SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Skyclarys 50 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg omaveloxolone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

Opaque hard capsule with “RTA 408” printed on the light green body in white ink and “50” printed on the blue cap in white ink. Capsules (size 0) are 21.7 ± 0.3 mm in length, and the outer diameter of the cap is 7.64 ± 0.06 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Omaveloxolone should be initiated and supervised by physicians with experience in the treatment of patients with Friedreich Ataxia.

Posology

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

Medicine lost through emesis should not be replaced with an additional dose.

If a dose is missed, the next dose should be taken as usual the following day. A double dose should not be taken to make up for a missed dose.

Dose modifications for concomitant therapy

The recommended dosages for concomitant use of omaveloxolone with strong or moderate cytochrome P450 (CYP) 3A4 inhibitors or inducers are described in Table 1 (see sections 4.4 and 4.5).

Table 1: Recommended dosage modifications of omaveloxolone with concomitant use of CYP3A4 inhibitors

Concomitant Drug Class	**Dosage Recommendation**
Strong CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of Skyclarys to 50 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, coadministration with strong CYP3A4 inhibitors should be discontinued.
Moderate CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of Skyclarys to 100 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, further reduce the dosage of Skyclarys to 50 mg once daily.

Elderly
No dose adjustment is required based on age (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh Class A).

The dose should be reduced to 100 mg once daily with close monitoring for adverse reactions in patients with moderate hepatic impairment (Child-Pugh

Class B). Lowering to 50 mg once daily should be considered if adverse reactions emerge.

The use of the medicinal product should be avoided in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

Renal impairment
The effect of moderate and severe renal impairment on the pharmacokinetics of omaveloxolone has not been studied (see section 5.2).

Paediatric population
The safety and efficacy of Skyclarys in children and adolescents aged less than 16 years have not yet been established. No data are available.

Method of administration

This medicinal product is for oral use.

Omaveloxolone should be taken on an empty stomach at least 1 hour before or 2 hours after eating (see sections 4.5 and 5.2).

Skyclarys capsules should be swallowed whole.

For patients who are unable to swallow whole capsules, Skyclarys capsules may be opened, and the entire contents sprinkled onto 2 tablespoons of apple puree. Patients should consume all the medicine/food mixture immediately on an empty stomach at least 1 hour before or 2 hours after eating. It should not be stored for future use (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Elevation of aminotransferases

Treatment with omaveloxolone in clinical trials with patients with Friedreich's ataxia has been associated with elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (see section 4.8). On-treatment aminotransferase elevations of $\geq 3 \times$ the upper limit of normal (ULN) were reported in 29.4% of patients, with maximal values occurring in the majority of patients within the first 12 weeks of treatment. Initial increases were followed by a trend toward normalization.

ALT, AST, and bilirubin should be monitored prior to initiation of omaveloxolone, monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated. If ALT or AST increases to > 5 × the ULN, omaveloxolone should be immediately discontinued, and liver function tests should be repeated as soon as possible. If laboratory abnormalities stabilize or resolve, omaveloxolone can be reinitiated. If ALT or AST increases to > 3 × the ULN and bilirubin increases to > 2 × the ULN, omaveloxolone should be immediately discontinued and liver function tests should be repeated. Testing should be continued as appropriate. When laboratory abnormalities stabilize or resolve, Skyclarys may be reinitiated with an appropriate frequency of monitoring liver function.

Drug interactions

Omaveloxolone is primarily metabolised by CYP3A4 (see section 5.2). Concomitant use of strong or moderate CYP3A4 inhibitors may significantly increase the systemic exposure of omaveloxolone (see section 4.5). If concomitant use of strong or moderate CYP3A4 inhibitors is unavoidable, dose reduction of omaveloxolone with monitoring should be considered (see section 4.2).

Concomitant use of omaveloxolone with strong or moderate CYP3A4 inducers may significantly decrease the exposure of omaveloxolone (see section 4.5), which may reduce the effectiveness of omaveloxolone. Patients treated with omaveloxolone should be warned to avoid concomitant use of CYP3A4 inducers while taking omaveloxolone. Alternative medicinal products should be considered if possible (see sections 4.2 and 4.5).

