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EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR

SKYCLARYS (Omaveloxolone)

RMP version number:	2.0
Data lock point (DLP) for this RMP:	31 Jan 2025
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QPPV name: Jan Petracek, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s deputy QPPV on behalf of the QPPV. The electronic signature is available on file.

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

Not applicable - no other versions of the omaveloxolone EU RMP are currently under evaluation.

Details of currently approved RMP

Version number:	1.0
Approved with procedure:	EMEA/H/C/006084/0000
Date of approval:	12 Dec 2023

Rationale for submitting an updated RMP

The MAH has changed from Reata Ireland to Biogen and therefore the EU RMP has been changed to the Biogen template. In addition to the above rationale, a summary of the significant changes implemented is provided in the table below:

Module	Rationale for update	Summary of significant changes
Part I	Pharmacotherapeutic group (ATC Code) published by WHO on 27 Dec 2024.	ATC code: N07XX25 under Pharmacotherapeutic group of Other nervous system drugs.
Part II Module SI	Not applicable	Not applicable
Part II Module SII	Non-clinical part of the safety specification updated.	Updated with results from a 2-year carcinogenicity study (RTA-P-21070).
Part II Module SIII	Not applicable	Not applicable
Part II Module SIV	Not applicable	Not applicable
Part II Module SV	Post-authorisation information updated.	Section was updated with post-authorisation exposure information.
Part II Module SVI	Not applicable	Not applicable
Part II Module SVII	Updated risks considered important for inclusion in list of safety concerns and updated search strategies.	Added malignancy as a new Important Potential Risk.
Part II Module SVIII	Summary of Safety concerns updated.	Added malignancy as an Important Potential Risk.

Module	Rationale for update	Summary of significant changes
Part III	Postmarketing registry of omaveloxolone for FA milestone updates available.	Section was updated with change in milestone dates for PASS study. Updated to include a new planned study to characterise malignancy
Part IV	Not applicable	Not applicable
Part V	Updated routine risk minimisation and Pharmacovigilance activities.	Section was updated to include Malignancy risk minimisation measures and Pharmacovigilance activities.
Part VI	Summary of the RMP for Skyclarys was updated.	Section updated to include Malignancy as an important potential risk.
Part VII	Annexes updated.	Annex 2 was updated with change in milestone dates for PASS study. Annex 3 was updated for Part C to include P296FA401 (408-C-2301) PASS Protocol Ver 6.0. Annex 4 was updated with the most recent follow-up forms for DILI and CHF. Annex 7 was updated with new literature references. Annex 8 was updated with summary of changes to the RMP over time.

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PART VII - ANNEXES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the plasma concentration versus time Curve
AUC0-24	Area Under the Concentration vs time curve from 0 to 24 hours
BCRP	Breast cancer resistance protein
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CHF	Congestive Heart Failure
CKD	Chronic kidney disease
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CYP	Cytochrome P450 (isoenzyme)
DILI	Drug-Induced Liver Injury
EAP	Early Access Programme
EC	Ethics Committee
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESKD	End-Stage Kidney Disease
EU	European Union
FA	Friedreich's Ataxia
FA-GCC	Friedreich's Ataxia Global Clinical Consortium
FARA	Friedreich's Ataxia Research Alliance
FDA	Food and Drug Administration
GD	Gestation Day
GGT	Gamma-Glutamyl transferase
GLP	Good Laboratory Practice
hERG	human Ether-á-go-go-Related Gene
IC50	half maximal Inhibitory Concentration
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISS	Integrated Summary of Safety
IUD	Intrauterine device

Abbreviation	Definition
Kim-1	Kidney injury molecule 1
LOAEL	Lowest observed adverse event level
MAH	Marketing Authorisation Holder
MHRD	Maximum Human Recommended Dose
NGAL	Neutrophil gelatinase-associated lipocalin
NOAEL	No Observed Adverse Effect Level
Nrf2	Nuclear factor erythroid 2-related factor 2
NT-proBNP	N-terminal pro B-type natriuretic peptide
PASS	Post Authorisation Safety Study
PIL	Patient information leaflet
PK	Pharmacokinetic(s)
PND	Post Natal Day
PPND	pre- and postnatal development
QD	Once daily
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCr	serum creatinine
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA query
Study 1402	Study 408-C-1402 (which consists of Part 1, Part 2, and Extension)
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TK	Toxicokinetic
ULN	Upper Limit of Normal
UNIFAI	UNIFIED Natural History Study
US/USA	United States (of America)

PART I: PRODUCT(S) OVERVIEW

Table 1: Product Overview

Active substance (INN or common name)	omaveloxolone
Pharmacotherapeutic groups (ATC Code)	N07XX25
Marketing Authorisation Applicant	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	01
Invented name in the European Economic Area (EEA)	Skyclarys
Marketing authorisation procedure	Centralized
Brief description of the product	**Chemical class:** Synthetic triterpenoid
	Summary of mode 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 2-related factor 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.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	https://www.ema.europa.eu/en/medicines/human/EPAR/skyclarys
Indication(s) in the EEA	**Current:** Omaveloxolone is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

Dosage in the EEA	**Current:** The recommended dose is 150 mg (3 hard capsules of 50 mg each) once daily. Omaveloxolone should be taken on an empty stomach at least 1 hour before eating or 2 hours after eating. Omaveloxolone capsules should be swallowed whole. For patients who are unable to swallow whole capsules, omaveloxolone capsules may be opened, and the entire contents sprinkled onto 2 tablespoons of apple puree. Patients should consume all the drug/food mixture immediately on an empty stomach at least 1 hour before eating or 2 hours after eating. Do not store for future use. 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. Medication lost through emesis should not be replaced with an additional dose. The recommended dosages for concomitant use of omaveloxolone with strong or moderate cytochrome P450 (CYP)3A4 inhibitors and inducers are described in sections 4.2, 4.4, and 4.5 of the SmPC. The recommended dosages for patients with hepatic impairment are described in section 4.2 of the SmPC.
Pharmaceutical form(s) and strengths	**Current *(if applicable)*:** Omaveloxolone capsules are supplied as opaque, hard capsules containing 50 mg of omaveloxolone as follows: Omaveloxolone 50 mg capsules have a light green body and blue cap, printed with “RTA 408” on the body in white ink and “50” on the cap in white ink.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1 Epidemiology of Friedreich's ataxia in adults and adolescents aged 16 years and older

Incidence

Friedreich's ataxia (FA) is a rare, genetic neuromuscular disorder.

Prevalence

The average calculated prevalence where patients were diagnosed by clinical/molecular/genetic methods (1994-2017) is 0.5 per 100,000 (0.05/10,000) [Buesch and Zhang 2022].

Demographics of the population in the proposed indication, age, gender, racial and/or ethnic origin and risk factors for the disease

According to recent literature, onset of FA after the age of 24 is considered to be late onset [Reetz 2018; Rummey 2022], while very late onset is considered to be onset after the age of 40 [Fearon 2020; Rummey 2022; Tamaroff 2022]. Notably, a comparative study found no phenotypic differences between late onset and very late onset FA [Lecocq 2016]. Within the FA population, most patients have FA onset by the age of 24. Among a dataset of 1115 individuals with FA, 89% had FA onset ≤ 24 years and 11% had late onset FA (age > 24 years), with age of onset in this late onset group ranging from 28 to 40 years [Rummey 2022]. In a separate large database of 650 individuals with FA, 83% had FA onset ≤ 24 years and 17% had late onset FA (age > 24 years), with age of onset in this late onset group ranging from 25 to 65 years [Reetz 2018]. Ultimately, FA leads to a shortened life expectancy, and the average age of death is 36.5 years based on a large retrospective study [Tsou 2011].

FA is the most common inherited ataxia in individuals of Western European origin and is also found in those of North African and Middle Eastern origin, but it has not been reported in other ethnic groups [Pandolfo 2008]. There is no gender difference in the prevalence of this neurodegenerative disorder [Parkinson 2013].

The main existing treatment options

Other than omaveloxolone, there are no effective therapies specifically for the treatment of FA. Clinical studies with weak exogenous antioxidants, such as coenzyme Q10 derivatives, and various antioxidant cocktails containing supplements, such as vitamin E (or derivatives), have not resulted in physiological improvements nor have they affected disease progression [Marmolino 2011].

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Diagnosis of FA usually occurs in childhood to early adulthood and is confirmed by molecular genetic testing. The disease typically presents with signs of loss of coordination (ataxia) in the

arms and legs, fatigue (energy deprivation and muscle loss), vision, hearing and speech impairment, aggressive scoliosis, diabetes mellitus, hypertrophic cardiomyopathy, and arrhythmia. These symptoms are not present in all affected individuals. The intellectual capabilities of affected individuals remain completely intact. The majority of patients have disease onset before 15 years of age, with a mean duration until wheelchair use of 11.5 years (25^{th}, 75^{th} percentiles 8.6 years, 16.2 years) after the onset of first symptoms [Rummey 2020] and a median survival of 34 to 37 years after disease onset [Klockgether and Evert 1998].

Important co-morbidities

As the disease progresses, affected individuals may develop dysarthria, foot deformities (pes cavus), and scoliosis. Cardiomyopathy and diabetes mellitus are also potential comorbidities in patients with FA.

Genetics

FA is an autosomal recessive cerebellar ataxia caused by triplet-repeat expansions in the frataxin gene. The causative mutation is a trinucleotide (GAA) repeat expansion in the first intron of the gene, leading to impaired transcription of frataxin. Frataxin is involved in iron homeostasis and may protect mitochondria from oxidative damage. Consequently, frataxin mutations result in a phenotype of mitochondrial iron overload and oxidative stress. The pathological consequences of frataxin deficiency include a severe disruption of iron-sulfur cluster biosynthesis, mitochondrial iron overload coupled to cellular iron dysregulation, and an increased sensitivity to oxidative stress [Dürr 2002].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Toxicity

The nonclinical program was designed and conducted to support the chronic administration of omaveloxolone at a daily dose of up to 150 mg (the maximum recommended human dose [MHRD]) in patients with FA. The results of this program support the safe use of omaveloxolone in patients.

Nonclinical safety of omaveloxolone was evaluated in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3 (R2)- and good laboratory practice (GLP)-compliant studies, including oral repeated dose toxicity (rodent and nonrodent) and genotoxicity studies (bacterial reverse mutation, chromosomal aberration, rat liver comet, and micronucleus). In the chronic GLP toxicity studies (i.e., 6-month rat and 9-month monkey), 3-month interim necropsies were included. Studies were also conducted to assess the potential effects of omaveloxolone on male and female fertility (rats), embryofetal development (rats and rabbits), and pre- and postnatal development (rats). The toxicity studies of omaveloxolone included appropriate toxicokinetic (TK) monitoring using validated bioanalytical methods and analytical assays. Based on the results from in vitro studies, omaveloxolone metabolism in the rat and monkey were qualitatively similar to that in humans, thus justifying these species for use in the pivotal toxicity studies.

The systemic toxicity potential of omaveloxolone has been evaluated in multiple nonclinical GLP toxicity studies in rats, minipigs, and monkeys after oral and dermal (which produces meaningful systemic exposure to omaveloxolone in animals) administration. The primary target organs for omaveloxolone observed in the rat and monkey include the liver (increased liver weight, hepatocellular hypertrophy, and bile duct hypertrophy and hyperplasia) and kidney (tubular degeneration/regeneration). These effects are mostly considered to be due to the known pharmacologic activity of omaveloxolone in animals and likely do not reflect off-target toxicity. In rats (but not monkeys or minipigs), minimal to mild squamous cell hyperplasia of the forestomach and/or the limiting ridge of the stomach was observed and was fully reversible on treatment discontinuation. The forestomach and limiting ridge of the stomach do not exist in humans, a monogastric species [Bertram 2013; Proctor 2007]. Therefore, this finding does not translate to humans and is not considered a relevant risk to humans. The clinical safety margin multiples were calculated as the ratio of exposure (based on the area under the plasma concentration vs time curve [AUC]) achieved at the no observed adverse effect level (NOAEL) to the exposure achieved at the MHRD of 150 mg in patients with FA. In the 6-month rat study, repeat daily oral administration of omaveloxolone resulted in observations of bile ductile hyperplasia and kidney tubular degeneration/regeneration, and a NOAEL was not determined. Overall, rats are more sensitive to the toxicologic effects of omaveloxolone than minipigs or monkeys. In rats, the NOAEL following 28 days or 13 weeks of daily oral administration was 3 mg/kg/day, corresponding to an AUC_{0-24} of approximately 2.0 hr*µg/mL. Following 6 months of oral administration to rats, adverse effects were observed at the lowest dose tested (0.3 mg/kg), which was associated with an AUC_{0-24} of approximately 0.3 hr*µg/mL. In monkeys, omaveloxolone was orally administered up to 100 mg/kg/day, as no further increases in exposure were observed above this dose level. An adverse finding of prolongation in activated partial thromboplastin time (aPTT) was observed in females at 100 mg/kg/day (with near complete

recovery after the withdrawal period), and thus, the NOAEL was 30 mg/kg/day. In males, aPTT was also increased at 100 mg/kg/day, but the increase was not as marked as in females, and it completely recovered after the withdrawal period; therefore, this was not considered adverse. Consistent with the tolerability and clinical safety profile of omaveloxolone in patients with FA administered the MHRD of 150 mg, a clinical safety multiple (based on AUC_{0-24}) of approximately 1.6 was achieved in monkeys at 30 mg/kg/day (i.e., the female monkey NOAEL) after 39 weeks of repeated daily oral dosing.

A GLP-compliant genotoxicity program was completed with omaveloxolone in vitro and in vivo (rat), and the overall weight of evidence indicated that omaveloxolone has a low genotoxicity risk to humans.

A GLP-compliant carcinogenicity study was performed to evaluate the carcinogenic potential of omaveloxolone, when administered once daily via oral gavage to rasH2 (hemizygous) mice for at least 26 weeks. Mice were assigned to 6 groups, and animals were dosed at doses of 5, 10, and 30 mg/kg/day (males) and 20, 50, and 100 mg/kg/day (females) via oral gavage once daily for up to 26 weeks. No omaveloxolone-related occurrence of neoplastic or non-neoplastic microscopic findings were noted in males administered up to 30 mg/kg/day and in females administered up to 100 mg/kg/day. Upon microscopic examination, no evidence of omaveloxolone-related carcinogenic effect was noted at any dose level. Oral gavage administration of 5, 10, or 30 mg/kg/day RTA 408 to male or 20, 50, or 100 mg/kg/day to female rasH2 hemizygous mice for 26 weeks was clinically well tolerated, had no effect on survival, and exhibited no evidence of any carcinogenic potential. Based on AUC of the highest doses tested and based on the survival and clinical observations, the calculated safety margins were 14.6 for males and 54.5 for females (based on estimated human AUC_{0-24} value of 1.18 hr*µg/mL in patients with FA administered 150 mg omaveloxolone.

