Risk Management Plan
for
Skyclarys 150 mg Capsules (Omaveloxolone)

MAH Name and Address
Reata Ireland Limited
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RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP	24 Mar 2022	Version number	1.0
Date of final sign off	12 Dec 2023		

Rationale for submitting an updated RMP: Not applicable
Summary of significant changes in this RMP: Not applicable
Other RMP versions under evaluation: Not applicable
Details of the currently approved RMP: Not applicable

1.8.2 Risk Management Plan

QPPV name

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{0-24}	area under the concentration vs time curve from 0 to 24 hours
BNP	B-type natriuretic peptide
CHF	congestive heart failure
C_{max}	maximum plasma concentration
CNS	central nervous system
CYP	cytochrome P450 (isoenzyme)
DILI	drug-induced liver injury
EPAR	European public assessment reports
ESKD	end-stage kidney disease
FA	Friedreich's ataxia
FDA	Food and Drug Administration
GD	gestation day
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
hERG	human ether-á-go-go-related gene
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISS	Integrated Summary of Safety
MHRD	maximum recommended human dose
NOAEL	no observed adverse effect level
Nrf2	nuclear factor erythroid 2-related factor 2
PK	pharmacokinetic(s)
RMP	risk management plan
SAE	serious adverse event
SmPC	summary of product characteristics
Study 1402	study 408-C-1402 (which consists of Part 1, Part 2, and Extension)
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US/USA	United States (of America)

PART I: PRODUCT OVERVIEW

Table Part I.1: Product Overview

Active substance (International Nonproprietary Name or common name)	omaveloxolone
Pharmacotherapeutic groups (ATC Code)	(Not yet assigned)
Marketing authorization applicant	Reata Ireland Limited
Medicinal products to which this Risk Management Plan (RMP) refers	01
Invented name in the European Economic Area (EEA)	Skyclarys
Marketing authorization 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	Skyclarys product information (section 1.3.1)
Indication in the EEA	**Current:** Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.
	Proposed: Not applicable

Dosage	**Current:** The recommended dose is 150 mg (3 hard capsules of 50 mg each) once daily. Skyclarys should be taken on an empty stomach at least 1 hour before eating. Skyclarys capsules should be swallowed whole and not crushed or chewed before swallowing. For patients who are unable to swallow whole capsules, Skyclarys capsules may be opened, and the entire contents sprinkled onto 2 tablespoons of applesauce. Patients should consume all the drug/food mixture immediately on an empty stomach at least 1 hour before 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 Skyclarys with strong or moderate cytochrome P450 - isotype 3A4 (CYP3A4) 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.
	Proposed: Not applicable
Pharmaceutical form and strengths	**Current:** Skyclarys capsules are supplied as opaque, hard capsules containing 50 mg of Skyclarys as follows: • Skyclarys 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.
	Proposed: Not applicable
Will the product be subject to additional monitoring in the European Union?	Yes

Part II: Module SI Epidemiology of the indication and target population

Indication

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

Incidence and Prevalence:

Friedreich's ataxia (FA) is a rare, genetic neuromuscular disorder. 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 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 (Rummey, 2022; Fearon, 2020). Notably, a comparative study found no phenotypic differences between late onset and very late onset FA (Lecocq, 2015). 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).

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 arrythmia. 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, 1998).

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 (Durr, 2002).

Main existing treatment options:

Other than Skyclarys, 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). Notably, prior clinical studies with exogenous antioxidants were unable to reduce the excess reactive oxygen species produced by the dysfunctional iron homeostasis and resulting mitochondrial damage (Di Prospero, 2007).

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.

Part II: Module SII Nonclinical 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 (ie, 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 (Proctor, 2007; Bertram, 2013). 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 (ie, 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.

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 (ie, 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 (ie, 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 rat is underway and will be completed by Q3-2025. The 2-year carcinogenicity study report will be submitted post-approval.

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

The key nonclinical safety findings and relevance to human usage are summarized below:

Key Nonclinical Safety Findings

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
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	Adequate safety margins above human exposure were established.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
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 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 and development toxicity (DART): 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 (AUC_{0-24} 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 (ie, thin body condition and red material in the pan) resulting in 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	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 6X that at the MHRD.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
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 (AUC_{0-24} of 0.314 hr*µg/mL on GD 19), and the developmental NOAEL was 10 mg/kg/day (AUC_{0-24} 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.	
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.

