14 December 2023
EMA/43636/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Skyclarys

International non-proprietary name: Omaveloxolone

Procedure No. EMEA/H/C/006084/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

9-HPT	9-hole peg test
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ADME	Absorption, distribution, metabolism, and excretion
ANCOVA	Analysis of covariance
ARE	Antioxidant response elements
ARP	All-randomised population
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
$AUC_{0-tlast}$	Area under the plasma concentration-time curve from time 0 to the last measurable concentration
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
BMI	Body mass index
BNP	Brain natriuretic peptide
BSEP	Bile salt export pump
CFU	Colony-forming units
CGIC	Clinical global impression of change
CI	Confidence interval
CK	Creatinine kinase
CL/(F)	(Apparent) clearance
$C_{max(ss)}$	Maximum observed plasma concentration (at steady-state)
CNS	Central nervous system
CPP	Critical process parameter
CQA	Critical quality attribute
C-QT	Concentration-QT
Ctrough	trough concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMF	Dimethylformamide

DoE	Design of experiments
DRF	Dose range finding
DSC	Differential scanning calorimetry
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EFD	Embryofetal developmental
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
E-R	Exposure-response
EU	European Union
F	Bioavailability
FA	Friedreich’s ataxia
FA-ADL	Friedreich’s ataxia activities of daily living
FA-COMS	Friedreich's ataxia clinical outcome measures; a Friedreich's ataxia natural history study
FARA	Friedreich’s Ataxia Research Alliance
(m)FARS	(modified) Friedreich's ataxia rating scale
FAS	Full analysis set
FDA	Food and Drug Administration
FTIR	Fourrier transform infrared spectroscopy
FXN	frataxin gene
GAA	guanine-adenine-adenine
GAA1 repeat length	length of a trinucleotide repeat composed of 1 guanine and 2 adenines in the guanosine-adenine-adenine 1 allele
GC	Gas chromatography
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practice
HDL	High-density lipoprotein
hERG	Human ether-a-go-go-related gene
H2O2	Hydrogen peroxide
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methyl cellulose
IC_{50}	50% inhibitory concentration
IPC	In-process control
IR	Infrared
ISR	Incurred sample reproducibility
IV	Intravenous

Ka	Absorption rate constant
Keap1	Kelch-like ECH-associated protein 1
KF	Karl Fischer titration
KIM-1	Kidney injury molecule-1
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LD	Lactation day
LDPE	Low density polyethylene
(V)LDL	(Very) Low-density lipoprotein
LLN	Lower limit of normal
(V)LOFA	(Very) late-onset FA
LS	Least squares
MAA	Marketing Authorisation Application
M17	Metabolite 17; 1,2-dihydro-29-OH omaveloxolone
M22	Metabolite 22; 1,2-dihydro-30-COOH omaveloxolone
M29	Metabolite 29; 1,2-epoxy omaveloxolone
MATE(1)(2-K)	Multidrug and toxin extrusion transporter (1) (2-K)
MAR	Missing at random
MDR1	Multidrug resistant transporter 1
MHRD	Maximum human recommended dose
MMRM	Mixed models repeated measures
mRNA	Messenger ribonucleic acid
MRT	Mean residence time
MS	Mass spectrometry
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotine amide dinucleotide phosphate
NGAL	Neutrophil gelatinase-associated lipocalin
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOAEL	No-observable-adverse-effect level
NOR	Normal operating range
Nrf2	Nuclear factor, erythroid 2 like 2
OAT(1)(3)	Organic anion transporter (1)(3)
OATP(1B1)(1B3)	Organic anion transporting polypeptide (1B1)(1B3)
OCT(1)(2)	Organic cation transporter (1)(2)
Omav	Omaveloxolone treatment group

Omav-Omav	Omaveloxolone-omaveloxolone treatment group
PAR	Proven acceptable range
PBBM	Physiologically based biopharmaceutical model
PBPK	Physiologically based pharmacokinetic(s)
PBT	Persistence, bioaccumulation, and toxicity
PD	Pharmacodynamic
PGIC	Patient global impression of change
Ph. Eur.	European Pharmacopoeia
P-gp	P-glycoprotein
PIP	Paediatric investigational plan
PK	Pharmacokinetic
Placebo-Omav	Placebo-omaveloxolone treatment group
popPK	Population pharmacokinetics
PPND	Pre- and post-natal developmental
PSD	Particle size distribution
PT	Preferred term
Q	Intercompartmental clearance
QD	Once daily
QTc(F)	Corrected QT interval by Fridericia's formula
QTPP	Quality target product profile
RH	Relative humidity
RRT	Relative retention time
RMP	Risk management plan
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Structure activity relationship
SCr	Serum creatinine
SmPC	Summary of product characteristics
SOC	system organ class
$t_{1/2}$	Apparent plasma terminal elimination half-life
TAMC	Total aerobic microbial count
tBHP	Tert-butyl hydroperoxide
T25FW	Timed 25-foot walk
TEAE	Treatment-emergent adverse event
TK	Toxicokinetics

t_{max}	Time to achieve maximum observed plasma concentration
TYMC	Total combined yeasts/moulds count
US	United States
ULN	upper limit of normal
UV	Ultraviolet
V_z/F	Apparent distribution volume
Vc/(F)	(Apparent) central distribution volume
Vp/(F)	(Apparent) peripheral distribution volume
XRPD	X-ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Reata Ireland Limited submitted on 28 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Skyclarys, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 February 2022.

Skyclarys, was designated as an orphan medicinal product EU/3/18/2037 on 27 June 2018 in the following condition: treatment of Friedreich's ataxia.

The applicant applied for the following indication: the treatment of Friedreich's ataxia (FA) in adults and adolescents aged 16 years and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0204/2022 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0204/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Skyclarys as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: http://www.ema.europa.eu/en/medicines/human/EPAR/Skyclarys

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to

the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance omaveloxolone contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice & protocol assistance

The applicant received the following scientific advice & protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
26 July 2018	EMA/CHMP/SAWP/481977/2018	*Susan Morgan* *Mario Miguel Rosa*
24 March 2022	EMA/SA/0000077358	*Livia Puljak* *Markku Pasanen*

The scientific advice & protocol assistance pertained to quality, non-clinical and clinical aspects:

EMA/CHMP/SAWP/481977/2018 - Quality, Non-clinical, Clinical

- The proposed synthesis for omaveloxolone drug substance; the proposed tests for the release and stability testing of the crystalline and amorphous omaveloxolone drug substance; the proposed tests for release and stability testing of the omaveloxolone drug product; the approach to include the executed commercial scale process validation for the drug substance in Section 3.2.S.4.5 of the Quality section of the MAA; the approach to include registration batches in the Quality section of the MAA, as well as a drug product process validation protocol that is planned to be executed prior to commercial launch in Section 3.2.P.3.5.
- Adequacy of the available safety pharmacology, genotoxicity, and repeat-dose toxicity studies, together with the planned reproductive and development studies, to support an MAA filing; the proposal to waive long-term carcinogenicity studies and to focus the carcinogenicity programme on evaluating the feasibility of a 6-month transgenic mouse carcinogenicity study.
- The primary endpoint of the phase 2 MOXIe trial; adequacy of the two-part MOXIe trial to support an MAA; adequacy of the safety database; the proposed clinical pharmacology study plan to support an MAA; adequacy of the clinical and epidemiological data on Friedreich's ataxia to support a paediatric study in the age range from 10 to 18 years.

EMA/SA/0000077358 - Quality, Non-clinical

- Starting materials; control strategy for genotoxic impurities; dissolution method.

  Adequacy of the non-clinical development programme; metabolites.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	28 November 2022
The procedure started on	28 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 March 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	05 April 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 August 2023
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 2 clinical sites (1 in Italy; 1 in Australia) and the sponsor (in the USA) between 20 March and 26 May 2023. The outcome of the inspection carried out was issued on	02 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint	19 November 2023

Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Skyclarys on	14 December 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	14 December 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Friedreich's ataxia (FA) is a rare, genetic, life-shortening, debilitating, and degenerative neuromuscular disorder.

2.1.2. Epidemiology

FA affects approximately 22,000 patients globally (Bürk, 2017). Studies suggest that FA is most observed in Caucasians, rare in sub-Saharan African populations (Koenig, 1998; Labuda, 2000) and very rare in Japan. In a 2013 study, Vankan synthesised available epidemiology studies that focused on different regions in Europe and concluded that approximately 2 in 100,000 people are affected by FA in Europe (Vankan, 2013).

2.1.3. Aetiology and pathogenesis

FA is caused by insufficient amounts of frataxin (FXN) protein. In most patients, the frataxin deficiency is caused by an expansion of a guanine-adenine-adenine (GAA) triplet repeat within the first intron of either allele of the FXN gene (Koeppen, 2011). FXN is required for the efficient synthesis of iron-sulfur clusters, cofactors that are important for the function of many proteins involved in fundamental cellular processes, such as mitochondrial energy production (Maio and Rouault, 2020). Furthermore, as FXN is a mitochondrial-targeted protein, its relative absence leads to dysfunction of multiple mitochondrial processes, such as a reduction in the activity of aconitase (a key enzyme in the tricarboxylic acid cycle), lower mitochondrial respiration, impaired mitochondrial adenosine triphosphate (ATP) production, and increased mitochondrial iron and oxidative stress (Poburski, 2016). Frataxin messenger ribonucleic acid (mRNA) levels are normally abundant in the spinal cord, dorsal root ganglia, heart, and other tissues with a high metabolic rate; tissues that are therefore susceptible to pathologies caused by diminished FXN expression (Campuzano, 1996; Jiralerspong, 1997; Poburski, 2016). The pathological consequences of frataxin deficiency include deficits in mitochondrial respiration and ATP production that ultimately lead to impaired neurologic function and neurodegeneration (Lodi, 1999; Dürr, 2002; Doni, 2021).

Substantial evidence demonstrates that Nrf2 (nuclear factor, erythroid 2 like 2) levels and activity are suppressed in cells from patients with FA and in preclinical animal models of the disease. In cells isolated from patients with FA, the levels of Nrf2 and its target genes are suppressed relative to levels in healthy controls. In cells and tissues from well-characterised animal models of FA, the levels of Nrf2 and its target genes are suppressed relative to levels in wild-type animals. These tissues included those primarily affected in FA, such as dorsal root ganglia, cerebellum, spinal cord, and heart. In cultured cells, silencing FXN gene expression by ribonucleic acid interference technology has been shown to suppress Nrf2 expression and activity in several cell types, including cells of neuronal origin. This direct effect suggests that Nrf2 suppression is an early event that occurs when FXN levels are insufficient. Collectively, the data demonstrate that impaired Nrf2 signalling, combined with frataxin deficiency, is a key contributor to mitochondrial dysfunction and the pathogenesis and progression of FA.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Ataxia is the most commonly presenting symptom in FA and is due to a combination of cerebellar and spinocerebellar degeneration, sensory neuropathy, and vestibular nerve involvement (Pandolfo, 2008). Nevertheless, the clinical phenotype of FA represents that of a multisystem disease encompassing not only characteristic neurological features, such as poor balance, impaired coordination, dysarthria, weakness, ocular fixation instability, deep sensory loss, and visual and hearing impairment, but also diverse non-neurological features such as hypertrophic cardiomyopathy, kyphoscoliosis, and foot deformities (Reetz, 2015).

For patients and their families, FA is a diagnosis with significant adverse impact on life expectancy and quality of life. One fifth of patients is younger than 5 years at onset. For the majority of patients, onset of symptoms occurs between 5 and 15 years of age, with a mean duration until loss of independent gait of 8 years and until wheelchair use of 11 to 14 years after disease onset (range 3 to 44 years), and a median survival of 34 to 37 years after disease onset (Klockgether, 1998; Bürk, 2017). Disease onset before the age of 20 and cardiac involvement are associated with faster progression of neurological symptoms. Most patients lose the ability to ambulate and are wheelchair-dependent by their mid-20s. 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). Cardiac dysfunction as a consequence of dilated cardiomyopathy and arrhythmias is widely accepted as the most common cause of mortality in patients with FA (Tsou, 2011).

With the identification of the genetic background, atypical forms of FA became identifiable. It then became evident that only 75% of patients could be diagnosed correctly as FA cases based on the original Harding criteria. Late onset FA (LOFA, onset after 25 years) or very late onset FA (VLOFA, onset after 40 years) have a slower progression. Non-neurological symptoms such as cardiomyopathy, diabetes, or skeletal deformities are less frequent. The phenotype is often more spastic with little or no ataxia. Therefore, FA should be considered in the diagnostic work-up even in individuals with onset after 60 years and absence of characteristic features (Bürk, 2017).

2.1.5. Management

Currently, there are no approved therapies for FA. The most recent consensus clinical management guidelines for FA recommend symptomatic treatment only (Corben, 2014; Zesiewicz, 2018).

Patient with FA are managed by multidisciplinary teams, including neurologists, cardiologists, physical therapist, social workers, and others. The standard of care for FA is similar globally and includes palliative and symptomatic treatments. Medications such as iron chelators, vitamin supplements, and frataxin level modifiers (Richardson, 2013) are used. Symptomatic treatments typically consist of physical therapy, the use of wheelchairs, or surgery (to correct skeletal deformations) in later stages of the disease (Richardson, 2013; Corben, 2014).

At a patient-focused drug development meeting on FA in 2017, patients expressed that while a cure for the disease is needed, a slowing or stopping of disease progression would be most valuable for the treatment of FA. Additionally, patients indicated in a survey that balance/walking, upper limb coordination, manual dexterity, and fatigue were major symptoms of the disease that contributed to the loss of independence in FA. Patients expressed that treatment of individual symptoms could have great impact on improving their quality of life (Friedreich's Ataxia "Voice of the Patient" report).

2.2. About the product

Omaveloxolone is an orally bioavailable triterpenoid analogue and a potent activator of the transcription factor, Nrf2. Omaveloxolone selectively and reversibly binds to Keap1 (Kelch-like ECH-associated protein 1), allowing for nuclear translocation of Nrf2 and transcription of its target genes. Nrf2 controls the expression of genes involved in mitochondrial function, redox balance, and inflammation. Omaveloxolone has been developed for the treatment of FA in adults and adolescents aged 16 years and older. The proposed dose regimen of omaveloxolone is 150 mg (3 hard capsules of 50 mg each) once daily.

2.3. Type of Application and aspects on development

The applicant claimed that the nonclinical, clinical, clinical pharmacology, and chemistry, manufacturing, and control development programs for omaveloxolone for treatment of FA were developed in consideration of ICH and regional regulatory guidance.

Two interactions with CHMP took place in terms of scientific advice/protocol assistance: a scientific advice finalised on 26 July 2018 (EMA/CHMP/SAWP/481977/2018), a follow up protocol assistance finalised on 24 March 2022 (EMA/SA/0000077358). Not all advice had been followed (see above).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing 50 mg of omaveloxolone as active substance.

Other ingredients are:

Capsule contents: pregelatinised starch, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and silica, colloidal anhydrous

Capsule shell: hypromellose, titanium dioxide, brilliant blue FCF, ferric oxide yellow

Printing ink: shellac, titanium dioxide

The product is available in high density polyethylene bottles with child-resistant, foil induction-sealed polypropylene closure, as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of omaveloxolone is N-((4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,9,12aheptamethyl-10,14-dioxo 1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)-2,2-difluoropropanamide corresponding to the molecular formula $C_{33}H_{44}F_2N_2O_3$. It has a relative molecular mass of 554.72 g/mol and the following structure:

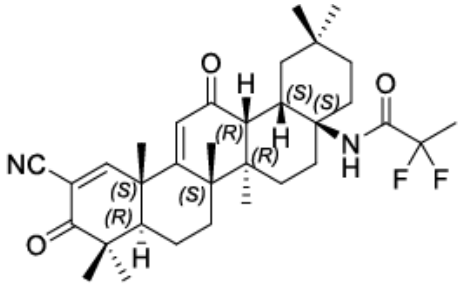


Figure 1: active substance structure

The chemical structure of omaveloxolone was elucidated by a combination of mass spectrometry, Fourier-transform infrared (FTIR) spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR, DEPT, COSY, HSQC), ultraviolet (UV)/visible spectroscopy, and elemental analysis.

The solid state properties of the active substance were measured by X-ray powder diffraction.

The absolute configuration has been confirmed by X-ray diffraction data for crystalline omaveloxolone (Form B).

Omaveloxolone is a white to off-white amorphous non hygroscopic solid. Omaveloxolone has been fully characterised providing information on its solubility in different pH aqueous media (pH 1-10), solubility in different organic solvents (freely soluble in acetone, practically insoluble in water and n-heptane), pKa, partition coefficient, melting range, specific optical rotation, Log D, Log P, stereochemistry, hygroscopicity, solid state – polymorphism and particle size distribution.

Omaveloxolone exhibits poor solubility in aqueous media in the physiological pH range. It is classified as BCS class IV compound.

Omaveloxolone exhibits stereoisomerism due to the presence of seven chiral centres. Absolute configuration has been confirmed by single crystal X-ray structural analysis. For the active substance, an optical rotation test is included in the specification, testing for stereoisomers is not considered necessary.

2.4.2.2. Manufacture, characterisation and process controls

Omaveloxolone is synthesised in seven main manufacturing steps, using well defined starting materials with acceptable specifications. Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials, reagents, and the isolated intermediates have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. A major objection was raised due to deficiencies and unclarities in the nitrosamine risk assessment of the active substance. The applicant adequately responded by providing an updated nitrosamine risk assessment reports covering all steps of the synthesis.

Changes introduced have been presented in sufficient detail and have been justified. The development of the manufacturing process is satisfactorily described discussing challenges and studies conducted to improve the process. The obtained side products have been identified and the process has been optimised to minimise their formation. The fate of potential impurities has been studied and a purge factor estimated either based on the batch data or spike/purge experiments. Normal operating ranges and set points for process parameters, process variable or IPC are presented in the dossier for each unit operation. Proven acceptable ranges have been established for some parameters typically based on univariant analysis. The development section provides a rationale for criticality of process parameters.

The active substance is packaged in a primary tag-tied low-density polyethylene (LDPE) bag inside a secondary heat-sealed aluminum laminate bag. The primary bag complies with EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for description/physical appearance (visual evaluation), identification (IR and HPLC), assay and related substances (HPLC), residual solvents (GC (headspace)), benzene (GC (headspace)), water content (KF), optical rotation (Ph.Eur.), crystal form (XRPD, Ph.Eur.), and particle size distribution (laser light diffraction).

The origin and fate of potential genotoxic impurities have been discussed and supported by spike/purge studies. The control strategy for potential genotoxic impurities has been satisfactorily justified.

A major objection was raised to request additional justification for the proposed limits for some impurities. The acceptance criteria for these impurities have been tightened based on the available batch release data and stability data and/or justified by the applicant. This was considered adequate to resolve the major objection.

Class 1 and class 2A elemental impurities and lithium were demonstrated to be absent in 6 development batches and 3 registration batches of the active substance.

Based on microbiological purity results of three registration batches of the active substance and taking into consideration low water activity and the control of microbiological purity of the finished product, the omission of microbiological testing is accepted for the active substance.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and related substances testing has been presented.

Batch analysis data (3 registration batches and 4 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from 3 registration batches of active substance from the proposed manufacturers stored in the intended commercial package (reduced scale, identical materials of construction) for up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one representative batch. Forced degradation studies under thermal, photolytic, acid, basic, and oxidative conditions were also provided on one representative batch.

The following parameters were tested: appearance, assay/related substances/purity, water content, crystal form (XRPD), particle size distribution (PSD) and water activity.

The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months stored protected from light in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product Skyclarys consists of immediate release opaque hard capsule with "RTA 408" printed on the light green body in white ink and "50" printed on the blue cap in white ink. Capsules (size 0) are 21.7 ± 0.3 mm in length, and the outer diameter of the cap is 7.64 ± 0.06 mm.

The solubility of omaveloxolone crystalline (Form B) and omaveloxolone amorphous was examined at 1-hour and 24-hour intervals in water and biorelevant media (SGF, FaSSIF-V2 and FeSSIF-V2) at 37°C. The solubility is low and a form change was observed after 24 hours under equilibrium solubility conditions for omaveloxolone amorphous.

Particle size of the active substance can potentially impact bioavailability as well. The active substance manufacturing process provides adequate controls to ensure a consistent active substance particle size distribution, and acceptance criteria for particle size distribution of the active substance are based on the particle size distribution of the clinical batches.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except silicified microcrystalline cellulose and the HPMC capsule shell. Silicified microcrystalline cellulose is a co-processed excipient consisting of microcrystalline cellulose and silica, colloidal anhydrous. The applicant is recommended to develop and implement an assay method for microcrystalline cellulose in the 'silicified microcrystalline cellulose', and amend the P.4.1 specification. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of the excipients with omaveloxolone has been demonstrated through stability studies on prototype formulations.

The quality target product profile (QTPP) and critical quality attributes (CQAs) of the finished product are provided. The pharmaceutical development activities were guided by the defined QTPP and focused on those CQAs that could be affected by a realistic change to the finished product formulation or manufacturing process.

The commercial capsule formulation was used for the pivotal clinical studies (Phase 2/Phase 3) in Friedrich's ataxia as well as various other Phase 1, 2, and 3 studies, including evaluation in other indications.

In addition to the proposed commercial 50 mg strength, also 2.5 mg and 10 mg strengths have been used during clinical development.

No overages are used in the manufacturing process.

According to the SmPC, the capsules may be opened and the content sprinkled onto apple sauce. A compatibility and stability study have been carried out to demonstrate that apple sauce does not affect the physical-chemical properties of the capsule content.

The primary packaging is high density polyethylene bottles with child-resistant, foil induction-sealed polypropylene closure, as described in section 6.5 of the SmPC. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process is a standard direct blending and encapsulation process and consists of four main steps: pre-lubrication blending, post-lubrication blending, capsule filling and packaging. The process is considered to be a standard manufacturing process.

An evaluation of the critical process parameters was performed during the manufacturing process development. The critical process parameters (CPPs) were identified. The in-process controls are considered sufficient. Holding times were established for the final blend intermediate and for the bulk product.

Process validation has not been provided, however a process performance qualification protocol was provided, which is acceptable for a standard manufacturing process for an immediate release formulation.

The in-process controls are adequate for this direct blending and encapsulation process for hard capsules.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description/physical appearance (visual evaluation), identification (HPLC, UV), assay and degradation products (HPLC), uniformity of dosage units (Ph.Eur., HPLC), water content (Ph.Eur., KF), dissolution (Ph.Eur., HPLC), microbiological quality (Ph.Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided and considering the applicant's response to the major objection on nitrosamine risk assessment for the active substance, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

A major objection was raised with respect to the microbiological quality of the finished product. In response, the applicant included a test for microbiological quality in the finished product specification (with periodic testing).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three registration/primary stability batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three batches of finished product of manufactured at the proposed commercial site, stored for up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradants, water content, dissolution, microbiology, crystallinity. The analytical procedures used are stability indicating. No significant changes or trends were observed in any of the parameters tested. All results were well within the proposed specifications, and amorphous form of the active substance was maintained at all times and conditions.

An in-use stability study has been performed simulating the intended use. It was concluded that declaration of an in-use shelf-life is not required.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study demonstrated that the finished product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 4 years with no special storage conditions, as stated in the SmPC (section 6.3), is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant adequately responded to three major objections by providing additional clarification on the nitrosamine risk assessment at active substance level, by further justification and tightening of the specified impurity limits in the active substance, and by implementing a specification and periodic testing for microbiological quality of the finished product.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the need to develop an assay method for microcrystalline cellulose and include acceptance criteria for it in the specification of the excipient silicified microcrystalline cellulose. This point is put forward and agreed as a recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following:

1. The applicant will develop an assay method for microcrystalline cellulose in addition to the assay of anhydrous colloidal silica to include in the specification for silicified microcrystalline cellulose.

2.5. Non-clinical aspects

2.5.1. Introduction

Omaveloxolone (also known as RTA 408) is a small molecule, novel, potent, orally bioavailable Nrf2 activator. It selectively and reversibly binds to Keap1, resulting in the activation of Nrf2, a transcription factor that modulates the expression of genes that normalise mitochondrial function, restore redox balance, and reduce inflammation. Omaveloxolone is intended as a treatment of FA where patients have suppressed levels and activity of Nrf2.

Non-clinical studies have been conducted in compliance with ICH guideline M3(R2) that addressed the pharmacology, pharmacokinetics (PK), and safety pharmacology of omaveloxolone, and included a complete battery of GLP compliant repeat-dose toxicity, reproductive toxicity, genotoxicity studies, and a 6-month carcinogenicity study in rasH2 mice. The non-clinical programme was designed and conducted to support the chronic daily oral administration of 150 mg omaveloxolone in patients with FA.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro and *in vivo* pharmacology studies were performed to demonstrate and characterise the antioxidative, mitochondrial bioenergetic and anti-inflammatory phenotype of omaveloxolone. The effects of omaveloxolone on activation of Nrf2 *in vitro* was tested in numerous studies; only the studies supporting the current marketing authorisation application (MAA) are discussed/presented in detail.