A GLP-compliant carcinogenicity study was performed to evaluate the carcinogenic potential of omaveloxolone when administered daily by oral gavage to male and female Sprague-Dawley rats for up to 104 weeks, and to determine the TK of omaveloxolone when administered daily by oral gavage to Sprague-Dawley rats (Study RTA-P-21070). The study was terminated early at 87 weeks for males and 85 weeks for females, due to animal attrition not caused by omaveloxolone. Male rats were administered 0.1, 0.3, or 1 mg/kg/day omaveloxolone. Female rats were administered 0.3, 1, or 3 mg/kg/day omaveloxolone. A reverse osmosis water control group and a sesame oil vehicle control group were included. Toxicokinetic animals were included for both control and treated groups. No evidence of omaveloxolone-related mortality or effect on survival was noted. Omaveloxolone-related lower mean body weights were observed for males administered ≥ 0.3 mg/kg/day and females administered 3 mg/kg/day, compared with the vehicle control group. Mean body weight decreases, relative to vehicle controls, reached a maximum of -14% or -13% in males administered ≥ 0.3 mg/kg/day or females administered 3 mg/kg/day, respectively. Omaveloxolone-related effects on incidences of neoplastic findings were noted in the liver (females, 3 mg/kg), mammary gland (females, 1, 3 mg/kg), testis (males, 1 mg/kg), and rectum (rectal-anal transition zone) [females, 3 mg/kg]. Effects on the incidences of non-neoplastic, proliferative findings were noted in the liver (bile ducts), nonglandular stomach, rectum, and esophagus; and effects on the incidence of non-neoplastic, non-proliferative findings were noted in the kidney (exacerbation of chronic progressive nephropathy, a known background finding in aged rats). The doses associated with no neoplastic lesions were ≤ 0.3 mg/kg/day in males and 0.3 mg/kg/day in females. Mean AUC_{0-24} during Week 26 for males administered 0.3

mg/kg/day was 163 h*ng/mL. Mean AUC_{0-24} during Week 26 for females administered 0.3 mg/kg/day was 278 h*ng/mL. Margins were less than the exposure at the maximum recommended human dose (MRHD).

In the fertility and early embryonic development toxicity study in rats, the NOAEL for reproductive and fertility indices was 10 mg/kg/day, based on the highest dose of omaveloxolone evaluated. However, the NOAEL for early embryonic development was 3 mg/kg/day, based upon increased pre- and post-implantation loss, increased resorptions (early and late), decreased number of implantation sites, and decreased number of viable embryos observed at 10 mg/kg/day. In the rat embryofetal toxicity study, no adverse effects were observed, and the NOAEL was 10 mg/kg/day, which was the highest dose evaluated and based on AUC, produced exposure approximately 6.3-fold the exposure at the MHRD.

In the rabbit embryofetal development toxicity study, early deliveries and abortions were observed and were associated with maternal toxicity (i.e., decreased gestational body weights and food consumption) with a NOAEL of 3 mg/kg/day; no fetal malformations were observed, and the NOAEL produced exposure below (0.3-fold) the exposure at the MHRD.

In the pre- and postnatal development (PPND) toxicity study in rats, the maternal NOAEL was the highest dose evaluated (i.e., 10 mg/kg/day), whereas the NOAEL for reproductive function was 3 mg/kg/day, due to increased stillborn pups and decreased pup survivals. In the F1 generation, the NOAEL was also 3 mg/kg/day due to decreased mean body weights and reduced number of corpus lutea and implantation sites. No effects on behavioral function or other developmental findings were observed. The 3- and 10 mg/kg/day NOAEL doses produced exposure ratios, based on AUC, of approximately 2.0- and 6.3-fold, respectively, the MHRD of 150 mg.

Juvenile toxicity studies have not been conducted. No adverse effects on neurobehavior or central nervous systems were observed in GLP safety pharmacology and general GLP toxicity studies, nor bone or growth development deformities were observed in the developmental and reproductive toxicity studies.

In addition, the Sponsor had also explored the treatment of dermatologic and ophthalmologic diseases with omaveloxolone, and nonclinical GLP toxicity studies were performed to evaluate the potential local and systemic effects with dermal (up to 3 months in rats and minipigs) or topical ocular (up to 28 days in rabbits and monkeys) administration. Systemic exposures to omaveloxolone with topical dermal administration were quite high and similar to those observed following oral administration, and consequently, the findings provide additional information regarding systemic safety as well as potential dermal effects.

In addition to the completed 6-month carcinogenicity study in rasH2 mice, a 2-year carcinogenicity study in rats was completed in Q2 2025. The 2-year carcinogenicity study report is submitted to EMA as part of the requested post-approval measure.

In summary, the detailed nonclinical data support the safe use of omaveloxolone in patients.

Key safety findings from non-clinical studies with potential relevance to human usage are described in Table 2.

Table 2: Key safety findings from non-clinical studies and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity	
Single-dose toxicity: Single dose toxicity studies were not conducted with omaveloxolone. **Repeat-dose toxicity:** GLP-compliant toxicity studies with orally administered omaveloxolone were conducted in rats (28 days, 13 weeks, and 26 weeks of dosing) and monkeys (28 days, 13 weeks, and 39 weeks of dosing). The primary target organs in the rat (considered adverse) and monkey (not considered adverse) after oral omaveloxolone administration were the liver and kidney. Relative to monkeys, rats were more sensitive to omaveloxolone. Further, data from toxicity studies in rats indicate that the NOAEL (No observed adverse effect level) decreases with longer durations of dosing, with NOAELs of 30 mg/kg/day, 3 mg/kg/day, 3 mg/kg/day, and 0.3 mg/kg/day as the lowest observed adverse event level (LOAEL) with 14 days, 28 days, 13 weeks, and 6 months of dosing, respectively. The increased liver weights and adverse liver microscopic findings in rats were associated with moderate to marked increases in serum gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBL) at the high dose, all of which were reversible upon drug discontinuation. Monkeys, however, at systemic exposures 1.7- to 5.5-fold above those observed in patients with FA at the MHRD of 150 mg, had increased liver weights, which were not associated with adverse microscopic pathology or changes in serum GGT, ALT, or AST; and TBL was decreased from baseline, suggesting an overall increase in liver function. The renal tubular degeneration/regeneration observed in rats was consistent with remodeling and did not appear to have a negative functional impact, considering 1) the lack of concurrent changes in blood urea nitrogen (BUN) or serum creatinine (SCr), 2) the lack of any signs of chronic inflammation or fibrosis, and 3) the lack of consistent association with common urinary biomarkers, such as kidney injury molecule 1 (Kim-1) and neutrophil gelatinase-associated	Adequate safety margins above human exposure were established.

SAFETY FINDING	RELEVANCE TO HUMAN USE
lipocalin (NGAL). In the 36-week monkeys GLP toxicity study, at the Week 13 (interim) and Week 39 (terminal) collections, minimal to moderate dose-dependent prolongations in mean aPTT were observed in males and females (30- and 100-mg/kg/day groups), relative to pretest means. At the end of the recovery interval, prolongations in aPTT were mostly resolved in females (100 mg/kg/day group) and fully resolved in all other treatment groups.	
Reproductive/developmental toxicity	
A GLP-compliant study evaluated developmental toxicity, including the teratogenic potential, for omaveloxolone in rats (Table 2.6.7.13A; Study RTA P 18017). Time-mated female rats (n = 20/dose group) were dosed once daily from gestation day (GD) 6 through GD 17 at dose levels of 0 (vehicle), 1, 3, or 10 mg/kg/day by oral gavage in a sesame oil suspension at a dosing volume of 5 mL/kg. No effect of omaveloxolone was observed on any of the maternal and fetal parameters evaluated, including clinical observations; body weights and body weight changes; food consumption; ovarian and uterine parameters; fetal body weights; and external, visceral, or skeletal evaluations. The NOAEL for maternal toxicity, prenatal developmental toxicity, and teratogenic potential was 10 mg/kg/day (AUC0-24 of 7.38 hr*µg/mL on GD 17). A GLP-compliant study evaluated the developmental toxicity, including the teratogenic potential, for omaveloxolone in rabbits. Time-mated female New Zealand White rabbits (n = 20/dose group) were dosed once daily from GD 7 through GD 19 at dose levels of 0 (vehicle), 3, 10, or 30 mg/kg/day by oral gavage in a sesame oil. No maternal or developmental toxicity was observed at the 3 mg/kg/day dose of omaveloxolone. Poor pregnancy outcomes, including early deliveries and abortions, were observed at the 10 mg/kg/day dose of omaveloxolone. Two females administered 10 mg/kg/day omaveloxolone aborted and were euthanized on GD 26 and GD 27, respectively. Maternal toxicity was observed at the 30 mg/kg/day dose of omaveloxolone (i.e., thin body condition and red material in the pan) resulting in	Administration of omaveloxolone to pregnant female rats has led to an increase in stillbirths, reduced first generation pup survival, and decreased pup body weights as well as decreased reproductive function in F1 female pubs and delayed sexual maturation in F1 male pubs at exposure levels corresponding to 6 × that at the MHRD.

SAFETY FINDING	RELEVANCE TO HUMAN USE
significantly lower mean bodyweights over all the gestation periods. Embryofetal toxicity in the 30-mg/kg/day omaveloxolone dose group included an increase in post-implantation loss (-11.17%), increased total number of resorptions (early and late, 1.51 fetuses per doe), and number of late resorptions (0.7 fetuses per doe). In addition, lower male and female fetal body weights (-19% to -22%) were observed at the 30 mg/kg/day omaveloxolone dose. No omaveloxolone-related fetal external, visceral, and skeletal malformations or developmental variations (external and visceral) were observed at 30 mg/kg/day. The maternal NOAEL for omaveloxolone was 3 mg/kg/day (AUC0-24 of 0.314 hr*µg/mL on GD 19), and the developmental NOAEL was 10 mg/kg/day (AUC0-24 of 0.838 hr*µg/mL on GD 19). In a pre- and postnatal study with oral administration of omaveloxolone to rats, parental (P) time-mated female rats (n = 20/dose group) were dosed once daily from GD 6 through Lactation Day 20 at dose levels of 0 (vehicle), 1, 3, or 10 mg/kg/day by oral gavage in a sesame oil. The NOAEL for general toxicity in parental females was 10 mg/kg/day, the highest dose level evaluated. The NOAEL for reproductive function in parental females was 3 mg/kg/day, due to the increased percent of litters with stillborn pups and reduced F1 pup survival to post-natal day (PND) 28 observed in the 10-mg/kg/day dose group. The NOAEL for F1 male and female general toxicity and fertility and reproductive parameters was 3 mg/kg/day, due to the decreased mean body weights and reduced mean numbers of corpora lutea and implantation sites in the 10-mg/kg/day dose group. Dose-dependent increases in omaveloxolone plasma concentrations were observed in pups, both due to excretion of omaveloxolone in milk as well as placental transfer. Effects were directly linked to exposure to omaveloxolone and was not observed as secondary to maternal toxicity.	
Genotoxicity	
A GLP-compliant genotoxicity program was completed for omaveloxolone in 2 in vitro genetic toxicity tests and 2 in vivo genotoxicity studies in rats. In the in vitro systems, incubations were	Omaveloxolone is negative for genotoxic potential in human subjects.

SAFETY FINDING	RELEVANCE TO HUMAN USE
performed up to the maximum recommended concentrations (i.e., cytotoxic concentrations or concentrations that exceeded the visible limit of solubility). The weight of evidence indicates that omaveloxolone likely has a low genotoxicity risk to human subjects.	
Carcinogenicity	
The carcinogenicity potential of omaveloxolone was investigated in a 26-week carcinogenicity study in rasH2 mice. No evidence of RTA 408-related carcinogenic effect was noted at any dose level upon microscopic examination. In conclusion, oral gavage administration of 5, 10, or 30 mg/kg/day RTA 408 to male or 20, 50, or 100 mg/kg/day to female rasH2 hemizygous mice for 26 weeks was clinically well tolerated, had no effect on survival, and exhibited no evidence of any carcinogenic potential. Based on AUC of the highest doses tested and based on the survival and clinical observations, safety margins of 14.6 and 54.5 in males and females, respectively (calculated based on estimated human AUC0-24 value of 1.18 hr*µg/mL in patients with FA administered 150 mg omaveloxolone). Omaveloxolone was administered in a carcinogenicity study in rats at levels of 0.1, 0.3, or 1 mg/kg/day for up to 87 weeks in males, or 0.3, 1, or 3 mg/kg/day for up to 85 weeks in females. Incidences of neoplastic findings were noted in the liver (bile ducts), mammary, testis, and rectum (rectal-anal transition zone). There were no neoplastic findings in males at ≤ 0.3 mg/kg/day and no neoplastic findings in females at 0.3 mg/kg/day. The AUC-based safety margins were less than the human exposure at the MRHD. The final reports of these 2 studies will be submitted as post-approval deliverables.	Potential targets for tumorigenesis were identified in the rat. The testes findings are considered of limited risk to humans based on accepted literature supporting the limited risk in humans [Creasy 2012]. For the liver (bile ducts), mammary and rectum (rectal-anal transition zone) findings there is no available accepted literature to support the limited risk in humans.
Safety pharmacology	
A GLP-compliant study determined the inhibitory potential of omaveloxolone on the rapidly activating inward rectifying potassium current conducted by the hERG channel. The hERG channel, stably expressed in the human embryonic kidney 293 (HEK293) cell line, was used to evaluate the effect of omaveloxolone on inward rectifying potassium current (IKr) using whole-cell patch clamp electrophysiology.	The 0.75 µM omaveloxolone concentration corresponds to approximately 188X the unbound $C_{max,ss}$ in patients with FA administered the MHRD of 150 mg (i.e., 4.00 nM). No specific risks were identified based on the in vivo safety pharmacology studies.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Superfusion of omaveloxolone at concentrations of 0.75 and 1.2 µM produced minimal concentration-dependent blockage of hERG current, with mean±SD inhibition of approximately 6.72%±4.24% and 21.5%±5.4%, respectively, compared to 0.675%±2.120% for the vehicle control.	
Other toxicity-related information or data	
Nephrotoxicity: Tubular degeneration/regeneration in male and female rats after 1 month at omaveloxolone doses ≥ 10 mg/kg/day (oral), 3 months (dermal ≥ 0.3% omaveloxolone lotion in males; 8% omaveloxolone lotion in females), and 6 months at doses ≥ 0.3 mg/kg/day (oral). In monkeys, minimal focal kidney tubular epithelial degeneration/regeneration was also observed in 2 of 4 males and 1 of 4 females at the highest dosage tested (100 mg/kg/day oral) after 9 months of administration. In minipigs, meaningful systemic exposures were achieved in the dermal GLP toxicity studies, but no omaveloxolone-related kidney findings were observed.	Adequate safety margins above human exposure were established in minipigs. Rats were more sensitive to omaveloxolone and nephrotoxicity was observed, however, a safety margin above MHRD was not achieved in the 6-month GLP toxicity study.
Hepatotoxicity: The systemic toxicity potential of omaveloxolone has been evaluated in multiple nonclinical GLP toxicity studies in rats, minipigs, and monkeys after oral and dermal (which produces meaningful systemic exposure to omaveloxolone in animals) administration. The primary target organs for omaveloxolone observed in rats and monkeys (but not minipigs) include the liver (increased liver weight, hepatocellular hypertrophy, bile duct hypertrophy and hyperplasia). Exposure-dependent increase in liver weight in rats and monkeys (but not minipigs), associated with dose-dependent centrilobular to pan lobular hepatocellular hypertrophy. In general, due to their higher sensitivity to omaveloxolone, rats, but not monkeys or minipigs, had hepatocellular hypertrophy at high systemic omaveloxolone exposure levels (i.e., AUC_{0-24} > 1 hr*µg/mL) with minimal individual hepatocyte necrosis (except for 3-month oral and dermal studies) and changes in liver clinical chemistry markers, (i.e., increases of TBL, GGT, ALT, and AST). Bile duct hyperplasia was only observed in monkeys at 30	Hepatotoxicity is observed in both rats and monkeys. However, in rats, liver effects are observed at or below clinically relevant dose levels.