1.8.2 Risk Management Plan

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
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 (ie, 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, (ie, increases of TBL, GGT, ALT, and AST). Bile duct hyperplasia was only observed in monkeys at 30 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.	Hepatotoxicity is observed in both rats and monkeys. However, in rats, liver effects are observed at or below clinically relevant dose levels.
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 performed up to the maximum recommended concentrations (ie, 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.	Omaveloxolone is negative for genotoxic potential in 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 AUC_{0-24} value of 1.18 hr*µg/mL in patients with FA administered 150 mg omaveloxolone). Also, a 2-year carcinogenicity study in rats is currently underway. In agreement with the FDA, the final reports of these 2 studies will be submitted as post-approval deliverables.	Unknown

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
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 (ie, bacterial reverse mutation, chromosomal aberration, rat liver comet, and micronucleus). In the chronic GLP toxicity studies (ie, 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.
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. 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.	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 (ie, 4.00 nM). No specific risks were identified based on the in vivo safety pharmacology studies.

Nonclinical 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 (ie, 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 (ie, itraconazole, as well as a perpetrator of drug-drug interactions with sensitive substrates for CYP2C8 (ie, repaglinide), CYP3A4/5 (ie., midazolam), breast cancer resistance protein (BCRP) (ie., rosuvastatin), or P-gp (ie., 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.

Nonclinical 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 Part II: Module SII-1: 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
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 postnatal 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 Part II: Module SIII.1 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 Part II: Module SIII.1: 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	408-C-1303	0	11

1.8.2 Risk Management Plan

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
conducted in patients with oncologic indications	408-C-1401	0	41

Abbreviation: FA=Friedreich's ataxia; Study 1402=Reata 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. (Table Part II: Module SIII.1):

- 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 Part II: Module SIII.3) 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 Part II: Module SIII.3) includes data from all omaveloxolone-treated patients (no placebo-treated patients), regardless of dose, from all studies in patients with FA (ie, Study 1402 Part 1, Part 2, and Extension). All phases of treatment are included (ie, 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 Part II: Module SIII.2: 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 Part II: Module SIII.3: 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 Part II: Module SIII.4: 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 Part II: Module SIII.5) and geographical region and ethnic origin (Table Part II: Module SIII.6).

Table Part II: Module SIII.5: 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%)
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 Part II: Module SIII.6: 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

Reata 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, Reata 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 Program

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 (eg, 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 Part II: Module SIV.1: 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, 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.

1.8.2 Risk Management Plan

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for Exclusion	Is it Considered to Be Included as Missing Information?	Rationale
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 heart failure when levels exceed 200 pg/mL.	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 Skyclarys. (Part II: Module SVII)
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)	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 **Error! Reference source not found.**.

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for Exclusion	Is it Considered to Be Included as Missing Information?	Rationale
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 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 (eg, repaglinide, midazolam,	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.	No	Skyclarys SmPC section 4.2 provides recommended dose modifications with concomitant use of use of CYP3A4 inhibitors and inducers.

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for Exclusion	Is it Considered to Be Included as Missing Information?	Rationale
sildenafil) b. Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (eg, carbamazepine, phenytoin, ciprofloxacin, grapefruit juice) c. Substrates for p-glycoprotein transporter (eg, ambrisentan, digoxin)	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.		Skyclarys SmPC section 4.5 provides information on interactions for CYP3A4 inhibitors, inducers, and substrates, CYP2C8 substrates, and BCRP substrates. Skyclarys SmPC section 4.6 provides guidance on concomitant use of hormonal contraceptives with Skyclarys.
History of clinically significant liver disease (eg, 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	No	Safety of patients in this population will be monitored via routine pharmacovigilance.

1.8.2 Risk Management Plan

Population- and/or Study Medication-Specific Exclusion Criterion	Reason for Exclusion	Is it Considered to Be Included as Missing Information?	Rationale
	FA caused by a genetic deficiency of frataxin only, not caused by other human mitochondrial mutations.		
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.
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 Programs

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 Programs

Table Part II: Module SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

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:	
Patients with 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 ≥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.
Patients with 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.