Omaveloxolone was tested in two assays to assess its ability to activate Nrf2 using reporter constructs containing verified antioxidant response elements (ARE), which are the DNA sequences that Nrf2 recognises and binds to in the promoter region of its target genes. One of the reporters tested was controlled by an ARE derived from the human Nqo1 gene and the other reporter was derived from the rat glutathione S-transferase alpha 2 ARE sequence. In both reporter assays, dose-dependent increases in luciferase activity were observed. Omaveloxolone also dose-dependently increased mRNA levels of Nrf2 target genes including Hmox1, Nqo1, Gclm, and Txnrd1 in normal human mesangial cells, Nqo1, Gclc, and Txnrd1 in RAW264.7 mouse macrophages and Nqo1 enzymatic activity in RAW264.7 mouse macrophages (studies RTA400-R-1114 and RTA400-R-1202).

The ability of omaveloxolone to increase Nrf2 activity was evaluated in cells of central nervous system (CNS) origin from mice and humans, namely neurons, microglia, and astrocytes. Treatment with omaveloxolone resulted in concentration-dependent increases in Nrf2 target gene (i.e., Nqo1 and Gclm or Gclc) expression (studies RTA400-R-1123 and RTA400-R-1704).

In C2C12 mouse myoblasts, omaveloxolone dose-dependently increased the expression of Nrf2 target gene mRNA (i.e., Nqo1 and Gclm) and the levels of total glutathione and concentration-dependently decreased the levels of cellular Reactive oxygen species (ROS) (study RTA400-R-1513). In a similar study at higher concentrations omaveloxolone increased the expression of Nrf2 target genes (i.e., Nqo1, Gclm, Txnrd1, Fth1, and Hmox1) in C2C12 mouse myoblasts (study RTA400-R-1701).

In human retinal pigment epithelial cells omaveloxolone protected against hydrogen peroxide (H2O2)-induced cell injury via Nrf2 activation by increasing the expression of its downstream genes including Ho-1, Nqo1, Sod2, catalase, Grx1, and Trx1 (reference: Liu et al., 2016).

The effects of omaveloxolone on mitochondrial function was tested *in vitro* in conditions with and without oxidative stress. Treatment of unstressed C2C12 myoblasts with omaveloxolone at concentrations of 1.6 to 12.5 nM that activate Nrf2 resulted in significant increases in basal respiration, ATP-linked respiration, maximal respiration, and spare respiratory capacity (i.e., the cells ability to respond to stress) (study RTA400-R-2005). These results were replicated confirming the effects of omaveloxolone on mitochondrial function in C2C12 myoblasts (study RTA400-R-1607). To evaluate the effect of omaveloxolone under conditions of oxidative stress, C2C12 myoblasts were challenged with tert-butyl hydroperoxide (tBHP). Pretreatment of the myoblasts with omaveloxolone resulted in significant and concentration-dependent increases in mitochondrial function parameters to near control level (study RTA400-R-2005). Furthermore, data from experiments in which Nrf2 levels were suppressed by clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 technology demonstrated that Nrf2 was required for omaveloxolone-mediated improvements in mitochondrial function (study RTA400-R-2008). To more

closely mimic the oxidative stress that is observed in cells from patients with FA, C2C12 myoblasts were challenged with a combination of buthionine sulfoximine and ferric ammonium citrate, which results in depletion of glutathione and increases in iron concentrations, respectively, thereby increasing levels of ROS and decreasing mitochondrial function. Pretreatment of the myoblasts with omaveloxolone prior to initiation of the oxidative stress challenge resulted in significant and concentration-dependent increases in mitochondrial function parameters (study No RTA400-R-2005).

The effects of omaveloxolone on inflammation was evaluated *in vitro*. Pretreatment with omaveloxolone at 0.1 to 25 nM dose-dependently decreased IFN-γ-induced nitric oxide production in RAW 264.7 macrophages with an average 50% inhibitory concentration (IC_{50}) of 3.8 nM (study RTA400-R-1113). Also, in IFN-γ-challenged RAW 264.7 macrophages, pretreatment with omaveloxolone at 0.8 to 100 nM significantly decreased the mRNA levels of cyclooxygenase 2, inducible nitric oxide synthase, chemokine C-C motif ligand 2 and chemokine C-C motif ligand 5 (study RTA400-R-1202). Similar suppression of inflammatory cytokines was also observed with omaveloxolone in lipopolysaccharide-stimulated mouse BV-2 microglial cells. Omaveloxolone at 3.1 to 25 nM significantly and concentration-dependently suppressed the mRNA levels of chemokine C-C motif ligand 2, IL-6 and TNF-α (study RTA400-R-1704).

Omaveloxolone was evaluated in multiple cell-based models of FA. Treatment of hFXNI154F murine embryonic fibroblast with omaveloxolone increased the expression of Nrf2 target genes and restored expression of suppressed Nrf2 target genes. In lymphoblastoid cell lines and dermal fibroblasts derived from patients with FA or healthy donors omaveloxolone also increased expression of Nrf2 target genes including Nqo1 and Gclm (study RTA400-R-1515). Additionally, treatment of hFXNI154F murine embryonic fibroblast with omaveloxolone increased glutathione levels at concentrations which corresponds to the concentrations that increase the expression of Gclm and Gclc, two genes involved in glutathione synthesis (study No RTA400-R-1523). Nrf2 is known to regulate a number of genes involved in iron metabolism including the genes that encode ferritin, a key iron storage protein. Therefore, omaveloxolone was shown to increase the expression of the genes that encode ferritin subunits (Fth1 and Ftl) in dermal fibroblasts derived from patients with FA (study RTA400-R-2212).
Omaveloxolone alleviated oxidative stress in fibroblasts from patients with FA by returning rates of lipid peroxidation, mitochondrial ROS generation and glutathione levels to control values. In cells from patients with FA omaveloxolone protected against hydrogen peroxide (H2O2)-induced decreased mitochondrial membrane potential. Fibroblasts from patients with FA were highly susceptible to cell death upon exposure to H2O2 however, incubation with omaveloxolone restored cell viability to a level similar to that of normal healthy control cells. In cerebellar granule neurons harvested from the knock-in/knockout and YG8R mouse models of FA and in fibroblasts isolated from patients with FA levels of nicotinamide adenine dinucleotide (NADH), a critical substrate for mitochondrial respiratory complex I, were significantly decreased compared to their wild-type or healthy donor counterparts. However, when the cells were incubated with omaveloxolone, NADH levels were restored to normal levels (reference: Abeti et al., 2018).

The effect of omaveloxolone on mitochondrial respiration was assessed in FA patient fibroblasts challenged with tBHP. Treatment with tBHP significantly reduced maximal respiration and spare respiratory capacity however, treatment with omaveloxolone rescued both of these parameters of mitochondrial function (study RTA400-R-2104). A similar increase in mitochondrial function following treatment with omaveloxolone has been observed in hFXNI154F murine embryonic fibroblasts (study RTA400-R-1514).

Six circulating metabolites of omaveloxolone were observed and identified in human plasma namely M14, M15, M17, M22, M23 and M28. The metabolites were evaluated for pharmacological activity using the primary *in vitro* assay that quantifies the suppression of IFN-γ-induced NO production in RAW264.7

macrophages and showed that the omaveloxolone metabolites possessed minimal to no pharmacological activity relative to parent (study RTA400-R-1617).

The ability of omaveloxolone to induce expression of Nrf2 target genes *in vivo* was demonstrated using tissues collected from healthy omaveloxolone-treated mice, rats and monkeys. Oral dosing with omaveloxolone generally increased the mRNA levels of various Nrf2 target genes in multiple tissues, including brain, in a dose-dependent manner. Transcriptional upregulation of Nrf2 target genes by omaveloxolone also resulted in functional increases in the antioxidative response, as manifested by dose-dependent increases in Nqo1, glutathione S-transferase, and glutathione reductase enzyme activity in rodent and monkey tissues (study RTA408-P-1206).

Single and repeat oral doses of omaveloxolone at 10, 30 and 100 mg/kg to monkeys demonstrated a well-characterised and dose-proportional PK and tissue distribution profile, which was associated with Nrf2 activation. Systemic exposures to omaveloxolone that produce Nrf2 activation in monkeys were readily achievable in FA patients after oral administration of at least 80 mg of the compound (reference: Reisman et al., 2019).

Because well-established animal models of FA are not commercially available, omaveloxolone was tested in several rodent models of neurological disease. In the mouse experimental autoimmune encephalomyelitis model of multiple sclerosis, omaveloxolone significantly decreased clinical manifestations of the disease (e.g. overall severity of hind-limb weakness and paralysis), improved overall survival, and decreased inflammation and demyelination in the spinal cord (reference: Wei et al., 2017). In a rat model of temporal lobe epilepsy, omaveloxolone significantly decreased the frequency of seizures and also prevented neuronal cell death in rats with status epilepticus, which was associated with significant and dose-dependent increases in both total glutathione and ATP levels in the cortex and hippocampus (reference: Shekh-Ahmad et al., 2018).

2.5.2.2. Secondary pharmacodynamic studies

Omaveloxolone at 200 and 2000 nM was evaluated in an *in vitro* screening panel to assess any potential effects on major off-target receptors, ion channels, transporters, and enzymes. No significant inhibition or stimulation (i.e., higher than 50%) of any of the targets tested was observed at either concentration of omaveloxolone (study RTA-P-18007).

Concentrations of 200 and 2000 nM omaveloxolone corresponded to approximately 51- to 516-times, respectively, the unbound maximum observed plasma concentration (C_{max}) in patients with FA administered the maximum human recommended dose of 150 mg (i.e., 3.87 nM). Thus, omaveloxolone showed no meaningful off-target activity when tested against a panel of receptors, ion channels, transporters and enzymes.

2.5.2.3. Safety pharmacology programme

The potential effects of omaveloxolone on the CNS were evaluated in Sprague-Dawley rats. In a Functional Observation Battery study, a single-dose oral administration of omaveloxolone to rats (10/sex/group) at 3, 10, and 30 mg/kg did not produce mortality, clinical observations, or effects on any of the neurobehavioral measures tested. Slight decreases in body weight gain were observed at 24 hours post dose in males and females following the 30 mg/kg treatment (study RTA408-P-1115).

A single dose of omaveloxolone at 3, 10, and 30 mg/kg by oral gavage did not produce mortality, adverse clinical observations, or effects on any of the pulmonary parameters (respiratory rate, tidal volume, and minute volume) measured by whole-body plethysmography in Sprague-Dawley rats (8/sex/group) (study RTA408-P-1116).

Plasma concentrations were not quantified in the CNS and respiratory safety pharmacology studies. Therefore, the sex-combined C_{max} after a single 30 mg/kg oral (i.e 820 ng/mL) dose determined in the 28-day GLP rat toxicity study (study RTA408-P-1103) was used to determine a margin of exposure. The mean C_{max} after a single 30 mg/kg oral dose in rats corresponded to approximately 11-times the total c_{max} at steady state ($C_{max,ss}$) in patients with FA administered the maximum human recommended dose of (MHRD) 150 mg (i.e. 71.5 ng/mL).

In vitro, the effect of omaveloxolone at concentrations of 0.75 and 1.2 µM was tested on the IKr current in HEK293 cells using whole-cell patch clamp electrophysiology methods. Superfusion of omaveloxolone at concentrations of 0.75 and 1.2 µM produced a concentration-dependent increase in inhibition of Human Ether-a-go-go-Related Gene (hERG)-mediated potassium currents of approximately 6.72 and 21.5%, respectively. The 0.75 µM omaveloxolone concentration corresponds to approximately 193-times the steady-state maximum free plasma drug concentration in patients with *FA* administered the MHRD of 150 mg (i.e., 3.87 nM) (study RTA408-P-1114).

In a dedicated cardiovascular safety pharmacology study omaveloxolone administered orally as a single dose to telemetered cynomolgus monkeys (4/sex/group) at dose levels of 10, 30, and 100 mg/kg according to a Latin square design, did not produce mortality, clinical signs, or result in meaningful changes in body weight, body temperature, blood pressure, or qualitative or quantitative (PR, RR, QRS, uncorrected QT intervals) electrocardiogram (ECG) parameters. The overall mean for corrected QT interval (QTc) from 0 to 5 hours following the 100 mg/kg treatment was statistically significant and was increased by approximately 1.6% compared to the vehicle control (study RTA408-P-1113). However, due to the low risk based on *in vitro* data and no indication of a QT prolonging effect of omaveloxolone based on C-QTc evaluation in healthy volunteers, this matter is not further pursued. Plasma concentrations were not quantified in this study. Therefore, the sex-combined C_{max} after a single 100 mg/kg oral dose (i.e., 219 ng/mL) determined in the 9-month GLP toxicity study (study RTA408-P-1205) was used to determine a margin of exposure. The mean total C_{max} at the 100 mg/kg dose corresponded to approximately 3-times the total $C_{max,ss}$ in patients with FA administered the MHRD of 150 mg (i.e. 71.5 ng/mL).

Cardiovascular safety of omaveloxolone was also evaluated as part of the pivotal 4- (5/sex/group) and 39-week (9/sex/group) repeat-dose toxicology studies in monkey by means of intermittent ECG recordings. Omaveloxolone induced no treatment-related changes on qualitative or quantitative ECG parameters following oral gavage at doses of 0 (vehicle), 10, 30 and 100 mg/kg/day for 1- or 9-months to monkey (study RTA408-P-1104 and RTA408-P-1205). The mean C_{max} after a single 100 mg/kg (i.e. 227 (4-week study) and 219 ng/mL (39-week study)) oral dose corresponded to 3-times the C_{max} in patients with FA administered the MHRD of 150 mg (i.e. 71.5 ng/mL).

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic (PD) drug-drug interactions (DDI) studies were presented.

2.5.3. Pharmacokinetics

PK of omaveloxolone was studied in mice, rats, rabbits, and monkeys. The toxicokinetics (TK) of omaveloxolone in rabbit, rat and monkey after repeated administration were assessed from pivotal toxicology studies carried out in accordance with GLP consistent with the ICH guideline S3A. The rat and monkey were selected as the relevant test species in the pivotal toxicology studies.

Methods of analysis

Bioanalysis in the pivotal toxicity studies were conducted with a demonstrated fit for purpose LC-MS/MS method.

Incurred sample reproducibility (ISR) for rat plasma was confirmed in the 28-day repeat-dose toxicity study RTA408-P-1103. ISR for monkey plasma was confirmed in the 28-day repeat-dose toxicity study RTA408-P-1104. ISR for mouse plasma was confirmed in the 26-week repeat-dose carcinogenicity study RTA-P-21001. For all three cases more than 90% of the re-analysed samples were within 20% of the original result. This confirms a robust bioanalytical method. An evaluation of ISR in rabbit plasma could not be found.

One bioanalytical method was fully validated for omaveloxolone in rat and monkey plasma (RTA-408-P-1102 and RTA408-P-1102), however when using this method on study samples, it was not robust. Hence, a new method (new sample extraction procedure) was developed and validated. This method was used for study samples thereafter. The LC-MS/MS method was also validated in rat milk. Amendment I provided extended stability for freeze/thaw and long-term storage at -70°C. Moreover, the recovery was determined to be approximately 100%. Amendment II characterised the lower recovery, when not adding 0.5% sodium bisulfite to the milk at the time of sampling.

In study RTA408-P-1204 (26-week in rat, finalised 15th October 2013), the analytical run history contains no failed runs out of 14 and reanalysis appear limited and adequately justified. Similarly, in study RTA408-P-1205 (39-week in monkey, finalised 10th October 2013), the analytical run history contains only 3 failed runs out of 34 and reanalysis appear limited, well-described and adequately justified.

Absorption

In vitro, omaveloxolone was shown to have low permeability in Caco-2 cell monolayers, and whereas it was not a substrate of Breast cancer resistance protein (BCRP) it may be a weak P-gp substrate.

Absorption PK parameters were investigated in toxicological species, including mice, rats, rabbits, and monkeys following single and repeated daily oral administration. Following a single oral administration of a suspension formulation in sesame oil at doses of 10 to 100 mg/kg, the C_{max} of omaveloxolone were observed within 1 to 2 hours in mice and within 4 to 8 hours in rats, rabbits, and monkeys. On a dose-normalised basis, omaveloxolone C_{max} and area under the concentration-time curve (AUC) were higher in rasH2 mice and rats relative to C57BL/6 mice, rabbits, and monkeys after a single oral administration. Systemic exposure to omaveloxolone was generally similar in males and females across species. Exposure to omaveloxolone following repeated daily oral administration increased slightly (≤2-fold) compared to a single administration. Oral administration of omaveloxolone over a dose range from 3 to 100 mg/kg generally produced a dose-proportional increase in systemic exposure in all species. Above 100 mg/kg in the pivotal toxicity species (i.e., 100 to 800 mg/kg in monkeys; 500 to 2000 mg/kg in rats), systemic exposure to omaveloxolone did not increase with dose, suggesting saturation of absorption. No consistent or meaningful differences in systemic exposure were observed between pregnant and non-pregnant females on a dose-

normalised basis across the dose range tested, and dose proportional increases in exposure with no apparent accumulation following repeated administration was observed in pregnant rats and rabbits.

Absorption following oral and intravenous (IV) administration in monkeys was investigated as part of the QWBA study, as presented under the distribution section. Data suggests that omaveloxolone has a very low oral bioavailability in monkeys of approximately 3.41% and further that it is extensively metabolised after both oral dosing and IV administration. After both oral and IV administration, an initial rapid elimination of total radioactivity was observed after 120 h and 8 h post-dose for oral and IV administration, respectively, with corresponding half-lives of 22.6 h and 3.02 h. A slower terminal elimination phase between 168 and 504 h with a half-life of 166 h was observed after oral dosing, whereas a half-life of 17.6 h between 8 and 48 h was observed after IV administration. Unchanged omaveloxolone was more rapidly cleared with an initial half-live of 12.3 hours through 96h, and a terminal half-life of approximately 128 h between 96 and 240 hours following oral administration. After IV administration, unchanged omaveloxolone remained measurable through 240 hours for 2 of the 3 animals and through 336 hours for 1 animal and was eliminated rapidly from systemic circulation with a mean total body clearance of 21.0 ± 3.0 mL/min/kg. Between 1 and 8 hours, an initial elimination phase was defined by a mean half-life of 3.23 h, whereas after approximately 96 hours, the elimination curve was defined by a slower mean half-life of 48.8 h. The mean (±SD) apparent volume of distribution (V_z/F) of omaveloxolone was 87.8 ± 10.7 L/kg, which is similar to the volume of total body water. The mean residence time (MRT) for omaveloxolone after oral and IV dosing was approximately 34.3 hours and 9.18 hours, respectively.

No PK investigation in rats following IV administration has been performed by the applicant, and a full metabolic profile in rat has not been presented to the same extend as in monkeys, e.g., on oral bioavailability and excretion. However, the current documentation on PK parameters in rats is accepted as sufficient considering that monkeys are considered the pivotal toxicological species and more relevant for clinical translatability, and therefore, it is not considered warranted to request further animal studies to investigate the PK profile in rats.

Distribution

By means of ultracentrifugation omaveloxolone was shown to be highly bound to plasma protein in the seven species tested. In rank order, the overall mean percentages of omaveloxolone bound to plasma proteins were 92.7, 94.7, 94.8, 95.2, 96.0, 96.9 and 99.6% for mice, rats, monkeys, dogs, rabbits, humans and minipigs, respectively. Omaveloxolone partitions mostly into plasma. In rank order, the overall mean blood-to-plasma concentration ratios of omaveloxolone were 0.687, 0.694, 0.768, 0.777, 0.792, 0.802, and 0.850 for rats, humans, mice, dogs, rabbits, monkeys, and minipigs, respectively (study RTA408-P-1124).

The distribution of omaveloxolone after oral administration to mice, rats, and monkeys was assessed using LC/MS/MS quantitation of omaveloxolone in selected tissues. Repeated oral dosing of omaveloxolone to mice, rats, and monkeys for 14 days at doses of 10, 30, and 100 mg/kg demonstrated that plasma omaveloxolone concentrations increased with dose level across species. Overall, omaveloxolone concentrations in tissues were generally similar or increased relative to plasma concentrations. In mice and rats, distribution after 4 hours was greatest in the liver with concentrations approximately 5- to 17-fold higher than plasma omaveloxolone concentrations, while concentrations in brain and lung were within 2-fold of the plasma concentrations. In monkeys, 24 hours following the last administered dose, tissue distribution was highest in lung (approximately 6- to 16-fold plasma omaveloxolone concentrations), followed by liver and brain (study RTA408-P-1131, RTA408-P-1121 and RTA408-P-1132).

Organs and tissue distribution of radioactivity of [^{14}C] omaveloxolone following administration of a single oral dose (100 mg/kg, 60 µCi/kg) to monkeys was investigated by a combined quantitative whole-body autoradiography evaluation and LSC analysis. Radioactivity was observed in most tissues, including adrenal glands, brain, eyes, fat, kidneys, liver, lungs, heart, skin, and gonads. Highest levels of radioactivity were observed within the gastrointestinal tract. Peak radioactivity, outside of the gastrointestinal tract, was observed between 8 and 30 hours. Further, [14C] omaveloxolone-derived radioactivity did not appear to specifically bind to melanin-containing tissues (i.e., eyes and skin) (study RTA-P-18011).

Omaveloxolone-derived radioactivity did not appear to specifically bind to melanin-containing tissues in monkey and no concern for phototoxicity was identified. Hence, the lack of a specific study in pigmented rats is accepted.

In a pre- and postnatal development (PPND) study parental time-mated female rats were dosed once daily from Gestation Day 6 through Lactation Day (LD) 20 at dose levels of 0 (vehicle), 1, 3, or 10 mg/kg/day by oral gavage. Omaveloxolone is excreted into milk as concentrations were quantified in milk of lactating rats on LD 12. The plasma omaveloxolone concentrations in pups 6 hours after dose administration to dams on LD 4 indicates that the pups were exposed systemically to omaveloxolone upon ingestion of milk containing omaveloxolone (study RTA-P-18019). No data on placental transfer were presented.

Metabolism

In vitro metabolism studies of omaveloxolone in liver microsomes from C57BL/6 mice, Sprague Dawley rats, cynomolgus monkeys, and humans revealed that omaveloxolone is extensively metabolised to 41 metabolites, with <3% and approximately 12% of omaveloxolone remaining after a 60-minute incubation with primate and rodent microsomes, respectively. Qualitatively, the omaveloxolone metabolites formed *in vitro* were consistent across species, with no unique human metabolites observed. Incubation of omaveloxolone in a panel of recombinant human CYP (rCYP) enzymes implicated rCYP2C8 and rCYP3A4 as enzymes contributing to omaveloxolone metabolism. Overall, CYP3A4 was identified as the major contributing enzyme to the *in vitro* metabolism of omaveloxolone in human liver microsomes.

In vivo in monkeys, metabolism also appears to be mediated primarily by oxidation and reduction. Definitive metabolite identification in monkey plasma after oral administration was not possible due to very low exposure and limited quantities of monkey plasma samples. According to the applicant, the data did suggest that the major human metabolite, M17, was present in monkey plasma at levels greater than those observed in human plasma, however, as it co-eluted with another metabolite (M15), a direct quantitative comparison was not possible. The major human metabolite M22 was detected in monkey plasma but could not be quantified (below LOQ). It was detected in bile in monkeys, demonstrating that the monkey has the metabolic capacity to produce M22, however, only in low amounts. Omaveloxolone and its metabolites were primarily excreted via feces both after oral and IV dosing in monkeys while minimal radioactivity was recovered in urine. Omaveloxolone was not quantifiable in feces after an IV dose, suggesting complete metabolism of omaveloxolone, while omaveloxolone accounted for 7.61% of dose in feces after oral administration. In conclusion, M22 is considered a disproportionate human metabolite in monkeys.

To investigate the presence and comparable quantities of M17 and M22 in different species, serum samples from rasH2 mice, CD-1 mice, rats, and monkeys were taken after oral administration at steady state and compared to the metabolites measured in FA patients. A mixed-matrix methodology was used to account for potential matrix-related effects in LC/MS response, where blank plasma of the comparative species was added to each sample (e.g., blank monkey plasma added to human pooled plasma samples and vice versa). All metabolites observed in patient plasma were also observed in monkey, rat and mouse plasma. In

monkeys at 100 mg/kg/day, which is the no-observable-adverse-effect level (NOAEL) in the 9 months repeat dose study, the metabolite ratio to FA patients were 25.6% and 6770% for M22 and M17, respectively. In CD-1 mice dosed with 100/50 mg/kg/day, all metabolites were higher than or similar to plasma levels in patients with FA, including the major human plasma metabolites M17 and M22. However, at 10 and 30 mg/kg/day, M22 was only 6.78% and 11.7% of patient levels. In rasH2 mouse plasma after a 100-mg/kg/day dose, both major human metabolites (i.e., M22 and M17) were observed at levels that are similar to or higher than patients with FA (i.e., 102% and 5230%, respectively, in males; 88.3% and 1720%, respectively, in females). Of note, the high dose for females in the 26-week carcinogenicity study is 100 mg/kg/day. In rats at an oral dose level of 10 mg/kg/day, M17 and M22 were detected at levels of 75.1% and 16.6% in male rats compared to levels in FA patients. Thus, M22 is also considered a disproportionate human metabolite in rats.

The *in vitro* pharmacological activity of omaveloxolone metabolites, e.g., M22 and M17, was compared to that of the parent compound in terms of suppression of interferon gamma (IFNγ)-induced NO production. Omaveloxolone was 62- to >1422-times more potent than all metabolites in the assay, indicating that the metabolites possess minimal to no pharmacologic activity relative to omaveloxolone.