SAFETY FINDING	RELEVANCE TO HUMAN USE
and 100 mg/kg/day in the chronic 9-month oral GLP toxicity study and was not observed in any minipigs dosed dermally with omaveloxolone lotion (up to the highest dose tested of 8% omaveloxolone lotion) twice daily for 13 weeks. These liver findings were generally reversible or shown to be in the process of reversing at the end of the recovery period.	
Juvenile toxicity: A formal juvenile toxicity study was not conducted. The nonclinical safety of omaveloxolone was evaluated in a battery of GLP-compliant studies including oral repeated dose toxicity (rodent and non-rodent) and genotoxicity studies (i.e., bacterial reverse mutation, chromosomal aberration, rat liver comet, and micronucleus). In the chronic GLP toxicity studies (i.e., 6-month rat and 9-month monkey), 3-month interim necropsies were included. Studies were also conducted to assess the potential effects of omaveloxolone on male and female fertility (rats), embryofetal development (rats and rabbits), and pre- and post-natal development (PPND) (rats). No adverse effects on neurobehavior or central nervous systems nor bone or growth development deformities were observed in the developmental and reproductive toxicity studies or in the GLP toxicity studies. Further, any potential effects on reproductive systems have been adequately assessed and described in the reproductive toxicology package. Additionally, the target organs of toxicity were identified in the pivotal GLP toxicity studies and included liver, kidney, and the gastrointestinal tract. These target organs are fully or near fully developed at birth, and any additional assessment in a juvenile animal study is unlikely to yield new safety information for these target organs.	The proposed patient population is 16 years of age and older, which is supported by the 9-month GLP monkey study (and the monkey embryofetal and infant development study) that provides coverage from human equivalence of age 12 and older.

Non-Clinical Drug-Drug Interaction Studies

The potential for omaveloxolone to inhibit CYP450 enzymes in human liver microsomes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 [using 2 different substrates]) was thoroughly evaluated.

Omaveloxolone directly inhibited CYP2C8 with an IC_{50} (half maximal inhibitory concentration) value of 0.67 μM and CYP3A4/5 (midazolam 1'-hydroxylation) with IC_{50} values of 0.7 μM and 0.8 μM in replicate experiments. The data revealed that omaveloxolone was a mixed inhibitor of

CYP2C8 and CYP3A4/5 (midazolam 1'-hydroxylation) with K_i (inhibition constant) values of approximately 0.5 μM for each enzyme. At 3 μM, the highest concentration evaluated in this study, omaveloxolone directly inhibited CYP2B6 by 25%, CYP2C9 by 33%, and CYP3A4/5 (testosterone 6β-hydroxylation, replicate experiments) by 32% and 41%, respectively. Omaveloxolone caused no or slight direct inhibition of CYP1A2, CYP2C19, or CYP2D6. In addition, omaveloxolone caused no or slight metabolism-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

To support the observed steady-state maximum plasma concentration (C_{max}) at the therapeutic dose (i.e., 150 mg) for omaveloxolone in patients with FA, an additional CYP450 enzyme inhibition study assessed higher concentrations for CYP450s where an IC_{50} value was not previously defined. Omaveloxolone was incubated with CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 (testosterone) to determine inhibitory potential.

Human liver microsomes, pooled from 200 individuals, were incubated with probe substrates in the presence or absence of omaveloxolone at concentrations from 0.01 to 10 μM. Substrate metabolite concentrations were quantified by LC/MS/MS. To distinguish between metabolism-dependent and time-dependent inhibition, omaveloxolone was pre-incubated with human liver microsomes for 30 minutes with and without an nicotinamide adenine dinucleotide phosphate, reduced (NADPH)-generating system, respectively, prior to probe substrate addition. Direct and metabolism-dependent inhibitors of cytochrome P450 isoenzyme (CYP) enzymes were included as positive controls.

Omaveloxolone directly inhibited CYP2C9 and CYP3A4/5 (testosterone) with IC_{50} values of 4.8 and 4.9 μM, respectively. In contrast, less than 50% direct inhibition was observed for CYP1A2 (up to 11%), CYP2B6 (up to 43%), CYP2C19 (up to 31%), and CYP2D6 (up to 27%); reported as > 10 μM. No evidence of metabolism or time dependent inhibition by omaveloxolone was observed for any of the CYP enzymes evaluated except for CYP1A2. CYP1A2 caused no metabolism dependent inhibition, but minimal time dependent inhibition was found. Inhibition of CYP1A2, at the highest omaveloxolone concentration tested (10 μM), was approximately 25% after pre-incubation in the absence of nicotinamide adenine dinucleotide phosphate, reduced, and an IC_{50} value was not determined. Based on the in vitro data, clinical drug-drug interaction studies were conducted to determine whether omaveloxolone was a victim of drug-drug interactions with a CYP3A4/5 inhibitor (i.e., itraconazole, as well as a perpetrator of drug-drug interactions with sensitive substrates for CYP2C8 (i.e., repaglinide), CYP3A4/5 (i.e., midazolam), breast cancer resistance protein (BCRP) (i.e., rosuvastatin), or P-gp (i.e., digoxin). Clinical study results confirmed that omaveloxolone is a substrate for CYP3A4; however, no other meaningful interactions were observed. Concomitant administration of moderate or strong CYP3A4 inhibitors and CYP3A4 inducers should be avoided. If concomitant use cannot be avoided dose reductions with monitoring can be considered (see SmPC section 4.2). For strong CYP3A4 inhibitors, considering the 4-fold increase in exposure, the available dose strength of omaveloxolone capsules (50 mg), and the available safety information from doses up to 300 mg (Study 1402 Part 1), it is recommended a reduced omaveloxolone dose of 50 mg once daily (QD) with close monitoring for adverse reactions when coadministration of omaveloxolone with strong CYP3A4 is unavoidable. If coadministration cannot be avoided with moderate CYP3A4 inhibitors, a reduced dose of omaveloxolone of 100 mg QD with close monitoring for adverse reactions is recommended.

Non-Clinical Summary

A comprehensive nonclinical development program compliant with the ICH M3 (R2) was completed. It addressed the pharmacology, pharmacokinetics (PK), and safety pharmacology of omaveloxolone, and included a complete battery of GLP-compliant repeat-dose toxicity, carcinogenicity, reproductive toxicity, and genotoxicity studies. The nonclinical program was designed and conducted to support the chronic daily oral administration of omaveloxolone. The results of this program support the safe use of omaveloxolone at a dose level of 150 mg MHRD in patients with FA.

Overall, rats are more sensitive to the toxicologic effects of omaveloxolone than minipigs or monkeys. In rats, the NOAEL following 28 days or 13 weeks of daily oral administration was 3 mg/kg/day, corresponding to an AUC_{0-24} of approximately 2.0 hr*µg/mL. Following 6 months of oral administration to rats, adverse effects were observed at the lowest dose tested (0.3 mg/kg), which was associated with an AUC_{0-24} of approximately 0.3 hr*µg/mL. Similar systemic exposure was achieved in rats at the lowest dose tested in a 13-week topical dermal toxicity study of omaveloxolone lotion, with similar adverse effects observed in males but not females in the low-dose group. In monkeys, the NOAEL following 28 days or 13 weeks of daily oral administration was at least 100 mg/kg/day, and the NOAEL following 9 months of daily oral administration was 30 mg/kg/day, corresponding to an AUC_{0-24} of approximately 2.0 hr*µg/mL. In a 13-week minipig dermal GLP toxicity study, the NOAEL was the MFD of 8% omaveloxolone lotion (twice daily by topical administration) with systemic exposures up to 1.7 hr*µg/mL.

Across studies, the adverse liver findings in rats were reversible upon drug discontinuation and were associated with moderate to marked increases in serum GGT, ALT, AST, and TBL. While ALT, AST, and GGT induction can be confounded by Nrf2 pharmacology, the profile in rats where exposures exceed clinical exposures is suggestive of hepatotoxicity. Specifically, no adverse effects on the liver occurred in monkeys, and the adverse effects on the liver in rats do not occur at systemic exposures (based on AUC_{0-24}) observed in patients with FA at the MHRD of 150 mg. In patients with FA, there was no difference between omaveloxolone- and placebo-treated groups in the incidence of treatment-emergent adverse events (TEAEs) of interest reported in the hepatobiliary disorders SOC or any reported hepatic serious adverse events (SAEs).

Based on the entirety of the data, the nonclinical study results support the marketing authorization of omaveloxolone in patients with FA.

The calculated safety margins based on the exposure ratios at the MHRD are presented in the table below.

Table 3: Human Safety Margins for Omaveloxolone

Species/Study	**Animal NOAEL**	**Animal AUC_{0-24} (hr*µg/mL)[ab]**	**Human Safety Margins at MHRD of 150 mg**
			Based on AUC[bc]
Rat 28-day	3	1.9	1.6

Species/Study	Animal NOAEL	Animal AUC_{0-24} (hr*µg/mL)[ab]	Human Safety Margins at MHRD of 150 mg
			Based on AUC[bc]
Rat 3-month	3	2.3	1.9
Rat 6-month	< 0.3[c]	< 0.3	< 0.3
Monkey 28-day	100	5.7	4.8
Monkey 3-month	100	6.5	5.5
Monkey 9-month	30	2.0	1.7
Rat genotoxicity (micronucleus)	2000	3.9	3.3
Rat fertility/developmental	3	2.4	2.0
Rat Embryofetal	10	7.4	6.3
Rabbit Embryofetal	3 (maternal)	0.3	0.3
	10 (fetus)	0.8	0.7
Rat Pre- and post-natal development	3	2.4	2.0

NOAEL = no observed adverse effect level, AUC = area under the curve, MHRD = maximum human recommended dose.
[a]Values represent the mean AUC after repeated administration for males and females combined, when appropriate.
[b]Safety margins calculated based on estimated human AUC_{0-24} value of 1.18 hr*µg/mL in patients with FA administered 150 mg omaveloxolone (Study REAT-PMX-OMAV-2081).
[c]LOAEL
Source: Module 2.4 Nonclinical Overview.

In summary, nonclinical data do not suggest a potential for the important potential risk of drug-induced liver injury (DILI), nor suggest fetal malformations at exposures less than the MHRD exposures. However, maternal toxicity was observed in the rabbit embryofetal assessment at exposures levels below that at the MHRD. However, information on the possible impact for use in pregnant and lactating women is considered as missing information. Nonclinical data that have relevance for human usage include the drug-drug interaction studies that provide evidence for the identified risk safety with concomitant use with strong/moderate CYP3A4 inhibitors and the potential risk for loss of efficacy with concomitant use with CYP3A4 inducers.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The clinical safety profile of omaveloxolone has been studied in approximately 400 patients and healthy subjects, including 5 PK studies and 6 other clinical studies in FA, mitochondrial myopathy, and oncology. In the FA population, 172 unique patients, which included a total of 33 patients < 18 years of age, were enrolled and evaluated to assess the safety and efficacy of omaveloxolone.

Table 4 shows the number of individuals exposed to omaveloxolone capsules, during the clinical development program. More than 800 patients and healthy subjects were exposed to omaveloxolone across the entire omaveloxolone development program, including two topical formulations. Of those, more than 400 subjects were exposed to the proposed commercial formulation for omaveloxolone.

Table 4: Total Exposure to Omaveloxolone

Safety Data for Capsule Formulation of Omaveloxolone N = 444			
Clinical Study Group	**Studies Included**	**Placebo (n = 82)**	**Omaveloxolone (n = 424)**
Healthy subjects	408-C-1703	0	34
	408-C-1804	0	32
	408-C-1805	0	8
	408-C-1806	0	61
	408-C-2106	0	32
Placebo-controlled studies conducted in patients with FA	1402 Part 2	52	51[a]
	1402 Part 1	17	52[a]
Open-label studies conducted in patients with FA	Study 1402 Extension	62[b]	87
Placebo-controlled studies conducted in patients with mitochondrial myopathies	408-C-1403	13	40
Open-label studies conducted in patients with oncologic indications	408-C-1303	0	11
	408-C-1401	0	41

Abbreviation: FA = Friedreich's ataxia; Study 1402 = clinical study 408-C-1402 (Part 1, Part 2, and/or Extension).
[a] Totals include number of unique patients.
[b] All patients enrolled in Study 1402 Extension (n = 149) first completed either Study 1402 Part 1 or Study 1402 Part 2. The number given in the placebo column represents patients who were on placebo in either Study 1402 Part 1 or Part 2; these patients received omaveloxolone in Study 1402 Extension.
Sources: Module 5.2; ISS Table 8; Study 408-C-2106 CSR Table 14.1.1

The clinical safety focuses on safety information derived from the following 3 studies to support the proposed indication for the treatment of FA in adults and adolescents aged ≥ 16.

- Study 408-C-1402 (hereafter referred to as "Study 1402") Part 1 was a completed, dose-ranging, randomized, double-blind, placebo-controlled study of omaveloxolone treatment in patients with FA. A total of 69 patients aged 16 to ≤ 40 years were enrolled in a 3:1 ratio, with 52 randomized to omaveloxolone (6 each to the 2.5/5-mg, 10-mg, 20-mg, 40-mg, and 80-mg groups; 12 to the 160-mg group; 10 to the 300-mg group), and 17 to placebo. Treatment was administered for 12 weeks to determine an appropriate dose of omaveloxolone to be used in Study 1402 Part 2.
- Study 1402 Part 2 was a completed, randomized, double-blind, placebo-controlled study, which evaluated the efficacy and safety of omaveloxolone 150 mg in 103 patients with FA for up to 48 weeks of treatment. Patients were randomized 1:1 to omaveloxolone or placebo.
- Study 408-C-1402 Extension is an ongoing, open-label extension study to assess the long-term safety of omaveloxolone in patients with FA who previously participated in Study 1402 Part 1 or Part 2. At the time of the interim database lock (24 March 2022), a total of 149 patients were enrolled, with a maximum omaveloxolone treatment duration of 3.4 years (in Study 1402 Extension), and 4.3 years combined exposure with the Study Part 2 duration.

The primary safety analysis set is the Primary Placebo-Controlled Analysis Set A (hereafter referred to as Analysis Set A, Table 5) which includes data from the randomized, double-blind, placebo-controlled Study 1402 Part 2.

The FA Overall Omaveloxolone Exposure Integrated Analysis Set C (hereafter referred to as Analysis Set C; Table 6) includes data from all omaveloxolone-treated patients (no placebo-treated patients), regardless of dose, from all studies in patients with FA (i.e., Study 1402 Part 1, Part 2, and Extension). All phases of treatment are included (i.e., on or after treatment). In these analyses, doses are assessed categorically, as 5 to 20 mg, 40 to 80 mg, 150/160 mg, and 300 mg, and were combined to characterize patients treated with any omaveloxolone dose for any duration. This analysis set was assessed to confirm the safety profile of Analysis Set A.

Table 5: Number of Patients in the Primary Placebo-Controlled Analysis Set A by Study, Treatment, and Dose Level

Study Number	Omaveloxolone 150 mg	Placebo	Total Patients
408-C-1402 Part 2	51	52	103

Source: Study 1402 Part 2 CSR, Table 14.1.1.1

Table 6: Number of Patients in the FA Analysis Set C by Study, Treatment, Formulation, and Dose Level

	Omaveloxolone							
Study Number	**5 mg[a]**	**10 mg**	**20 mg**	**40 mg**	**80 mg**	**150/160 mg**	**300 mg**	**All Treated**
408-C-1402 Part 1	6	6	6	6	6	12	10	52
408-C-1402 Part 2	NA	NA	NA	NA	NA	51 (43 also in Study 1402 Extension	NA	51
408-C-1402 Extension[b]	NA	NA	NA	NA	NA	149	NA	149 (Interim Data Cut: 24 March 2022)
Total Patients	6	6	6	6	6	159[c]	10	165[c]

[a] All patients who were randomized to 2.5 mg were titrated up to 5 mg. For purposes of data presentation 5 mg is used.
[b] Study is ongoing, Interim Database lock 24 March 2022.
[c] Total includes number of unique patients.
Source: Study 1402 Part 1 CSR, Table 14.1.1; Study 1402 Part 2 CSR, Table 14.1.1.1; Study 1402 Extension Interim CSR 2022, Table 14.1.1.1.

The Placebo-Controlled Integrated FA Analysis Set B (hereafter referred to as Analysis Set B) includes data from the double-blind treatment phase for both Study 1402 Part 1 and Part 2 for the treatment of patients with FA. This analysis set includes patients treated with either placebo or the omaveloxolone recommended dose (160 mg from Study 1402 Part 1, 150 mg from Study 1402 Part 2), and includes the same assessments as Analysis Set A. Summaries included placebo and omaveloxolone doses of 150/160 mg pooled. This analysis set was assessed to confirm the safety profile of Analysis Set A.

The Long-Term Safety Study 1402 Subgroup Set D (hereafter referred to as "Analysis Set D") includes all omaveloxolone-treated patients (no placebo-treated patients) who enrolled in Study 1402 Part 2 and were randomized to omaveloxolone. Patients who completed Study 1402 Part 1 and patients who were randomized to placebo in Study 1402 Part 2 are not included in this subgroup. The results summarize the entire patient exposure on omaveloxolone in Study 1402 Part 2 and Extension. This analysis set was assessed to confirm the long-term safety of omaveloxolone 150 mg treatment.

The FA Exposure Analysis Set E (hereafter referred to as "Analysis Set E") consists of patients with ≥ 48 weeks exposure to omaveloxolone 150 mg, ≥ 96 weeks exposure to omaveloxolone 150 mg, and ≥ 144 weeks exposure to omaveloxolone 150 mg. The results summarize the entire patient exposure on omaveloxolone in Study 1402 Part 2 and the Study 1402 Extension.

The Placebo-Controlled Integrated All Analysis Set X (hereafter referred to as "Analysis Set X") is defined as patients who received at least 1 dose of study drug (omaveloxolone or placebo) in a randomized placebo-controlled study. Data from patients who received 150 mg omaveloxolone, 160 mg omaveloxolone, or placebo in any part of Study 1402 are included. The purpose of this

analysis set is to summarize safety findings from all placebo-controlled studies included in the Integrated Summary of Safety (ISS). Table 7 shows the exposure in Analysis Sets A and C (All Patients).

Table 7: Exposure in Analysis Sets A and C (All Patients)

Analysis Set	N[b]	Duration of Study Drug Exposure		
		Median Exposure (years)	> 0.92 Patient Years (> 48 Weeks) n (%) Patients[a]	> 1.84 Patient Years (> 96 Weeks) n (%) Patients[a]
Analysis Set A				
Omaveloxolone 150 mg (n = 51)	51	0.92	20 (40.0%)	0
Placebo (n = 52)	52	0.92	27 (51.9%)	0
Analysis Set C				
Omaveloxolone				
5 to 20 mg (n = 18)	18	0.23	0	0
40 to 80 mg (n = 12)	12	0.23	0	0
150/160 mg (n = 159)	167	2.77	137 (82.0%)	125 (74.9%)
300 mg (n = 10)	10	0.23	0	0
Combined (n = 165)	207	2.72	137 (66.2%)	125 (60.4%)

[a] Percentages are based on the number of non-missing observations.
[b] N is the number of exposure measurements. For patients who started omaveloxolone in Study 1402 Part 1 and entered Study 1402 Extension, exposure was calculated separately for the double-blind and Study 1402 Extension studies. These patients are counted in multiple dose groups if they changed dose level when entering the Study 1402 Extension. All other patients had 1 observation. For patients who started omaveloxolone in Study 1402 Part 2 and entered Study 1402 Extension, exposure was calculated across both studies when entering Study 1402 Extension.
Source: ISS Table 5.1.1.1, 5.1.2.1

The tables below present the exposure of omaveloxolone by age group (Table 8) and geographical region and ethnic origin (Table 9).

Table 8: Exposure by Age Group (Analysis Set A)

Age (years)	< 18 years		≥ 18 years	
	Omaveloxolone	Placebo	Omaveloxolone	Placebo
Analysis Set A				
N	9	15	42	37
Mean (SD)	16.6 (0.53)	16.5 (0.52)	24.9 (5.71)	27.1 (7.34)
Median	17.0	17.0	23.0	26.0
Min, Max	16, 17	16, 17	18, 39	18, 40
Male: N (%)	3 (33.3%)	10 (66.7%)	17 (40.5%)	25 (67.6%)

Age (years)	< 18 years		≥ 18 years	
	Omaveloxolone	Placebo	Omaveloxolone	Placebo
Analysis Set A				
Female: N (%)	6 (66.7%)	5 (33.3%)	25 (59.5%)	12 (32.4%)

Abbreviations: Max = maximum; Min = minimum.
Note: Percentages are based on the number of patients with data.
Source: ISS Table 2.1.1.1

Table 9: Exposure by Geographic Region, Race and Ethnicity (Analysis Set A)

Geographic Region				
	USA		Ex-USA[a]	
	Omaveloxolone (N = 36)	Placebo (N = 35)	Omaveloxolone (N = 15)	Placebo (N = 17)
Race, n (%)				
White	35 (97.2%)	33 (94.3%)	15 (100%)	17 (100%)
Non-White	1 (2.8%)	2 (5.7%)	0	0
Ethnicity, n (%)				
Not Hispanic or Latino	34 (94.4%)	32 (91.4%)	15 (100%)	17 (100%)
Hispanic or Latino	2 (5.6%)	3 (8.6%)	0	0

Abbreviation: USA = United States of America
[a] Other countries include United Kingdom, Austria, Italy, and Australia
Note: Percentages are based on the number of patients with data.
Source: ISS Table 2.1.1.3

The MAH has conducted 2 open-label oncology studies (408-C-1401 and 408-C-1303) in which omaveloxolone was studied as an oral dose form in patients with advanced solid tumors. Additionally, the MAH has conducted 4 clinical studies (408-C-1305, 408-C-1306, 408-C-1307, and 408-C-1309) in which omaveloxolone was tested topically (using an eyedrop or lotion formulation), and patients had no appreciable systemic exposure. These studies do not contribute to the assessment of safety for orally administered omaveloxolone and are not integrated in the pooled safety database.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the FA development programme

The main exclusion criteria and under-represented populations in the clinical program were reviewed to identify factors that could influence differences in the safety profile of the product as reported in clinical studies compared to treatment of the target population (FA). The exclusion criteria for the pivotal Phase 2 study in the FA clinical development program, Study 1402 Part 2, are presented below, classified by routine (e.g., common safety criteria used in interventional clinical studies and/or those that may mask the effect of the intervention), and population-/study medication-specific exclusion criteria.

Routine Exclusion Criteria:

- Prior participation in a study with omaveloxolone.
- Known active fungal, bacterial, and/or viral infection, including HIV or hepatitis virus (B or C).
- Known or suspected active drug or alcohol abuse, as per Investigator judgment.
- Any abnormal laboratory test value or clinically significant preexisting medical condition that, in the opinion of the Investigator, would have put the patient at risk by study enrollment.
- Participation in any other interventional clinical study within 30 days prior to Study Day 1.
- Cognitive impairment that could preclude ability to comply with study procedures.
- Unable to comply with the requirements of the study protocol or were unsuitable for the study for any reason, in the opinion of the Investigator.
- Used antioxidant supplements, including but not limited to idebenone, CoQ10, nicotinamide, and vitamin E, above the recommended daily allowance, within 14 days prior to Study Day 1 or planned to take any of these supplements during the time of study participation.
- History of thromboembolic events within the past 5 years.
- Administered anticoagulant therapy within 30 days prior to Study Day 1.
- Had clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations > 1.5 × the upper limit of normal (ULN) of AST or ALT. Levels above this threshold were allowable, if attributable to muscle injury.

Table 10 shows the FA population and study specific exclusion criteria.

Table 10: FA Population- and Study-Specific Exclusion Criteria

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Uncontrolled diabetes (hemoglobin A1c > 11.0%)	Patients with uncontrolled diabetes are generally non-compliant with medication adherence and therefore would confound safety and efficacy assessments of omaveloxolone [Polonsky and Henry 2016].	No	Prevalence of diabetes in the FA-COMS natural history database is 8.7% (96/1099 patients) [Tamaroff 2022]. In Study 1402 Part 2, a total 11/103 (10.6%) enrolled patients were diabetic and prediabetic; 9 of these patients were assigned to the omaveloxolone group and 2 patients to the placebo group. No patients were excluded due to the criteria of HbA1c > 11%. Safety of patients in this population will be monitored via routine pharmacovigilance.
B-type natriuretic peptide (BNP) level > 200 pg/mL	In patients with type 2 diabetes and Stage 4 CKD, adjudicated heart failure events were observed in 96/1088 patients (8.8%) randomized to a structural analogue of omaveloxolone. Baseline BNP > 200 pg/mL was identified as a risk factor contributing to the excess in observed adjudicated heart failure events in patients with Stage 4 CKD treated with a structural analogue of omaveloxolone and has been excluded in the FA population. BNP is a biomarker of fluid status and possible pre-existing	No	Elevated baseline BNP > 200 pg/mL may be a risk factor for developing congestive heart failure (CHF). BNP > 200 pg/mL should trigger evaluation for signs and symptoms of fluid overload and heart failure, as it is a non-specific marker. CHF is an important potential risk for omaveloxolone. (Part II: Module SVII)

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	heart failure when levels exceed 200 pg/mL.		
Have 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 FA, including but not limited to any of the following: a. Clinically significant congenital or acquired valvular disease b. Pericardial constriction (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit) c. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit) d. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina) e. History of hospitalization for heart failure in the last five years f. Cardiac insufficiency, defined as New York Heart Association Class > 2 g. History of atrial fibrillation h. History of unstable arrhythmias	In patients with type 2 diabetes and Stage 4 CKD, adjudicated heart failure events were observed in 96/1088 (8.8%) patients randomized to a structural analog of omaveloxolone, compared to 55/1097 patients (5.0%) randomized to placebo. Pre-existing heart failure was identified as a risk factor contributing to the excess in observed adjudicated heart failure events in patients treated with a structural analogue of omaveloxolone and has been excluded for the studies in FA.	No	Pre-existing symptomatic heart failure is a risk factor for developing CHF in studies with a structural analog of omaveloxolone. Safety of patients in this population will be monitored via routine pharmacovigilance. See Annex 3.

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
i. Have a left ventricular ejection fraction ≥ 40% (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)			
Administered any of the following drugs within 7 days prior to Study Day 1 or planned to take any of these drugs during the time of study participation: a. Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil) b. Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice) c. Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)	Omaveloxolone is a CYP3A4 substrate. Strong or moderate CYP3A4 inhibitors may significantly increase the systemic exposure of omaveloxolone. Co-administration of omaveloxolone with strong or moderate CYP3A4 inducers may significantly decrease exposure of omaveloxolone, which may reduce the effectiveness of omaveloxolone. Omaveloxolone is a weak inducer of CYP3A4 and CYP2C8. Concomitant use with omaveloxolone can reduce the exposure of CYP3A4 and CYP2C8 substrates which may reduce the activity of these substrates.	No	Omaveloxolone SmPC section 4.2 provides recommended dose modifications with concomitant use of use of CYP3A4 inhibitors and inducers. Omaveloxolone SmPC section 4.5 provides information on interactions for CYP3A4 inhibitors, inducers, and substrates, CYP2C8 substrates, and BCRP substrates. Omaveloxolone SmPC section 4.6 provides guidance on concomitant use of hormonal contraceptives with omaveloxolone.

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), or had, at Screening, clinically relevant deviations in laboratory tests including any one of the following: a. ALT and/or AST > 1.5-fold ULN b. Bilirubin > 1.2-fold ULN c. Alkaline phosphatase > 2-fold ULN d. Albumin < lower limit of normal	Patients with FA with clinically significant liver disease were excluded from clinical studies to avoid enrolling very sick patients, which could confound safety assessments with regards to elevations in transaminases and liver function tests.	No	The recommended dosage for patients with hepatic impairment is described in section 4.2 of the SmPC.
Previously documented mitochondrial respiratory chain disease	Both mitochondrial respiratory chain disease and FA are caused by mitochondrial dysfunction. Mitochondrial respiratory chain disease was excluded to assess the effect of omaveloxolone in FA caused by a genetic deficiency of frataxin only, not caused by other human mitochondrial mutations.	No	Safety of patients in this population will be monitored via routine pharmacovigilance.
Scheduled surgical treatment for scoliosis or foot deformity during the study	Surgical treatment for scoliosis or foot deformity improves mobility in patients with FA and would confound efficacy and safety assessments of omaveloxolone in patients with FA.	No	Safety of patients in this population will be monitored via routine pharmacovigilance.

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Significant current suicidal ideation within 1 month prior to Screening Visit as per Investigator judgment or any history of suicide attempts	Depression and its symptoms are prevalent and clinically relevant among patients with FA; thus, these patients were excluded from the study as it may interfere with efficacy and safety assessments of omaveloxolone in patients with FA.	No	Safety of patients in this population will be monitored via routine pharmacovigilance.
Pregnant or breastfeeding	Pregnant and lactating women have not been included in omaveloxolone clinical studies. As per protocol, if a woman became pregnant during a clinical study, the study drug was stopped, and the subject was discontinued. There are no adequate data from the use of omaveloxolone in pregnant or lactating women.	No	Safety of patients in this population will be monitored via routine pharmacovigilance.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; CHF = congestive heart failure; CKD = chronic kidney disease; FA = Friedreich's ataxia; HbA1c = hemoglobin A1c; SmPC = summary of product characteristics; ULN = upper limit of normal

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

FA is a rare disease; 172 unique patients, including 33 patients < 18 years of age were enrolled and evaluated to assess the safety and efficacy of omaveloxolone in this patient population. The maximum duration a patient has been exposed during the clinical development is 3.4 years (in Study 1402 Extension), and 4.3 years combined exposure with the Study 1402 Part 2 duration. The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, or those that may disproportionately affect populations excluded from the clinical development program.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 11.

Table 11: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women/ breastfeeding women	Not included in the clinical development program for omaveloxolone. No pregnancy occurred in any part of Study 1402 as of 24 March 2022.
Patients with relevant comorbidities: • Hepatic impairment	Omaveloxolone is excreted predominantly via the feces. In subjects with 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 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. 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 of the SmPC.
Patients with relevant comorbidities: • Renal impairment	Omaveloxolone is excreted predominantly via the feces, with minimal urinary excretion (0.1%). Thus, a formal renal impairment PK study was not conducted. Population pharmacokinetic analysis confirmed that eGFR values $\geq$ 63 mL/min/1.73m^2 did not have a significant effect on the PK of omaveloxolone. The effect of moderate or severe renal impairment on the PK of omaveloxolone. The effect of moderate or severe renal impairment on the PK of omaveloxolone is unknown.