1.8.2 Risk Management Plan

Type of Special Population	Exposure
Patients with 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 Skyclarys SmPC has appropriate warnings regarding fluid overload and congestive heart failure 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) (Module SVII.3.1).
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 studies	None
Population 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 genetics	None
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-Authorization Experience

Omaveloxolone was approved for commercial use in the United States of America on 28 February 2023. However, at the data lock for this RMP commercial product was not yet available. Thus, there is not any post-authorization experience with omaveloxolone.

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Not applicable

SV.1.2 Exposure

Not applicable

Part II: Module SVI Additional Requirements for the Safety Specification

SVI.1 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 (eg, 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) (ie., 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 B-type natriuretic peptide (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 (eg, 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 $AUC_{0-\infty}$ (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 Skyclarys 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 Skyclarys 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 Skyclarys to 50 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, coadministration with strong CYP3A4 inhibitors should be discontinued.
Moderate CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of Skyclarys to 100 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, further reduce the dosage of Skyclarys to 50 mg once daily.

- **Potential loss of efficacy with concomitant use with strong or moderate CYP3A4 inducers:** Concomitant use of Skyclarys with strong or moderate CYP3A4 inducers may significantly decrease the exposure of omaveloxolone, which may reduce the effectiveness of Skyclarys. 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 Skyclarys with strong or moderate CYP3A4 inducers is described in section 4.4 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 B-type natriuretic peptide (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 Skyclarys 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 Skyclarys, 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 (Skyclarys, n=37; placebo, n=37), weight loss of at least 5% from baseline was observed in32.4% of Skyclarys-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. Skyclarys 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

1. 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.

Risk-benefit impact:

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 (Zhang, 2006; Nrf2 Activator Pharmacology Summary Report, 2020; Lewis, 2021). 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 (Pompella, 2007; McGill, 2016).

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.

2. 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.

Risk-benefit impact:

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.

3. 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.

Risk-benefit impact:

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 Skyclarys should not be used during pregnancy and in women of childbearing potential not using contraception.

4. 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.

Risk-benefit impact:

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

Not applicable as this is the first RMP for omaveloxolone.

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

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 Skyclarys. 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 Skyclarys 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.

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 (Zhang, 2006; Nrf2 Activator Pharmacology Summary Report, 2020;Lewis, 2021). Nrf2 is an important regulator of glutathione production and mitochondrial energy metabolism (Harvey, 2009; Holmstrom, 2016), and ALT, AST, and GGT have been shown to contribute to these processes at the biochemical level (Pompella, 2007; McGill, 2016).

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

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. Skyclarys treatment should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with Skyclarys 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.

SVII.3.2 Presentation of the Missing Information

1. Missing information: Use in pregnancy

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 the Safety Concerns

Table Part II: Module SVIII.1: Summary of Safety Concerns

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

Part III Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will include use of Standard Medical Follow-up Questionnaires (SMFQ) as follows:

Specific adverse reaction follow-up questionnaires for safety concerns:

- 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

Reata is proposing additional pharmacovigilance activities to manage and further characterize some of the safety concerns of omaveloxolone. This will include the following proposals:

Study Title: An Observational, Multinational, Post-Marketing Registry of Omaveloxolone-Treated Patients with Friedreich's Ataxia (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 post-marketing registry will collect data from omaveloxolone-naïve patients with FA who are prescribed omaveloxolone and treated per its approved label. The primary objectives of this registry 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 registry 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 (registry) of patients with FA who are treated with omaveloxolone per its approved label.

The FA-Global Clinical Consortium (FA-GCC) platform will be used to contact physicians and enroll patients.

- The enrollment period will start from product launch of omaveloxolone in the first participating country and following ethics committee (EC) approval of the protocol.
- Each patient will be followed for five years, up to 60 days after discontinuation of omaveloxolone treatment, loss to follow-up, or death, whichever occurs first.
- Routine visits are expected to be scheduled according to the omaveloxolone prescribing label. If any additional assessments are performed, they will be collected in between the routine visits.
- The schedule of assessments is based on anticipated visits as per the prescribing label and the Friedreich's Ataxia Global Clinical Consortium UNIFIED Natural History Study (UNIFAI). No additional visits are expected solely for this registry. 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 will be included in the registry. Due to the rarity of FA and the already established infrastructure of the FA-GCC, patients for this registry will be identified and enrolled via the FA-GCC natural history platform.