In conclusion, M22 is considered a disproportionate human metabolite in pivotal non-clinical species (i.e. rats and monkeys). Qualitatively, it is detected in all animal species. It holds no *in vitro* pharmacological activity compared to omaveloxolone, and it is structurally similar to other metabolites, such as M17, M15 and M23 (C29/C30 metabolites). Total exposure to C29/C30 metabolites shows that monkeys are exposed to higher amounts than humans (2.48 hr*ng/mL vs 0.187 hr*ng/mL, respectively). M22 is furthermore observed in levels above those in humans in both rasH2 and CD-1 mice. In silico, M22 did not fire any positive alerts for mutagenic potential and when tested in a non-GLP Ames test, it was considered negative under the study conditions (see the metabolite section under toxicology below for the safety assessment of M17 and M22). Based on the available information, higher exposure in patients to M22 compared to monkeys and rats is not likely to result in any additional observed toxicity.

Excretion

Excretion was assessed in monkeys following IV and oral dosing of [14C] omaveloxolone. In oral dosed monkeys the total mean radioactivity recovery was 51.81% of the total dose at study termination (504 hours after administration), comprised of 14.39% in urine, 15.62% in feces, 18.84% in the cage rinses, and an additional 2.96% in the final cage wipe. Considering that the urine excretion in the IV group was minimal, it is likely that most of the radioactivity found in the urine at the early timepoints was due to fecal contamination. Additionally, most of the radioactivity collected in the cage rinses at the early time intervals would be due to the soft fecal material not collected in the feces separator. Therefore, the data indicate that feces is the primary route of elimination following an oral dose.

In orally dosed and bile-duct cannulated monkeys the total mean radioactivity recovery was 17.91% from biliary excretion over the total collection period of 168 hours. The intervals with the highest amounts of biliary excretion were at 8 to 24 and 24 to 48 hours after administration with 5.19% and 5.91% of total radioactive dose at these intervals, respectively.

In IV dosed monkeys the total mean radioactivity recovery was 84.44% of the total dose at study termination (504 hours post dose), with 5.17% in urine, 70.23% in feces, 8.10% in cage rinses, and an additional 0.94% in the final cage wipe. The primary route of elimination was in the feces with the bulk of radioactivity being eliminated within 72 hours after dosing. By 168 hours after administration, the total daily elimination was less than 1% of the total radioactive dose.

Hence, the study demonstrated that the primary route of excretion was via the hepatobiliary/fecal route with little radioactivity (approximately 5%) being excreted into urine. Oral administration of [14C] omaveloxolone to bile duct-cannulated monkeys showed approximately 18% of the total dose being excreted into bile.

No data on excretion of mice and rats were presented.

Pharmacokinetic drug interactions

The potential effect of omaveloxolone on CYP450 and transporter test systems was undertaken to determine the potential for PK DDI. In addition, inhibition of CYP450 enzymes with the M17 and M22 metabolites was also evaluated.

Omaveloxolone was a mixed inhibitor of CYP2C8 and CYP3A4/5 with Ki values of approximately 0.5 µM for each enzyme (study RTA408-P-1106). To evaluate the potential for inhibition at the observed $C_{max, ss}$ at the therapeutic dose for omaveloxolone in patients with FA, an additional CYP450 enzyme inhibition study assessed higher concentrations of omaveloxolone for CYP450s where an IC_{50} value was not previously defined. Omaveloxolone directly inhibited CYP2C9 and CYP3A4/5 with IC_{50} values of 4.8 and 4.9 µM, respectively (study RTA-P-17011). Omaveloxolone did not induce CYP450 (CYP1A2, CYP2B6, and CYP3A4/5) enzyme activity in primary human hepatocytes at concentrations where cytotoxicity was not observed (up to 3 µM). At 5 µM omaveloxolone, where cytotoxicity of primary human hepatocytes was observed induction of approximately 4-fold was observed for CYP3A4/5 (study RTA408-P-1107).

Omaveloxolone inhibited the systemic transporters MDR1 (multidrug resistant transporter 1), OCT1 (Organic cation transporter 1), OAT1 (Organic anion transporter 1) and OATP1B3 (Organic anion transporting polypeptide 1B3) with IC_{50} values of 0.706, 0.945, 2.27 and 3.47 µM, respectively. Omaveloxolone displayed little to no inhibitory effects on the systemic transporters BCRP, BSEP (bile salt export pump), OAT3 (Organic anion transporter 3), OATP1B1 (Organic anion transporting polypeptide 1B1), OCT2 (Organic cation transporter 2), MATE1 (Multidrug and toxin extrusion transporter 1) or MATE2-K (Multidrug and toxin extrusion transporter 2-K). In addition, in OATP1B1- and OATP1B3-transfected cells, the uptake of omaveloxolone was comparable to that of control cells, indicating that omaveloxolone is not a substrate of OATP1B1 or OATP1B3 (studies RTA408-P-1209 and RTA-P-17012).

The two major human metabolites M17 and M22 were also evaluated *in vitro* for CYP inhibition potential at concentrations up to 10 µM and did not show any meaningful inhibition (study RTA-P-20022).

In addition, according to the EMA `*Guideline on the investigation of drug interactions*` *(CPMP/EWP/560/95/Rev. 1 Corr. 2**)* for clinical relevance of intestinal exposure interactions, the concentration range should be sufficient for determining a Ki ≤ 0.1-fold the maximum expected dose taken at one occasion /250 mL. Therefore, following calculation was performed:

Intestinal exposure

Ki ≤ 0.1-fold the maximum expected dose taken at one occasion /250 mL

0.1×150mg/250mL = 0.1×0.6 = 0.06 mg/mL = 108.16 µM

the concentration range should be sufficient for determining a Ki ≤ 108.16 µM

Due to poor solubility of omaveloxolone in aqueous media in the physiological pH range, it was not feasible to prepare omaveloxolone assay medium with higher concentration than 30 µM when investigating intestinal exposure interactions *in vitro*. Omaveloxolone concentration 30 µM inhibited BCRP by less than 50% (IC_{50} > 30 µM), while omaveloxolone concentration 5 µM displayed little to no inhibitory effects on the BSEP, OAT3,

OATP1B1, and OCT2. Performed *in vitro* studies are considered sufficient with regard to omaveloxolone poor solubility in aqueous media in the physiological pH range.

Other pharmacokinetic studies

Studies for ophthalmology and dermatology indications were presented by the applicant. However, taking into consideration the present application is for oral administration only, these studies were deemed not relevant and hence, they were not assessed in detail.

2.5.4. Toxicology

The systemic toxicity potential of omaveloxolone has been evaluated in multiple nonclinical GLP toxicity studies in rasH2 mice, rats, and monkeys after oral administration as well as in rats and minipigs after dermal administration, after which systemic exposure has been demonstrated comparable to levels observed after oral administration. Rats and monkeys were identified as the pivotal toxicity species, in which the toxicity profile of omaveloxolone has extensively been investigated. A large difference was observed in the ability of the two species to adapt to omaveloxolone-related effects, and toxicity was more pronounced in rats than in monkeys. Based on the general toxicity observed at almost all dose levels in the rats in the repeat- dose studies, which was not organ-specific in nature, it is acknowledged that rats appear to be very sensitive to treatment with omaveloxolone and are therefore not considered an appropriate non-clinical species to investigate the toxicological profile of omaveloxolone. Monkeys have in general been shown to more closely resemble human PK and physiology and are thus, considered the most relevant non-clinical species. Monkeys were chosen as the non-rodent non-clinical species in the omaveloxolone testing programme as dogs have previously been shown to develop species-specific gastrointestinal toxicity following repeated dosing with the chemically related substance, bardoxolone methyl. Toxicology studies were generally conducted using omaveloxolone formulated as a suspension in sesame oil, in contrast to the clinical formulation as hard capsules. A PK study in monkeys with amorphous omaveloxolone powder (with no excipients) in a loose-filled capsule were however performed demonstrating that systemic exposure to omaveloxolone, based on AUC, was approximately 25% to 50% of the exposure observed with a suspension. The suspension formulation is therefore considered to represent a worst-case level of exposure in toxicology studies, and it is acceptable that toxicity studies have been conducted with a sesame oil suspension as vehicle. Furthermore, the formulation intended for marketing authorisation, the hard capsules, contains common excipients only, i.e., novel excipients which would require further non-clinical testing are not used.

2.5.4.1. Single dose toxicity

No single dose toxicity studies have been conducted.

2.5.4.2. Repeat dose toxicity

The applicant conducted an extensive toxicology programme (190 unique nonclinical studies in total) encompassing several animal species (including different strains) and routes of administration. Duration and design of studies complies with ICH M3 Guideline for the chronic treatment. It is noted that majority of studies were conducted in 2012 and some (e.g., reproductive toxicology) later in 2019/2020. Some discrepancies were identified between batches used in non-clinical testing, which are addressed in section on Impurities below.

The primary target organs for omaveloxolone observed in rats and monkeys included the liver, kidney, and gastrointestinal tract. To elucidate the liver and kidney findings, two 14-days repeat dose oral studies in rats were performed to characterise the liver findings as well as explore potential biomarkers for the kidney effects. It is noted that NOAELs in rats decreases with increasing duration of the studies, which may be observed as a progression of effects over time due to chronic pharmacologically mediated Nfr2 upregulation.

Exposure-dependent increases in liver weight were observed in rats and monkeys, which were associated with dose-dependent centrilobular to panlobular hepatocellular hypertrophy. Further, minimal individual hepatocyte necrosis and changes in liver clinical chemistry markers indicative of liver injury (i.e., increases of total bilirubin, gamma-glutamyl transferase [GGT], alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) was observed in rats, as well as minimal to moderate biliary changes, including bile ductule hypertrophy and hyperplasia. These liver findings were generally reversible or shown to be in the process of reversing at the end of the recovery period. The liver weight increases, and hepatocellular hypertrophy were in general accompanied by increased levels of glycogen as well as increases in the smooth endoplasmatic reticulum as observed in the 14 days mechanistic rat studies. No ultrastructural evidence of peroxisome proliferation, mitochondrial abnormalities, abnormalities of other organelles, or lipid accumulation was observed. No microscopic correlates for the increased liver weights were observed at the end of the 39-week monkey study, supporting that liver weight increases in monkeys were not associated with any adverse liver findings as those observed in rats. The biliary hyperplasia observed in the rat was considered of low severity (minimal to mild) at ≥1 mg/kg in the 6 months study compared to minimal to severe in the 13-week study at ≥3 mg/kg. It has furthermore been observed not to affect functionality (e.g., cholestasis) and it has been linked mechanistically to choleresis in rats. Only minimal to mild bile duct hyperplasia was observed in monkeys at ≥30 mg/kg after 9 months treatment, resulting in higher exposure margins, indicating that monkeys are less sensitive to the adaptation of the liver changes. The liver effects do not seem to progress over time; however, they are observed to increase in severity in rats with dose and is not considered adaptive at higher dose levels. Aside from the liver effects, it appears that coagulation parameters may be affected in animals as increases in activated partial thromboplastin time was observed in monkeys. Also, lower erythrocyte mass and iron deficiency was observed as a consequence of treatment. Pharmacological activation of Nrf2 also resulted in increases in cholesterol levels as well as low-density lipoprotein (LDL) cholesterol in rats in the 6 months study. Mechanistically, Nrf2 is known to influence several factors that may impact cholesterol synthesis including fatty acid oxidation, nicotine amide dinucleotide phosphate (NADPH) production, and redox balance, and these effects are also observed in patients.

Squamous epithelial hyperplasia of mostly minimal to mild severity was observed in rats in the non-glandular squamous portion of the stomach (forestomach) and/or the limiting ridge of the stomach. The effects were fully reversible in the 28-day and 6-month oral and 13-week dermal GLP toxicity studies. One male rat at the high dose (3 mg/kg/day) in the 6-month chronic rat oral GLP toxicity study had squamous epithelial hyperplasia, which was associated with a squamous cell carcinoma involving the non-glandular and glandular stomach. Reversible squamous epithelial hyperplasia has also been observed in other, anatomically adjacent structures (i.e., oesophagus and larynx) in the 28-days and 6 months oral studies in rats as well as the 13-week dermal study. In the 3-month interim group of the 9-month monkey oral GLP toxicity study, squamous epithelial hyperplasia was observed in the oesophagus and larynx of monkeys, but not in the stomach. Similar findings were not present at the 9-month terminal sacrifice suggesting a transient response. The applicant states that the findings in monkey could be related to nonspecific, mechanical irritation related to oral gavage treatment in that study. However, hyperplasia in the oesophagus and larynx was not present in the control animals or any other treatment groups, indicating that the finding could be treatment related. The same is the case for the 6 months rat study; hyperplasia in larynx and oesophagus is limited to the high dose

treatment group, with no observations in the control group. The incidence of hyperplasia in different tissues observed across different species is further evaluated under the Carcinogenicity section below.

Tubular degeneration/regeneration was observed in rat kidneys following treatment with omaveloxolone as early as after 14 days of daily oral administration. It was mostly minimal/mild in severity but was accompanied by tubular epithelial cell necrosis and proteinuria at clinically relevant dose levels in the oral dosing studies (e.g., 1 mg/kg/day in the 6-months GLP study). With short treatment duration (e.g., 14 days of oral dosing), tubular degeneration/regeneration in rats was reversible with a 28-day treatment-free period (Study TA12-213); however, with an oral treatment duration of ≥28 days or a dermal treatment duration of 13 weeks, the effects did not reverse following a 28-day (oral studies) or a 2-month (dermal studies) recovery period. No changes in blood urea nitrogen (BUN) or serum creatinine (SCr) levels as well as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) was observed in rats. Tubular degeneration/regeneration was not observed in monkeys through 3 months of administration, but only observed as minimal focal tubular epithelial degeneration/regeneration without associated proteinuria after 9 months treatment in the high dose group (100 mg/kg/day), which was reversible after 28 days of recovery. No changes in BUN or SCr was observed in monkeys.

Mild cardiac myofiber degeneration/necrosis was observed in rats primarily at the highest dose level (30 mg/kg/day) in the 13-week oral study with a single incident at 10 mg/kg/day, which was associated with minimal to mild subacute/chronic inflammation and led to pre-term mortalities. No findings of cardiomyopathy were observed in rats at up to 3 mg/kg/day in the 6 months study. The applicant states that cardiomyopathy is a common background finding in the heart of aging rats but may be difficult to differentiate from treatment-induced myocardial changes. In the study report for the 13-week rat study, it is stated that microscopic pathology consistent with cardiomyopathy was present in males and/or females in all dose groups including controls in the 13-week oral rat study. However, in the unscheduled deaths, myofiber degeneration/necrosis was diffuse and associated with interstitial subacute/chronic inflammation and basophilic extracellular matrix and it is described in the study report that the findings may potentially be omaveloxolone-related. Furthermore, in the 28-days study in rasH2 mice, 3 male mice at the highest dose level (300 mg/kg/day) were found dead prior to scheduled sacrifice, with the cause of death attributed to light to moderate degeneration/necrosis of cardiac myocytes in the heart.

The treatment-related findings from the repeat dose toxicity studies are further discussed under "Discussion of non-clinical aspects" in relation to clinical relevance.

Interspecies comparison

An interspecies comparison between the exposure measured in animals (steady state AUC measured over 24 h) compared to the human AUC at steady state, measured over 24 h, revealed that findings in repeat dose toxicity studies in rats in general occur close to or below the recommended human dose level (i.e., ratios of <0.3 – 1.6). On the other hand, monkeys seem less sensitive to omaveloxolone-induced findings, ranging from exposure ratios of 2 – 5.5. Whereas developmental findings were generally observed at dose levels that also induced maternal toxicity, reprotoxic effects were observed in the F1 pups at a lower dose level than that at which maternal toxicity occurred in the rat the PPND study. The findings are further discussed below for the PPND in rats. Safety margins to developmental effects were in general low, and use of omaveloxolone during pregnancy is not recommended, as described in the summary of product characteristics (SmPC) sections 4.6 and 5.3.

2.5.4.3. Genotoxicity

Omaveloxolone was tested positive for clastogenic genotoxicity in a GLP-compliant *in vitro* mammalian chromosome aberration test in human peripheral blood lymphocytes. Omaveloxolone was however negative in the bacterial reverse mutation assay (Ames test) *in vitro* and was also considered negative *in vivo* in both the rat bone marrow erythrocyte micronucleus assay and the rat liver Comet Assay, as it was not observed to increase the incidence of micronucleated erythrocytes or induce DNA damage in liver cells. In spite of the positive *in vitro* chromosome aberration assay, the overall weight of evidence, including two negative GLP-compliant *in vivo* tests in rats, indicates a low genotoxic potential of omaveloxolone.

2.5.4.4. Carcinogenicity

In the 26-week carcinogenicity study in rasH2 transgenic mice, no non-neoplastic or neoplastic adverse treatment-related findings are reported in doses up to 30 and 100 mg/kg/day in males and females, respectively. Though several incidences of bronchoalveolar adenomas are observed, especially in the high dose group in males compared to concurrent controls (20%), it is accepted that the findings were within historical control ranges (24%) and these types of neoplasms are reported as common among this strain of mice. The other neoplastic findings were generally considered non-dose-response related and of low incidence within historical control ranges. Thus, treatment with omaveloxolone is not considered associated with an increased risk for carcinogenicity in rasH2 mice. Considering the NOAELs at the highest doses tested, safety margins of 14.6 for males and 54.5 for females was determined, compared to an exposure of 1.18 hr*µg/mL (area under the plasma concentration-time curve from time 0 to 24 hours [$AUC_{0\text{-}24hr}$]) in FA patients at clinically recommended dose levels.

As already presented and discussed under the Repeat-dose toxicity section, several findings of squamous epithelial hyperplasia in the nonglandular and glandular stomach, bile ductules, larynx and oesophagus have been observed in rats, which in one male rat in the 6 months repeat dose study progressed to malignant squamous cell carcinoma in the nonglandular portion of the stomach. Furthermore, hyperplasia of the larynx and oesophagus have been observed in monkeys at the interim 13-week investigations, whereas the observation had reversed by the end of the 9 months repeat dose study. Unlike the 26-week study, in the 28-days dose range finding (DRF) study in rasH2 mice, hyperplasia was observed in the tongue, oesophagus, nonglandular and glandular stomach in males at ≥30 mg/kg and at ≥100 mg/kg in females. For the incidence of hyperplasia of the larynx and oesophagus in both monkeys, rasH2 mice and rats, no observations were reported in the control groups, indicating that the effect was treatment related. While the argument presented by the applicant, that observations in the nonglandular part of the stomach is not clinically relevant, is in general supported, and while the rat does seem like a sensitive species in comparison to monkeys, the observed level of omaveloxolone-induced hyperplasia in many different tissues and in different species is of concern, as the clinical long-term implications for potentially sensitive patients are not clear. Given the overall negative genotoxic potential of omaveloxolone, a non-genotoxic mechanism of action for carcinogenic effect could be considered for the observed hyperplasia in rodent and non-rodent species. No long-term carcinogenicity study has been performed in a second species (rats) prior to MAA submission. The applicant has confirmed that a 2-year carcinogenicity study in rats is ongoing and that a final report will be submitted in September 2025, which will support the conclusion on the carcinogenic potential for omaveloxolone. As the submitted carcinogenicity study in rasH2 mice did not show any findings of hyperplasia or neoplastic findings, it is considered acceptable that that the available data for omaveloxolone points to a negligible risk for (non-genotoxic) carcinogenicity and that the planned 2-year carcinogenicity

study in rats are submitted as a post-authorisation measure variation by September 2025, which is also in line with the EMA scientific advice provided in March 2022 (EMA/SA/0000077358).

Mechanistically, the applicant has referred to investigations linking pharmacological activation of Nrf2 with hyperplasia/hyperkeratosis of squamous epithelium and gastrointestinal effects in animals. The applicant has submitted several investigations which show that genetically decreased levels of Keap1 can lead to hyperkeratosis and obstructive lesions within the upper digestive tract. The same mechanistic considerations can be assumed to occur for pharmacological agents that inhibit Keap1 with subsequent activation of Nrf2, such as omaveloxolone. None of the investigations have however correlated the reduction/inhibition of Keap1 and subsequent hyperplasia/hyperkeratosis with tumour formation. Some studies have correlated mutations in Keap1 or Nrf2 in human tumour cells, leading to high levels of sustained Nrf2 activity, with increased proliferation, chemoresistance and poor survival. Therefore, the applicant conducted a study investigating the correlation between the pharmacological effect on Keap1 inhibition/Nrf2 activation and promotion of cancer growth or therapeutic resistance in comparison with the effect of genetically modified levels of Keap1. According to the applicant, pharmacological Nrf2 activators do not have the same effect as Keap1 loss or mutation on cancer cell growth and survival as omaveloxolone did not increase cell proliferation or survival. On the contrary, several investigations point to chemopreventive properties of Nrf2 activators due to the reduction of oxidative stress and inflammation in the microenvironment of established tumours.

2.5.4.5. Reproductive and developmental toxicity

Male and female fertility were investigated in rats, including early embryonic development, however, no TK analysis was performed. Embryofetal developmental (EFD) toxicity in rats and rabbits were conducted, including TK analysis in both species. PPND toxicity was investigated in rats and concentrations of omaveloxolone were determined in milk and in pup plasma samples. No juvenile studies were conducted with omaveloxolone, which is acceptable (see below).

In a GLP-compliant fertility study in male and female CD rats (Study RTA-P-18016), no effects on fertility were observed in male rats up to 10 mg/kg/day. In female rats, an increase in pre- and post-implantation loss, resorptions (early and late), and a decrease in the number of implantation sites and the number of viable embryos was observed at 10 mg/kg/day. The NOAEL for female fertility and early embryonic toxicity is therefore 3 mg/kg/day, corresponding to 2-fold the human exposure at the MHRD of 150 mg. It is noted that the fertility study does not follow the recommendation on the duration of the study for the female fertility. To conclude on the oestrous cycle, data from 2 or 3 cycles are needed to exclude intra- and inter-animal variability. The study director has however compared the data with the historical control instead of baseline cycle data of the enrolled females, which is acceptable. Of note, an increase in seminiferous tubule degeneration and cellular debris in the lumen of the epididymis in rasH2 mice was observed in the 28 days DRF study at the highest dose tested (300/150 mg/kg/day). No TK was measured in the study, however, in the definitive 26-week rasH2 mice carcinogenicity study, the highest dose tested (30 mg/kg/day) corresponded to an exposure margin of 14.6. Therefore, the male fertility findings in the DRF study in rasH2 mice are considered not clinically relevant.

In a non-GLP DRF study for the EFD study in rats, toxicity was investigated in 5 females per dose group at 1, 3, 10 or 30 mg/kg/day (Study RTA-P-18014). While maternal toxicity was observed ≥ 10 mg/kg/day (increased liver weights), developmental toxicities were observed at 30 mg/kg/day, such as a decrease in number of viable fetuses, litter size, gravid uterine weight (-50%), and fetal body weight (males, females, and sexes combined; -19.8%, -21.0%, and -20.0%, respectively), and increased percent of post-implantation loss and the number of early and late resorptions compared to concurrent controls. In the GLP-

compliant pivotal EFD study in 20 female rats per group, no effects were observed on either the maternal or fetal parameters evaluated at dose levels up to 10 mg/kg/day. The overall NOAEL for EFD effects in the rat is considered 10 mg/kg/day, corresponding to an exposure margin of 6.3.

In a GLP-compliant EFD study in 20 female rabbits per dose group, maternal toxicity was observed at 30 mg/kg/day consisting of few/absent/tan discolored feces, thin body condition and reduced food consumption. This resulted in lower mean gestation body weights beginning on GD 16 and continuing for the remainder of the study. Two females aborted at 10 mg/kg/day and were euthanised and further 3 females aborted and were euthanised at 30 mg/kg/day. Furthermore, embryofetal toxicity was observed at 30 mg/kg/day, including increased in post-implantation loss, number of resorptions and number of late resorptions as well as lower male and female fetal body weights. At the dose of 30 mg/kg/day, a statistically significant increased litter incidence (87.5%) of unilateral full rib (variation) was observed in comparison to concurrent controls (litter incidence of 42.1%). The variation was considered treatment-related and was reported to be slightly outside recent historical control data (litter incidence of 84.2%). The applicant does not consider the variation adverse due to the slight magnitude of difference from the historical control data, and they argue that it would have no impact on fetal viability, which is accepted. The maternal NOAEL is considered 3 mg/kg/day and the developmental NOAEL is considered 10 mg/kg/day in rabbits, corresponding to exposure margins of 0.3 and 0.7, respectively.