Lipid abnormalities

Treatment with omaveloxolone has been associated with increases in low-density lipoprotein (LDL) cholesterol and decreases in high-density lipoprotein (HDL) cholesterol. Lipid parameters should be assessed prior to initiation of omaveloxolone and should be monitored periodically during treatment. Lipid abnormalities should be managed according to standard clinical guidelines.

Elevation of B-type natriuretic peptide (BNP)

Treatment with omaveloxolone has been associated with increases in BNP but without any concurrent increase in blood pressure or associated events of fluid overload or congestive heart failure. In Study 1, a total of 13.7% of patients treated with Skyclarys had an increase from baseline in BNP and a BNP above the ULN (100 pg/mL), compared to 3.8% of patients who received placebo. The incidence of elevation of BNP above 200 pg/mL was 3.9% in patients treated with Skyclarys. Whether the elevations in BNP in Study 1 are related to Skyclarys or cardiac disease associated with Friedreich’s ataxia is unclear.

In a study with a related compound in diabetic patients with chronic kidney disease (CKD), excess heart failure events due to fluid overload were observed among patients with stage IV CKD. Baseline BNP > 200 pg/mL and prior hospitalization for

congestive heart failure were identified as risk factors for heart failure among patients who had stage IV CKD but not in patients who had stage 3b CKD.

Cardiomyopathy and diabetes mellitus are common in patients with Friedreich's ataxia. BNP should be monitored prior to and periodically during treatment. Patients should be advised of the signs and symptoms of congestive heart failure associated with fluid overload, such as sudden weight gain (≥ 1.4 kg in 1 day or ≥ 2.3 kg in 1 week), peripheral oedema, and shortness of breath. If signs and symptoms of fluid overload develop, BNP (or NT-proBNP) should be monitored and managed according to standard clinical guidance. Treatment with Skyclarys should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with Skyclarys should be discontinued. Per clinical judgment, more frequent monitoring of patients with a recent hospitalization for fluid overload due to underlying cardiomyopathy, diabetic stage IV CKD, or other aetiologies is strongly recommended.

Body weight decrease

Treatment with Skyclarys has been associated with mild decreases in body weight. Advise patients to monitor their weight regularly. Further evaluate the patient if unexplained or clinically significant body weight decrease occurs.

Hypersensitivity reactions

Skyclarys is associated with a risk of hypersensitivity reactions including urticaria and rash (see section 4.8).
In the randomized, double-blind, placebo-controlled trial of 51 patients treated with Skyclarys 150 mg/day for 48 weeks, the frequency of hypersensitivity events was very common (≥ 1/10). All events were non-serious and all events reported in participants receiving omaveloxolone were mild in severity. The average time to onset for the omaveloxolone group was 135 days (minimum: 3 days, maximum: 360 days, median: 95 days). Hypersensitivity reactions including urticaria and rash have also been reported in the post-marketing setting and other clinical trials. In the post-marketing setting, one serious case of drug hypersensitivity has been reported, all events reported in other clinical trials were mild to moderate in severity. If a hypersensitivity reaction occurs, appropriate measures should be initiated if needed. Patients should be informed of the signs and symptoms of hypersensitivity.

Skyclarys contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free.'

4.5 Interaction with other medicinal products and other forms of interaction

Omaveloxolone is a substrate of CYP3A4. Co-administration of strong or moderate CYP3A4 inhibitors or CYP3A4 inducers will affect the pharmacokinetics of omaveloxolone.

Effect of other medicines on pharmacokinetics of omaveloxolone

Strong or moderate CYP3A4 inhibitors
In a clinical study, co-administration of Skyclarys with itraconazole, a strong CYP3A4 inhibitor, increased the area under the curve ($AUC_{0\text{-}inf}$) and maximal plasma concentration (C_{max}) by approximately 4-fold and 3-fold, respectively. In a clinical study with healthy subjects, co-administration of verapamil (120 mg once daily) increased the AUC and C_{max} by 1.24-fold and 1.28-fold, respectively. Verapamil is a known moderate CYP3A4 inhibitor and inhibitor of the P-gp transporter. If concomitant use of strong or moderate CYP3A4 inhibitors is unavoidable, dosage reduction of Skyclarys should be considered with monitoring (see sections 4.2 and 4.4). Some examples of strong and moderate CYP3A4 inhibitors are clarithromycin, itraconazole, ketoconazole, ciprofloxacin, cyclosporine, fluconazole, and fluvoxamine.

As grapefruit and grapefruit juice are inhibitors of CYP3A4, patients should be warned to avoid these while taking Skyclarys (see section 4.4).

Strong or moderate CYP3A4 inducers
In a clinical study, co-administration of omaveloxolone with efavirenz, a moderate CYP3A4 inducer, decreased the area under the curve ($AUC_{0\text{-}inf}$) and maximal plasma concentration (C_{max}) by approximately 49% and 38%, respectively. Due to potential loss of efficacy, patients treated with Skyclarys should be warned to avoid use of strong or moderate CYP3A4 inducers while taking Skyclarys and alternatives should be considered if possible. Some examples of strong or moderate CYP3A4 inducers are carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John’s wort, and efavirenz.

Effect of omaveloxolone on other medicinal products

The following were evaluated in clinical studies with omaveloxolone 150 mg in healthy subjects:

CYP3A4 substrates
The AUC of midazolam, a CYP3A4 substrate, was reduced by approximately 45% when co-administered with omaveloxolone, indicating that omaveloxolone is a weak inducer of CYP3A4 and can reduce the exposure of CYP3A4 substrates. Concomitant use with Skyclarys may reduce the efficacy of hormonal contraceptives. Advise patients to avoid concomitant use with combined hormonal contraceptives (e.g., pill, patch, ring), implants, and progestin only pills (see section 4.6).

CYP2C8 substrates
The AUC of repaglinide, a CYP2C8 substrate, was reduced by approximately 35% when co-administered with omaveloxolone, indicating that

omaveloxolone is a weak inducer of CYP2C8 and can reduce the exposure of CYP2C8 substrates.

BCRP substrates
The AUC of rosuvastatin, a BCRP and OATP1B1 substrate, was reduced by approximately 30% when co-administered with omaveloxolone, indicating that omaveloxolone is a weak inducer of BCRP and can reduce the exposure of BCRP substrates.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of omaveloxolone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Skyclarys should not be used during pregnancy or in women of childbearing potential not using contraception. Patients should use effective contraception prior to starting treatment with Skyclarys, during treatment, and for 28 days following discontinuation of treatment.

Skyclarys may decrease the efficacy of hormonal contraceptives (see section 4.5). Advise patients to avoid concomitant use with combined hormonal contraceptives (e.g., pill, patch, ring). Counsel females using hormonal contraceptives to use an alternative contraceptive method (e.g., non-hormonal intrauterine system) or additional non-hormonal contraceptive (e.g., condoms) during concomitant use and for 28 days after discontinuation of Skyclarys.

Breast-feeding

There are no data on the presence of omaveloxolone in human milk. Omaveloxolone is present in the milk of lactating rats and resulted in treatment-related effects in offspring (see section 5.3). A risk to the newborn infant cannot be excluded. Skyclarys should not be used during breast-feeding.

Fertility

There are no data on the effects of Skyclarys on human fertility. Animal data did not indicate impairment of parent male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Omaveloxolone may have a minor influence on the ability to drive and use machines. Fatigue may occur following administration of omaveloxolone (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most frequently occurring adverse reactions observed with Skyclarys are ALT increased and headache (37.3% each); weight decreased (34.0%); nausea (33.3%); AST increased and fatigue (21.6% each); diarrhoea (19.6%); oropharyngeal pain (17.6%); vomiting (15.7%), back pain, muscle spasms, and influenza (13.7% each); and decreased appetite (11.8%).

Tabulated list of adverse reactions

The adverse reactions observed in the randomized, double-blind, placebo-controlled trial in 51 patients treated with Skyclarys 150 mg/day for 48 weeks (median exposure 0.92 patient years) are listed in Table 2 by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Selected adverse reactions are further decribed in following Table 2.

Table 2 Adverse reactions

System Organ Class	Preferred Term	Frequency Category
Infections and infestations	Influenza	Very common
	Urinary tract infection	Common
Immune system disorders	Hypersensitivity including urticaria and rash [a]	Very common
Metabolism and nutrition disorders	Decreased appetite	Very common
	Hypertriglyceridemia	Common
	Very low density lipoprotein increased	Common
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Very common
Gastrointestinal disorders	Nausea	Very common
	Diarrhoea	Very common
	Vomiting	Very common
	Abdominal upper pain	Common
	Abdominal pain	Common

System Organ Class	Preferred Term	Frequency Category
Hepatobiliary disorders	ALT increased	Very common
	AST increased	Very common
	GGT increased	Common
Musculoskeletal and connective tissue disorders	Back pain	Very common
	Muscle spasms	Very common
Reproductive system and breast disorders	Dysmenorrhoea	Common
General disorders and administration site conditions	Fatigue	Very common
Investigations	BNP increased[b]	Common
	Weight decreased[c]	Very common

[a] Cases have been reported in the post-marketing setting with unknown frequency
[b] Based on laboratory evaluations with values > 200 pg/mL.
[c] Based on weight measured in the clinic with on-treatment weight loss ≥ 5%.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; GGT=gamma glutamyltransferase.

Description of selected adverse reactions

Gastrointestinal disorders
Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, nausea occurred in 33.3% of patients, diarrhoea in 19.6% of patients, vomiting in 15.7% of patients, abdominal upper pain in 9.8% of patients, and abdominal pain in 7.8% of patients. All events were assessed as either mild or moderate in severity, and 75.8% of the events occurred within the first 12 weeks of therapy.

Aminotransferase elevations
Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, adverse reactions of aminotransferase elevations included: ALT increased in 37.3% of patients, AST increased in 21.6% of patients, and gamma glutamyltransferase (GGT) increased in 5.9% of patients. Treatment interruptions due to aminotransferase elevations occurred in 11.8% of all Skyclarys-treated patients. One patient (2%) was discontinued for aminotransferase elevation per protocol.

In patients treated with Skyclarys, the incidence of on-treatment elevations of ALT or AST ≥ 3 × the ULN was 29.4%, with 15.7% experiencing elevations ≥ 5 × the ULN. Elevations of ≥ 3 × the ULN were generally transient and reversible, with 80% of these patients experiencing maximal levels within the first 12 weeks of treatment. None of these patients had ALT or AST levels ≥ 3 × the ULN at the withdrawal visit. Mean values generally decreased towards baseline with continued treatment or after interruption in therapy. No patient had concomitant elevation of total bilirubin > 1.5 × the ULN.

Elevation of BNP
In the randomized, double-blind, placebo-controlled study, increases in laboratory evaluations of BNP were observed in patients treated with Skyclarys. Mean BNP values were elevated at Week 4, and remained elevated through Week 48, with peak

mean elevations at Week 24. Mean BNP values remained below the ULN (< 100 pg/mL). A total of 13.7% of patients treated with Skyclarys had an increase from baseline in BNP and a BNP above the ULN (100 pg/mL), compared to 3.8% of patients who received placebo; 3.9% of patients had BNP values that exceeded 200 pg/mL while on treatment. There were no discontinuations due to BNP elevation.

Lipid abnormalities
Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, hypertriglyceridaemia was reported in 3.9% of patients, very low-density lipoprotein increased was reported in 3.9% of patients, and hypercholesterolaemia was reported in 2.0% of patients. At Week 48 in the Skyclarys treatment group, mean LDL increased by approximately 25 mg/dL and mean HDL decreased by approximately 5 mg/dL. After withdrawal of Skyclarys, mean LDL and HDL levels returned to baseline.

Weight decreased
In the randomized, double-blind, placebo-controlled study, weight decrease was reported for 2.0% of patients treated with Skyclarys and 1.9% of patients treated with placebo. No serious adverse reactions or discontinuations due to decreased appetite or weight decrease were reported in either treatment group.

Decrease in body weight was observed after Week 24. The mean weight decrease relative to baseline was 1.35 kg (SD 3.585 kg) in the Skyclarys group and the mean weight increase relative to baseline was 1.17 kg (SD 4.108 kg) in the placebo group after 48 weeks of treatment. Among all patients with baseline BMI < 25 kg/m^2 across both treatment groups (Skyclarys, n=37; placebo, n=37), weight loss of at least 5% from baseline was observed in 32.4% of Skyclarys-treated patients versus 2.7% of placebo-treated patients.

Paediatric population

Based on evaluation of Skyclarys in randomized, placebo-controlled trials, the safety profile of Skyclarys in paediatric patients aged 16 to less than 18 years (n=24) was consistent with the safety profile in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific antidote for Skyclarys. For patients who experience overdose, closely monitor and provide appropriate supportive treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs. ATC code: N07XX25

Mechanism of action

The precise mechanism by which omaveloxolone exerts its therapeutic effect in patients with Friedreich's ataxia is unknown. Omaveloxolone has been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. There is substantial evidence that Nrf2 levels and activity are suppressed in cells from patients with Friedreich's ataxia.

Pharmacodynamic effects

Omaveloxolone binds to Kelch-like ECH-associated protein 1 (Keap1), a protein that regulates the activity of Nrf2. Binding to Keap1 allows nuclear translocation of Nrf2 and transcription of its target genes. In fibroblasts isolated from patients with Friedreich's ataxia, omaveloxolone was shown to restore Nrf2 protein levels and increase Nrf2 activity. Omaveloxolone was also shown to rescue mitochondrial dysfunction and restore redox balance in these cells, as well as in neurons from mouse models of Friedreich's ataxia. Evidence of pharmacodynamic activity was observed in omaveloxolone-treated patients, with dose-dependent changes in the products of Nrf2 target genes, serum ferritin and GGT, across the dose range of 20 mg to 300 mg. Patients who received omaveloxolone 160 mg generally showed the largest increase from baseline for these serum markers.

Effect of omaveloxolone on the QT interval

In a randomized, double-blind, placebo- and active-controlled, 3-way crossover TQTc study in healthy subjects, omaveloxolone and its major metabolites (M17 and M22) alone or combined did not cause a clinically significant QTc prolongation as the upper bound of the 2-sided 90% CI estimate was below the regulatory threshold of concern of 10 msec. The mean omaveloxolone C_{max} of 319.4 ng/mL in the study was 4.5-fold the predicted mean steady-state C_{max} (71.5ng/mL) in FA patients and covers the worst-case clinical exposure scenario of a 4.5-fold increase in C_{max}, if omaveloxolone is administered with food.

Clinical efficacy and safety

The efficacy and safety of Skyclarys were evaluated as a treatment for Friedreich's ataxia in two parts of a randomized, double-blind, placebo-controlled, study (Study 1 [NCT02255435; EudraCT 2015-002762-23]) and in an ongoing, open-label extension to Study 1.

Study 1 Part 2

Study 1 Part 2 was a randomized, double-blind, placebo-controlled, multicentre study to evaluate the safety and efficacy of Skyclarys in patients with Friedreich's ataxia for 48 weeks of treatment. A total of 103 patients including 24 adolescents were randomized (1:1) to Skyclarys 150 mg/day (N=51) or placebo (N=52). Patients were excluded from Study 1 if they had BNP levels > 200 pg/mL prior to study entry, or a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia. Additionally, patients were excluded from Study 1 if they had a history of clinically significant liver disease (eg, fibrosis, cirrhosis, hepatitis) or clinically relevant deviations in laboratory tests at screening including ALT and/or AST > 1.5-fold ULN, bilirubin > 1.2-fold ULN, alkaline phosphatase > 2-fold ULN, or albumin < lower limit of normal (LLN). Randomization was stratified by pes cavus status. Pes cavus population was defined as having a loss of lateral support and was determined if light from a flashlight could be seen under the patient's arch when barefoot and weight bearing. The primary efficacy endpoint was change in the modified Friedreich's Ataxia Rating Scale (mFARS) score compared to placebo at Week 48 for patients without pes cavus (ie, the full analysis set [FAS]; n=82). The mFARS is a clinical assessment tool to assess patient function, which consists of 4 domains to evaluate bulbar function, upper limb coordination, lower limb coordination, and upright stability. The mFARS has a maximum score of 99, with a lower score on the mFARS signifying lesser physical impairment. In the FAS, 53.7% were male. The mean age was 23.9 years at study entry, and the mean age of Friedreich's ataxia onset was 15.5 years. Baseline mFARS and Friedreich's ataxia-Activities of Daily Living (FA-ADL) scores were 39.83 and 10.29 points, respectively. Mean GAA1 repeat length was 714.8. At study entry, 92.7% of patients were ambulatory, 37.8% had a history of cardiomyopathy, and 2.4% had a history of diabetes mellitus.

Treatment with Skyclarys significantly improved mFARS scores, with a least squares mean difference of -2.41 (standard error 0.955) relative to placebo (p=0.0138) (Table 3). All components of the mFARS assessment, including ability to swallow (bulbar), upper limb coordination, lower limb coordination, and upright stability, favoured Skyclarys over placebo.

Table 3 Study 1 Part 2: mFARS Results (FAS)

	Skyclarys (N=40)	**Placebo (N=42)**
Total mFARS		
Baseline		
n	40	42
Mean (SD)	40.95 (10.394)	38.78 (11.025)
Week 48		
n	34	41
Mean (SD)	39.17 (10.019)	39.54 (11.568)

	Skyclarys (N=40)	Placebo (N=42)
Week 48 Change from baseline		
LS Mean (SE)	-1.56 (0.689)	0.85 (0.640)
LS Mean Difference (SE)	-2.41 (0.955)	-
p-value vs. placebo	0.0138	

Abbreviations: FAS=Full Analysis Set; LS=least squares; mFARS=modified Friedreich's ataxia rating scale.
Note: mFARS scores can range from 0 to 99 points. Within each section of the mFARS, the minimum score is 0. The maximum score for each section is as follows: 11 points for Bulbar Function, 36 points for Upper Limb Coordination, 16 points for Lower Limb Coordination, and 36 points for Upright Stability.

In the All Randomized Population (N=103), which included all patients regardless of pes cavus status, Skyclarys improved mFARS scores relative to placebo, with a least squares mean difference of 1.94 (standard error 0.894) (nominal p=0.0331).

In exploratory subgroup analyses, point estimates for changes in mFARS consistently favoured Skyclarys relative to placebo across subgroups based on baseline age, ambulatory status, and GAA1 repeat length (Table 4).

Table 4 Study 1 Part 2: Change in mFARS at Week 48 in subgroups (FAS)

Subgroup	Least Squares Mean Difference[a] (95% CI)	P-Value
Age		
< 18 years (n=20)	-4.21 (-8.48, 0.06)	0.0532
≥ 18 years (n=62)	-1.59 (-3.77. 0.58)	0.1486
GAA1 repeat length ≥ 675		
Yes (n=39)	-4.27 (-6.96, -1.58)	0.0024
No (n=28)	-1.95 (-5.20, 1.29)	0.2325
Ambulatory status		
Non-ambulatory (n=6)	-4.57 (-11.41, 2.27)	0.1864
Ambulatory (n=76)	-2.20 (-4.22, -0.18)	0.0336

Abbreviations: CI=confidence interval; FAS=Full Analysis Set; GAA1 repeat length=length of the trinucleotide repeats in the GAA1 allele composed of 1 guanine and 2 adenines; mFARS=modified Friedreich's ataxia rating scale.
[a] Least squares mean difference is Skyclarys □ placebo.

Although Study 1 was not powered to detect a difference in the key secondary endpoints, Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC), PGIC and CGIC scores at Week 48 were numerically improved in patients treated with Skyclarys relative to placebo in the primary analysis population (least squares [LS] mean difference in PGIC= -0.43, LS mean difference in CGIC= -0.13). Additionally, treatment of patients with Skyclarys resulted in numerically improved FA-ADL scores relative to placebo, with an LS mean difference of -1.30 points (standard error=0.629).

In a post hoc, propensity-matched analysis of long term open-label treatment with Skyclarys, patients treated with Skyclarys had lower mFARS scores at 3 years, as compared to a matched natural history group. This exploratory analysis should be interpreted cautiously given the limitations of data collected outside of a controlled study, which may be subject to confounding.

Paediatric population

The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with Skyclarys in the paediatric population aged 2 years to less than 16 years in treatment of Friedreich's ataxia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Omaveloxolone was absorbed after oral administration in healthy fasted subjects with peak plasma concentrations typically observed 7 to 14 hours post dose. Patients with Friedreich's ataxia demonstrated a 2.3-fold faster absorption of omaveloxolone than fasted healthy subjects.

Co-administration of a high-fat meal resulted in a small increase (1.15-fold) in area under the plasma concentration vs time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) but caused a 4.5-fold increase in C_{max} compared to fasted conditions. It is recommended that Skyclarys be taken without food.

Omaveloxolone C_{max} and $AUC_{0\text{-}inf}$ were similar when capsule contents were sprinkled on apple puree or when administered as intact capsules. The median time to achieve C_{max} (t_{max}) of omaveloxolone was shortened from approximately 10 hours to 6 hours when sprinkled on apple puree (see section 4.2).

The absolute or relative bioavailability of omaveloxolone has not been determined.

Linearity/non-linearity

The total plasma omaveloxolone exposure (AUC) increased in a dose-dependent and dose proportional manner, but C_{max} increased in a less than dose proportional manner in healthy fasted subjects.

Distribution

Omaveloxolone is 97% bound to protein in human plasma. Omaveloxolone shows low to moderate membrane permeability. The average apparent volume of distribution is 7361 L (105 L/kg).

Biotransformation

Following a single oral dose of [^{14}C]-omaveloxolone administered to healthy male subjects, omaveloxolone was found to be eliminated by metabolism via CYP3A4 to a series of 30 metabolites, of which 7 metabolites were quantified and identified. Metabolites M22 and M17 were major plasma metabolites that accounted for 18.6% and 10.9% of total plasma radioactivity, respectively.

The other metabolites were minor, each accounting for less than 10% of total plasma radioactivity exposure. None of the metabolites has meaningful pharmacological activity.

Elimination

Following a single oral dose of radio-labeled omaveloxolone administered to healthy male subjects, approximately 92.5% of the dosed radioactivity was recovered within a 528-hour collection period: 92.4% via the faeces and 0.1% via the urine. The majority (90.7%) of the administered dose was recovered in the faeces within 96 hours after administration.

The average apparent plasma clearance of omaveloxolone is 109 L/hr and the average apparent plasma terminal half-life is 58 hours (32-94 hours).

Pharmacokinetic/pharmacodynamic relationship(s)

Effect of age, sex, and body weight on omaveloxolone pharmacokinetics
Population pharmacokinetic analyses indicate that there is no clinically meaningful effect of age (16-71 years), sex, or body weight on the pharmacokinetics of omaveloxolone and no dose adjustments based on these factors are necessary.

Patients with renal impairment

Population pharmacokinetic analysis confirmed that estimated glomerular filtration rate values $\geq$ 63 mL/min/1.73 m^2 did not have a significant effect on the pharmacokinetics of omaveloxolone. The effect of moderate or severe renal impairment on the pharmacokinetics of omaveloxolone is unknown.

Patients with hepatic impairment

In subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C), omaveloxolone clearance was reduced, resulting in higher plasma exposure of omaveloxolone. Subjects with moderate hepatic impairment exhibited up to a 65% increase in AUC and an 83% increase in C_{max} compared to subjects with normal hepatic function. In subjects with severe hepatic impairment, the AUC for omaveloxolone was increased by 117% as compared to subjects with normal hepatic function. However, the data in subjects with severe hepatic impairment are limited. In subjects with mild hepatic impairment (Child-Pugh Class A), there was no change in AUC and only a 29% increase in C_{max}. The recommended dosage for patients with hepatic impairment is described in section 4.2.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, and carcinogenic potential.

Based on a panel of *in vitro* and *in vivo* mutagenicity tests, omaveloxolone is considered of low genotoxic potential. Omaveloxolone was not carcinogenic in a 6-month carcinogenicity study in rasH2 mice up to doses corresponding to approximately 14.6 and 54.5 times in males and females, respectively, the maximum human recommended dose (MHRD) and systemic exposure (AUC) in patients with Friedreich's ataxia.

Preclinical data revealed toxicities related to omaveloxolone. In rats, findings of irreversible kidney injury (multifocal renal tubular degeneration/regeneration accompanied by proteinuria) were observed at clinically relevant dose levels in rats after 28 days of daily oral exposure up to 6 months. Furthermore, reversible observations of hyperplasia of the GI tract (forestomach, oesophagus, larynx) was observed in rats and monkeys already after 28 days of dosing, up to 6 or 9 months in rats and monkeys, respectively. In one male rat from the high dose group at 6 months dosing, the squamous epithelial hyperplasia was associated with a squamous cell carcinoma involving the non-glandular and glandular stomach.

Fertility and early embryonic development

Omaveloxolone, administered at oral doses of 1, 3, and 10 mg/kg/day to male rats for 28 days before mating and throughout the mating period and to female rats from 14 days before mating, throughout mating, and until gestation day 7 did not alter male or female fertility. However, pre- and post-implantation embryonic loss, resorptions, and a decrease in the number of viable embryos occurred at the dose corresponding to approximately 6 times the maximum human recommended dose (MHRD) based on systemic exposure. No effects on pre- and post-implantation loss occurred at approximately 2 times the MHRD based on systemic exposure.

Embryo-foetal development

In an embryo-foetal toxicity study in rats, no maternal toxicity or embryo-foetal abnormalities were detected in rats at an oral dose corresponding to approximately 6 times the MHRD based on systemic exposure. However, at doses achieving exposure levels 19 times the MHRD, post-implantation loss, resorptions as well as decreases in number of viable fetuses, litter size, and foetal body weight were observed in rats. Embryo-foetal assessment in rabbits demonstrated maternal toxicity that was associated with early deliveries and interruptions of pregnancy as well as low foetal body weights at a dose level corresponding to exposures lower (0.7-fold) than those at the MHRD; however, in the same study, no foetal malformations were observed at approximately 1.4 times the MHRD based on systemic exposure.

Pre- and post-natal development

In a pre- and post-natal evaluation in rats, administration of omaveloxolone during the period of organogenesis through lactation at doses of 1, 3, and 10 mg/kg/day was associated with an increased

percentage of litters with stillborn pups, reduced first generation pup survival, and decreased mean pup body weights. Decreased reproductive function (reduced mean numbers of corpora lutea and implantation sites) were observed in F1 females and delayed sexual maturation was observed in F1 males at a dose level of approximately 6 times the MHRD based on systemic exposure. No adverse reactions were observed at a dose of approximately 2 times the MHRD based on systemic exposure. Dose-dependent increases in omaveloxolone plasma concentrations were observed in pups, due to excretion of omaveloxolone in milk. Effects were directly linked to exposure to omaveloxolone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Pregelatinized maize starch
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Silica, colloidal anhydrous

Capsule shell

Hypromellose
Titanium dioxide (E171)
Brilliant Blue FCF (E133)
Ferric oxide yellow (E172)

Printing ink
Shellac (E904)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene bottles with child-resistant, foil induction-sealed polypropylene closure.

Pack size of 90 capsules.
Pack size of 270 (3 packs of 90) capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 22407/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/04/2025

10 DATE OF REVISION OF THE TEXT

17/12/2025