Milestones: Protocol submission, start of data collection, annual progress reports, end of data collection, final study report

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: 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	-	-	-	-
Category 3 - Required additional pharmacovigilance activities				
An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia	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 Q3 2024 Annually starting Q4 2025 Q1 2031 Q2 2031

Part IV Plans for Post-Authorization 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 Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important potential risk: 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. (See SmPC section 4.4). PIL section 2: If you have problems with your liver, your doctor may decide to change the dose or not start treatment with Skyclarys. Your doctor will decide on whether to discontinue Skyclarys 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 Skyclarys should be continued. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription

1.8.2 Risk Management Plan

Safety Concern	Routine Risk Minimization Activities
Important potential risk: 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 Skyclarys should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with Skyclarys should be discontinued. Per clinical judgment, more frequent monitoring of patients with a recent hospitalization for fluid overload due to underlying cardiomyopathy, diabetic stage IV CKD, or other 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 Skyclarys. 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 Skyclarys. Your doctor will decide on treatment and whether Skyclarys 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 Skyclarys should be continued. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription

1.8.2 Risk Management Plan

Safety Concern	Routine Risk Minimization Activities
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: Skyclarys should not be used during pregnancy or in women of childbearing potential not using contraception. Patients should use effective contraception prior to starting treatment with Skyclarys, during treatment, and for 1 month following discontinuation of treatment. Skyclarys may decrease the efficacy of hormonal contraceptives (see section 4.5). Advise patients to avoid concomitant use with combined hormonal contraceptives (eg, pill, patch, ring). Counsel females using hormonal contraceptives to use an alternative contraceptive method (eg, non-hormonal intrauterine system) or additional non-hormonal contraceptive (eg, condoms) during concomitant use and for 28 days after discontinuation of Skyclarys. Skyclarys should not be used while breast-feeding. PIL section 2: You should not take Skyclarys 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 Skyclarys. Using Skyclarys 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 Skyclarys treatment and for 28 days after stopping treatment with Skyclarys. Talk to your doctor about the most suitable birth control for you. Do not breast-feed your baby while you are being treated with Skyclarys. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription
Missing information: 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 Minimization 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 Minimization Measures

Table Part V 3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important potential risk: Drug-induced liver injury	Routine risk minimization 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. (See SmPC section 4.4). PIL section 2: If you have problems with your liver, your doctor may decide to change the dose or not start treatment with Skyclarys. Your doctor will decide on whether to discontinue Skyclarys 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 Skyclarys should be continued. Restricted medical prescription Additional risk minimization measures: None	Routine Pharmacovigilance Activities 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: Q2 2031
Important potential risk: Congestive heart failure	Routine risk minimization 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 Skyclarys should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with Skyclarys should be	Routine Pharmacovigilance Activities 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: Q2 2031

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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 Skyclarys. 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 Skyclarys. Your doctor will decide on treatment and whether Skyclarys 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 Skyclarys should be continued. Restricted medical prescription Additional risk minimization measures: None	
Missing information: Use in pregnancy	Routine risk minimization measures: SmPC section 4.6. PIL section 2 SmPC section 4.6: Skyclarys should not be used during pregnancy or in women of childbearing potential not using contraception. Patients should use effective contraception prior to starting treatment with Skyclarys, during treatment, and for 28 days following discontinuation of treatment. Skyclarys may decrease the efficacy of hormonal contraceptives (see section 4.5). Advise patients to avoid concomitant use with combined hormonal contraceptives (eg, pill, patch, ring). Counsel females using hormonal contraceptives to use an alternative contraceptive method (eg, non-hormonal intrauterine system) or additional non-hormonal contraceptive (eg, condoms) during concomitant use and for 28 days after discontinuation of Skyclarys.	Routine Pharmacovigilance Activities

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Skyclarys should not be used while breast-feeding. PIL section 2: You should not take Skyclarys 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 Skyclarys. Using Skyclarys 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 Skyclarys treatment and for 28 days after stopping treatment with Skyclarys. Talk to your doctor about the most suitable birth control for you. Do not breast-feed your baby while you are being treated with Skyclarys. Restricted medical prescription Additional risk minimization measures: None	
Missing information: Long-term safety	Routine risk minimization measures: NA Additional risk minimization measures: None	Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: None. Additional Pharmacovigilance Activities: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia.