In the PPND study in rats (1, 3 and 10 mg/kg/day oral dosing), omaveloxolone-related observations in parental (F0) females administered 10 mg/kg/day included decreased mean body weights, decreased mean food consumption, and increased macroscopic observations of enlarged livers. The study director however concluded that the differences were not considered adverse. Thus, the parental NOAEL is determined at 10 mg/kg/day. In F1 offspring, omaveloxolone-related toxicity was observed in pups at 10 mg/kg/day, including an increased percentage of litters with stillborn pups, reduced first generation pup survival, decreased mean pup body weights, an increased age of attaining preputial separation in male pups as well as a decreased mean numbers of corpora lutea and implantation sites in female pups. In relation to the recent authorisation of Skyclarys by FDA, it is noted that FDA has included the following text in the Prescribing Information under 8.1: "*Oral administration of omaveloxolone (0, 1, 3, or 10 mg/kg/day) to rats throughout pregnancy and lactation resulted in an increase in stillbirths and impaired neurobehavioral function (increased locomotor activity and learning and memory deficits) in offspring at all doses…*". Effects on learning and memory were investigated in the PPND study using a step-through passive avoidance test, which did not reveal any treatment-related effects. It is accepted that the PPND study did not include specific tests methods investigating complex learning tasks such as the water maze (as specified in ICH S5 (R3)), as ICH S5 (R2) was in force at the time of conduct of the study, which does not include any specific requirements on test methods for investigating effects on learning and memory. The only observation of potential neurobehavioral impairment in the PPND study (RTA-P-18019) arises from the observation of increases in basic movement count and total distance in males at the highest dose group and females at all dose levels. However, the impairment is only observed during the first or first two 5-minute intervals post-dose, respectively, and otherwise is not observed again during the rest of the observation period for up to 60 minutes. Therefore, it is assessed that the effect should not be observed as adverse, and it is not considered warranted to include the observation in the SmPC. Additionally, though omaveloxolone is able to penetrate the blood-brain barrier, it appears there is a low risk for off-target activity in the CNS based on the negative outcome in a SafetyScreen44 Panel study (Study RTA-P-18007) when tested against a panel of receptors, ion channels, transporters, and enzymes.

TK investigations in the study demonstrated that omaveloxolone is excreted in the milk of lactating dams, and increasing doses of omaveloxolone is measured in the plasma of the pups, correlating to dose levels

administered to the dams. Based on the findings in the F1 offspring, the developmental NOAEL in rats is considered 3 mg/kg/day. Using the TK data in the definitive EFD rat study, the AUC at 3 and 10 mg/kg/day is 2.44 and 7.38 h*µg/ml, corresponding to exposure margins of 2.1 and 6.3.

Skyclarys is indicated for the treatment of FA in adults and adolescents aged 16 years and older. No justification for omission of juvenile animal studies was provided by the applicant. However, considering the target organs of toxicity (gastrointestinal tract, liver and kidney) identified in the young and adult animals in pivotal repeat-dose toxicity studies, no higher sensitivity to toxicity in comparison to adults is expected as these organs are already fully developed in the proposed paediatric population (16-18 years). It is therefore accepted that no non-clinical studies in juvenile animals have been conducted to support the indication. Moreover, studies in rats and monkeys were initiated at age of animals corresponding to 12-16 years of age in humans and thus submitted studies sufficiently cover toxicity profile for the aimed paediatric population. The juvenile population group (16-18 years) is furthermore included in the clinical trial studies. This is in accordance with the PIP (EMEA-C1-002487-PIP01-18).

2.5.4.6. Toxicokinetic data

See PK section on absorption.

2.5.4.7. Local tolerance

A full dermal toxicological package as well as ocular studies were conducted by the applicant in relation to another indication (psoriasis) and have been submitted by the applicant in this MAA as supportive information. No local tolerance was observed in connection with dermal application of omaveloxolone in a GLP-compliant 13-weeks study in rats. Hyperplasia in the gastrointestinal tract and surrounding tissues was observed in rats and monkeys in the repeat-dose studies, which the applicant argued was procedure-related after oral gavage administration. A further discussion is included in the repeat dose toxicity and carcinogenicity sections above.

2.5.4.8. Other toxicity studies

Considering the type of molecule (small molecule), investigations of antigenicity and immunotoxicity are not required for omaveloxolone.

Dependence

Omaveloxolone is a Nrf2 activator, intended for treatment of FA, which is a rare autosomal recessive neurodegenerative disorder that leads to degeneration and demyelination of spinocerebellar dorsal root ganglion neurons and primarily affects the central and peripheral nervous system. Distribution to the CNS is observed, as described above in the Distribution section. The potential for misuse is described in the risk management plan (RMP) Part II, module SVI. According to the applicant, there were no off-target effects with a broad range of receptors (G protein-coupled receptors and nuclear receptors), ion channels, transporters, and enzymes in assays commercially available as the SafetyScreen44™ Panel (Eurofins Cerep-Panlabs) (Study RTA-P-18007) up to 2000 nM ~500X MoS (C_{max}, unbound). No CNS effects were observed neither in safety pharmacology study nor in repeat-dose toxicity studies. Overall, these data indicate that omaveloxolone shows no meaningful off-target CNS activity and no additional studies or assessment on dependence potential is warranted.

Metabolites

Two major metabolites have been identified in humans: M22 (TX304579) and M17 (TX304571). M17 is observed at higher levels in rats and monkey plasma compared to patients, and the toxicity profile is considered to be covered by the toxicological assessment of omaveloxolone. Furthermore, in silico evaluations using Leadscope Genetox Statistical Model Applier Version 2.3.3 and Derek Nexus 6.0.1 did not fire any positive alerts for mutagenicity for M17, classifying the substance as class 5 according to ICH M7. As described in the PK section on metabolites above, M22 is considered a disproportionate metabolite, as it has been quantified in higher amounts in humans compared to monkeys and rats. No dedicated repeat-dose studies have been conducted with M22 to assess the toxicity. An *in silico* evaluation was also conducted for M22 using Leadscope Genetox Statistical Models and Lhasa Derek Nexus, which did not identify any alerting mutagenic structures. A non-GLP, non-guideline Ames test, using only 4 strains of *S. typhimurium* and concentrations up to 100 µg/plate, was performed with M22. The applicant argues that technical and logistic challenges did not allow for higher amounts to be tested. Under the study conditions, M22 was negative for bacterial mutagenicity. Taking all information provided into account, as also discussed in the section on metabolites under PK, the higher exposure in patients to M22 compared to monkeys and rats is not likely to result in any additional observed toxicity, and it is accepted that no further information is provided in order to qualify M22.

Impurities

From the list of potential impurities, only three were identified as potential bacterial mutagens based on in silico evaluations of the substances; classifying them as class 3 impurities according to ICH M7The majority of the remaining impurities were identified as class 5 impurities according to ICH M7 based on negative in silico predictions using Lhasa Derek Nexus and Leadscope modelling tools. Some impurities fired a positive alert using one of the tools, however, as the alert was based on the same structural feature as that contained in the parent compound or a structural similar analogue for which negative Ames data is available, the positive prediction was rejected and the impurities were classified as class 4 impurities. This is acceptable.

The applicant referred to impurity profiles in the pivotal repeat-dose toxicology studies in rats and monkeys to toxicologically qualify the proposed limits.

The majority of the repeat-dose toxicology studies were conducted in 2012 and some (e.g., reproductive toxicology) later in 2019/2020. When comparing the batch impurity profile, it is noteworthy that no impurities were detected in the reproductive toxicology studies in rats and rabbits (batch G-17-016 using method QAL-SM-1824.01 from Study 20-EDHP-2043) while impurities were found in the 28-day and 9-month repeat-dose toxicity studies in monkeys used for impurity qualification and DP specification. To account for differences in the analytical methods used in the different repeat-dose studies, some older batches were reanalysed using the proposed commercial analytical method. Impurities were previously calculated based on w/w values at D150 and considered as acceptable further justification has been provided referring to Study RTA-P-20021 "Exposure Margin Determination for RTA 408 and Identified Metabolites in Mixed-Matrix-Normalized Monkey and Human Plasma". It is agreed that provided study data indicates that the metabolite's exposure is adequately covered in animals (assuming to be 0.84/day mg at 30 mg) and the proposed acceptance criteria of 0.25% in drug substance and 0.3% in drug product (0.45 mg/day or 0.009 mg/kg/day for 50 kg patient at MDD of 150 mg) are toxicologically justified.

Phototoxicity

The applicant has adequately demonstrated that omaveloxolone does not absorb light over the wavelength range of 290 to 700 nm (maximum absorption at 242 nm). The maximum molar absorptivity at 332 nm of 87

$L \cdot mol^{-1}\ cm^{-1}$ is less than 1000 $L \cdot mol^{-1}\ cm^{-1}$ and thus, the requirement for further phototoxicity investigations according to ICH S10 is not triggered.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1: Environmental risk assessment of omaveloxolone

Substance (INN/Invented Name): omaveloxolone					
CAS-number (if available): -					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	5.23			Potential PBT Yes
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow} at pH 6.8 (OECD 123)	5.23			B
	BCF (OECD 305)	-			B/not B
Persistence	DT50 or ready biodegradability (OECD 301 or 308)	-			P/not P
Toxicity	NOEC or CMR	-			T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0015	µg/L			> 0.01 threshold N
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = $DT_{50,\ sediment}$ = $DT_{50,\ whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	

An initial persistence, bioaccumulation and toxicity (PBT) screening was performed by the applicant for omaveloxolone, identifying a logPow value of 5.23 using the OECD 123 GLP method via slow stirring. Though

omaveloxolone is an ionisable compound with a pKa of 7.26 and logDow should have been determined at 3 different pH values according to guidance, it is accepted that logPow is only identified at pH 6.8 as the identified logPow is above the PBT trigger limit. As the logPow is above both trigger limits 3 and 4.5, a definitive PBT assessment should be performed according to the ERA guideline (EMEA/CHMP/SWP/4447/00 corr 2* and EMA/CHMP/SWP/44609/2010 Rev. 1).

When the trigger value of log Kow > 4.5 is met, a definitive PBT assessment should be conducted, consisting of sequentially testing and evaluating persistence, then bioaccumulation, then toxicity. First, it should be tested if the substance is readily biodegradable (OECD 301). If not, OECD 308 and/or OECD 307 or OECD 309 study should be performed to evaluate the P criterion. If the P criterion is fulfilled, an assessment of bioaccumulation should be performed by conducting an OECD 305 study (bioaccumulation in fish). Finally, an assessment of toxicity should be performed according to the ERA guidelines, i.e., conducting chronic toxicity studies in algae/cyanobacteria (OECD 201), then Daphnia (OECD 211) and then fish (OECD 210).

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of omaveloxolone to the environment. The applicant has committed to submit the required definitive PBT assessment during the post-authorisation phase following a tiered approach no later than 1st June 2025.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The effect of omaveloxolone to restore Nrf2 levels and activity, rescue mitochondrial dysfunction, restore redox balance, and suppress inflammation were adequately characterised in PD *in vitro* models of FA and *in vivo* relevant animal models.

Nrf2 is a transcription factor that regulates many aspects of cellular metabolism, redox balance and bioenergetics. Omaveloxolone was shown to activate Nrf2 target genes including Nqo1, Hmox1, Gclm, Txnrd1, Gclc and Fth1 in a variety of murine and human cell lines. Omaveloxolone promoted improved mitochondrial function when tested *in vitro* in conditions with and without oxidative stress in C2C12 mouse myoblasts and such activity is lost in test systems with targeted deletion of Nrf2. Omaveloxolone suppressed inflammatory cytokines e.g., and TNF-γ and IFN-γ in a variety of cell lines. In multiple cell-based models of FA including in cells isolated from patients with FA omaveloxolone activated Nrf2, restored mitochondrial function, increased substrate availability for the mitochondrial electron transport chain, restored redox balance and protected mitochondria and cells from the deleterious effects of oxidative stress.

In vivo omaveloxolone was shown to induce expression of Nrf2 target genes using tissues collected from healthy omaveloxolone-treated mice, rats and monkeys. From preliminary data on PD and PK clinical doses of 150 mg, which are associated with meaningful improvements in neurological function in patients with FA, generated plasma omaveloxolone concentrations after oral dosing that were consistent with those that had been shown to significantly induce Nrf2 target genes in monkeys. Because well-established animal models of Friedreich's ataxia are not commercially available, omaveloxolone was tested in several rodent models of neurological disease and demonstrated efficacy *in vivo* in the experimental autoimmune encephalomyelitis mouse model of multiple sclerosis and in a mouse model of epilepsy.

The number of *in vivo* efficacy studies of omaveloxolone in the dossier was rather limited. From the scientific literature it is generally recognised that no well-established and optimal animal models to study Friedreich's

ataxia are currently available. On one side conditional murine knockout models that reproduce key elements of the human disease have been utilised but they lack the genetic background. On the other side animal models expressing the mutation in patients of FA including GAA repeat expansion-based knock-in and transgenic mice have also been used however, these models only show a very mild phenotype of the disease. Although relying mainly on *in vitro* studies proof of concept and mode of action of omaveloxolone in the disease to be treated and the proposed indication was considered satisfactorily demonstrated.

In vitro studies with omaveloxolone showed low activity against a broad panel of receptors, ion channels, transporters and enzymes at doses far exceeding concentrations in patients with FA administered the MRHD of 150 mg.

The safety pharmacology programme demonstrated that there were no omaveloxolone-related adverse effects on the CNS or respiratory function of the rat. Omaveloxolone had no meaningful effect in the *in vitro* hERG assay and ECG parameters collected after single- and repeat-dose in monkeys identified no safety concern with regard to risk for QT prolongation at the doses tested. Hence, the *in vitro* and *in vivo* studies in rats and monkeys suggest omaveloxolone is unlikely to adversely affect the central nervous, respiratory, or cardiovascular systems in humans when given up to 150 mg daily.

Pharmacokinetics

The bioanalytical programme for omaveloxolone appear to have been well in control, when used in the GLP-compliant pivotal repeat-dose toxicity studies.

Extensive PK investigations have been performed in monkeys to elucidate ADME characteristics. Limited PK investigations have been performed in rats, and information on absorption and excretion is considered missing. It is however accepted that the PK profile in rats is not further investigated, as it appears that monkeys are more clinically relevant. Rats are more sensitive to omaveloxolone compared to monkeys based on the general toxicity observed in rats. However, data presented by the applicant indicates that the toxicity profile in rats may be of limited clinical relevance.

PK DDI studies of omaveloxolone were considered to be adequate.

Toxicology

Hepatic toxicity

Findings related to liver injury was observed in both mice and rats but were most pronounced in rats. The applicant provided a comprehensive discussion on the liver findings and the potential responsible mechanisms. As observed in the 14 days mechanistic rat studies liver weight increases and hepatocellular hypertrophy were in general accompanied by increased levels of glycogen as well as increases in the smooth endoplasmic reticulum. The applicant argues that the glycogen change may be due to altered transcription of genes involved in glycogen storage/lysis while changes in smooth endoplasmic reticulum may be due to increased expression of several cytoprotective enzymes, specifically the known primary Nrf2 target genes. Further, the applicant argues that the observed bile ductule hypertrophy and hyperplasia may be an adaptive physiological response due to omaveloxolone-mediated activation of Nrf2 receptors in the bile ductule, which induces glutathione synthesis and thus affects glutathione-dependent bile flow. Thus, oral administration of omaveloxolone activates Nrf2 and induces expression of enzymes important in the synthesis and homeostasis of glutathione, which, in turn, increases osmotic forces driving bile flow. In the clinic, drug-induced liver injury (DILI) is an important potential risk and will be followed by a PASS registry study. It is also contraindicated in patients with severe or moderate hepatic impairment as described in the SmPC. The liver findings in rats are not considered adaptive, and the severity of adversity depends on the organism's capacity to adapt to

treatment-related effects. The effect is therefore considered a potential clinical risk for patients but is adequately reflected in the SmPC and RMP.

Renal toxicity

Irreversible tubular degeneration/regeneration was observed in rat kidneys following treatment with omaveloxolone after 28 days of daily oral administration and was accompanied by tubular epithelial cell necrosis and proteinuria at clinically relevant dose levels in the oral dosing studies (e.g., 1 mg/kg/day in the 6-months GLP study). According to the applicant, literature indicates that similar findings of tubular degeneration/regeneration have been reported as background findings in rats with incidence increasing with age. The applicant also argues that the finding is suggestive of a remodeling process and that the findings reflect the low tolerability of rats towards omaveloxolone. Furthermore, no findings of negative functional impact have been observed, such as changes in BUN or SCr levels, and in addition, they were not associated with signs of chronic inflammation or fibrosis up to 6 months of daily oral administration. In the mechanistic 14-days studies, potential urinary biomarkers for kidney effects were explored, e.g., KIM-1 and NGAL. Though increased urinary KIM-1 levels were associated with mild to moderate tubular degeneration/regeneration in Study TA12-213, no cell death was observed, and increase in KIM-1 was not consistently associated with observations of histological changes in every animal. In monkeys treated up to 9 months, minimal to mild tubular degeneration/regeneration with no apparent effect on kidney function, chronic inflammation or fibrosis was observed at 4-fold MHRD. At dose levels corresponding to 1.7-fold MHRD, no signs of kidney toxicity were observed. In addition, the applicant has presented several publications in rats and mice that show an improvement in kidney function upon treatment with omaveloxolone analogs in animal models of kidney injury, specifically showing a reduction in tubular interstitial inflammation and fibrosis. Mechanistically, this is associated with reduction of albumin, and it is argued that Nrf2 activators reduce kidney injury by protecting the tubules from the damaging effects of excessive albumin. No sign of glomerular injury was observed in the 28-day repeat- dose study in rats, which, according to the applicant, would have been expected as proteinuria is known to occur mainly due to increased glomerular filtration rate or damage to the glomerular filtration barrier. The applicant therefore states that it is unlikely that the proteinuria in rats was caused by glomerular injury, but speculates that it may be caused by megalin, a protein that is involved in the tubular reabsorption of albumin. In the clinical trials, no fibrosis has been observed in patients treated with omaveloxolone. In contrast, an improvement in kidney function has been observed. Based on the data and rationale provided by the applicant and considering that the monkey appears to be the most relevant non-clinical species, it is accepted that the clinical risk of kidney injury appears to be low.

Cardiac toxicity

An increased risk of cardiomyopathy is reported in FA patients and cardiomyopathy accounts for about half of deaths in advanced stages of the disease, mainly affecting young patients below the age of 40 years (Delatycki and Corben, 2012[1]; Bürk 2017[2]). Furthermore, congestive heart failure is included in the safety specification as an important potential risk. According to Mathis, 2022[3], Nrf2 activating xenobiotics (e.g., bardaloxone) have been associated with negative myocardial pathologies, resulting in termination of multiple clinical trials and induction of cardiomyocyte hypertrophy and heart failure after chronic Nrf2 upregulation in animal studies. For bardoxolone, it has been shown that sustained increases of Nrf2 resulted in injured kidneys and proteinuria, possibly linked mechanistically with the inactivation of Keap1 suppression. Due to the concerns regarding the role of exogenous Nrf2 activation by pharmaceutical compounds in the potential

[1] Delatycki MB and Corben LA. Clinical features of Friedreich ataxia. J Child Neurol. 2012 Sep;27(9):1133-7.
[2] Bürk Cerebellum & Ataxias (2017) 4:4 DOI 10.1186/s40673-017-0062-x
[3] Mathis, B.J.; Kato, H.; Hiramatsu, Y. Induction of Cardiac Pathology: Endogenous versus Exogenous Nrf2 Upregulation. Cells 2022, 11, 3855. https://doi.org/ 10.3390/cells11233855

increased risk of cardiomyopathy in a FA patient population already at risk, the applicant was asked to thoroughly discuss the pharmacological mode of action in relation to the observations in animals and the clinical implications.

In monkeys, no cardiotoxic findings were observed in repeat- dose studies for up to 9 months at 4-fold the MHRD in FA patients, also with no cardiovascular findings in the safety pharmacology studies. Also, no cardiotoxic findings were observed in minipigs at clinically relevant dose levels. Two findings of cardiomyopathy were observed in rodents; one in the 28-days non-GLP dose range finding study in Tg-rasH2 mice and one in the non-GLP 13-weeks study in rats. Both occurred at high non-clinically relevant dose levels, and the effect was not observed in the GLP studies of longer duration. The applicant argued that Tg-rasH2 mice are not a good model for general toxicity, which is acknowledged. Rats have been shown to be more sensitive to omaveloxolone than monkeys, and it is accepted that the effects in rats at high dose levels may not be clinically relevant. Further, the applicant argued that the non-clinical models included in the article by Mathis, 2022, which is based on genetic inactivation of Nrf2, is not reflective of pharmacologically induced Nrf2 activation. Therefore, the results referred in Mathis, 2022 should be interpreted with care, when translating these to the effects of pharmacologically mediated Nrf2 activation.

B-type natriuretic peptide (BNP) is identified as an important regulator of vascular resistance, blood pressure, and natriuresis, promoting increased downstream vasodilation and natriuresis, thereby reducing cardiac hypertrophy and fibrosis and promoting renal protection (Okamoto, 2019[4]). However, Okamoto, 2019 has also described that the cardiac release of BNP represents an important compensatory mechanism during cardiac overload and pathogenesis of heart failure, with elevated plasma BNP levels correlating with the severity of heart failure and fluid retention. The applicant has referenced literature supporting that low levels of BNP are associated with metabolic risk factors such as obesity, lipid profiles and metabolic syndrome, and increases in BNP can be correlated with improvement in associated metabolic parameters. In a study in C57BL/6J mice fed high-fat diet for 12 weeks, the effects of 2 different omaveloxolone analogues administered PO (15 mg/kg/day RTA 403; 25 and 50 mg/kg/day RTA 405) were assessed in relation to body weight, Nrf2 activation, and BNP expression (Study RTA-P-19008). In the study, the omaveloxolone analogues attenuated or reduced weight gain, which was correlated with BNP upregulation in treated mice. No cardiac hypertrophy or increased heart weights was observed during the study. The applicant therefore concludes that the omaveloxolone analogues prevent cardiac hypertrophy while increasing BNP expression due to their beneficial effect on metabolic risk factors in the mouse model. According to the applicant, the non-clinical data furthermore indicates that omaveloxolone/Nrf2-mediated changes in metabolism may be responsible for increased BNP expression and associated increase in BNP observed in clinical trials with omaveloxolone, and that increased BNP levels should therefore not be observed as an indicator of cardiac injury during treatment with omaveloxolone, but rather a protective effect. As no signs of fluid overload or heart failure was observed in the clinical or non-clinical studies following treatment with omaveloxolone, it is accepted that the slight increase in BNP should be viewed as a part of metabolic reprogramming rather than cardiotoxicity.

Overall, it seems unlikely that the singular observations of cardiotoxicity in rodent studies at high dose levels are translatable to humans. Taking the mechanistic considerations as well as the supportive non-clinical and clinical information into account, from a non-clinical point of view, it does not appear that omaveloxolone is likely to increase the cardiovascular risk for FA patients.

[4] Okamoto R, Ali Y, Hashizume R, et al. BNP as a major player in the heart-kidney connection. Int J Mol Sci 2019; 20:3581.

Carcinogenicity

Several findings of squamous epithelial hyperplasia in the nonglandular and glandular stomach, bile ductules, larynx and oesophagus have been observed in rats, which in one male rat in the 6-month repeat-dose study progressed to malignant squamous cell carcinoma in the nonglandular portion of the stomach. Hyperplasia was also observed in monkeys (larynx and oesophagus) and rasH2 mice (tongue, oesophagus, nonglandular and glandular stomach). For the incidence of hyperplasia of the larynx and oesophagus in both monkeys, rasH2 mice and rats, no observations were reported in the control groups, indicating that the effect was treatment related. The applicant however adequately argued that mechanistically, the induction of hyperplasia can be accounted for; also, there is no evidence that the hyperplasia will develop into tumours. On the contrary, the applicant submitted data indicating that Nrf2 activators may have chemopreventive properties as they are able to reduce the level of oxidative stress and inflammation in the microenvironment of established tumours. A final report for a full 2-year carcinogenicity study in rats will be submitted in September 2025, which will support the conclusion on the carcinogenic potential for omaveloxolone.

The non-clinical findings are correctly reflected in SmPC (section 4.6 and 5.3) and the RMP.

Ecotoxicity/environmental risk assessment

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of omaveloxolone to the environment.

The applicant commits to perform the following studies as follow-up measures: definitive PBT assessment following a tiered approach no later than 1st June 2025.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary PD studies provided adequate evidence that omaveloxolone is a potent Nrf2 activator and thus, induces a mitochondrial bioenergetic, antioxidative, and anti-inflammatory phenotype which may be beneficial in patients with FA. Proof of concept, mechanism of action and mode of action of omaveloxolone were demonstrated despite a limited number of *in vivo* efficacy studies. When assessed against a panel of receptors, ion channels, transporters and enzymes no significant off-target activity of omaveloxolone at clinically relevant doses was observed. *In vitro* and *in vivo* safety studies in rats and monkeys suggest omaveloxolone is unlikely to adversely affect the central nervous, respiratory, or cardiovascular systems in humans when given up to 150 mg daily. Studies on PD DDI were not conducted.

The PK of omaveloxolone appears to be well described in monkeys, which is also considered to be the most clinically relevant non-clinical species. It is accepted that no further PK data is provided for rats.

Large differences in susceptibility to omaveloxolone-induced effects were observed between the two pivotal toxicity species, monkeys and rats. Reversible signs of liver toxicity were observed in rats at clinically relevant dose levels (increased liver weight, hepatocyte necrosis, increases of total bilirubin, GGT, ALT, and AST). Similar effects were also observed in monkeys, however, not to the same extent. Irreversible tubular degeneration/regeneration in the kidneys of rats were observed at clinically relevant dose levels, which was accompanied by tubular epithelial cell necrosis and proteinuria, however, in monkeys, only reversible minimal focal tubular epithelial degeneration/regeneration without associated proteinuria was observed after 9 months treatment. Hyperplasia was observed in several tissues in both rats and monkeys, where hyperplasia in one instance progressed to a squamous cell carcinoma involving the non-glandular and glandular stomach in one rat. Based on the available data, it seems there is a low risk that the observed hyperplasia will develop

into tumours and the clinical risk appears to be low. However, a final report will be submitted for a 2-year carcinogenicity study in September 2025 to confirm the carcinogenic potential. Observations of mild cardiac myofiber degeneration/necrosis in rats and rasH2 mice at the highest dose level tested raised concern, as cardiomyopathy, including effects on kidney, could be related to the pharmacological mode of action. However, the applicant provided a thorough discussion on available data and mechanistic considerations regarding Nrf2 activation, and overall, it does not appear that omaveloxolone is likely to increase the cardiovascular risk for FA patients from a non-clinical point of view. The SmPC section 4.6 and 5.3 and the RMP have been amended by the applicant and there are no further comments.

From a non-clinical point of view, the application is considered approvable.

The CHMP recommends the following measures in relation to the non-clinical issues:

- The applicant should submit the final report for the 2-year carcinogenicity study in rats in no later than September 2025and update the risk assessment according to the results.
- The applicant should submit the required definitive PBT assessment following a tiered approach no later than 1st June 2025.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Identifier NCT# EudraCT#	Study Design (Duration) Status Database Lock	Location (s)	Treatment	Number of Patients Enrolled Adolescents (<18 years old)
Study 1402 Part 1 NCT02255435 EudraCT 2015-002762-23	Randomized, double-blind, dose-ranging Placebo-controlled (16 weeks: 12 weeks on treatment plus 4 weeks off treatment) Completed 27 Jun 2017 (final)	United States, Austria, and Australia	Omav: 2.5 mg for 2 weeks followed by dose escalation to 5 mg/10 mg/ 20 mg/40 mg/ 80 mg/160 mg/ 300 mg, oral, QD Placebo, oral, QD	69: 52 Omav/17 placebo 9: 6 Omav/3 placebo
Study 1402 Part 2 NCT02255435 EudraCT 2015-002762-23	Pivotal study Randomized, double-blind, parallel-group Placebo-controlled (52 weeks: 48 weeks on treatment plus 4 weeks off treatment) Completed 12 Nov 2019 (final)	United States, Austria, Italy, United Kingdom, and Australia	Omav: 150 mg, oral, QD Placebo, oral, QD	103: 51 Omav/52 placebo 24: 9 Omav/15 placebo
Study 1402 Extension NCT02255435 EudraCT 2015-002762-23	Open-label, long-term extended access Median Omav treatment duration is currently 2.75 years [exposure in Study 1402 Extension only] Ongoing 24 March 2022 (interim)	United States, Austria, Italy, United Kingdom, and Australia	Omav: 150 mg, oral, QD	149 Omav (Placebo-Omav = 106; Omav-Omav = 43) 11 Omav

Abbreviations: EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; NCT=National Clinical Trial (number; the ClinicalTrials.gov identifier); Omav=omaveloxolone; Omav-Omav=omaveloxolone - omaveloxolone (the set of patients randomised to omaveloxolone in Study 1402 Part 2 who then continued with omaveloxolone treatment in Study 1402 Extension); Placebo-Omav=placebo - omaveloxolone (patients from Study 1402 Part 1 and patients randomised to placebo in Study 1402 Part 2 who then all received treatment with omaveloxolone in Study 1402 Extension); QD=once daily.

Study Identifier/Phase	Type of Study	Number of Healthy Subjects/Patients	Dose Form(s) Studied	Duration of Treatment
408-C-1703/ Phase 1	Biopharmaceutic and Clinical Pharmacology Part 1: Food effect Part 2: Dose proportionality	34 Omav Part 1: 16 Part 2: 18	50, 100, and 150 mg	Part 1: single dose in each period (fasted or fed), with confinement for 6 days after dosing (each period) Part 2: single dose, with confinement for 6 days after dosing
408-C-1805/ Phase 1	Clinical Pharmacology: AME	8 Omav	150 mg	Single dose, with maximum stay through Day 23
408-C-1806/ Phase 1	Clinical Pharmacology: DDI Part 1: midazolam, repaglinide, metformin, rosuvastatin/digoxin cocktail Part 2: gemfibrozil Part 3: itraconazole Part 4: verapamil	61 Omav Part 1: 16 Parts 2, 3, and 4: 15 each	150 mg	Part 1: approximately 9 weeks total duration of study with QD Omav on Days 12 to 27 Parts 2, 3, and 4: 8 weeks total duration of study with QD Omav on Days 1 and 13
408-C-1804/ Phase 1	Clinical Pharmacology: Hepatic impairment	32 Omav	150 mg	Single dose, with follow-up through Day 15
Total Patients		135 Omav		

Abbreviations: AME=absorption, metabolism, and excretion; DDI=drug-drug interaction; Omav=omaveloxolone; QD=once daily.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalysis

The concentration of omaveloxolone in plasma was determined using validated LC-MS/MS methods. PK-samples from clinical studies were measured in three laboratories (Abbvie, Q2 solution and Covance) and the bioanalytical methods was validated in each laboratory. The bioanalytical method of Abbvie was validated however with some deficiencies. The bioanalytical methods of Q2 Solutions and Covance passed all validation criteria and were demonstrated to be selective, linear, robust, and reliable. The in-study QC samples, the data of back-calculated calibration standards and ISR results demonstrated reliable performance of these methods during analysis of study samples. Samples were analysed under conditions and within periods covered by the stability studies. The Abbvie method was cross validated with the method of Q2 Solutions.

The PK of omaveloxolone was mainly determined with the two reliable bioanalytical methods of Q2 solutions and Covance. DDI probe substrates were also quantified with validated LC-MS/MS methods.

Population PK model

The population PK (popPK) analysis was performed with a nonlinear mixed effects modelling approach using NONMEM version 7.4.3 with first-order conditional estimation with interaction.

The popPK model (report REAT-PMX-OMAV-2081) was developed for omaveloxolone using the results from 5 studies (408-C-1402, 408-C-1403, 408-C-1703, 408-C-1804, and 408-C-1806) with data from healthy subjects and patients with FA and mitochondrial myopathy with the purpose of identifying intrinsic and extrinsic factors that affect omaveloxolone concentrations in plasma of adult healthy subjects and patients with FA. Number of subjects, measurable observations, and below the lower assay limit of quantification observations across studies are summarised by study, number of subjects, and measurable observations excluded from the analysis in Table 2.

Table 2: Plasma concentrations in the PK analysis dataset

Study	Subjects (No. of Excluded Subjects)	Measurable Observations (No. of Excluded Observations)	BLQ Observations
408-C-1402	102 (1)	718 (11)	8
408-C-1403	38 (0)	244 (10)	5
408-C-1703	34 (0)	831 (3)	47
408-C-1804	32 (0)	658 (0)	35
408-C-1806	45 (0)	884 (1)	45
Total	251 (1)	3310 (25)	140

Abbreviations: BLQ=below the lower assay limit of quantitation; PK=pharmacokinetic.

Eight continuous covariates (age, body weight, estimated glomerular filtration rate (eGFR), albumin, alkaline phosphatase, ALT, AST, and bilirubin) and 7 categorical covariates (sex, food status (fasted/fed), race, renal impairment status, CYP3A4 inducers and proton pump inhibitors) were tested in the popPK analysis with significance levels of 0.01 and 0.001 in the forward addition and backward elimination procedure, respectively.

The final popPK model of omaveloxolone was described by a 2-compartment disposition model with first-order absorption, and linear clearance (CL) including baseline age and baseline alkaline phosphatase (ALP) effect on CL, healthy subject effect on absorption rate constant (Ka), and food status on Ka and bioavailability (F). The exponent for the effect of age on apparent clearance (CL/F) of -0.2767 suggested a lower CL in older patients. The exponent for the effect of baseline ALP on CL/F of -0.3393 suggested a higher CL in subjects with lower baseline ALP levels. The parameter estimates for the final popPK model are presented in Table 3.

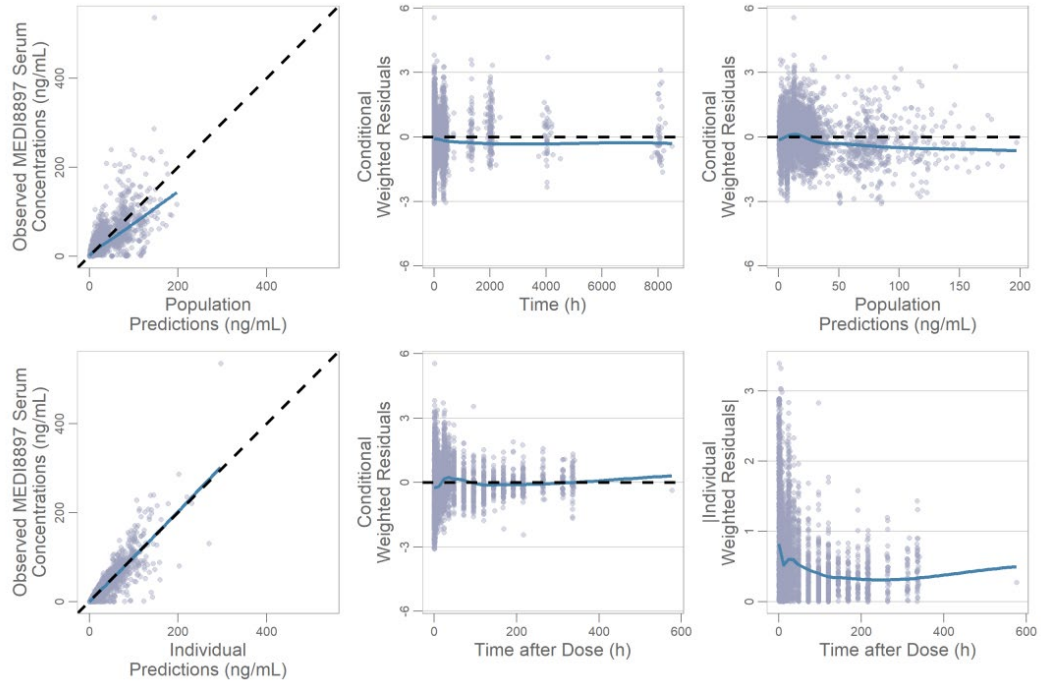
Table 3: Final model parameters estimates for omaveloxolone PK

Parameters	Estimates	%RSE	95% CI	
Apparent clearance (CL/F, L/h)	108.8	3	102.5 – 115	
Baseline age effect on CL	$CL_i = \left({Age_i}/{34}\right)^{-0.2767}$	29	-0.4354 – -0.1179	
Baseline ALP effect on CL	$CL_i = \left({ALP_i}/{69}\right)^{-0.3393}$	30	-0.5381 – -0.1404	
Apparent central volume of distribution (Vc/F, L)	409.7	11	323.9 – 495.5	
Apparent intercompartmental clearance (Q/F, L/h)	81.88	13	60.47 – 103.3	
Apparent peripheral volume of distribution (Vp/F, L)	6951	12	5355 – 8547	
Absorption rate constant (Ka, 1/h)	0.1001	18	0.06386 – 0.1363	
Healthy subject effect on absorption (KAINDIC)	Ka*(1 – 0.5559)	13	-0.703 – -0.4089	
Food effect on absorption (KAFED)	Ka*(1 + 5.081)	29	2.181 – 7.981	
Food effect on relative bioavailability (F1FED)	F*(1 + 0. 2394)	50	0.005933 – 0.473	
Random effects	**Estimates (%CV)**	**%RSE**	**95% CI**	**Shrinkage (%)**
IIV on Vc	79	8	0.4424 - 0.8198	24
ηVc-ηCL correlation	-	r=0.0333		
IIV on CL	42	6	0.1352 - 0.2152	5
ηVc-ηVp correlation	-	r=0.0481		
ηCL-ηVp correlation	-	r=0.0478		
IIV on Vp	98	9	0.6226 - 1.293	12
ηVc-ηQ correlation	-	r=0		
ηCL-ηQ correlation	-	r=0.0361		
ηVp-ηQ correlation	-	r=0.0178		
IIV on Q	84	13	0.3462 - 1.08	12
IIV on Ka	47	10	0.1069 - 0.2492	27
Residual error	**Estimates**	**%RSE**	**95% CI**	
Proportional error	34.47	3.0	32.5 - 36.45	

Abbreviations: η=eta; %CV=percentage of coefficient of variation; %RSE=percentage of relative standard error; ALP=alkaline phosphatase; CI=confidence interval; CL=clearance; F=bioavailability; IIV=interindividual variability; Ka=absorption rate constant; Q=intercompartmental clearance; Vc=central volume of distribution; Vp=peripheral volume of distribution

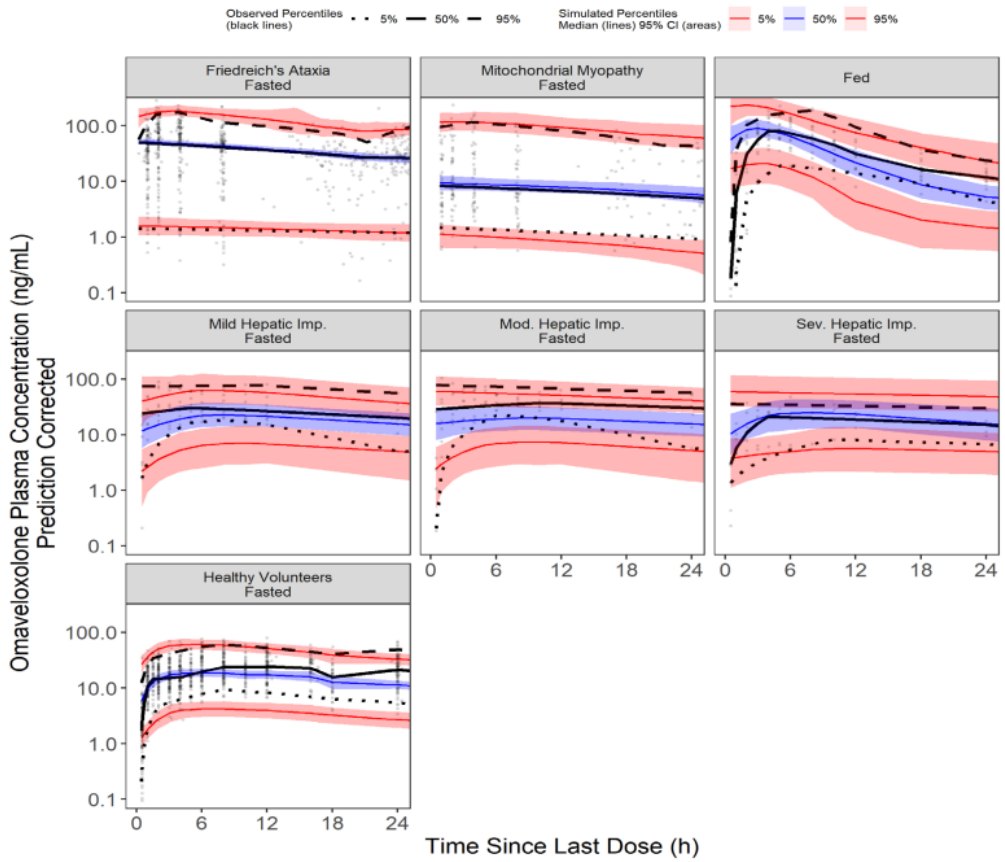
Goodness-of-fit (GOF) plots and selected pcVPCs are presented in Figure 2 and Figure 3.

Figure 2: GOF plots for the final model by administration route



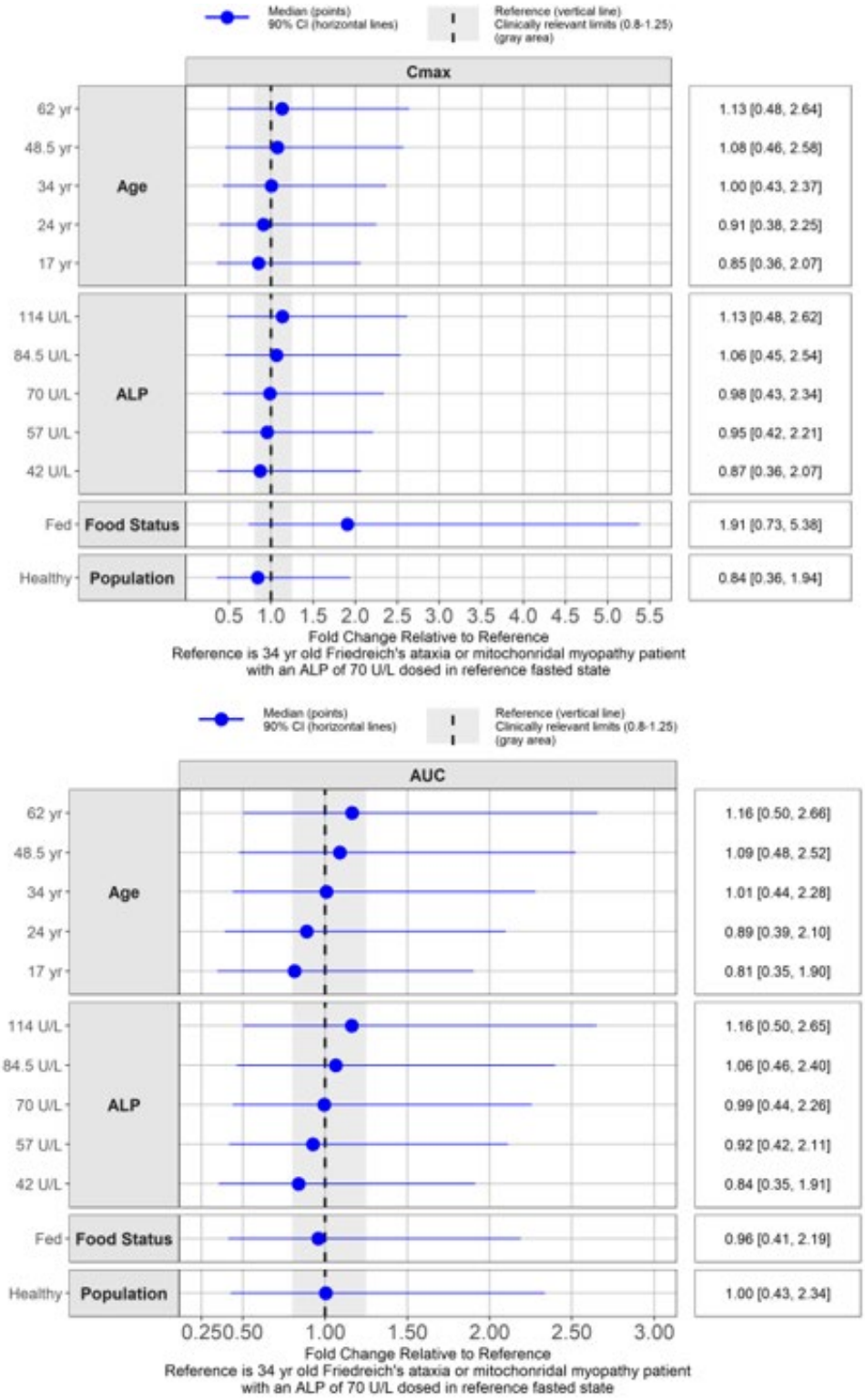
Dots are individual data. Solid red lines are smoothed LOESS lines. Dashed lines are lines of identity. Abbreviation: GOF=goodness-of-fit; LOESS: locally weighted scatterplot smoothing.

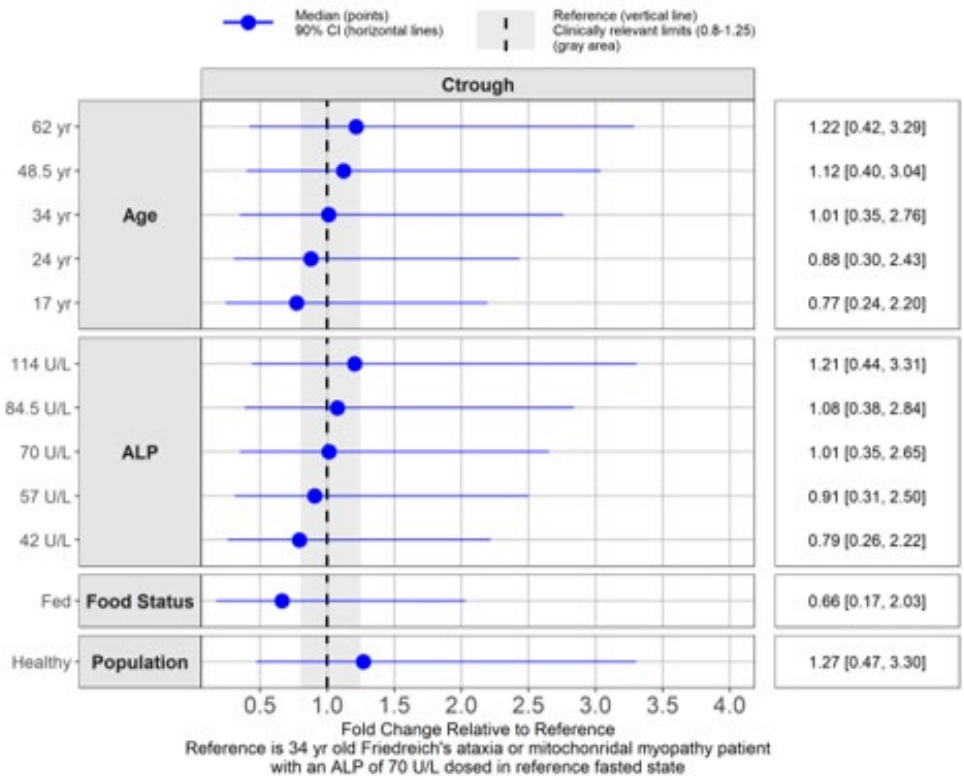
Figure 3: Prediction-corrected VPC



Impact of covariates on exposure metrics were evaluated by univariate and multivariate analyses. The results of univariate analysis are depicted below.

Figure 4: Forest plots for univariate assessment of C_{max}, AUC, C_{trough} of omaveloxolone





Abbreviations: ALP=alkaline phosphatase; AUC= area under the plasma concentration vs time curve; C_{max}= maximum plasma concentration; C_{trough}= trough plasma concentration; popPK=population pharmacokinetics; CI=confidence interval Note: Reference is 34 yr old Friedrich's Ataxia or mitochondrial myopathy patient with an ALP of 70 U/L dosed in the reference fasted state.
Note: Age and ALP values correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of the observed values from the popPK dataset.

Absorption

The permeability of omaveloxolone was determined to be low in *in vitro* permeability models and shown be a weak P-gp substrate. The solubility was also low and omaveloxolone was classified as a BCS class 4 type of compound. In the popPK analysis, the absorption could be described as a first-order process with an estimated ka of 0.044 hr-1 in healthy volunteers. The slow absorption of omaveloxolone is reflected in a large and variable time to achieve maximum observed plasma concentration (t_{max}) of 9 hr (4-36 hr) in the ADME (absorption, distribution, metabolism, and excretion) study 408-C-1805, see Table 4. Furthermore, secondary peaks were observed in several subjects, also contributing to t_{max} variability of omaveloxolone. In FA patients the ka was estimated to be increased by 2.3-fold, resulting in a reduction in t_{max} and an increase in C_{max} compared to healthy volunteers. The *in vivo* absorption of omaveloxolone was found to be solubility and dissolution rate limited according to (PBBM) physiologically based biopharmaceutical model and physiologically based pharmacokinetic(s) (PBPK) modelling.

Table 4: Single-dose PK parameters in healthy subjects

PK Parameters	Study 408-C-1805	Study 408-C-1703			Study 408-C-1804	Study 408-C-1806 (Part 2)	Study 408-C-1806 (Part 3)	Study 408-C-1806 (Part 4)
Dose (N)	**150 mg (N=8)**	**50 mg Fasted (N=10)[a]**	**100 mg Fasted (N=8)**	**150 mg Fasted (N=16)**	**150 mg (N=12)[b]**	**150 mg (N=14)**	**150 mg (N=15)[c]**	**150 mg (N=15)**
C_{max} (ng/mL) *Geo Mean (CV%)*	3.75 (63.3)	18.8 (52.9)	26.2 (38.5)	25.4 (51.3)	40.7 (32.4)	33.7 (46.6)	43.0 (41.8)	33.2 (45.6)
$AUC_{(0-\infty)}$ (ng*h/mL) *Geo Mean (CV%)*	183 (25.7)	513 (36.4)[a]	1125 (46.4)	1117 (48.4)	1630 (34.8)[b]	1440 (47.8)	1730 (50.7)[c]	1530 (43.8)
t_{max} (h) *Median (min, max)*	9.00 (4.00-36.00)	5.5 (1.00, 8.00)	10.00 (8.00, 12.00)	11.00 (3.00, 24.00)	7.00 (1.00, 24.00)	14.29 (1.00, 24.43)	12.00 (2.00, 24.00)	12 (1.00, 24.00)
$t_{½}$ (h) *Mean (SD)*	50.2 (14.2)	34.63 (7.27)[a]	33.71 (6.95)	31.52 (5.62)	87.9 (13.7)[b]	67.8 (12.2)	93.7 (29.4)[c]	66.2 (10.4)
CL/F (L/h) *Mean (SD)*	842 (218)	103 (32.5)[a]	95.94 (36.0)	148 (71.9)	96.8 (30.6)[b]	114 (51.3)	96.1 (44.7)[c]	108 (58.0)
Vz/F (L) *Mean (SD)*	62800 (29800)	5083.6 (1947)[a]	4522.2 (1788)	6631.6 (3241)	12200 (3660)[b]	11400 (6010)	12600 (6170)[c]	10100 (4800)

Abbreviations: $AUC_{0-\infty}$=area under the plasma concentration vs time curve from time zero extrapolated to infinity; CL/F=apparent total plasma clearance after extravascular administration; C_{max}=maximum plasma concentration; CV%=percent coefficient of variation; Geo Mean=geometric mean; max=maximum; min=minimum; N=number of subjects; PK=pharmacokinetic(s); $t_{½}$=apparent plasma terminal elimination half-life; t_{max}=time to achieve C_{max}; V_z/F=apparent volume of distribution during the terminal elimination phase after extravascular administration.
[a] Study 408-C-1703, 50 mg Fasted, N =9 for $AUC_{(0-\infty)}$, $t_{1/2}$, CL/F, and Vz/F
[b] Study 408-C-1804, Normal hepatic function subjects, N = 11 for $AUC_{(0-\infty)}$, $t_{1/2}$, CL/F, and Vz/F
[c] Study 408-C-1806 Part 3, N = 14 for $AUC_{(0-\infty)}$, $t_{1/2}$, CL/F, and Vz/F

Bioavailability: The absolute oral bioavailability of omaveloxolone has not been determined. The bioavailability of omaveloxolone was estimated by PBPK modelling to 20%.

Bioequivalence: The drug formulation for the marketed product is the same which was used in the pivotal clinical study. In the clinical study 408-C-2106, another method of administration was evaluated in healthy subjects. It was shown that a single dose of capsule content sprinkled on applesauce was bioequivalent with the standard method of administration of omaveloxolone (Table 5).

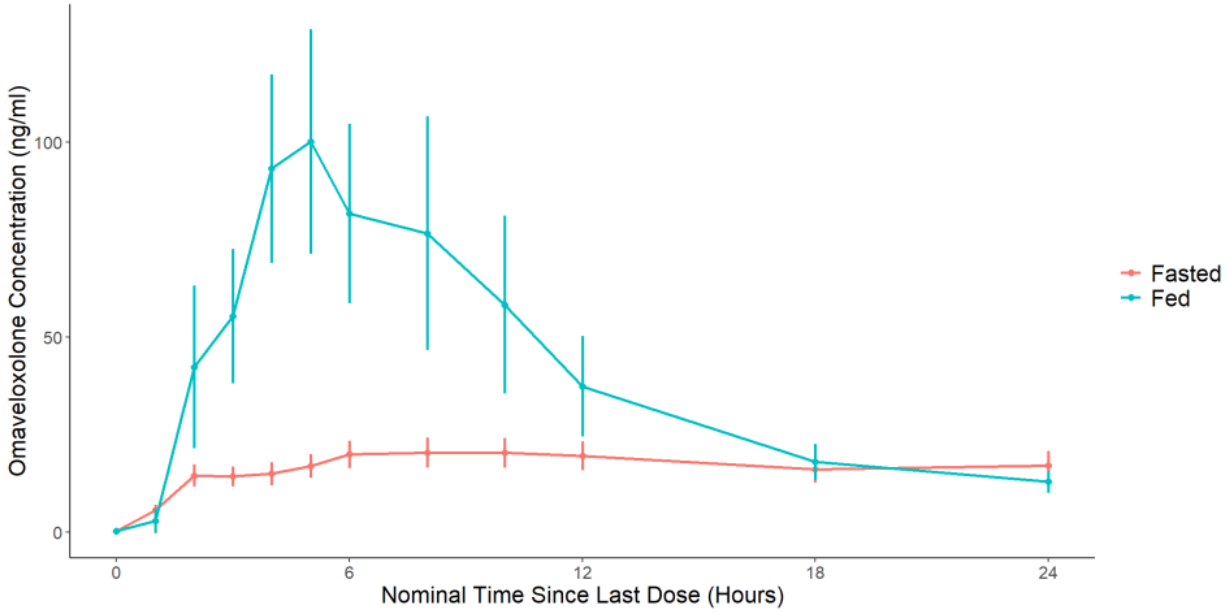
Table 5: Summary of statistical comparison of plasma omaveloxolone PK parameters for a 150 mg dose of omaveloxolone sprinkled in applesauce (treatment B) versus a 150 mg dose of omaveloxolone intact capsules (treatment A)

	Treatment B (Test)		Treatment A (Reference)				
Parameter	n	Geometric LSMs	n	Geometric LSMs	GMR (%)	90% Confidence Interval	Intra-subjec CV%
C_{max} (ng/mL)	32	31.16	31	32.43	96.09	84.80 - 108.89	29.65
AUC_{0-t} (hr•ng/mL)	32	1374	31	1508	91.13	81.66 - 101.70	25.92
$AUC_{0-\infty}$ (hr•ng/mL)	32	1426	31	1560	91.37	81.95 - 101.87	25.68

Treatment B: A single oral dose of 150 mg omaveloxolone capsules (3 x 50 mg) sprinkled on applesauce (test)
Treatment A: A single oral dose of 150 mg omaveloxolone intact capsules (3 x 50 mg) (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from ANOVA.
Geometric Mean Ratio (GMR) = 100 x (test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.

Influence of food: Influence of food was evaluated in the clinical study 408-C1703. Administration of omaveloxolone with a high-fat meal resulted in a 351% (4.5-fold) increase in mean C_{max} and a 15% increase in mean area under the concentration time curve from time zero extrapolated to infinity (AUC_{0-inf}) as compared to fasting conditions, see Figure 5. In the pivotal clinical studies in FA patients, omaveloxolone was administered in fasted state. Secondary peaks were observed in the plasma concentration time curve under fasted conditions and are likely the result of delayed absorption.

Figure 5: Comparison of mean plasma omaveloxone concentrations versus time since the last dose for healthy subjects under fasted and fed conditions following a single 150mg dose.



Note: Coloured lines are mean ± confidence intervals.

Distribution

The apparent steady state volume of distribution (Vss/F) of omaveloxolone was estimated by popPK modelling to 7361 L, very large. Plasma protein binding of omaveloxolone is 97% over the tested

concentration range from 10 to 2000 ng/mL. The blood-to-plasma ratio of omaveloxolone 0.694 and was also not concentration dependent in the concentration range from 10 to 2000 ng/mL.

Elimination

Omaveloxolone is mainly eliminated by metabolism and fecal excretion. The average Cl/F was estimated by popPK modelling to 108.8 L/hr (high), and the average half-life ($t_{1/2}$) estimated to 57 hr.

The human ADME properties of omaveloxolone was evaluated in the clinical study 408-C1805 in healthy subjects. A single oral dose of 150 mg omaveloxolone containing [14C]-labelled omaveloxolone was administered, see Figure 7 and Table 6. Human mass-balance data shows that after 96 hours postdose 90.7% of radioactivity from [14C]-labelled omaveloxolone was excreted in feces, see Figure 7. Of the excreted material in feces 40.3% was unchanged [14C]-omaveloxolone. Less than 1.1% of the radioactive dose of omaveloxolone was excreted renally.

Figure 6: Arithmetic mean (+SD) concentration profiles of plasma omaveloxolone, plasma total radioactivity, and whole blood total radioactivity (PK population)

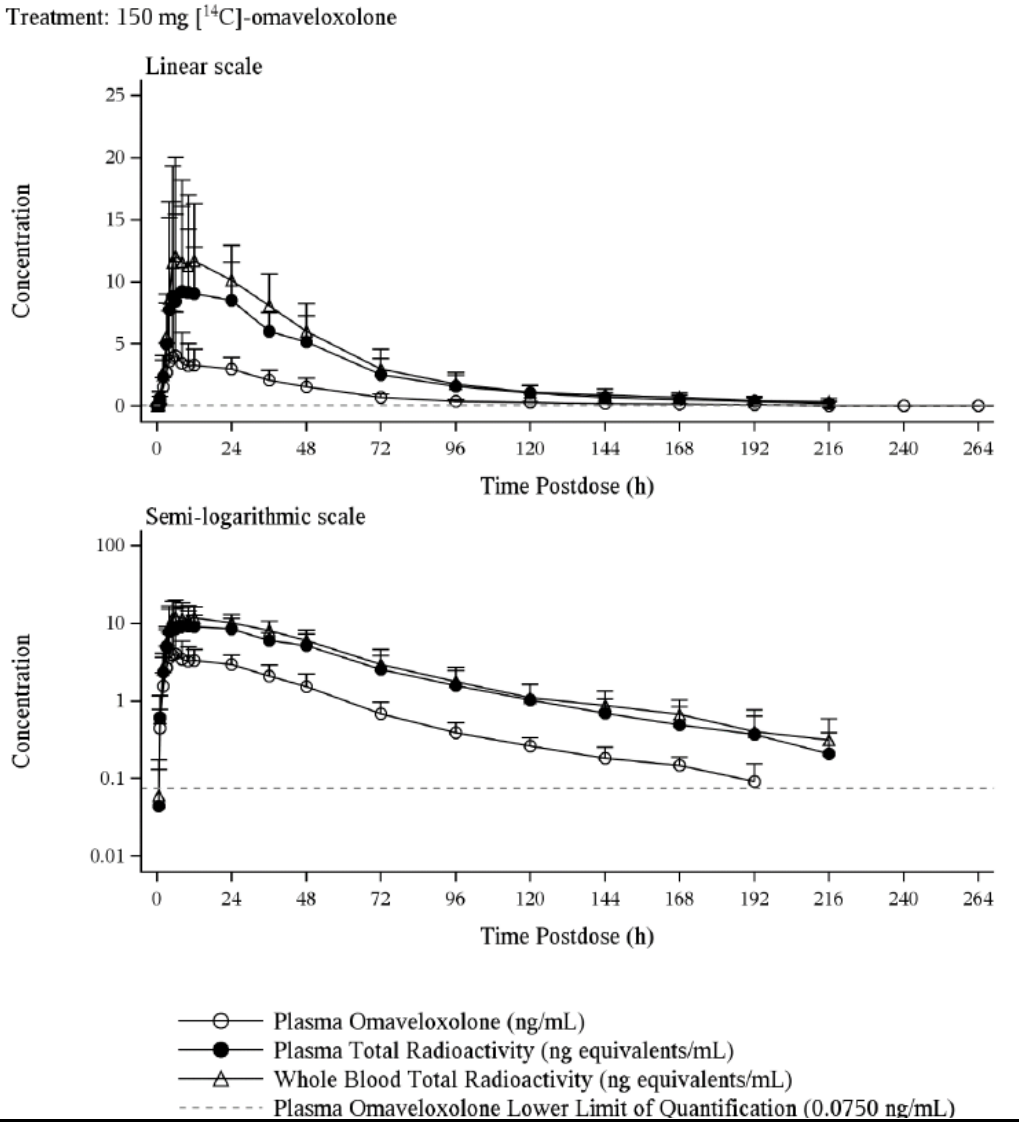


Table 6: Summary of pharmacokinetic parameters for omaveloxolone following a single oral dose.

Parameter	Plasma Omaveloxolone	Plasma Total Radioactivity	Whole Blood Total Radioactivity
AUC_{0-t} (h*ng/mL)[a]	175 (27.3)	515 (42.7)	632 (44.4)
$AUC_{0-\infty}$ (h*ng/mL)[a]	183 (25.7)	606 (30.9)	745 (33.8)
C_{max} (ng/mL)[a]	3.75 (63.3)	9.80 (55.2)	11.9 (49.7)
t_{max} (h)[b]	9.00 (4.00-36.00)	24.00 (5.00-48.00)	12.01 (6.00-36.00)
t½ (h)	48.4 (29.9)	54.1 (38.5)	56.3 (56.7)
CL/F (L/h)	818 (25.7)	–	–
V_z/F (L)	57200 (48.3)	–	–
$AUC_{0-\infty}$ (Blood/Plasma Total Radioactivity Ratio)	–	–	1.23
$AUC_{0-\infty}$ (Plasma Omaveloxolone/Total Radioactivity Ratio)	–	0.311 (8.5)	–

Abbreviations: AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-\infty}$ Blood/Plasma Total Radioactivity Ratio=$AUC_{0-\infty}$ of total radioactivity in whole blood relative to $AUC_{0-\infty}$ of total radioactivity in plasma; $AUC_{0-\infty}$ Plasma Omaveloxolone/Total Radioactivity Ratio=$AUC_{0-\infty}$ of non-radiolabeled omaveloxolone in plasma relative to $AUC_{0-\infty}$ of total radioactivity in plasma; CL/F=apparent total plasma clearance; C_{max}=maximum observed plasma concentration; CV=coefficient of variation; t½=apparent plasma terminal elimination half-life; t_{max}=time to achieve maximum observed plasma concentration; V_z/F=apparent distribution volume.

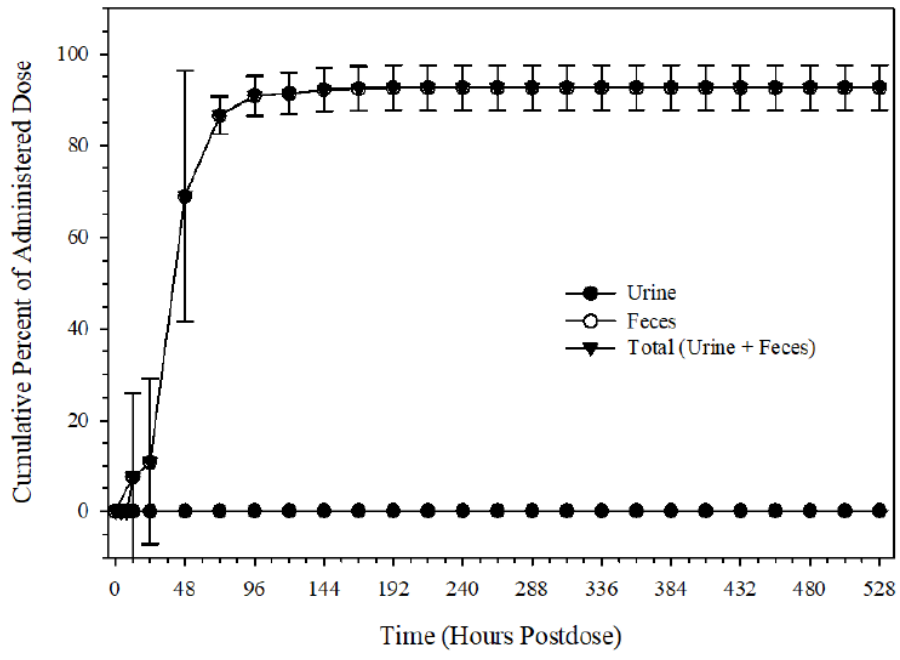
[a] For total radioactivity AUCs and Cmax units are (h*ng/Eq/mL) and (ng/Eq/mL), respectively

[b] Median (minimum-maximum).

Source: 408-C-1805 CSR, Tables 14.2.1-1 to 14.2.1-3.

Geometric mean (CV%) data are presented.

Figure 7: Arithmetic mean (SD) cumulative percent of radioactive dose recovered in urine and feces at specified intervals after a single oral dose of ^{14}C-omaveloxolone.

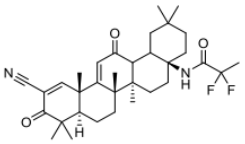
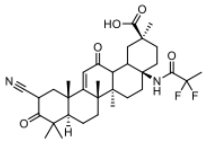
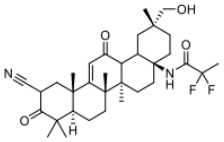


Abbreviations: CSR=clinical study report; SD=standard deviation.

Omaveloxolone is metabolised to 30 metabolites, of which seven were identified. The major omaveloxolone metabolites identified in plasma were the M22 metabolite and M17 metabolite, accounting for 18.6% and

10.9%, respectively, of total plasma radioactivity (Table 7). All the identified metabolites were inactive. Metabolism of omaveloxolone is oxidative and mainly mediated by CYP3A with a minor contribution of CYP2C8 and CYP2J2. *In vitro* clearance data with CYP3A inhibitor ketoconazole indicates that CYP3A metabolism accounts for 89% of omaveloxolone metabolism.

Table 7: Summary of metabolites in humans following a single oral dose of ^{14}C-omaveloxolone (only the major metabolites are presented here).

Component Designation	Chemical Name	Structure	Plasma		Feces[a] (% Total Dose)
			$AUC_{0\text{-}168hr}$ (hr*µg-Eq/g)	% Total Plasma Radioactivity	
Omaveloxolone	Omaveloxolone		0.0585	10.5%	40.3%
TX304579 (M22)[b]	**1,2-dihydro-30-COOH omaveloxolone**		**0.104**	**18.6%**	**ND[c]**
TX304571 (M17)[b]	**1,2-dihydro-29-OH omaveloxolone**		**0.0607**	**10.9%**	**ND**

a Urine metabolites are not presented. There were 17 urine metabolites, which individually accounted for <0.01% of the dose and were well below the limit for identification. In addition to low abundances, low ionisation efficiencies and lack of substantive product ion spectra confounded metabolite identification.
b Major huma metabolites (ie. > 10% of total radioactivity in plasma based of AUC are bolded).
c ND, not detected.

Interconversion: Omaveloxolone possesses one potential epimerizable centre, C13. Chiral interconversion of omaveloxolone is not expected in humans.

PK of metabolites: Exposure $AUC_{0\text{-}168\ hr}$ of the inactive major metabolites of omaveloxolone was determined after single dosing of omaveloxolone. The major metabolites appear to be formation rate-limited from the comparable plasma profile of total radioactivity and plasma profile of omaveloxolone.

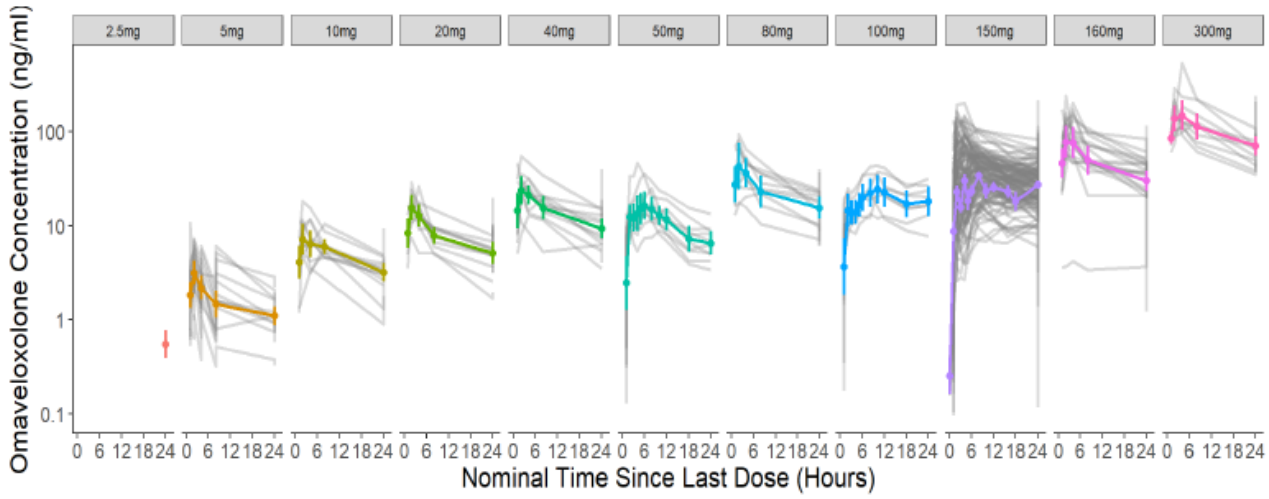
Consequences of possible genetic polymorphism: The major elimination pathways of omaveloxolone do not involve polymorphically expressed drug metabolizing enzyme or drug transporters.

Dose proportionality and time dependencies

Dose-proportionality was evaluated in the clinical study 408-C-1703 in healthy volunteers after single dose administration of omaveloxolone. Dose-proportionality was evaluated with a power model, and it was demonstrated from a dose of 50 mg to 150 mg of omaveloxolone using the Hummel criteria for area under the concentration-time curve from time 0 to the time of the last measurable concentration ($AUC_{0\text{-}tlast}$), $AUC_{0\text{-}inf}$ but not for C_{max}. PK-data from the dose-ranging study 408-C-1402 in FA patient after 14 days repeated dose of omaveloxolone indicates a dose proportional increase in AUCss up to highest dose evaluated 300 mg, see

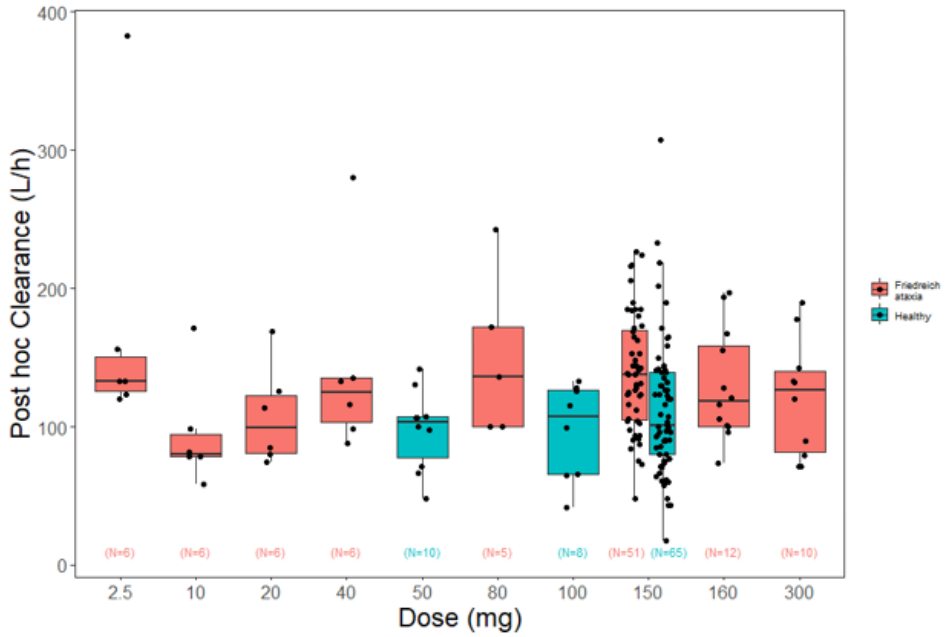
Figure 8. Consistent clearance values were found across doses in healthy subject and FA patients (Figure 9).

Figure 8: Plasma omaveloxone concentrations versus time since the last dose, stratified by dose level (semilogarithmic)



Gray lines are individual subject profiles within each dose level. Coloured lines are mean ±confidence intervals

Figure 9: Post hoc clearance vs. dose in healthy subjects (studies 408—1703 and 408-C-1806) and FA patients from study 1402 Part 1 and Part 2



Abbreviations: FA=Friedreich's ataxia
Note: Horizontal lines represent the median; boxes represent the interquartile range (IQR; 25th to 75th percentiles); whiskers represent 1.5*IQR; black circles represent individual observations. Healthy subjects include fasted subjects from studies 408-C-1703, 408-C-1804 (normal hepatic function only), and 408-C-1806 (omaveloxolone only). FA patients in the 2.5 mg dose group also include data from patients who escalated to 5 mg after at least 2 weeks of dosing.

Time-dependency of omaveloxolone was evaluated in the clinical DDI-study 408-C-1806, Part 1. In the study steady state of omaveloxolone is reached at least after 17 days of once daily (QD) administration of omaveloxolone, as mean plasma C_{trough} of omaveloxolone did not increase after 1 week of additional dosing.

The time-dependency of omaveloxolone PK in FA patients was evaluated through a popPK modelling approach. After repeat dosing of 150 mg QD omaveloxolone in FA patient a mean accumulation ratio of C_{max} and AUC was estimated to 1.7 and 2.3. PBPK modelling indicate that autoinduction leads to increased clearance with a predicted CL/F for omaveloxolone at steady-state is 179 L/h, versus CL/F of 108 L/h following single-dose administration.

Intra- and inter-individual variability

The estimated inter-individual variability (%CV) in the Cl/F (42%) and in Vc/F (79%) and Vp/F (98%) of omaveloxolone were moderate to high in the popPK analysis. The inter-individual variability (%CV) of ka (47%) and of intercompartmental clearance (Q) (84%) were also moderate to high. Intra-individual variability has not been determined.

Pharmacokinetics in target population

The PK of omaveloxolone is comparable between FA patients and healthy volunteers with regards to Cl/F and Vss/F. A higher ka (2.3-fold) of omaveloxolone was seen in the target population (FA patients) versus healthy volunteers. The increase in ka is likely due to less strict fasting conditions in the clinical studies in FA patients i.e., a food effect.

Special populations

Impaired renal function: The PK of omaveloxolone was not assessed in a dedicated clinical study in patients with renal impairment. Renal excretion of omaveloxolone was found to be a very minor (< 1.1%) elimination pathway. The popPK analysis indicates that eGFR is not an important covariate for determining omaveloxolone PK. Subjects with moderate and severe renal impairment were not included in the popPK analysis and the range of eGFR in subjects included in the popPK dataset was from 63.4 to 141 ml/min/1.73 m2.