Type of special population	Exposure
Patients with relevant comorbidities: • Cardiovascular impairment	Patients with a prior history of left-sided heart disease and/or clinically significant cardiac disease were excluded in the FA studies (Module SIV.1). Cardiovascular safety was evaluated due to cardiovascular SAEs, including fluid overload, increased blood pressure, and heart failure, which were observed in a previous clinical study with a structural analog of omaveloxolone in patients with type 2 diabetes mellitus and Stage 4 CKD (Study 402-C-0903). Of note, risk factors for these events were identified and used as population selection criteria to mitigate cardiovascular risks in patients in subsequent studies with a structural analogue of omaveloxolone. Based on review of Study 1402 Part 2, clinical data for TEAEs, as well as review of relevant imaging and laboratory studies, a risk for cardiac disorders was not identified. The small increases in BNP that were observed for omaveloxolone-treated patients were not associated with fluid overload or heart failure and may be considered indicative of improvements in metabolism, rather than fluid retention. There were no cardiac adverse effects based on review of clinical ECG and echocardiographic data. Although Stage 4 CKD is not a typical comorbidity of FA, this type of patient may exist. Accordingly, the omaveloxolone SmPC has appropriate warnings regarding fluid overload and CHF in patients with Stage 4 CKD and advises that patients should be counselled on the signs and symptoms of CHF. See SmPC sections 4.4 and 4.8; PIL section 2 and 4 and Module SVII.3.1.
Patients with relevant comorbidities: • Immunocompromised patients	Not included in the clinical development program for omaveloxolone (Module SIV.1).
Patients with a disease severity different from inclusion criteria in clinical trials	None
Patients with relevant different race and ethnic origin	**Number of subjects by race in the FA patient population (Analysis Set A):** White: 50 (98.0%) Non-White: 1 (2.0%) **Number of subjects by ethnicity in the FA patient population (Analysis Set A):** Non-Hispanic or Latino: 49 (96.1%) Hispanic or Latino: 2 (3.9%)
Subpopulations carrying relevant genetic polymorphisms	None

Type of special population	Exposure
Pediatric patients	33 patients < 18 years of age were enrolled and evaluated to assess the safety and efficacy of omaveloxolone in this patient population. For the treatment of FA, omaveloxolone has been studied in pediatric patients 16 to < 18 years of age. A total of 24 patients younger than 18 years were included (Part II: Module SIII).
Other	None

Abbreviations: AE = adverse event; AUC = area under the plasma concentration versus time curve; CKD = chronic kidney disease; C_{max} = maximum plasma concentration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FA = Friedreich's ataxia; SAE = serious adverse event; SmPC = summary of product characteristics
Source: ISS Table 2.1.1.3

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The MAH collects data on sales patients for omaveloxolone in its internal database. The data include the number of patients who were sold omaveloxolone during the month. The total sales to patients by month is the best available cumulative number of exposed patients in the postmarket setting. All data are available on a monthly basis.

Individual-level data are not available for precise patient-time calculation. Estimated cumulative patient-years of exposure were calculated by summing the total number of sales patients each month during the reporting period and dividing by 12 (months in a year).

SV.1.2 Exposure

Cumulative postmarketing exposure to omaveloxolone is presented in Table 12.

Table 12: Estimated Cumulative Postmarketing Patient Exposure by Region

Region	Cumulative IBD to 31 Jan 2025	
	Number of Patients	PY
EU	672	415.83
RoW	1220	1458.54
Total Exposed	**1892**	**1874.37**

The MAH has initiated an EAP. The cumulative EAP exposure as of 31 Jan 2025 to omaveloxolone is 830 patients (183.3 PY).

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Omaveloxolone crosses the blood brain barrier but is not expected to be subject to abuse or a potential for misuse for illegal purposes.

Multiple nonclinical studies were reviewed to assess the potential for drug abuse liability. Omaveloxolone (200 µM and 2000 µM) was tested in vitro in a panel of receptors, ion channels, transporters, and enzymes that included multiple central nervous system (CNS) targets (SafetyScreen44™ panel) (Study RTA-P-18007; Module 2.6.2, section 3.1) and in a GLP CNS safety pharmacology study in rats. The results of the study demonstrated that omaveloxolone did not significantly inhibit any reference compound receptor binding or enzyme activity. Concentrations of 200 and 2000 nM omaveloxolone correspond to approximately 50- and 500X, respectively, the free drug C_{max} in patients with FA when administered the MHRD of 150 mg.

Note that in the SafetyScreen44™ study, results for benzodiazepine and serotonin 2A (5-HT2A) receptors indicated negative percent inhibition values at 200 and 2000 nM of -31.8% and -44.3%, respectively, for benzodiazepine and -37.0% and -68.6%, respectively, for 5-HT2A. These values were considered to be technical artifacts of the assay, as it states the following in the Results Interpretation Guide within the study report (Study RTA-P-18007): “Low to moderate negative values have no real meaning and are attributable to variability of the signal around the control level. High negative values (≥ 50%) that are sometimes obtained with high concentrations of test compounds are generally attributable to nonspecific effects of the test compounds in the assays.”

Furthermore, no effects were observed in the CNS safety pharmacology study in rats up to the highest dose tested (30 mg/kg). The mean C_{max} at the 30-mg/kg oral dose in rats corresponds to approximately 11.5X the mean C_{max} at steady state, in patients with FA administered the MHRD of 150 mg. Further, in clinical studies with omaveloxolone, no psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) were reported.

Based on its mechanism of action, omaveloxolone is not considered a drug for potential abuse, and, as such, a drug abuse study was concluded to be unnecessary.

Analysis Sets A to C were queried for events possibly related to abuse potential. No patients reported any events from the Medical Dictionary for Regulatory Activities Drug abuse and dependence standardized MedDRA query. Thus, the review of TEAEs from omaveloxolone clinical studies provides no evidence for any abuse potential for omaveloxolone.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

This section is consistent with the Summary of Product Characteristics (SmPC) (i.e., contraindications, warnings and precautions, limitations on use, and adverse drug reactions [ADRs]/undesirable effects) of omaveloxolone. A summary of the identified and potential risks for omaveloxolone with the rationale whether the risk is or is not considered important is included. Details for the important identified and potential risks and missing information that (1) may have potential impact on the risk-benefit assessment and/or public health or (2) may require either further characterization or evaluation, or implementation of specific risk minimization activities are further characterized. Safety concerns for omaveloxolone are derived from the pivotal Study 1402 Part 2 and the ongoing long-term Study 1402 Extension in patients with FA and supplemented with clinical study experience from its overall clinical development program. The data are presented herein by the pooled data in patients with FA in patients 16 years of age and older, unless otherwise specified.

SVII.1 Identification of safety concerns in the initial RMP submission

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	DILI CHF
Missing information	Use in pregnancy Long-term safety

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following risks are not considered Important for inclusion in the list of safety concerns in the RMP. The events below are those reported in ≥ 5% of omaveloxolone-treated patients and ≥ 5% the placebo rate in the FA population (*risk not an ADR in the SmPC):

- ALT increased
- AST increased
- GGT increased
- Headache
- Influenza
- Urinary tract infection
- Nausea
- Diarrhoea
- Abdominal pain upper

- Abdominal pain
- Back pain
- Muscle spasms
- Fatigue
- Oropharyngeal pain
- Decreased appetite
- Dysmenorrhoea
- Safety with concomitant use with strong or moderate CYP3A4 inhibitors*
- Potential loss of efficacy with concomitant use with strong or moderate CYP3A4 inducers*
- Use in patients with hepatic impairment*
- Elevation of BNP
- Lipid abnormalities
- Body weight decrease

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):

- **Alanine aminotransferase (ALT) increased:** A higher incidence of the TEAEs of ALT increased was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events of ALT increased 37.3% to 1.9%, related events 37.3% to 0%). All events were mild to moderate in severity, 1 patient discontinued treatment due to this adverse event (AE), and dose interruptions were required in 11.8% (n = 6) patients. Increases in ALT were not associated with increases in bilirubin or with any clinical evidence of liver injury. No cases meeting Hy's law criteria have been reported with omaveloxolone treatment.
- **Aspartate aminotransferase (AST) increased:** A higher incidence of the TEAEs of AST increased was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events of AST increased 21.6% to 1.9%, related events 21.6% to 0%). All events were mild to moderate in severity, 1 patient discontinued treatment due to this AE, and dose interruptions were required in 5.9% (n = 3) patients. Increases in AST were not associated with increases in bilirubin or with any clinical evidence of liver injury. No cases meeting Hy's law criteria have been reported with omaveloxolone treatment.

- **Gamma-glutamyl transferase (GGT) increased:** A higher incidence of the TEAEs of GGT increased was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events of GGT increased 5.9% to 0%, related events 5.9% to 0%). All events were mild to moderate in severity, no patient discontinued treatment due to this AE, and dose interruptions were required in 3.9% (n = 2). Increases in GGT were not associated with increases in bilirubin or with any clinical evidence of liver injury. No cases meeting Hy's law criteria have been reported with omaveloxolone treatment.
- **Headache:** A higher incidence of headache was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 37.3% to 25.0%, related events 17.6% to 7.7%). All events were mild to moderate in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Influenza:** A higher incidence of influenza was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 13.7% to 3.8%, no related events). All events were mild to moderate in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Urinary tract infection:** A higher incidence of urinary tract infection was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 7.8% to 0%, no related events). All events were mild in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Nausea:** A higher incidence of nausea was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 33.3% to 13.5%, 17.6 % to 5.8% related events). All events were mild to moderate in severity, no patient discontinued treatment, and dose interruptions were required in 2.0% (n = 1) patients. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Diarrhoea:** A higher incidence of diarrhoea was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 19.6% to 9.6%, related events 11.8% to 0%). All events were mild to moderate in severity, no patient discontinued treatment, and dose interruptions were required in 2.0% (n = 1) patients. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.

- **Abdominal pain upper:** A higher incidence of abdominal pain upper was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 9.8% to 1.9%, related events 5.9% to 0%). All events were mild in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Abdominal pain:** A higher incidence of abdominal pain upper was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 7.8% to 1.9%, related events 3.9% to 1.9%). All events were mild to moderate in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Back pain:** A higher incidence of back pain was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 13.7% to 7.7%, no related events). All events were mild to moderate in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Muscle spasms:** A higher incidence of muscle spasms was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 13.7% to 5.8%, related events 9.8% to 3.8%). All events were mild to moderate in severity, 1 patient discontinued treatment due to this AE, and dose interruptions were required in 2.0% (n = 1) patients. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Fatigue:** A higher incidence of fatigue was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 21.6% to 13.5%, related events 13.7% to 7.7%). All events were mild to moderate in severity, 1 patient discontinued treatment due to this AE, and dose interruptions were required in 2.0% (n = 1) patients. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Oropharyngeal pain:** A higher incidence of oropharyngeal pain was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 17.6% to 5.8%, related events 2.0% to 1.9%). All events were mild to moderate in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Decreased appetite:** A higher incidence of decreased appetite was observed in omaveloxolone-treated patients compared to placebo-treated patients in the

Placebo-Controlled Analysis Set A (All events 11.8% to 3.8%, related events 5.9% to 1.9%). All events were mild in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.

- **Dysmenorrhoea:** A higher incidence of dysmenorrhoea was observed in omaveloxolone-treated patients compared to placebo-treated patients in the Placebo-Controlled Analysis Set A (All events 5.9% to 0%, no related events). All events were mild in severity and did not result in dose interruption or treatment discontinuation. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.
- **Safety with concomitant use with strong or moderate CYP3A4 inhibitors:** An increase in systemic exposure of omaveloxolone was observed in healthy subjects following co-administration with multiple oral doses of itraconazole (strong CYP3A4 inhibitor) compared with omaveloxolone administered alone (approximately 4- and 3-fold increases in AUC0-∞ (area under the plasma concentration) vs C_{max} (time curve from time 0 extrapolated to infinity), respectively). In a clinical study with healthy subjects, co-administration of verapamil with omaveloxolone at steady state increased the AUC by approximately 1.24-fold and C_{max} by approximately 1.28-fold. Verapamil is a known moderate CYP3A4 inhibitor and inhibitor of the P-gp transporter.

  The recommended dosage for concomitant use of omaveloxolone with strong or moderate CYP3A4 inhibitors are described in section 4.2 of the SmPC. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.

Recommended Dosage of Omaveloxolone with Concomitant Use of Strong or Moderate CYP3A4 Inhibitors

Concomitant Drug Class	Dosage
Strong CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of omaveloxolone 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 omaveloxolone s to 100 mg once daily with close monitoring for adverse reactions.

Concomitant Drug Class	Dosage
	• If adverse reactions emerge, further reduce the dosage of omaveloxolone to 50 mg once daily.

- **Potential loss of efficacy with concomitant use with strong or moderate CYP3A4 inducers:** Concomitant use of omaveloxolone with strong or moderate CYP3A4 inducers may significantly decrease the exposure of omaveloxolone, which may reduce the effectiveness of omaveloxolone. Use of omaveloxolone with strong or moderate CYP3A4 inducers should be avoided. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.

  The recommended dosage for concomitant use of omaveloxolone with strong or moderate CYP3A4 inducers is described in section 4.2 of the SmPC. 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).

- **Elevation of BNP:** Slight increases in laboratory evaluations of BNP were observed in patients treated with omaveloxolone in the Placebo-Controlled Analysis Set A. Two patients (3.8%) had BNP values that exceeded 200 pg/mL. Overall, mean BNP values remained below the ULN (< 100 pg/mL). The increases in BNP were not associated with any concurrent increases in blood pressure or associated events of fluid overload or cardiac failure. There were no discontinuations due to BNP elevation. SmPC section 4.4 provides guidance on monitoring BNP and signs and symptoms of CHF associated with fluid overload. PIL section 2 advises patients to contact their doctor immediately if they have signs and symptoms of CHF, sudden weight gain, swelling of legs, ankles, or feet, and shortness of breath (see Part II: Module SVII). This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.

- **Lipid abnormalities:** In the Placebo-Controlled Analysis Set A, hypertriglyceridemia was reported in (3.9%) patients, very low-density lipoprotein increased was reported in (3.9%) patients, and hypercholesterolaemia was reported in (2.0%) patient. No serious adverse reactions or discontinuations occurred as a result of lipid abnormalities. In the placebo group, no adverse reactions of lipid abnormalities were reported. At Week 48 in the omaveloxolone treatment group, mean low-density lipoprotein (LDL) increased by approximately 25 mg/dL and mean high-density lipoprotein (HDL) decreased by approximately 5 mg/dL at Week 48. After withdrawal of omaveloxolone, mean low-density lipoprotein and high-density lipoprotein levels returned to baseline. Lipids parameters should be assessed prior to initiation of omaveloxolone therapy, monitored periodically during treatment, and managed according to standard clinical guidelines. This identified risk does not have

an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.

- **Weight decreased:** In the randomized, double-blind, placebo-controlled study, weight decrease was reported for (2.0%) patient treated with omaveloxolone, and no 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 (SD 3.585) kg in the omaveloxolone group and the mean weight increase relative to baseline was 1.17 (SD 4.108) in the placebo group after 48 weeks of treatment. Among all patients with baseline body mass index (BMI) < 25 kg/m^2 across both treatment groups (omaveloxolone, n = 37; placebo, n = 37), weight loss of at least 5% from baseline was observed in32.4% of omaveloxolone-treated patients versus (2.7% of placebo-treated patients.