PART VI Summary of the Risk Management Plan for Skyclarys

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

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

This summary of the RMP for Skyclarys 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 Skyclarys's RMP.

I. The Medicine and What It Is Used For

Skyclarys 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 Skyclarys's benefits can be found in Skyclarys'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 Minimize or Further Characterize the Risks

Important risks of Skyclarys, together with measures to minimize such risks and the proposed studies for learning more about Skyclarys's 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 (eg, 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 Skyclarys is not yet available, it is listed under "missing information" below.

II.A. List of Important Risks and Missing Information

Important risks of Skyclarys 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 Skyclarys. 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 (eg, on the long-term safety of the medicine).

Table Part VI.1: List of Important Risks and Missing Information

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

II.B. Summary of Important Risks

Important potential risk: Drug-induced liver injury	
Evidence for linking the risk to the medicine	Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, adverse reactions of aminotransferase elevations included: ALT increased in 37.3% of patients, AST increased in 21.6% of patients, and 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 Skyclarys. 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.
Risk minimisation measures	Routine risk minimization 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. (See SmPC section 4.4). PIL section 2: If you have problems with your liver, your doctor may decide to change the dose or not start treatment with Skyclarys. Your doctor will decide on whether to discontinue Skyclarys 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 Skyclarys should be continued. Restricted medical prescription Additional risk minimization measures: None

1.8.2 Risk Management Plan

Additional pharmacovigilance activities	Additional pharmacovigilance activities: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia

Important potential risk: 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 minimization measures	Routine risk minimization 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 Skyclarys should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with Skyclarys should be discontinued. Per clinical judgment, more frequent monitoring of patients with a recent hospitalization for fluid overload due to underlying cardiomyopathy, diabetic stage IV CKD, or other 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 Skyclarys. 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 Skyclarys. Your doctor will decide on treatment and whether Skyclarys 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 Skyclarys should be continued. Restricted medical prescription Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia

Missing information: Use in pregnancy	
Risk minimisation measures	Routine risk minimization measures: SmPC section 4.6. PIL section 2 SmPC section 4.6: Skyclarys should not be used during pregnancy or in women of childbearing potential not using contraception. Patients should use effective contraception prior to starting treatment with Skyclarys, during treatment, and for 28 days following discontinuation of treatment. Skyclarys may decrease the efficacy of hormonal contraceptives (see section 4.5). Advise patients to avoid concomitant use with combined hormonal contraceptives (eg, pill, patch, ring). Counsel females using hormonal contraceptives to use an alternative contraceptive method (eg, non-hormonal intrauterine system) or additional non-hormonal contraceptive (eg, condoms) during concomitant use and for 28 days after discontinuation of Skyclarys. Skyclarys should not be used while breast-feeding. PIL section 2: You should not take Skyclarys 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 Skyclarys. Using Skyclarys 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 Skyclarys treatment and for 28 days after stopping treatment with Skyclarys. Talk to your doctor about the most suitable birth control for you. Do not breast-feed your baby while you are being treated with Skyclarys.

	Restricted medical prescription Additional risk minimization measures: None

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimization measures: None Additional risk minimization 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-Authorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

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

II.C.2. Other Studies in Post-Authorization Development Plan

Reata 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 (**Error! Reference source not found.**). Reata 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 (**Error! Reference source not found.**).

Part VII Annexes

List of Annexes

Annex 4 Specific Adverse Drug Reaction Follow-Up Forms

1.8.2 Risk Management Plan

Drug Induced Liver Injury- Safety Medical Follow-up Query Form

To be utilized to collect initial or follow-up information on all Post-Marketing adverse event reports falling under the MedDRA System Organ Class of Hepatobiliary Disorders or reports of increased ALT, AST, GGT and/or Total Bilirubin above normal limits

Reata Global DS database # or Medical Information Call Center #: _____

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: _____

☐ Race/ethnicity: _____

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: _____

1.8.2 Risk Management Plan

Clinical Symptoms	
Please specify start and stop date of symptom. ☐ Fatigue *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Decreased appetite *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Nausea *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Vomiting *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Jaundice *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.	☐ Abdominal pain *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Fever *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Rash *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Eosinophilia *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Other: _____ *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ 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: Click or tap to enter a date.

Findings & conclusions:

Lab results: _____ Date: Click or tap to enter a 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: Click or tap to enter a date.