Impaired hepatic function: The PK of omaveloxolone in hepatic impaired patients was assessed in the clinical study 408-C-1804, see Table 8 and Table 9. Hepatic impairment classification was based on Child-Pugh score and each healthy subject with normal hepatic function was demographically matched (1:1) by sex, age (±10 years), and body mass index (BMI, ±20%) to a completed hepatic impairment subject. In the group of patients with mild impairment, only a limited increase in omaveloxolone exposure was found compared to subjects with normal hepatic function (Table 9). Patients with moderate hepatic impairment had 65%, 56%, and 83% higher $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 to the time of the last measurable concentration ($AUC_{0\text{-}tlast}$), and C_{max} values, respectively, than subject with normal hepatic function. Patients with severe hepatic impairment had a 117% increase in $AUC_{0\text{-}inf}$ compared to the normal hepatic group. The $AUC_{0\text{-}tlast}$ values were 27% higher, while C_{max} was 32% lower, for the severe impairment group compared to the normal group. The mean $t_{1/2}$ was increased in patients with moderate and severe hepatic impairment (Table 8).

Table 8: Summary of the PK parameters for omaveloxolone following a single oral dose.

Parameter	Normal Hepatic Function (N = 12)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 7)	Severe Hepatic Impairment (N = 5)
AUC_{0-t} (h*ng/mL)	1570 (34.5)	1610 (60.1)	2270 (55.8)	1840 (41.6)
$AUC_{0-\infty}$ (h*ng/mL)	1630 (34.8)	1710 (57.5)	2490 (59.5)	2550 (47.4)
C_{max} (ng/mL)	40.7 (32.4)	49.5 (58.1)	61.6 (28.6)	28.2 (60.7)
T_{max}[a] (h)	7.00 (1.00-24.00)	2.00 (1.00-12.00)	8.00 (1.00-24.00)	6.00 (2.00-24.00)
$t_{1/2}$ (h)	86.8 (17.4)	83.8 (60.3)	119 (28.8)	187 (37.0)
CL/F (L/h)	92.1 (34.8)	87.8 (57.5)	60.2 (59.5)	58.8 (47.4)
V_z/F (L)	11500 (39.9)	10600 (95.9)	10300 (64.6)	13100 (63.8)

Geometric mean (CV%) data are presented Abbreviations: AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration time curve from time zero extrapolated to infinity; CL/F = apparent total plasma clearance; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects; t1/2 = apparent plasma terminal elimination half-life; t_{max} = time of the maximum observed concentration; Vz/F = apparent volume of distribution during the terminal phase. a Median (min-max)

Table 9: Statistical summary of the PK parameters of omaveloxolone

Comparison	Parameter	Test n	Test GLSM	Reference n	Reference GLSM	Ratio of GLSMs (90% CI) (Test : Reference)
Mild Hepatic Impairment (Test) vs Normal Hepatic Function (Reference)	$AUC_{0-\infty}$ (h*ng/mL)	8	1710	8	1690	1.01 (0.663, 1.54)
	AUC_{0-t} (h*ng/mL)	8	1610	8	1630	0.990 (0.649, 1.51)
	C_{max} (ng/mL)	8	49.5	8	38.3	1.29 (0.786, 2.12)
Moderate Hepatic Impairment (Test) vs Normal Hepatic Function (Reference)	$AUC_{0-\infty}$ (h*ng/mL)	7	2490	7	1510	1.65 (1.13, 2.42)
	AUC_{0-t} (h*ng/mL)	7	2270	7	1460	1.56 (1.06, 2.30)
	C_{max} (ng/mL)	7	61.6	7	33.6	1.83 (1.41, 2.38)
Severe Hepatic Impairment (Test) vs Normal Hepatic Function (Reference)	$AUC_{0-\infty}$ (h*ng/mL)	3	2550	3	1170	2.17 (1.25, 3.77)
	AUC_{0-t} (h*ng/mL)	5	1840	5	1440	1.27 (0.782, 2.07)
	C_{max} (ng/mL)	5	28.2	5	41.6	0.677 (0.356, 1.29)

Abbreviations: AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time zero extrapolated to infinity; CI = confidence interval; C_{max} = maximum observed plasma concentration; GLSM = geometric least squares mean; n = number of observations Data were analysed using paired t-test. The ratio and corresponding confidence limits are back-transformed from the difference and confidence limits calculated on the loge scale

Gender, race, bodyweight, and age

The effect of the intrinsic factors; gender, race, body weight and age on omaveloxolone PK were evaluated by popPK modelling. Baseline age (median age in popPK dataset was 34 years; age range 16-71 years including 6 elderly subjects, > 65 years) was found to have a significant influence on Cl/F. CL was reduced by age. This change in CL/F was considered of no clinical relevance. Gender, race (white and black Americans) and body weight were found not to impact omaveloxolone exposure.

Pharmacokinetic interaction studies

Perpetrator DDI: Omaveloxolone is an *in vitro* inhibitor of the CYP3A (midazolam, K_i: 0.49 µM) and CYP2C8 (K_i: 0.55 µM) enzymes. For CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 the IC_{50} was above 3 µM, the highest concentration of omaveloxolone tested in the assay. On basis of mRNA and partly enzyme activity

data, it was shown that omaveloxolone is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, UGTs and drug transporters. Omaveloxolone was identified as an *in vitro* CYP3A inducer (4 fold) and a CYP2C19 weak inducer (2.7 fold). Omaveloxolone is an *in vitro* inhibitor of the drug transporter P-gp (IC_{50}: 0.71 µM), OAT1 (IC_{50}: 2.3 µM), OATP1B3 (IC_{50}: 3.5 µM) and OCT1 (IC_{50}: 0.95 µM). For BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K the IC_{50} was above 5 µM and 30 µM, the highest concentration of omaveloxolone tested in the assays. The metabolite M22 do not inhibit (IC_{50} > 10 µM) any of the 7 major drug metabolizing CYP450 enzymes. The metabolite M17 was a weak time-dependent inhibitor of CYP3A (IC50: 4.0 µM (preincubation)/ 9.1 µM).

Victim DDI: Omaveloxolone is primarily metabolised *in vitro* by CYP3A4 with a minor contribution from CYP2C8 and CYP2J2. It was also shown to be a weak substrate for the drug transporter P-gp. Finally, omaveloxolone was shown not to be a substrate of the drug transporters BCRP, OATP1B1 and OATP1B3.

DDI with omaveloxolone were assessed in the clinical study 408-C-1806 performed in healthy subjects.

Perpetrator DDI: Administration of a single dose of 150 mg omaveloxolone with the CYP3A sensitive substrate midazolam resulted in a 45% decrease in mean $AUC_{0\text{-}inf}$ and 35% decrease in mean C_{max} of midazolam compared with midazolam administration alone. Omaveloxolone also decreases the CYP2C8 sensitive substrate repaglinide mean $AUC_{0\text{-}inf}$ and mean C_{max} with 35% and 24%, also suggesting some modest induction effects. The BCRP and OATP1B1/OATP1B3 sensitive substrate rosuvastatin's mean $AUC_{0\text{-}inf}$ and mean C_{max} were decreased 31% and 40% by co-administration with omaveloxolone, suggesting some modest induction effects of omaveloxolone on BCRP. No clinically relevant interactions were observed by co-administration of omaveloxolone with the two drug transporter sensitive substrates for OCT-1 (metformin) and P-gp (digoxin), (study 408-C-1806).

Victim DDI: Co-administration of 150 mg omaveloxolone with the strong CYP3A and P-gp inhibitor itraconazole results in a 312% increase in mean $AUC_{0\text{-}inf}$ and a 177% increase in mean C_{max} of omaveloxolone compared with administration of omaveloxolone alone. Co-administration of omaveloxolone with the P-gp and moderate CYP3A inhibitor verapamil, dose of 120 mg QD, resulted in a 24% and 28% increase in the mean $AUC_{0\text{-}inf}$ and mean C_{max} of omaveloxolone. The exposure of omaveloxolone was not substantially impacted by co-administration with the CYP2C8 inhibitor gemfibrozil (study 408-C-1806).

In silico evaluation of drug-drug interaction by PBPK modelling: Omaveloxolone victim DDI involving the CYP3A enzyme was further explored using PBPK modelling (Table 10). The PBPK model simulated interaction between omaveloxolone and itraconazole was slightly higher than the observed clinical interaction. *Victim DDI:* PBPK model simulation demonstrates that omaveloxolone exposure, as a CYP3A substrate, is significantly impacted by co-administration with a moderate and strong CYP3A inhibitors or moderate and strong CYP3A inducers, Table 10. The simulated interaction between omaveloxolone and the mild CYP3A inhibitor cimetidine was found to be of no clinical relevance.

Table 10: Summary of predicted geometric mean (90%CI) AUC and Cmax ratios for omaveloxolone in the absence and presence of CYP3A4 inhibitors and induces in healthy volunteers.

Omaveloxolone Dose	150 mg SD		150 mg QD	
Perpetrator	$AUC_{0-\infty}$ Ratio	C_{max} Ratio	AUC_{0-24h} Ratio	C_{max} Ratio
Itraconazole (200 mg for 14 days)	7.27 (6.63-7.97)	2.52 (2.42-2.63)	5.54 (4.63-5.23)	4.92 (5.17-5.93)
Fluconazole (200 mg QD)	3.37 (3.30-3.51)	3.03 (2.95-3.11)	3.40 (3.30-3.51)	3.03 (2.95-3.11)
Cimetidine (400 mg BID)	1.15 (1.14-1.16)	1.10 (1.09-1.11)	1.14 (1.13-1.15)	1.14 (1.12-1.15)
Rifampin (600 mg QD)	0.07 (0.06-0.08)	0.14 (0.13-0.15)	0.10 (0.08-0.11)	0.12 (0..11-0.14)
Efavirenz (600 mg QD)	0.29 (0.27-0.32)	0.49 (0.47-0.52)	0.39 (0.36-0..42)	0.46 (0.43-0.49)

Exposure relevant for safety evaluation

The relevant steady state exposure of omaveloxolone in FA patients for safety evaluation was estimated with a popPK simulation approach based partially on PK-data from FA patients. The approach provides an omaveloxolone AUCss of 1180 h*ng/mL and a $C_{max, ss}$ of 71.5 ng/ml in FA patients.

2.6.2.2. Pharmacodynamics

Mechanism of action

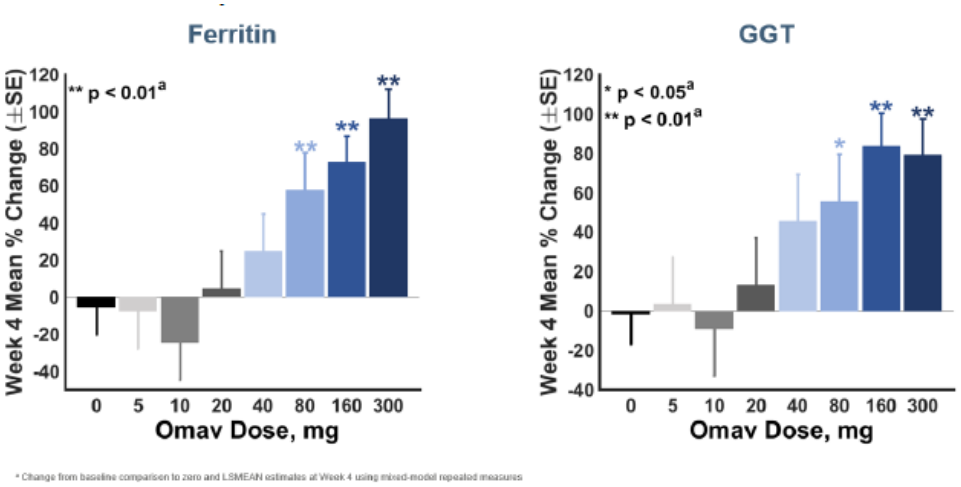
Omaveloxolone is a novel, orally bioavailable Nrf2 activator. It selectively and reversibly binds to Keap1, resulting in the activation of Nrf2, a transcription factor that modulates the expression of genes involved in regulating mitochondrial function, oxidative stress, and inflammation.

Primary pharmacology

PD activity (Nrf2 target gene induction) was assessed by analysing serum levels of ferritin, GGT, ALT, AST, and creatinine kinase (CK), which are regulated by Nrf2.

Dose-dependent induction of direct Nrf2 transcriptional target proteins, ferritin and GGT, was observed at omaveloxolone doses as low as 20 mg and reached statistical significance from baseline at doses of 80 mg and higher (Figure 10).

Figure 10: Nrf2 target gene induction in omaveloxolone-treated FA patients (Study 408-C-1402, part 1)

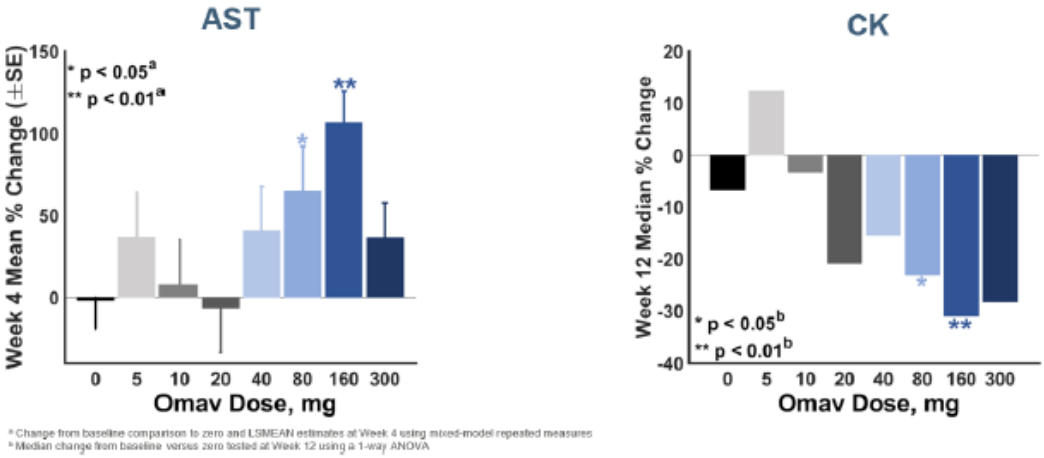


[a] Change from baseline comparison to zero and LSMEAN estimates at Week 4 using mixed-model repeated measures

Abbreviations: FA=Friedreich's ataxia; GGT=gamma-glutamyltransferase; Nrf2=nuclear factor erythroid-derived 2-related factor 2; Omav=omaveloxolone; SE=standard error.
Source: Lynch, 2018.

Two markers of cellular metabolism, AST and CK, were monitored to assess improvements in mitochondrial function. AST delivers substrate to the mitochondria for energy production as part of the malate shuttle, and CK is involved in the utilisation of ATP throughout cells. Dose-dependent modulation of AST and CK was observed with statistically significant changes from baseline observed at doses of 80 and 160 mg (Figure 11), demonstrating that the optimal median decreases in CK were observed at omaveloxolone doses of 80 to 160 mg.

Figure 11: Mitochondrial function improvements in omaveloxolone-treated FA patients (Study 408-C-1402, part 1)



[a] Change from baseline comparison to zero and LSMEAN estimates at Week 4 using mixed-model repeated measures
[b] Median change from baseline versus zero tested at Week 12 using a 1-way ANOVA

Abbreviations: AST=aspartate aminotransferase; CK=creatine kinase; FA=Friedreich's ataxia; Omav=omaveloxolone; SE=standard error.
Source: Lynch, 2018.

Dose finding

Study 408-C-1402 was a 2-part, Phase 2 study to evaluate the safety, efficacy, and PD of omaveloxolone in patients with FA. Study 1402 Part 1 was a randomised, placebo-controlled, double-blind, dose-ranging study

to evaluate the safety, efficacy, and PD activity of omaveloxolone at 2.5, 5, 10, 20, 40, 80, 160, and 300 mg in patients with FA. The primary objectives of Part 1 were to evaluate the change in peak work during maximal exercise testing and the safety and tolerability of omaveloxolone. The characterisation of PK and the evaluation of PD markers of activity in platelet, cheek swab, and muscle samples were exploratory objectives. Sparse blood samples were collected to assess omaveloxolone plasma concentrations in Study 1402 Part 1 with serial collection at Week 2 (predose and 1, 2, 4, and 8 hours after study drug administration) and predose collection at Weeks 8 and 12.

A cohort consisted of the next 8 eligible patients randomised 3:1 to omaveloxolone at the cohort specific dose (n=6) or placebo (n=2). Approximately 9 cohorts were to be enrolled in Part 1 of the study to allow for adequate dose-ranging for selection of a dose of omaveloxolone to be used in Part 2. Prior to opening each cohort in Part 1 for enrolment, the Sponsor evaluated all available data from doses studied in Part 1 to determine if enough information was available to select doses for Part 2 of the study. Once enrolment began in Part 2, no additional cohorts were enrolled in Part 1.

From the doses evaluated in Part 1 of Study 408-C-1402, the 160-mg dose of omaveloxolone was considered optimal based on Data Safety Monitoring Board and Sponsor assessment of available safety, efficacy, and PD data. Available capsule strengths of omaveloxolone (2.5 mg, 10 mg, and 50 mg capsules) require 4 capsules daily for a 160-mg dose, but only 3 capsules daily are required for a 150-mg dose. Based on the efficacy and safety responses as well as the pharmacological response, an omaveloxolone dose of 150 mg was selected for Study 1402 Part 2 because it differs by less than 10% from the 160 mg dose that was evaluated in Part 1. The 150-mg dose is therefore expected to provide similar pharmacologic response while affording a reduction in the number and complexity of capsules that patients are required to swallow once each day for 48 weeks during Part 2.

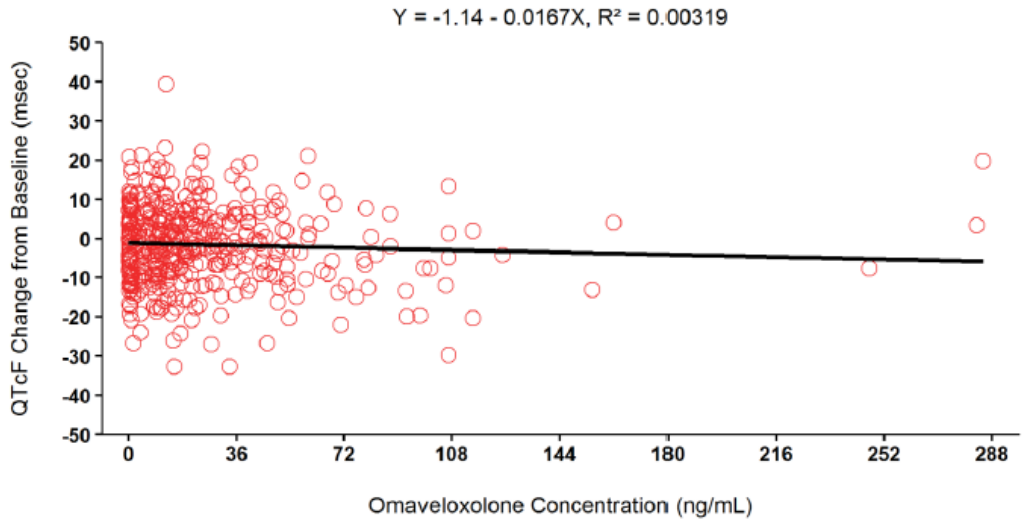
Efficacy results from of Part 2 confirmed that 150 mg is a safe and effective dose for the treatment of FA.

Secondary pharmacology

The objectives of this C-QT analysis were to evaluate the relationship between plasma omaveloxolone concentrations and corrected QT by Fridericia's formula (QTcF) interval in HV; and to predict omaveloxolone-related changes in ΔQTcF interval in HV receiving the therapeutic dose of omaveloxolone (150 mg QD administered in the fasted state) compared to the changes observed with higher exposures (150 mg QD administered in the fed state) in HV. Of note, the ECG data were not collected at peak concentrations (nor post-C_{max} for a delayed effect) in the fed state and thus not representative for a worst-case exposure, which is a guideline requirement. The applicant plans to conduct a thorough QTc study (study 2201) in healthy subjects in which the exposure will be 5-fold higher (study in fed state) than the observed steady state exposure in FA patients receiving 150 mg once daily.

Overall, the C-QT dataset used in the prespecified model included 488 matched PK and ECG samples from 64 subjects. The relationship between ΔQTcF and omaveloxolone concentration was slightly negative (slope of -0.0167 and R^2 = 0.00319) for the pooled studies (Figure 12). For reference, at the therapeutic dose of 150 mg QD (fasted) in patients with FA, the mean post hoc estimated $C_{max, ss}$ is 71.5 ng/mL (range: 37.4-144 ng/mL).

Figure 12: Scatter plot of QTcF change from baseline versus omaveloxolone concentration with linear regression.



QTcF: corrected QT by Fridericia's formula

Mean C_{max} and concentration-related ΔQTcF with 90% CI and bias-corrected 90% CI were predicted at 150 mg (fasted), 150 mg QD (fasted), 150 mg (fed), and 150 mg QD (fed) using the final model and the food effect sensitivity model with fasted data only; the summary of prediction results is displayed in Table 11. The upper bound of the bias-corrected 90% CI for concentration-related ΔQTcF at the highest predicted Cmax was 0.582 msec using the final model and 3.25 msec using the food effect sensitivity model from fasted data only. The upper bound of the 90% CI is below 10 msec for both models across the range of concentrations included in the analysis. Therefore, a 10-msec increase in corrected QT interval can be ruled out in HV receiving the therapeutic dose of omaveloxolone (150 mg QD [fasted]) in patients with FA and clinical worst-case exposures (150 mg single dose [fed] and 150 mg QD [fed]) in HV.

Table 11: Summary of bias-corrected 90% CI for AQTcF by dose level

Dose Regimen	Median Geometric Mean C_{max} (ng/mL)	Final Model (Model 1) Mean ΔQTcF and 90% CI (msec)	Fasted Data Only (Model 3) Mean ΔQTcF and 90% CI (msec)
150 mg single dose (fasted)	20.5	-0.419 (-1.01, 0.103)	0.0325 (-0.464, 0.577)
150 mg QD (fasted)	90.3	-1.84 (-4.43, 0.452)	0.143 (-2.04, 2.54)
150 mg single dose (fed)	96.5	-1.97 (-4.74, 0.484)	0.153 (-2.18, 2.71)
150 mg QD (fed)	116	-2.36 (-5.68, 0.582)	0.184 (-2.62, 3.25)

Abbreviations: ΔQTcF=baseline-corrected QT by Fridericia's formula; CI=confidence interval; C_{max}=maximum observed plasma concentration; QD=once daily.
Source: 4505-RPT001 Report, Table 3
90% bias-corrected CI is reported.

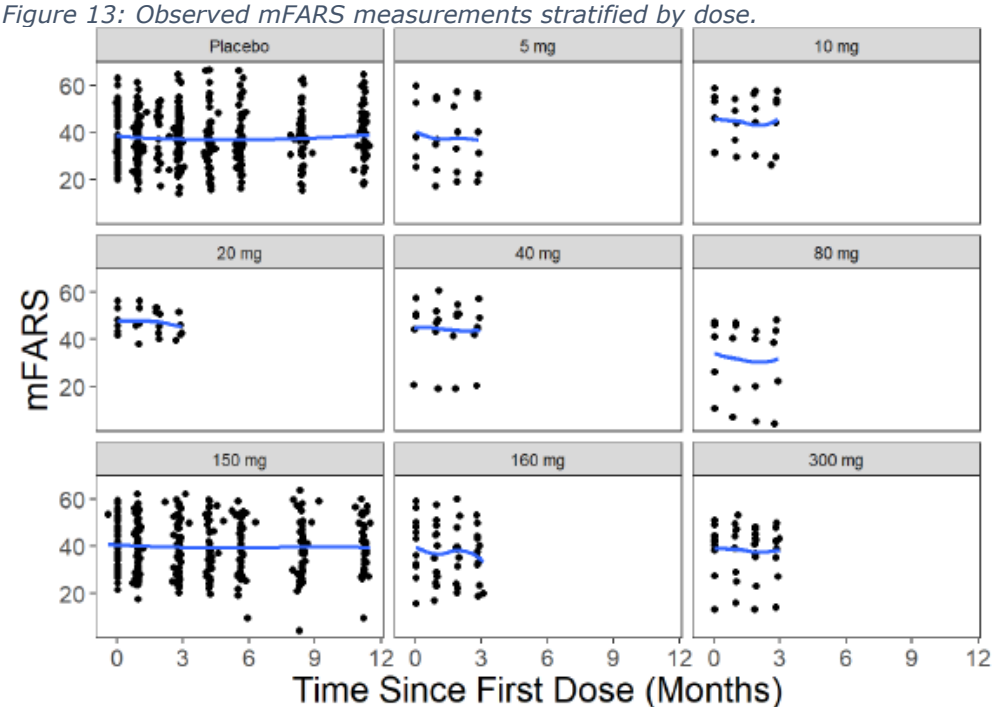
Relationship between plasma concentration and effect

Exposure-efficacy relationship

Longitudinal regression analyses were performed on the change in mFARS to assess drug effect.