  Patients are advised to monitor their weight regularly and tell their doctor if they have weight loss. Clinicians are advised to further evaluate the patient if unexplained or clinically significant body weight decreases occurs. Omaveloxolone contains sodium. This medicinal product contains less than 1 mmol (23 mg) per dose, that is to say essentially 'sodium free'. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk.

- **Use in 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 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. In subjects with mild hepatic impairment (Child-Pugh Class A) there was no change in AUC and only a 29% increase in C_{max}. This identified risk does not have an impact on the risk-benefit balance of the product or implications for public health, and thus is not considered an important identified risk. The recommended dosage for patients with hepatic impairment is described in section 4.2 of SmPC. 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).

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The rationale for considering the remaining risks relevant for inclusion in the current list of safety concerns (at the time of initial MAA) is presented in Table 13.

Table 13: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk category	Risk-benefit impact
Important potential risk: DILI A higher incidence of ALT and AST increases were observed in omaveloxolone-treated patients (ALT: 19 [37.3%]; AST: 11 [21.6%]) compared to placebo-treated patients (ALT: 1 [1.9%]; AST: 1 [1.9%]). No serious adverse reactions of ALT/AST elevations were reported. Increases in ALT and AST led to treatment discontinuation in 1 patient (2.0%). A majority of patients had elevations that remained below 3 × ULN, with maximal values occurring within the first 12 weeks of treatment. Initial increases were followed by a trend toward normalization.	The elevations in ALT, AST, and GGT observed in omaveloxolone-treated patients are considered to be associated with activation of Nrf2, resulting in increases in glutathione biosynthesis and mitochondrial energy metabolism [Lewis 2021; Zhang 2006]. Nrf2 is an important regulator of glutathione production and mitochondrial energy metabolism [Harvey 2009; Holmström 2016], and ALT, AST, and GGT have been shown to contribute to these processes at the biochemical level [McGill 2016; Pompella 2007]. Clinical evidence of DILI, namely elevation of ALT/AST ≥ 3 × ULN combined with the elevation of TBL ≥ 2 × ULN, was not observed with omaveloxolone treatment. No cases meeting Hy's law criteria have been reported with omaveloxolone treatment. Given that the omaveloxolone-exposed number of patients is relatively limited, DILI is an important potential risk.

Risk category	Risk-benefit impact
Important potential risk: CHF Congestive heart failure has not been reported in patients with FA treated with omaveloxolone in the primary placebo-controlled study. In a randomized study with a structural analog of omaveloxolone with a similar mechanism of action, in patients with type 2 diabetes associated with Stage 4 chronic kidney disease (CKD), adjudicated heart failure events were reported in 96/1088 patients (8.8%) randomized to the structural analog of omaveloxolone, vs 55/1097 patients (5.0%) randomized to placebo. The excess in heart failure events occurred within the first 4 weeks after beginning treatment and were often preceded by evidence of fluid overload. Several risk factors (history of heart failure and elevated baseline BNP levels [> 200 pg/mL]) and risk minimization measures (including careful monitoring of weight and BNP levels) were identified and implemented in subsequent clinical studies, including FA studies. Patients with BNP levels > 200 pg/mL prior to study entry or a history of clinically significant left-sided heart disease were excluded from the studies of patients with omaveloxolone. This phenomenon occurred specifically in the setting of type 2 diabetes mellitus and Stage 4 CKD.	Based on review of Study 1402 Part 2, clinical data for TEAEs, as well as review of relevant imaging and laboratory studies, a risk for CHF was not identified. The small increases in BNP that were observed for omaveloxolone-treated patients were not associated with fluid overload or heart failure and may be considered indicative of improvements in metabolism, rather than fluid retention. Omaveloxolone treatment did not result in an increase in blood pressure. There were no cardiac adverse effects based on review of clinical ECG and echocardiographic data. As characterized in the literature, patients with FA have minimal risk of advanced kidney disease and have a distinct cardiomyopathy characterized by reduced cardiac contractility in the end stages of disease. Although Stage 4 CKD is not a typical comorbidity of FA, this type of patient may exist. The benefit of omaveloxolone as an effective treatment for FA, a condition with increased mortality outweighs the important potential risk of CHF, which can be managed in clinical practice through monitoring and management.
Missing information: Use in pregnancy Animal data have shown reproductive toxicity (Part II: Module SII). It is unknown if omaveloxolone crosses the placental barrier. Although not anticipated from animal data, at this time there is no information on human primary and secondary pregnancy outcomes after exposure in utero. Women and men of childbearing age are well within the target age range of treatment with omaveloxolone, and thus, pregnancy exposures in the post-marketing setting, both in utero and via partner, can be expected.	No data in humans have been obtained relating to primary and secondary pregnancy outcomes or lactation, and patients are generally diagnosed with FA during their reproductive years. The benefit of omaveloxolone as an effective treatment for FA, a condition with increased mortality, outweighs the missing information on pregnancy. This missing information can be managed in clinical practice by advising patients that omaveloxolone should not be used during pregnancy and in women of childbearing potential not using contraception.

Risk category	Risk-benefit impact
Missing information: Long-term safety Omaveloxolone is expected to possibly be a life-long treatment for chronic disease. The primary FA pivotal study was 48 weeks in length, with the possibility for patients to have entered into a long-term safety study until omaveloxolone is commercialized. Although no long-term safety concerns are anticipated, the long-term safety of omaveloxolone use in patients with FA has yet to be fully characterized.	The benefit of omaveloxolone as an effective treatment for FA, a condition with increased mortality, outweighs the missing information on the long-term use of omaveloxolone in this population.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.2.1 Newly identified safety concerns

Malignancy is a new important potential risk. Malignancy was assessed as an important potential risk given the nonclinical study RTA-P-21070 findings, the uncertainty of a possible mechanism for the observed malignancies, the serious and significant consequences that could result from malignancy and that the omaveloxolone exposed number of patients is relatively limited. There is currently insufficient clinical evidence to conclude a causal relationship between malignancy and omaveloxolone.

SVII.2.2 Reclassification of existing safety concerns

Not applicable – no safety concerns have been reclassified or removed in the current EU RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

1. Important potential risk: DILI

Relevant MedDRA terms: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ narrow)

Potential mechanisms:

Nonclinical data indicates that omaveloxolone regulates the transcription of ALT and AST in multiple organs and suggests that the transient increases in transaminase levels observed in humans are related to the pharmacology of the drug and not due to liver toxicity.

Evidence source(s) and strength of evidence:

A higher incidence of ALT and AST increases were observed in omaveloxolone-treated patients (ALT: 19 [37.3%]; AST: 11 [21.6%]) compared to placebo-treated patients (ALT:1 [1.9%]; AST: 1 [1.9%]). No serious adverse reactions of ALT/AST elevations were reported.

Increases in ALT and AST led to treatment discontinuation in 1 patient (2.0%). A majority of patients had elevations that remained below 3 × ULN, with maximal values occurring within the first 12 weeks of treatment. Initial increases were followed by a trend toward normalization.

Characterization of the risk:

In patients with FA, elevations in liver enzymes were the most common TEAEs associated with omaveloxolone. Majority of events were mild, transient, and reversible, with maximal values occurring within the first 12 weeks of treatment. Initial increases were followed by a trend toward normalization.

Risk factors and risk groups:

Patients with pre-existing hepatobiliary disease, acute viral infections affecting the liver, and patients taking concomitant medications known to be associated with aminotransferase elevations or liver injury.

Preventability:

The SmPC advises healthcare professionals that ALT/AST and TBL be assessed prior to treatment initiation, monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated during treatment with omaveloxolone. If ALT or AST increases to > 5 × ULN or if ALT or AST increases to > 3 × ULN and bilirubin increases to > 2 × ULN, treatment with omaveloxolone should be immediately discontinued and liver function tests should be repeated. Testing should be continued as appropriate. When laboratory abnormalities stabilize or resolve, omaveloxolone may be reinitiated with an appropriate frequency of monitoring liver function.

Impact on the risk-benefit balance of the product:

The elevations in ALT, AST, and GGT observed in omaveloxolone-treated patients are considered to be associated with activation of Nrf2, resulting in increases in glutathione biosynthesis and mitochondrial energy metabolism [Lewis 2021; Zhang 2006]. Nrf2 is an important regulator of glutathione production and mitochondrial energy metabolism [Harvey 2009; Holmström 2016], and ALT, AST, and GGT have been shown to contribute to these processes at the biochemical level [McGill 2016; Pompella 2007].

Direct liver injury has not been observed in any clinical study of omaveloxolone. In addition, no Hy's law cases have been reported with omaveloxolone treatment. Increased ALT and increased AST are very common TEAEs associated with omaveloxolone-treated patients. With appropriate monitoring of liver function within the initial 3 months of therapy and periodically thereafter, the benefit of omaveloxolone as an effective treatment for FA, a condition with increased mortality outweighs the important potential risk of DILI.

Public health impact:

FA is a rare genetic disease estimated to affect 5000 people in the US and 22,000 patients globally (Part II: Module SI), and therefore the number of patients expected to be treated with omaveloxolone in clinical practice will be limited.

Health professionals and patients should be generally informed of the risk for aminotransferase elevations and the appropriate monitoring of liver function while under

treatment with omaveloxolone. The potential risk of DILI can be adequately managed in clinical practice and thus the public health impact of this potential risk is low.

2. Important potential risk: CHF

Relevant MedDRA terms: Cardiac failure (SMQ broad)

Potential mechanisms:

Available data from Study 402-C-0903 and other studies suggest that treatment with a structural analog of omaveloxolone with similar mechanism of action, can differentially affect fluid handling according to the clinical condition of patients and likely promote fluid retention in patients with Stage 4 renal dysfunction and other recognized risk factors associated with heart failure at baseline.

Evidence source(s) and strength of evidence:

Data from Study 402-C-0903, which was conducted to assess the efficacy of structural analogue of omaveloxolone relative to placebo in delaying progression to end stage kidney disease (ESKD) and cardiovascular deaths in patients with Stage 4 CKD and type 2 Diabetes receiving standard of care, indicated an increase in adjudicated heart failure events in patients receiving a structural analogue of omaveloxolone compared to placebo. This phenomenon occurred specifically in the setting of type 2 diabetes mellitus and Stage 4 CKD.

Characterization of the risk:

Congestive heart failure has not been reported in patients with FA treated with omaveloxolone. In a randomized study in patients with type 2 diabetes associated with Stage 4 CKD, adjudicated heart failure events were reported in 96/1088 patients (8.8%) randomized to a structural analog of omaveloxolone with a similar mechanism of action, vs 55/1097 patients (5.0%) randomized to placebo. The excess in heart failure events occurred within the first 4 weeks after beginning treatment and were often preceded by evidence of sodium retention and fluid overload. Several risk factors (history of heart failure and elevated baseline BNP levels [> 200 pg/mL]) and risk minimization measures (including careful monitoring of weight and BNP levels) were identified and implemented in subsequent clinical studies, including FA studies. Patients with BNP levels > 200 pg/mL prior to study entry or a history of clinically significant left-sided heart disease were excluded from the studies of patients with omaveloxolone.

Risk factors and risk groups:

Patients with type 2 diabetes mellitus and Stage 4 CKD with high baseline BNP levels and history of symptomatic CHF are at a potential risk for the development of CHF with omaveloxolone use.

Preventability:

The SmPC advises healthcare professionals to monitor BNP prior to and periodically during treatment. Patients should be informed about the signs and symptoms of CHF 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, prescribers should be advised to monitor BNP (or NT-proBNP) and manage according to standard clinical guidance. Omaveloxolone treatment should be interrupted during fluid

overload management. If fluid overload cannot be appropriately managed, treatment with omaveloxolone should be discontinued.

Impact on the risk-benefit balance of the product:

With appropriate mitigation efforts in the primary placebo-controlled FA study, no SAEs related to fluid overload or CHF have occurred. 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 CHF. The benefit of omaveloxolone as an effective treatment for FA, a condition with increased mortality, outweighs the important potential risk of CHF that can be managed according to standard clinical guidance.

Public health impact:

FA is a rare genetic disease estimated to affect approximately 22,000 patients globally (Part II: Module SI), and therefore the number of patients expected to be treated with omaveloxolone in clinical practice will be limited. In addition, CHF can be generally well managed with standard clinical guidance and the public health impact of this potential risk is low.

3. Important potential risk: Malignancy

Relevant MedDRA terms: MedDRA SMQs Malignant or unspecified tumours (SMQ narrow).

Potential mechanisms

There is uncertainty of a possible mechanism for the observed malignancies. Literature data are sparse and did not indicate an association between omaveloxolone and malignancy. There are no epidemiology data on omaveloxolone and malignancy.

Evidence source(s) and strength of evidence

In the nonclinical study RTA-P-21070, a 104-Week Once Daily Oral Gavage Toxicity and Toxicokinetic Study with RTA 408 in Rats, neoplastic changes were observed in the liver (bile duct), mammary, testis, and the rectum (rectal-anal transition zone). A subsequent analysis of all available data including literature was performed. Based on the strength of evidence from the available non-clinical carcinogenicity data, there is evidence to suspect the possibility of a causal relationship with the medicinal product, but there is currently insufficient clinical evidence to conclude that this association is causal. Malignancy is considered an Important Potential Risk.

Characterization of the risk

As of 22 Apr 2022 (ISS DLP), there were no malignancy TEAEs in FA patients exposed to omaveloxolone in Study 408-C-1402 (MOXIe) Part 1, Part 2, or the open label extension. Until 28 May 2025, 10 events of malignancy, all in differing locations (abdominal, lung, prostate, renal, skin, tongue, neoplasm unspecified) were reported from postmarketing sources of which 8 events were considered serious.

The impact of developing a malignancy on quality of life can vary considerably between patients and is dependent on malignancy location, stage, and other co-morbidities affecting a patient's ability to tolerate treatment and is therefore difficult to assess outside of an individual case-by-case basis.

Risk factors and risk groups

Comorbidities unrelated to FA, including cancer, are mostly diagnosed in participants with long disease duration, and the incidences of these conditions are comparable to that observed in the age-matched general population.

Preventability

The SmPC section 5.3 (Preclinical safety data) includes results from the 2-year carcinogenicity study in the rat. The clinical relevance of these findings in humans is currently unknown.

Impact on the risk-benefit balance of the product

Based on the available non-clinical carcinogenicity data, there is evidence to suspect the possibility of a causal relationship with omaveloxolone and malignancy, but where there is currently insufficient clinical evidence to conclude that this association is causal. The benefit/risk profile for omaveloxolone remains positive for the treatment of FA.

Public health impact

FA is a rare genetic disease estimated to affect 5000 people in the US and 22,000 patients globally, therefore, the number of patients expected to be treated with omaveloxolone in clinical practice will be limited.

Health professionals and patients should be generally informed of the potential risk for malignancy and omaveloxolone.

SVII.3.2 Presentation of the missing information

1. **Missing information: Use in pregnancy**

   Relevant MedDRA terms: Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)

   Evidence source:

   Animal studies have shown reproductive toxicity (Part II: Module SII). However, there are no human data to assess the effects of omaveloxolone on pregnancy outcomes.

   Population in need of further characterization:

   Patients who become pregnant during the use or via partner use of omaveloxolone. This includes women of childbearing age and partners of such women who use omaveloxolone. This missing information will be monitored via routine pharmacovigilance.

2. **Missing information: Long-term safety**

   Evidence source:

   There are no long-term safety effects expected to be associated with the use of omaveloxolone in patients with FA. Given the rare nature of the disease, an adequately powered long-term safety outcome study may be difficult to accurately detect a safety signal. The pivotal FA study was 48 weeks in duration, with some patients entering a long-term safety extension study. This extension study will end for patients with FA upon commercial availability of omaveloxolone.

Population in need of further characterization:

Patients on long-term chronic omaveloxolone therapy beyond the length of the clinical experience. Missing information on long-term safety will be monitored by both routine and additional pharmacovigilance through a long-term safety registry (Part III.2).

PART II: MODULE SVIII - SUMMARY OF SAFETY CONCERNS

The omaveloxolone safety specification includes the following important identified risks, important potential risks and areas of missing information Table 14.

Table 14: Summary of safety concerns

Important identified risks	None
Important potential risks	Drug-induced liver injury Congestive heart failure Malignancy
Missing information	Use in pregnancy Long-term safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III: 1 Routine pharmacovigilance activities

The MAH employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise all of the safety concerns discussed in this EU RMP. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

In addition to adverse reactions reporting and signal detection activities, the following routine pharmacovigilance activities are also employed to provide further characterisation data for specific safety concerns.

Specific adverse reaction follow-up questionnaires:

- Important Potential Risk of Drug-induced liver injury: Drug-Induced Liver Injury

Important Potential Risk of Congestive Heart Failure: Congestive Heart Failure**Other forms of routine pharmacovigilance activities for safety concerns:**

- None

III. 2 Additional pharmacovigilance activities

Study Title: An Observational, Multinational, Post-Marketing Registry of Omaveloxolone-Treated Patients with Friedreich's Ataxia (296FA401) (408-C-2301).

Study short name: Post-Marketing Registry of Omaveloxolone for FA.

Rationale and study objectives: The goal of this study is to further characterize the long-term safety profile of omaveloxolone under real-world conditions, and to characterize FA clinical management and outcomes in omaveloxolone-treated patients. This postmarketing study will collect data from patients with FA enrolled in the Friedreich's Ataxia Global Clinical Consortium (FA-GCC) UNIFIED Natural History Study (UNIFAI) who are omaveloxolone naive and are prescribed omaveloxolone and treated per its approved label (omaveloxolone-naive cohort) or who initiated omaveloxolone treatment per its approved label following their enrollment in UNIFAI but less than 12 months prior to enrollment in this study (non-naive cohort). The primary objectives of this study are to assess the long-term safety of omaveloxolone as prescribed to patients with FA in the real-world setting and to document and characterize all CHF and DILI adverse events. The secondary objective of this study is to capture reasons and timing of treatment interruptions, treatment discontinuations, and drug overdose.

Study design: The objectives will be addressed in an observational, multi-country cohort study of patients with FA who are treated with omaveloxolone per its approved label.

The FA-Global Clinical Consortium (FA-GCC) UNIFIED Natural History Study (UNIFAI study) platform will be used to contact investigators and enroll patients.

- This study begins after product availability in a country that has approval for omaveloxolone, and when the first participating site begins enrollment, following the relevant ethics committee (EC) or institutional review board (IRB) approval of the protocol.
- End of study for completed patients is defined as completion of the 60-month visit; end of study for patients who discontinue treatment or discontinue from the study prior to the 60-month visit is defined as completion of the 60-day follow-up visit, if applicable.
- Routine visits are expected to be scheduled according to the omaveloxolone prescribing label.
- The schedule of assessments is based on anticipated visits as per the prescribing label and the UNIFAI study. The goal is to collect as much information as possible without imposing any additional burden on the patients and families.

Study population: Patients who initiate treatment with omaveloxolone per its approved label (omaveloxolone-naive cohort) or who have initiated omaveloxolone treatment per its approved label less than 12 months prior to enrollment in this study (non-naive cohort) will be included in the study. Due to the rarity of FA and the already established infrastructure of the UNIFAI study, patients for this study will be identified and enrolled via the sites of the UNIFAI study platform.

Milestones:

- Protocol submission: Q3 2023
- Start of data collection: Q4 2024
- Annual progress reports starting: Q1 2026
- End of data collection: Q1 2031
- Final study report: Q3 2031

III. 3 Summary table of additional pharmacovigilance activities

A summary of the studies included in the pharmacovigilance plan are summarised in Table 15.

Table 15: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None	-	-	-	-
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	-	-	-	-

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia **Status:** Ongoing	Primary objectives: To assess the long-term safety of omaveloxolone as prescribed to patients with FA in the real-world setting and to document and characterize all CHF and DILI adverse events. Secondary objective: To capture reasons and timing of treatment interruptions, treatment discontinuations, and drug overdose.	Long-term safety of omaveloxolone Drug-induced liver injury Congestive heart failure	Protocol submission Start of data collection Annual progress reports End of data collection: Final study report:	Q3 2023 Q4 2024 Annually starting Q1 2026 Q1 2031 Q3 2031
New Study Planned **Status:** Planned	To characterise the Important Potential Risk of malignancy in omaveloxolone-exposed patients with FA.	Malignancy	Feasibility assessment	Estimated Q1 2027

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V: 1 Routine risk minimisation measures

A description of the routine risk minimisation measures per safety concern are discussed in Table 16.

Table 16: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Potential Risks	
Drug-induced liver injury	**Routine risk communication:** SmPC sections 4.4. PIL sections 2 and 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4: 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. PIL section 2: If you have problems with your liver, your doctor may decide to change the dose or not start treatment with omaveloxolone. Your doctor will decide on whether to discontinue omaveloxolone if liver problems develop. PIL section 4: Based on your blood tests, your doctor may tell you that you have high liver enzymes. Your doctor will decide on treatment and whether omaveloxolone should be continued. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription.
Congestive heart failure	**Routine risk communication:** SmPC section 4.4. PIL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4: 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 one day or ≥ 2.3 kg in one 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 omaveloxolone should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with omaveloxolone should be discontinued. Per clinical judgment, more frequent monitoring of patients with a recent hospitalization for fluid

Safety concern	Routine risk minimisation activities
	overload due to underlying cardiomyopathy, diabetic stage IV CKD, or other etiologies is strongly recommended. PIL section 2: Your doctor will also test for BNP (B-type natriuretic protein, a blood test for heart problems) before you start taking omaveloxolone. Contact your doctor immediately if you have sudden weight gain, swelling of legs, ankles, or feet, or shortness of breath, which may be signs or symptoms of heart problems while taking omaveloxolone. Your doctor will decide on treatment and whether omaveloxolone should be continued. PIL section 4: Based on your blood tests, your doctor may tell you that you have increased BNP (a marker for heart problems). Your doctor will decide on treatment and whether omaveloxolone should be continued. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription.
Malignancy	**Routine risk communication:** • Include information on malignancy from the 2-year carcinogenicity study in rat in the SmPC section 5.3 (Preclinical safety data) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the product labeling:** None
Missing Information	
Use in pregnancy	**Routine risk communication:** SmPC section 4.6. PIL section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.6: Omaveloxolone 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 omaveloxolone, during treatment, and for 28 days following discontinuation of treatment. Omaveloxolone 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 omaveloxolone. Omaveloxolone should not be used while breast-feeding. PIL section 2: You should not take omaveloxolone if you are pregnant, think you may be pregnant, or are planning to have a baby. Tell your doctor immediately if you become pregnant while you are being treated with omaveloxolone

Safety concern	Routine risk minimisation activities
	Using omaveloxolone can reduce the effectiveness of hormonal birth control. You should use a different method of birth control, such as a non-hormonal IUD (intrauterine device) or barrier contraceptives such as condoms. A reliable method of birth control should be used during omaveloxolone treatment and for 28 days after stopping treatment with omaveloxolone. Talk to your doctor about the most suitable birth control for you. Do not breast-feed your baby while you are being treated with omaveloxolone. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription.
Long-term safety	**Routine risk communication:** NA **Routine risk minimization activities recommending specific clinical measures to address the risk:** NA **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription.

V. 2. Additional risk minimisation measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures.

Table 17: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Drug-induced liver injury	***Routine risk minimisation measures:*** SmPC section 4.4. PIL sections 2 and 4. SmPC section 4.4: 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	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*** Specific detailed adverse reaction follow-up questionnaire. ***Additional pharmacovigilance activities:*** An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia. Final study report: Q3 2031.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	> 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. PIL section 2: If you have problems with your liver, your doctor may decide to change the dose or not start treatment with omaveloxolone. Your doctor will decide on whether to discontinue omaveloxolone if liver problems develop. PIL section 4: Based on your blood tests, your doctor may tell you that you have high liver enzymes. Your doctor will decide on treatment and whether omaveloxolone should be continued. Restricted medical prescription. ***Additional risk minimisation measures:*** None.	
Congestive heart failure	***Routine risk minimisation measures:*** SmPC section 4.4. PIL sections 2 and 4 SmPC section 4.4: 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 one day or ≥ 2.3 kg in one 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 omaveloxolone should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with omaveloxolone 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 etiologies is strongly recommended.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*** Specific detailed adverse reaction follow-up questionnaire. ***Additional pharmacovigilance activities:*** An observational, multinational, postmarketing registry of omaveloxolone-treated patients with Friedreich's ataxia. Final study report: Q3 2031.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PIL section 2: Your doctor will also test for BNP (B-type natriuretic peptide, a blood test for heart problems) before you start taking omaveloxolone. Contact your doctor immediately if you have sudden weight gain, swelling of legs, ankles, or feet, or shortness of breath, which may be signs or symptoms of heart problems while taking omaveloxolone. Your doctor will decide on treatment and whether omaveloxolone should be continued. PIL section 4: Based on your blood tests, your doctor may tell you that you have increased BNP (a marker for heart problems). Your doctor will decide on treatment and whether omaveloxolone should be continued. Restricted medical prescription. ***Additional risk minimisation measures:*** None.	
Malignancy	***Routine risk minimization measures:*** • SmPC section 5.3 (Preclinical safety data) ***Additional risk minimisation measures:*** None.	***Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection*** None ***Additional Pharmacovigilance Activities***: New Study planned to characterise the Important Potential Risk of malignancy in omaveloxolone-exposed patients with FA. Feasibility assessment: Q1 2027.
Missing information		
Use in pregnancy	***Routine risk minimisation measures:*** SmPC section 4.6. PIL section 2 SmPC section 4.6: Omaveloxolone should not be used during pregnancy or in women of childbearing potential not using contraception. Patients	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	should use effective contraception prior to starting treatment with omaveloxolone, during treatment, and for 28 days following discontinuation of treatment. Omaveloxolone 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 omaveloxolone. Omaveloxolone should not be used while breast-feeding. PIL section 2: You should not take omaveloxolone if you are pregnant, think you may be pregnant, or are planning to have a baby. Tell your doctor immediately if you become pregnant while you are being treated with omaveloxolone. Using omaveloxolone can reduce the effectiveness of hormonal birth control. You should use a different method of birth control, such as a non-hormonal IUD (intrauterine device) or barrier contraceptives such as condoms. A reliable method of birth control should be used during omaveloxolone treatment and for 28 days after stopping treatment with omaveloxolone. Talk to your doctor about the most suitable birth control for you. Do not breast-feed your baby while you are being treated with omaveloxolone. Restricted medical prescription. ***Additional risk minimisation measures:*** None.	***Additional pharmacovigilance activities:*** None.
Long-term safety	***Routine risk minimisation measures:***	***Routine pharmacovigilance activities beyond adverse***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	NA ***<u>Additional risk minimisation measures:</u>*** None.	***<u>reactions reporting and signal detection:</u>*** None. ***<u>Additional pharmacovigilance activities:</u>*** An observational, multinational, postmarketing registry of omaveloxolone-treated patients with Friedreich's ataxia. Final study report: Q3 2031.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR SKYCLARYS (OMAVELOXOLONE)

This is a summary of the RMP for omaveloxolone. The RMP details important risks of omaveloxolone, how these risks can be minimized, and how more information will be obtained about omaveloxolone's risks and uncertainties (missing information).

Omaveloxolone's SmPC and its package leaflet give essential information to healthcare professionals and patients on how omaveloxolone should be used.

This summary of the RMP for omaveloxolone should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of omaveloxolone's RMP.

I. The medicine and what it is used for

Omaveloxolone is authorized for the treatment of FA in adults and adolescents aged 16 years and older It contains omaveloxolone as the active substance and it is given orally.

Further information about the evaluation of omaveloxolone's benefits can be found in omaveloxolone's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of omaveloxolone, together with measures to minimize such risks and the proposed studies for learning more about omaveloxolone risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about undesirable effects is collected continuously and regularly analyzed, including Periodic safety update report (PSUR) assessment, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of omaveloxolone is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of omaveloxolone are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of omaveloxolone. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term safety of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Drug-induced liver injury Congestive heart failure Malignancy
Missing information	Use in pregnancy Long-term safety

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Important Potential Risks	
Drug-induced liver injury	
Evidence for linking the risk to the medicine	Among patients treated with omaveloxolone 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 GGT increased in 5.9% of patients. One patient (2%) was discontinued for aminotransferase elevation > 8 × the ULN, as prespecified in the study protocol. The incidence of elevations of ALT or AST above 5x and 3x the ULN was 16% and 31%, respectively, in patients treated with omaveloxolone. Laboratory evaluations identified 69% of patients with aminotransferase elevations that were less than 3 × the ULN. These were generally transient and reversible, with maximal values occurring within the first 12 weeks of treatment. Mean values generally decreased towards baseline levels with continued treatment or after interruption in therapy.
Risk factors and risk groups	Patients with pre-existing hepatobiliary disease, acute viral infections affecting the liver, and patients taking concomitant medications known to be associated with transaminase elevations are at risk for development of transaminase elevation.