Findings & conclusions: _____

Diagnostic procedure 2: _____ Date: Click or tap to enter a date.

Findings & conclusions: _____

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

Risk Factors

1.8.2 Risk Management Plan

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: ☐ None ☐ Temporary discontinuation ☐ Permanent discontinuation ☐ Dose decreased ☐ Other: _____
Event Treatment
Please specify the therapeutic measures taken to treat the event: ☐ Medications, specify: _____ ☐ Treatment procedures, specify: _____ ☐ Other measures, specify: _____
Patient outcome: ☐ Unknown ☐ Resolved/Recovered ☐ Ongoing ☐ Resolved with sequelae
Form Completed By: _____ **Company:** _____ **Date:** Click or tap to enter a date.

Congestive Heart Failure - Safety Medical Follow-up Query Form

To be utilized to collect initial or follow-up information on all Post-Marketing adverse events reports that include those:

- **falling under the MedDRA System Organ Class of Cardiac Disorders,**
- **reports of worsening of cardiac function and/or heart failure,**
- **reports sudden weight gain (3 pounds or more of weight gain in one day, or 5 pounds or more of weight gain in a week), or peripheral edema, palpitations, or shortness of breath,**
- **reports of increased BNP or NT-proBNP above normal**

Reata Global DS database # or Medical Information Call Center # Case number: _____

Diagnosis of the event (incl. presumptive or differential): _____

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

Baseline Ejection fraction: _____

History of Friedreich's 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: _____

☐ Male

☐ Female

☐ Unknown

☐ Age at onset of event: _____

☐ Race/Ethnicity: _____

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

☐ Fatigue *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.	☐ Orthopnea *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.
☐ Chest Pain or Pressure *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.	☐ Persistent Cough/Wheezing *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.
☐ Abdominal Swelling *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.	☐ Lack of appetite *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.
☐ Shortness of breath	☐ Rapid Weight Gain

1.8.2 Risk Management Plan

Start/Stop Date: Click or tap to enter a date. to Click or tap to enter a date. ☐ Rapid/Irregular Heart Rate *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Impaired Thinking *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Pain (Shoulders, Neck, Arms, Jaw): _____ *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Dizziness or Fainting *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date.	*Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Dyspnea on exertion: *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Cough: *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Peripheral Edema (Legs, Ankles, Feet): _____ *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ Other: _____ *Start/Stop Date*: Click or tap to enter a date. to Click or tap to enter a date. ☐ 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: Click or tap to enter a date. Findings & conclusions: _____ Lab test: _____ Date: Click or tap to enter a date. Findings & conclusions: _____ Lab test: _____ Date: Click or tap to enter a date. Findings & conclusions: _____	
Exams & consultations	

1.8.2 Risk Management Plan

Please specify performed exams and provide the findings and conclusions.	
☐ Echocardiogram ☐ Pulse Oximetry ☐ Chest X-Ray ☐ Cardiac CT scan	☐ Cardiac MRI ☐ Coronary Angiogram ☐ Specialist consultation (Cardiologist) ☐ Other, specify: _____

Diagnostic Procedure Results *(Repeat rows as needed)*

Diagnostic procedure 1: _____ Date: Click or tap to enter a date.

Findings & conclusions: _____

Diagnostic procedure 2: _____ Date: Click or tap to enter a date.

Findings & conclusions: _____

Diagnostic procedure 3: _____ Date: Click or tap to enter a date.

Findings & conclusions: _____

Diagnostic procedure 4: _____ Date: Click or tap to enter a date.

Findings & conclusions: _____

Diagnostic procedure 5: _____ Date: Click or tap to enter a date.

Findings & conclusions: _____

Diagnostic procedure 6: _____ Date: Click or tap to enter a date.

Findings & conclusions: _____

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

1.8.2 Risk Management Plan

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

1.8.2 Risk Management Plan

☐ Yes ☐ No ☐ Unk: If yes, please list below (include start and stop dates): _____	
Action taken with Skyclarys	
☐ None ☐ Temporary discontinuation ☐ Permanent discontinuation	☐ Dose decreased ☐ Other: _____
Event Treatment *(Please specify the therapeutic measures taken to treat the event:*	
☐ 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: _____ Title:_____**Company:** _____ **Date:** _____	

Annex 6 Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable