) points on average for 42 participants on placebo. The key secondary endpoints, patient global impression of change (PGIC) and clinical global impression of change (CGIC), did not formally contribute to evidence for efficacy. The secondary endpoint of FA-activities of daily living (FA-ADL) was significantly improved in the omaveloxolone arm at week 48. Limitations of MOXIe Part 2 include:

- It is unclear whether the approximate 2-point difference observed between arms in mFARS (on a 93-point scale) constitutes a meaningful slowing of FA progression;
- More mFARS data were missing in the omaveloxolone arm, meaning the treatment effect could be overestimated due to attrition bias;
- There is a high risk of bias due to baseline imbalances in participant characteristics and potential unblinding due to the high gastrointestinal side effect burden in the omaveloxolone arm;
- Trial results cannot be generalised to patients with underlying diabetes or cardiac disease as they were excluded from the trial;
- Limited data preclude any meaningful conclusions regarding the impact of omaveloxolone on health-related quality of life (HRQoL); and
- The efficacy of omaveloxolone in clinically relevant subgroups is highly uncertain due to small sample size.

MOXIe Part 2 was followed by an open-label extension (OLE) period up to 144 weeks where 149 participants received a target dose of omaveloxolone 150mg o.d. alongside BSC. The Applicant presented MOXIe OLE data for three years and five years of follow-up. To evaluate the long-term efficacy of omaveloxolone compared to BSC, change in mFARS was compared between MOXIe OLE participants and propensity-matched participants from the Friedreich Ataxia Clinical Outcome Measures Study (FACOMS) registry who were receiving BSC only. At year three, MOXIe OLE participants had experienced slower progression. The least squares mean progression from baseline in mFARS was 3 (standard error [SE] 0.66) in MOXIe OLE participants compared to 6.61 in propensity-matched FACOMS participants. Limitations of MOXIe OLE and the propensity-matched analysis include:

- The longer-term observed outcomes on mFARS in the MOXle OLE cannot be attributed to causal effects of omeveloxolone due to the single-arm, open-label trial design as well as high proportions of missing mFARS observations after week 24;
- Patients who discontinued treatment in the MOXle OLE had more severe FA, introducing a risk of bias in favour of omeveloxolone; and
- Indirect treatment comparisons between MOXle OLE participants and FACOMS participants are uncertain due to a lack of matching of important prognostic covariates and the likelihood that BSC differed between the two populations.

## 2. Safety of omeveloxolone

The safety profile of omeveloxolone was derived from all omeveloxolone-treated participants across MOXle Part 2, MOXle OLE and the MOXle Part 1 study (n=165). The mean duration of omeveloxolone exposure in this cohort was 2.72 years. Omeveloxolone was generally well tolerated. In total, 15 participants (9%) permanently discontinued omeveloxolone due to treatment emergent adverse event (TEAE). The most common TEAEs were gastrointestinal disorders (38%, n=62) including nausea, diarrhoea, and vomiting. The CHMP note that the high gastrointestinal side effect burden related to omeveloxolone may have led to unblinding in MOXle Part 2. Headache was also common (31%, n=51), as were hepatic TEAEs including increases in alanine aminotransferase (29%, n=47) and aspartate aminotransferase (15%, n=25).

The SmPC recommends dose reduction to 100mg omeveloxolone o.d. and close monitoring for AE in patients with moderate hepatic impairment. The use of omeveloxolone is contraindicated in patients with severe hepatic impairment.

## 3. Cost effectiveness of omeveloxolone

The Applicant has compared the cost-effectiveness of omeveloxolone (alongside BSC) to BSC.

### *Methods*

A de novo regression-based model considers patient outcomes based on five mFARS health states (mFARS 0-19, 20-39, 40-59, 60-79, 80-93). Disease progression is modelled by predicting change in mFARS over time using long-term patient-level data from the FACOMS dataset. A weighted average of disease progression is estimated according to 'age of onset', a prognostic factor for speed of FA progression. Age of onset categories include  $\leq 7$  years, 8-

14 years, 15-24 years, and >24 years. Patients in the omaveloxolone arm enter the model on omaveloxolone treatment and remain on treatment until discontinuation (informed by the MOXle OLE). Individuals in the comparator arm enter the model receiving BSC only. The relative treatment effect is derived as a “rate ratio” of cumulative change in mFARS after three years of patients from the matched (via an unanchored propensity score nearest neighbour matching algorithm) FACOMS versus MOXle OLE population. Deaths recorded over twelve years in the European Friedreich’s Ataxia Consortium for Translational Studies (EFACTS) registry (Indelicato et al, 2024) are used to map mFARS to overall survival for each treatment arm. Costs and utilities are also determined by the projected mFARS score for each treatment arm and applied for each one-year cycle. A lifetime horizon is applied.

The Applicant used utility data derived from a vignette-based time trade-off (TTO) study. The Review Group identified a number of limitations of this vignette-based approach, notably: HRQOL using the SF-36 measure was collected in the MOXle Part 2 trial but not used to inform the cost-effectiveness model (CEM); EQ-5D-3L data were available from the EFACTS registry but not used in the CEM; and the methods used to generate utilities in the vignette study were not validated. The Applicant considered that the SF-36 and EQ-5D generated from MOXle Part 2 and EFACTS were not sensitive to changes in health status for mobility-impaired patients with FA. The Review Group consider that EQ-5D-3L data from the EFACTS registry demonstrate adequate sensitivity to change in both ambulatory and non-ambulatory patients with FA, supporting the use of this data in the NCPE adjusted base case. The model included drug acquisition costs, pharmacy fees and AE costs for omaveloxolone. Other healthcare resources were aggregated as mFARS-score specific costs and included routine medical visits and hospitalisations. Non-healthcare costs were included for caregiver support and home modifications.

*Results*

An incremental analysis of the costs and benefits of omaveloxolone (alongside BSC) versus BSC was presented by the Applicant. Results of the analysis are presented in Table 1.

**Table 1 Applicant base case incremental cost-effectiveness results<sup>a</sup>**

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	600,694	7.80	-	-	-
Omaveloxolone	2,763,926	9.38	2,163,233	1.58	1,364,848

**QALY:** quality adjusted life year; **ICER:** incremental cost effectiveness ratio; **BSC:** best supportive care

<sup>a</sup> Corresponding probabilistic ICER using 1,000 iterations =€1,384,050/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

The NCPE adjusted base case, which uses EQ-5D-3L utility data from the EFACTS registry rather than vignette TTO-generated utilities, is presented in Table 2.

**Table 2 NCPE adjusted base case incremental cost-effectiveness results<sup>a</sup>**

<b>Treatments</b>	<b>Total costs (€)</b>	<b>Total QALYs</b>	<b>Incremental costs (€)</b>	<b>Incremental QALYs</b>	<b>ICER (€/QALY)</b>
BSC	600,694	9.63	-	-	-
Oma <span>ve</span> loxolone	2,763,926	10.87	2,163,233	1.24	1,750,668

**BSC:** Best supportive care; **ICER:** Incremental cost effectiveness ratio; **QALY:** Quality-adjusted life year

<sup>a</sup> Corresponding probabilistic ICER using 1,000 iterations =€1,751,535/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcome.

### *Sensitivity analysis*

The Review Group consider that there is uncertainty in the reliability of the ICER relating to the relative treatment effect, relative dose intensity (RDI), and the application of a lifetime time horizon. The NCPE conducted targeted scenario analyses to test these uncertainties. The ICER fluctuated between €1.68 million and €1.98 million per QALY.

The probability of cost-effectiveness for omaveloxolone (alongside BSC) versus BSC in the Applicant and NCPE-adjusted base cases was 0% at thresholds of €20,000 per quality-adjusted life year (QALY) and €45,000 per QALY.

## **4. Budget impact of omaveloxolone**

The price to wholesaler of omaveloxolone is €23,200 per pack (90 x 50mg). The estimated cost per patient per year to the HSE for omaveloxolone is €280,380 (VAT not applicable on oral drugs). The Applicant predicted that 66 patients will be treated with omaveloxolone in year one, rising to 124 in year five. The five-year estimated cumulative (gross and net) drug budget impact for omaveloxolone is €134.3 million. Many of the BIM inputs are uncertain and there is considerable uncertainty associated with the budget impact estimate. The Applicant assumed that 61.67% of patients aged 16 years and older with FA are seen in clinical practice in Ireland and thus might be eligible for treatment with omaveloxolone. The Review Group consider that all patients aged 16 years and older with FA in Ireland might be eligible for treatment should omaveloxolone be reimbursed. A scenario analysis in which the

proportion of eligible patients increased to 100% resulted in a cumulative five-year gross and net drug budget impact of €214.6 million. The Applicant assumed a 55% market share for omaveloxolone in year one, increasing to 100% by year five. The Review Group consider the market shares underestimated as omaveloxolone will be the only licensed pharmacological treatment for FA if reimbursed. A scenario analysis in which the market shares were increased to 100% in all years resulted in a cumulative five-year drug budget impact of €163.2 million.

## **5. Patient Organisation Submission**

Patient organisation submissions were received for this submission from Friedreich's Ataxia Research Alliance (FARA) Ireland and Neuroataxia CLG t/a Ataxia Foundation Ireland.

## **6. Conclusion**

The NCPE recommends that omaveloxolone not be considered for reimbursement\*.

There is uncertainty regarding the clinical benefit of omaveloxolone and the probability of cost effectiveness at the €45,000 per QALY threshold is 0% in the Applicant and NCPE-adjusted base cases. There is a substantial five-year cumulative drug budget impact (gross and net), estimated to be over €134.3 million.

\*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.