Important Potential Risks	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC section 4.4. PIL section 2 and 4. SmPC section 4.4: 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. PIL section 2: If you have problems with your liver, your doctor may decide to change the dose or not start treatment with omaveloxolone Your doctor will decide on whether to discontinue omaveloxolone s if liver problems develop. PIL section 4: Based on your blood tests, your doctor may tell you that you have high liver enzymes. Your doctor will decide on treatment and whether omaveloxolone should be continued. Restricted medical prescription. ***Additional risk minimisation measures:*** None.
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia.
Congestive heart failure	
Evidence for linking the risk to the medicine	Congestive heart failure has not been reported in patients with FA treated with omaveloxolone. In a randomized study in patients with type 2 diabetes associated with Stage 4 CKD, adjudicated heart failure events were reported in 96/1088 patients (8.8%) randomized to a structural analog of omaveloxolone with a similar mechanism of action, vs 55/1097 patients (5.0%) randomized to placebo. The excess in heart failure events occurred within the first 4 weeks after beginning treatment and were often preceded by evidence of sodium retention and fluid overload. Elevated baseline BNP levels (> 200 pg/mL) and pre-existing heart failure were identified as the risk factors contributing to the excess in observed heart failure events. This phenomenon occurred specifically in the setting of type 2 diabetes mellitus and Stage 4 CKD with a structural analog of omaveloxolone.
Risk factors and risk groups	Patients with type 2 diabetes mellitus and Stage 4 CKD with high baseline BNP levels and history of symptomatic congestive heart failure are at a potential risk for the development of congestive heart failure with omaveloxolone use.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC section 4.4. PIL sections 2 and 4

Important Potential Risks	
	SmPC section 4.4: 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 one day or ≥ 2.3 kg in one 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 omaveloxolone should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with omaveloxolone 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 etiologies is strongly recommended. PIL section 2: Your doctor will also test for BNP (B-type natriuretic peptide, a blood test for heart problems) before you start taking omaveloxolone. Contact your doctor immediately if you have sudden weight gain, swelling of legs, ankles, or feet, or shortness of breath, which may be signs or symptoms of heart problems while taking omaveloxolone. Your doctor will decide on treatment and whether omaveloxolone should be continued. PIL section 4: Based on your blood tests, your doctor may tell you that you have increased BNP (a marker for heart problems). Your doctor will decide on treatment and whether omaveloxolone should be continued. Restricted medical prescription. ***Additional risk minimisation measures:*** None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia.
Malignancy	
Evidence for linking the risk to the medicine	In the nonclinical study RTA-P-21070, a 104-Week Once Daily Oral Gavage Toxicity and Toxicokinetic Study with RTA 408 in Rats, neoplastic changes were observed in the liver (bile duct), mammary, testis, and the rectum (rectal-anal transition zone). A subsequent analysis of all available data including literature was performed. Based on the strength of evidence from the available non-clinical carcinogenicity data, there is evidence to suspect the possibility of a causal relationship with the medicinal product, but there is currently insufficient clinical evidence to conclude that this association is causal. Malignancy is considered an Important Potential Risk.
Risk factors and risk groups	Comorbidities unrelated to FA, including cancer, are mostly diagnosed in participants with long disease duration, and the incidences of these conditions are comparable to that observed in the age-matched general population.

Important Potential Risks	
Risk minimisation measures	***Routine risk minimization measures*** Include information on malignancy from the 2-year carcinogenicity study in rat in the SmPC section 5.3 (Preclinical safety data). ***Additional risk minimization measures:*** None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities*** New Study planned to characterise the Important Potential Risk of malignancy in omaveloxolone-exposed patients with FA. Feasibility assessment: Q1 2027.

Missing Information	
Use in pregnancy	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC section 4.6. PIL section 2 SmPC section 4.6: Omaveloxolone s 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 omaveloxolone, during treatment, and for 28 days following discontinuation of treatment. Omaveloxolone 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 omaveloxolone. Omaveloxolone should not be used while breast-feeding. PIL section 2: You should not take omaveloxolone if you are pregnant, think you may be pregnant, or are planning to have a baby. Tell your doctor immediately if you become pregnant while you are being treated with omaveloxolone. Using omaveloxolone can reduce the effectiveness of hormonal birth control. You should use a different method of birth control, such as a non-hormonal IUD (intrauterine device) or barrier contraceptives such as condoms. A reliable method of birth control should be used during omaveloxolone treatment and for 28 days after stopping treatment with omaveloxolone. Talk to your doctor about the most suitable birth control for you.

Missing Information	
	Do not breast-feed your baby while you are being treated with omaveloxolone. Restricted medical prescription. ***Additional risk minimisation measures:*** None.
Long-term safety	
Risk minimisation measures	***Routine risk minimisation measures:*** None. ***Additional risk minimisation measures:*** None.
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no current studies which are conditions of the marketing authorization or specific obligation of omaveloxolone.

II.C.2 Other studies in post-authorisation development plan

The MAH is proposing an observational, multinational, post-marketing registry of omaveloxolone-treated patients with FA for 5 years which will provide longitudinal safety data after commercial launch (Annex 3). The MAH will work in close collaboration with the Friedreich's Ataxia Research Alliance (FARA) to use the data collection infrastructure set up for the Clinical Outcome Measures in FA-Global Clinical Consortium (FA-GCC) natural history studies. The safety registry will evaluate the long-term safety of omaveloxolone in patients with FA in the real-world setting and to further characterize the safety concerns of the important potential risks of DILI and CHF. The study will also capture reasons and timing of omaveloxolone treatment interruptions, discontinuations, and drug overdose. The protocol will be established and submitted for review to the health authority for feedback prior to the initiation of the registry. The registry is proposed to include subjects on commercial omaveloxolone. This will provide long-term data. Proposed size of the registry is 300 total subjects prescribed omaveloxolone. The safety data will be communicated to the health authority on a yearly basis (Annex 3).

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Adverse event follow up forms will be distributed for potential events of Drug-Induced Liver Injury and Congestive Heart Failure (see Part III [*Pharmacovigilance Plan*] of the EU RMP for details).

The follow up forms for distribution are provided in this Annex below:

- Skyclarys Drug Induced Liver Injury Data Collection Tool
- Skyclarys Congestive Heart Failure Data Collection Tool

Skyclarys Drug Induced Liver Injury Data Collection Tool

Case number: _____

Diagnosis (incl. presumptive or differential)

Baseline AST: _____ (normal range): _____

Baseline ALT: _____ (normal range): _____

Baseline Bilirubin: _____ (normal range): _____

Baseline GGT: _____ (normal range): _____

Sex:

☐ Male

☐ Female

☐ Unknown:

☐ Age at onset: _____

Time to onset of Hepatic Dysfunction and /or elevation in liver function tests (ALT, AST, GGT, and/or Total bilirubin) from start of Skyclarys: _____

Time to onset of event from last dose of Skyclarys: _____

Clinical Symptoms	
Please specify start and stop date of symptom. ☐ Fatigue *Start/Stop Date*: _____ to _____ ☐ Decreased appetite *Start/Stop Date*: _____ to _____ ☐ Nausea *Start/Stop Date*: _____ to _____ ☐ Vomiting *Start/Stop Date*: _____ to _____ ☐ Jaundice *Start/Stop Date*: _____ to _____	☐ Abdominal pain *Start/Stop Date*: _____ to _____ ☐ Fever *Start/Stop Date*: _____ to _____ ☐ Rash *Start/Stop Date*: _____ to _____ ☐ Eosinophilia *Start/Stop Date*: _____ to _____ ☐ Other: _____ *Start/Stop Date*: _____ to _____ ☐ None
Lab tests Performed	
Please specify performed tests and provide lab results with the values of baseline and up to the patient's recovery. ☐ Complete Blood Count ☐ Liver enzymes/transaminases (AST, ALT, ALP, & GGT) ☐ Bilirubin (Direct & Indirect) ☐ INR ☐ Complete metabolic panel (CMP)	☐ Viral hepatitis (A, B, C, & D, E, other), cytomegalovirus (CMV), infectious mononucleosis titres ☐ Autoimmune panel e.g., anti-mitochondrial antibodies, antinuclear antibodies (ANA), anti-actin antibodies, anti-microsomal antibodies, LE cells, rheumatoid factor, other ☐ Ceruloplasmin, alpha-1-antitrypsin, transferrin, CPK, LDH, ☐ Other, specify _____
Lab Test Results	
Include normal ranges (repeat rows as needed) Lab results: _____ Date: _____ Findings & conclusions: Lab results: _____ Date: _____ Findings & conclusions: _____	

Diagnostic Procedures

Please specify performed exams and provide the findings and conclusions.

☐ Abdominal, liver, gall bladder, or pelvic ultrasound
☐ Specialist consultation (gastroenterologist/hepatologist)
☐ Liver biopsy
☐ Other, specify _____

Diagnostic procedure 1: _____ Date: _____
Findings & conclusions: _____

Diagnostic procedure 2: _____ Date: _____
Findings & conclusions: _____

For fatal event, was an autopsy performed: ☐ Yes ☐ No ☐ Unknown (If yes, please, include the autopsy report)

Risk Factors

Please specify if the patient has any of the following risk factors:

☐ Yes ☐ No ☐ Unk - The case meets Hy's law criteria (*Hy's Law = 3 X ULN LT and/or AST + coexisting > 2 ULN bilirubin (in absence of >2ULN ALP) with no alternative cause other than suspect drug).*

☐ Yes ☐ No ☐ Unk - History of alcohol or recreational drug use, please, specify amount, frequency, and duration: _____

☐ Yes ☐ No ☐ Unk - History of gall bladder or liver disease

☐ Yes ☐ No ☐ Unk - History of hepatic, biliary, pancreatic, or other abdominal malignancy

☐ Yes ☐ No ☐ Unk - History of biliary cirrhosis or other autoimmune disease

☐ Yes ☐ No ☐ Unk - History of congestive heart failure (CHF). If yes, the ejection fraction/New York Hospital Association I-IV (NYHA) class: _____

☐ Yes ☐ No ☐ Unk - Wilson's disease or alpha-1-antitrypsin deficiency

☐ Yes ☐ No ☐ Unk - History suggestive of ischemic hepatitis e.g., recent major surgery or major blood loss/hypoperfusion

☐ Yes ☐ No ☐ Unk - Exposure to toxic chemicals: ☐ known hepatotoxins e.g., CCL4 ☐ Other, specify and provide results of toxicology screen: _____

☐ Yes ☐ No ☐ Unk - Previous drug induced liver injury (DILI), please provide details with symptoms including: _____ due to the drug(s): _____

☐ Other risk factors, specify: _____

Concomitant Medications ☐ Yes ☐ No ☐ Unk: If yes, please list below (include start and stop dates):

Action taken with Skyclarys for the event being described:
☐ None
☐ Temporary discontinuation
stop date: _____
restart date:_____
☐ Permanent discontinuation
☐ Dose decreased
☐ Other: _____

Event Treatment

Please specify the therapeutic measures taken to treat the event:
Event being treated: _____
☐ Medications, specify: _____
☐ Treatment procedures, specify: _____
☐ Other measures, specify: _____

Patient outcome: ☐ Unknown ☐ Resolved/Recovered ☐ Ongoing ☐ Resolved with sequelae
Form Completed By: _____ **Company**: _____ **Date**: _____

Skyclarys Congestive Heart Failure Data Collection Tool

Case number: _____

Diagnosis (incl. presumptive or differential): _____

Baseline cardiac function (NYHA Class/ AHA Stage): _____

Baseline Ejection fraction: _____

History of Friedrichs Ataxia Cardiomyopathy/Congestive Heart Failure:

Baseline BNP/ NT-proBNP levels: _____

Time to onset of event from first dose of Skyclarys: _____

Time to onset of event from last dose of Skyclarys: _____

Patient Sex:

☐ Male

☐ Female

☐ Unknown

☐ Age at onset: _____

Clinical symptoms *(Please include start / stop date)*

☐ Fatigue

Start/Stop Date:_____ to _____

☐ Chest Pain or Pressure

Start/Stop Date:_____ to _____

☐ Abdominal Swelling

Start/Stop Date:_____ to _____

☐ Shortness of breath

Start/Stop Date:_____ to _____

☐ Rapid/Irregular Heart Rate

Start/Stop Date:_____ to _____

☐ Impaired Thinking

Start/Stop Date:_____ to _____

☐ Pain (Shoulders, Neck, Arms, Jaw): _____

☐ Orthopnea

Start/Stop Date:_____ to _____

☐ Persistent Cough/Wheezing

Start/Stop Date:_____ to _____

☐ Lack of appetite

Start/Stop Date:_____ to _____

☐ Rapid Weight Gain

Start/Stop Date:_____ to _____

☐ Dyspnea on exertion:

Start/Stop Date:_____ to _____

☐ Cough:

Start/Stop Date:_____ to _____

☐ Peripheral Edema (Legs, Ankles, Feet): _____

Start/Stop Date:_____ to _____

Start/Stop Date:_____ to _____ ☐ Dizziness or Fainting *Start/Stop Date*:_____ to _____	☐ Other: _____ *Start/Stop Date*:_____ to _____ ☐ None
Lab tests *(Please specify performed tests and provide lab results with the values of baseline and up to the patient's recovery.*	
☐ Complete Blood Count ☐ Cardiac troponin ☐ BNP, NT-proBNP ☐ Creatinine kinase (CK) ☐ CK-MB ☐ INR	☐ Myoglobin ☐ Electrolyte Panel ☐ Bilirubin ☐ Complete metabolic panel (CMP) ☐ Other, specify: _____
Lab Results *(Repeat rows as needed) (Include normal ranges)* Lab test: _____ Date: _____ Findings & conclusions: _____ Lab test: _____ Date: _____ Findings & conclusions: _____ Lab test: _____ Date: _____ Findings & conclusions: _____	

Exams & consultations

Please specify performed exams and provide the findings and conclusions.

☐ Echocardiogram	☐ Cardiac MRI
☐ Pulse Oximetry	☐ Coronary Angiogram
☐ Chest X-Ray	☐ Specialist consultation (Cardiologist)
☐ Cardiac CT scan	☐ Other, specify: _____

Diagnostic Procedure Results *(Repeat rows as needed)*

Diagnostic procedure 1: _____ Date: _____

Findings & conclusions: _____

Diagnostic procedure 2: _____ Date: _____

Findings & conclusions: _____

Diagnostic procedure 3: _____ Date: _____

Findings & conclusions: _____

Diagnostic procedure 4: _____ Date: _____

Findings & conclusions: _____

Diagnostic procedure 5: _____ Date: _____

Findings & conclusions: _____

Diagnostic procedure 6: _____ Date: _____

Findings & conclusions: _____

For fatal event, was autopsy performed: ☐ Yes ☐ No ☐ Unknown (If yes, please, include the autopsy report)

Risk factors

Please specify if the patient has any of the following risk factors:

☐ Yes ☐ No ☐ Unk - History of Heart Attack

☐ Yes ☐ No ☐ Unk - History of Coronary Artery Disease

☐ Yes ☐ No ☐ Unk - History of Hypertension

☐ Yes ☐ No ☐ Unk - History of Myocarditis

☐ Yes ☐ No ☐ Unk - History of Valvular Heart Disease

☐ Yes ☐ No ☐ Unk - History of Congenital Heart Disease

☐ Yes ☐ No ☐ Unk - History of Arrhythmias

☐ Yes ☐ No ☐ Unk - History of Diabetes

☐ Yes ☐ No ☐ Unk - History of Hyperthyroidism/Hypothyroidism

☐ Yes ☐ No ☐ Unk - History of Obesity

☐ Yes ☐ No ☐ Unk - History of HIV

☐ Yes ☐ No ☐ Unk - History of alcohol or recreational drug use, please, specify amount, frequency, and duration: _____

☐ Yes ☐ No ☐ Unk - History of tobacco use, please, specify amount, frequency, and duration:

☐ Yes ☐ No ☐ Unk - History of congestive heart failure (CHF). If yes, the ejection fraction: _____

New York Hospital Association (NYHA) Class I-IV: _____

American Heart Association (AHA) Stage A-D: _____

☐ Other risk factors, specify: _____

Concomitant Medications

☐ Yes ☐ No ☐ Unk: If yes, please list below (include start and stop dates):

_____

Action taken with Skyclarys for the event being described

☐ None	☐ Dose decreased
☐ Temporary discontinuation:	☐ Other: _____
stop date: _____	
restart date:_____	
☐ Permanent discontinuation	

Event Treatment *(Please specify the therapeutic measures taken to treat the event):*

Event being treated: _____

☐ Medications, specify: _____

☐ Treatment procedures, specify: _____

Other measures, specify: _____

Patient Outcome

☐ Unknown ☐ Resolved/Recovered ☐ Ongoing ☐ Resolved with sequelae.

If resolved, please provide the time to resolution: _____

Form Completed By: _____ Company: _____ Date: _____

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.