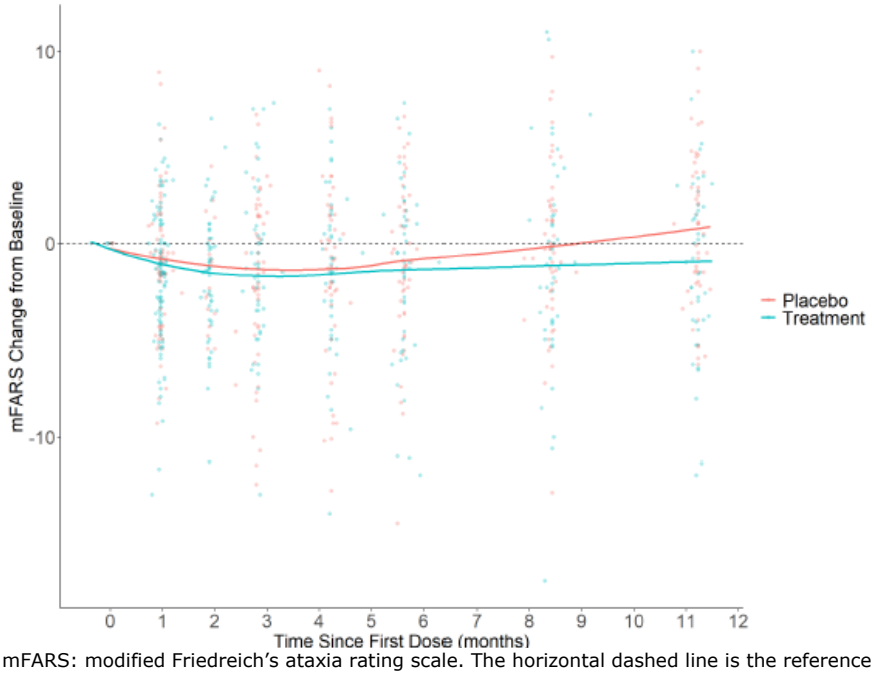
Observed mFARS measurements stratified by dose are shown in Figure 13 and Figure 14. Increases in mFARS scores represent a worsening in function. An analysis of natural disease progression in patients with FA showed that patients aged 16-40 years and >40 years at baseline had change from baseline mFARS scores of 1.11 and 0.47, respectively, over the first year of the study. Exploratory data analysis indicated a wide range of mFARS values and small changes in mFARS over the time course studied. In Figure 14, decreases in mFARS values versus placebo were observed over time with the largest changes in omaveloxolone-treated patients versus placebo occurring at 48 weeks.

Figure 13: Observed mFARS measurements stratified by dose.



mFARS: modified Friedreich's ataxia rating scale

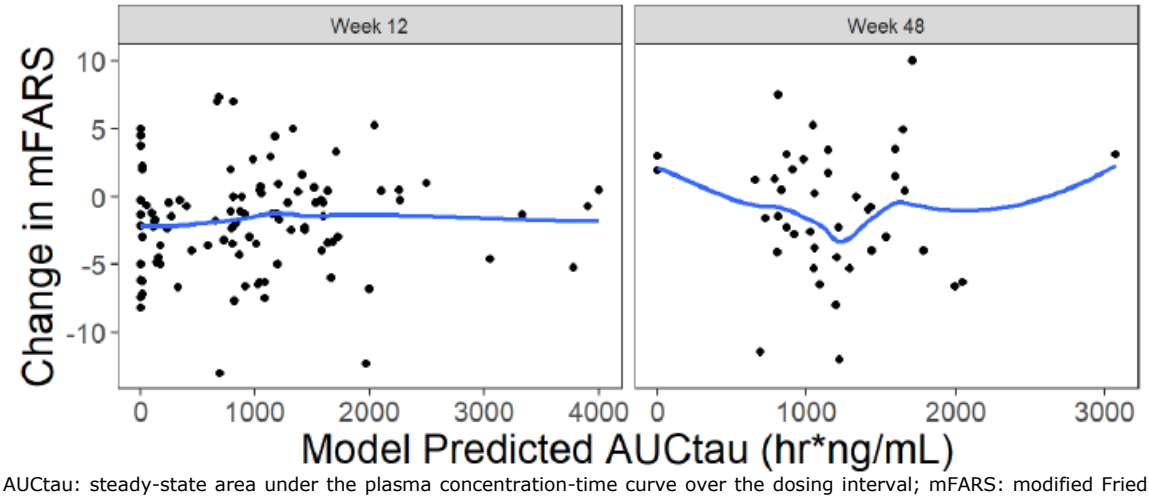
Figure 14: mFARS change from baseline stratified as placebo versus treatment.



mFARS: modified Friedreich's ataxia rating scale. The horizontal dashed line is the reference line

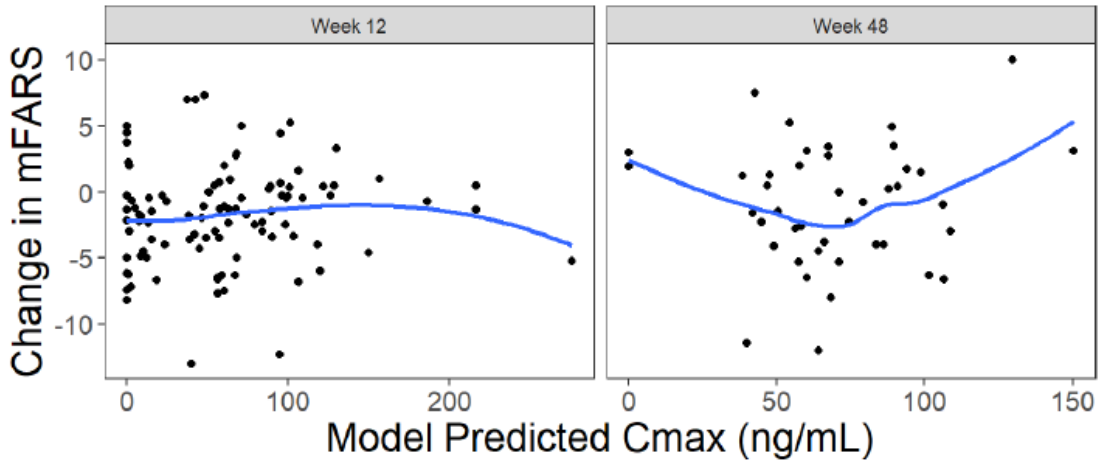
Exposure-mFARS analyses was performed using observed C_{max}, C_{trough}, and AUC as exposure metrics. Subjects from both Parts 1 and 2 (dose range: 2.5 mg QD to 300 mg QD) were included in this analysis. The majority of data are from the 150 mg QD population. The analyses showed no sign of an exposure-mFARS relationship (Figure 15, Figure 16, Figure 17).

Figure 15: Observed change from baseline in mFARS measurements versus model predicted AUCtau at weeks 12 and 48.



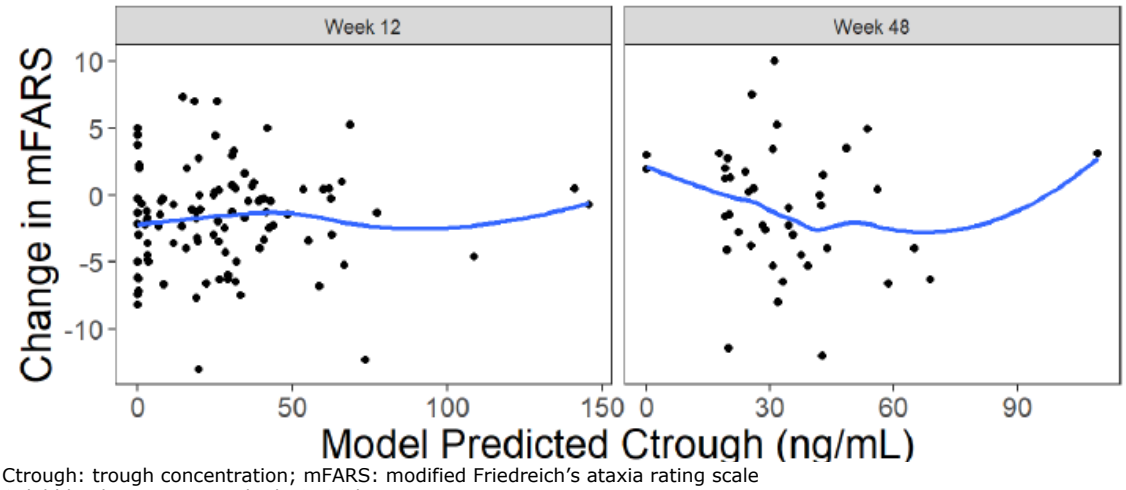
AUCtau: steady-state area under the plasma concentration-time curve over the dosing interval; mFARS: modified Friedreich's ataxia rating scale Solid blue lines are smoothed LOESS lines.

Figure 16: Observed change from baseline in mFARS measurements versus model predicted Cmax at weeks 12 and 48.



Cmax: maximum concentration; mFARS: modified Friedreich's ataxia rating scale
Solid blue lines are smoothed LOESS lines.

Figure 17: Observed change from baseline in mFARS measurements versus model predicted Ctrough at weeks 12 and 48.



Ctrough: trough concentration; mFARS: modified Friedreich's ataxia rating scale
Solid blue lines are smoothed LOESS lines.

Exposure-safety relationship

Cardiac events

Omaveloxolone AUCss, C_{max}, and dose level were evaluated individually to determine the strongest exposure predictor to be used in the exposure response (E-R) modelling. The results of the univariate analysis of exposure predictors indicated that C_{max} was the strongest predictor of the incidence of cardiac events. The 95% confidence interval (CI) includes 0 for slope, indicating that C_{max} is not significant. The parameter estimates for the final model are summarised in Table 12.

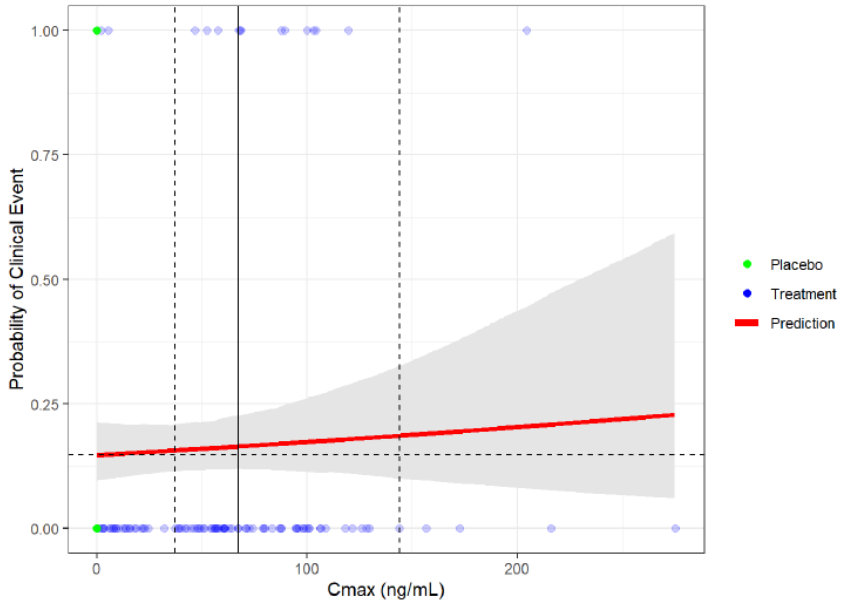
Table 12: Summary of the parameter estimates for the final cardiac event model.

Parameter	Estimate	RSE (%)	95% CI
Intercept	-1.75	27.2	-2.32 – -1.25
C_{max} slope	0.00196	0.4	-0.00654 – 0.00958

Source: OMAV-2081-ER-16oct2020-report.Rmd
Abbreviations: CI=confidence interval; C_{max}=maximum plasma concentration; RSE=relative standard error.
Note: The intercept is the probability of event for a reference individual on the logit scale (14.8%)

Figure 18 shows the observed and model-predicted probability of a cardiac event and indicates that C_{max} is not a strong predictor of event. The probability of a cardiac event is correlated with increasing C_{max}. The reference patient with FA in this analysis was a patient with FA on placebo who has a 14.8% probability of experiencing a cardiac event. Observed probabilities of having a cardiac adverse event (AE) was 14.7% for patients receiving 150 mg and 17.4% for patients receiving placebo. The mean (5th, 95th prediction interval) probability of a cardiac event for a patient receiving a 150-mg dose was 16.5% (11.9%, 20.9%) compared to 14.8% (9.7%, 21.4%) for placebo.

Figure 18: Observed and predicted cardiac events.



Source: OMAV-2081-ER-16oct2020-report.Rmd
Note: The solid red line is the predicted probability of experiencing a cardiac event. The gray-shaded area is the 95% CI of the model prediction. The 2 vertical dashed lines are the minimum and maximum C_{max} for the 150-mg dose level.
Abbreviations: CI=confidence interval; Cmax=maximum plasma concentration.

Infections and infestations

Omaveloxolone AUCss, C_{max}, and dose level were evaluated individually to determine the strongest exposure predictor to be used in the E-R modelling. Since C_{max} had the lowest Akaike information criterion, C_{max} was chosen as the exposure predictor for the initial model. The 95% CI does not include 0 for slope, indicating that C_{max} is significant. The parameter estimates for the final model are summarised in Table 13.

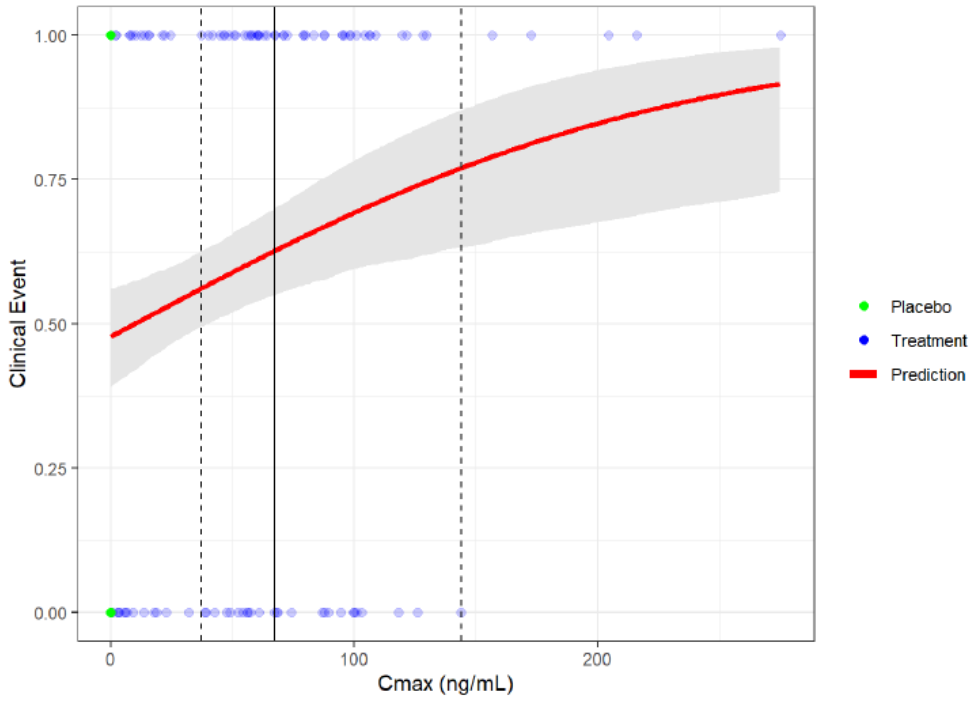
Table 13: Summary of the parameter estimates for the final infections and infestations event model.

Parameter	Estimate	RSE (%)	95% CI
Intercept	-0.0876	20.3	-0.483 – 0.304
C_{max} slope	0.00900	0.4	0.00227 – 0.0164

Source: OMAV-2081-ER-16oct2020-report.Rmd
Note: The intercept is the probability of event for a reference individual on the logit scale (47.8%).
Abbreviations: CI=confidence interval; C_{max}=maximum plasma concentration; RSE=relative standard error.

Figure 19 shows the observed and model-predicted probability of infections and infestations event and indicates that Cmax is a strong predictor of event. The probability of an infections and infestations event is correlated with increasing C_{max}. The reference patient with FA in this analysis was a patient with FA on placebo who had a 47.8% probability of experiencing an infections and infestations event. Observed probabilities of having an infections and infestations AE was 61.8% for patients receiving 150 mg and 47.8% for patients receiving placebo. The model-predicted mean (5th, 95th prediction interval) probability of an infections and infestations event for a subject receiving 150-mg dose was 62.6% (55.0%, 69.9%) compared to 47.8% (39.1%, 56.1%) for placebo.

Figure 19: Observed and predicted infections and infestation events.



Source: OMAV-2081-ER-16oct2020-report.Rmd
Note: The solid red line is the predicted probability of experiencing an infections and infestations event. The gray-shaded area is the 95% CI of the model prediction. The 2 vertical dashed lines are the minimum and maximum C_{max} for the 150-mg dose level.
Abbreviations: CI=confidence interval; C_{max}=maximum plasma concentration.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The PK of omaveloxolone was evaluated by modelling and simulation studies, *in vitro* studies and clinical pharmacology studies.

The concentration of omaveloxolone in plasma was determined using validated LC-MS/MS methods. The bioanalysis conducted in support of the omaveloxolone clinical programme is considered to be in accordance with regulatory requirements. Overall, all bioanalytical methods were usable and suitable for the determination of omaveloxolone in human plasma samples from clinical studies.

The popPK model (report REAT-PMX-OMAV-2081) was developed for omaveloxolone using the results from 5 studies (408-C-1402, 408-C-1403, 408-C-1703, 408-C-1804, and 408-C-1806) with data from healthy subjects and patients with FA and mitochondrial myopathy with the purpose of identifying intrinsic and extrinsic factors that affect omaveloxolone concentrations in plasma of adult healthy subjects and patients with FA. Age and ALP were statistically significant covariates in the SCM-procedure and used for simulations and generally well predicted in all age and ALP quartiles. Impact of covariates on PK exposure metrics (C_{trough}, AUC and C_{max}) is not considered sufficiently explored. Results of univariate and multivariate assessment of statistically significant covariates on exposure metrics (C_{trough}, AUC and C_{max}) indicated the only covariate with clinically relevant effect was prandial state where fed state gave rise to changes outside the 0.8-1.25 range most profound for C_{max}.

The PopPK model has major limitations and cannot be used to reliably predict the C_{max} and AUC in patients from the sparse sampling. The C_{trough} values (in addition to C_{max} and AUC) was used for E-R modelling of the probability of a cardiac event, of an infection or an infestation and did not result in new conclusions.

The ADME study (AME study) in healthy subjects shows that omaveloxolone is slowly absorbed, reflected in a large and variable t_{max} of 9 hr (4-36 hr). It is metabolised to a large extent and excreted predominantly in feces where a large part, 40.3%, of excreted material was [14C]-omaveloxolone. Exposure of omaveloxolone in the clinical ADME study (mass-balance study) was very low compared to other clinical studies with omaveloxolone resulting in 5–6-fold higher Cl/F and Vz/F values. Upon request, the applicant clarified that the main amount of faecal excreted omaveloxolone is attributed to non-absorbed omaveloxolone and not derived from systemic elimination e.g. biliary elimination. This conclusion is based on the high apparent clearance and dissolution studies showing a decreased rate of dissolution for the special formulation of omaveloxolone used in the ADME clinical study. The absolute bioavailability has not been determined for omaveloxolone. The applicant intends to use the clinical formulation as the final marketed product. It was demonstrated that omaveloxolone administered as capsule content sprinkled on applesauce was bioequivalent with the standard clinical capsule formulation.

Administration of omaveloxolone with a high-fat meal resulted in a 351% (4.5-fold) increase in C_{max} and a 15% increase in $AUC_{0\text{-}inf}$ as compared to fasting conditions. The large food effect is addressed in the SmPC where it is recommended that omaveloxolone is administered on an empty stomach at least one hour before or two hours after eating.

Omaveloxolone is 97% bound to plasma proteins and binding was concentration independent. It is widely distributed with an average Vdss of 7361 L. The average CL/F of omaveloxolone was estimated to 108.8 L/hr and the average $t_{1/2}$ was 57 hr.

Omaveloxolone was metabolised to two major inactive metabolites, M22 and M17, accounted for 18.6% and 10.9%, respectively, of total plasma radioactivity. PK of the major metabolites have not been determined. As the terminal profile of total radioactivity is comparable with that of parent compound, the major metabolites are not expected to accumulate more than what was observed for omaveloxolone. Metabolism of omaveloxolone was oxidative and mainly shown to be mediated *in vitro* by the CYP3A enzyme.

Dose-proportionality of $AUC_{0\text{-}inf}$ and AUC_{tlast} was demonstrated in healthy volunteers from a dose of 50 mg to 150 mg omaveloxolone, whereas C_{max} was found to be less-than dose proportional up to a dose of 150 mg. In FA patients, steady-state exposure appears to be dose-proportional up to a dose of 300 mg.

In healthy subjects, steady-state of omaveloxolone was reached after a minimum of 17 days repeated QD dosing. In FA patients, a mean accumulation ratio of C_{max} and AUC was estimated to 1.7 and 2.3. PBPK modelling predicts some degree of autoinduction.

PopPK estimated inter-individual variability in ka, apparent and intercompartmental clearance, and V/F were moderate to high. Data on intra-individual PK variability is not available.

Overall, the PK of omaveloxolone is comparable in FA patients and healthy volunteers. Differences related to absorption was shown in the popPK analysis; a 2.3-fold higher rate of absorption in FA patients leading to decreased t_{max} and increased C_{max} was reported. The difference in absorption between FA patients and fasted healthy volunteers was likely related to the less strict fasting conditions in FA patients i.e. a food-effect.

The PK of omaveloxolone has not been evaluated in a dedicated clinical study in renally impaired patients. The lack of a renal impairment study is justified by the applicant with the low level (< 1.1%) of renal excretion, the limited impact of PPB on plasma protein changes, and a comparable safety profile of the 300 mg omaveloxolone dose to the 150 mg commercial dose. According to EMA guidance for evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function, then also PK of drugs which are primarily hepatically eliminated can be affected in patients with renal impairment. The absence of PK data in moderate and severe renally impaired patient is stated in the SmPC. The applicant conducted a dedicated clinical study in patients with hepatic impairment. In patients with moderate and severe hepatic impairment, an increase in exposure of omaveloxolone compared to normal subjects was observed, whereas in patients with mild impairment no impact on exposure was found. The impact of hepatic impairment is reflected in the SmPC, which recommends reducing dose of omaveloxolone in patients with moderate hepatic impairment and avoid use in patients with severe hepatic impairment. Gender, body weight, and race (white and black Americans) did not have an impact on PK, whereas clearance was influenced by age. The applicant has justified that dose adjustment is not necessary in elderly despite the lower clearance in elderly. Only children in the age from 16 to 18 years were included in the clinical studies and no dose adjustment in this group is judged necessary by the applicant. This analysis is supported, and the information is included in the SmPC.

With regards to DDI, then relevant *in vitro* findings for omaveloxolone have been followed up except for CYP2C19 by clinical studies and further evaluated with PBPK modelling. In the follow-up induction study, CYP2C19 was induced by omaveloxolone. The applicant is requested on basis of this *in vitro* finding, to evaluate according to the DDI guideline the potential for relevant clinical interactions with CYP2C19 substrate (**REC**).

A reduction in mean $AUC_{0\text{-}inf}$ of the CYP3A substrate midazolam of 45% was observed when co-administered with omaveloxolone, indicating that it is a weak inducer of the CYP3A enzyme. Furthermore, also a weak decrease in exposure of the CYP2C8 substrate repaglinide and the BCRP and OATP1B1/OATP1B3 substrate rosuvastatin was found. These DDI of omaveloxolone on other drugs are adequately reflected in the SmPC. *In vitro,* omaveloxolone was shown to be a CYP3A inhibitor and a P-gp inhibitor. Based on the clinical

midazolam interaction study, performed at steady state, omaveloxolone is a net inducer of CYP3A. Further analysis shows, that when starting treatment with omaveloxolone, there is a potential for intestinal inhibition, but not hepatic inhibition, of CYP3A and P-gp by omaveloxolone. Further evaluation of this DDI potential by PBPK modelling using the CYP3A and the P-gp sensitive substrates, midazolam and digoxin, shows that no initial DDI is predicted between omaveloxolone and the CYP3A and P-gp sensitive substrates. A qualification report to assess the predictive performance of Simcyp Simulator V18 for intestinal CYP3A4 inhibition (using alfentanil, midazolam and simvastatin) indicated that the model platform could be considered to give reasonably accurate prediction of CYP3A4-mediated DDIs following both IV and oral dosing. Likewise, a qualification report to assess the P-gp-mediated DDIs involving digoxin and dabigatran etexilate as the P-gp substrates and ritonavir, verapamil, clarithromycin, ketoconazole, and quinidine as P-gp inhibitors, indicated that the model platform would give predictions with reasonable accuracy. In conclusion, the PBPK simulations indicated that negligible DDI was predicted between single oral doses of midazolam (CYP3A4 substrate), digoxin (P-gp substrate), and dabigatran (P-gp substrate) and a single oral dose of 150 mg of omaveloxolone. Although the model is not considered sufficiently qualified for SmPC recommendations, further investigation of the intestinal inhibition potential of omaveloxolone towards CYP3A4 and P-glycoprotein in a clinical study, is not considered necessary.
Co-administration of omaveloxolone with the strong CYP3A and P-gp inhibitor itraconazole leads to a 312% (4.1-fold) increase in mean $AUC_{0\text{-}inf}$ omaveloxolone. The overall data provided shows that omaveloxolone is primarily a sensitive CYP3A substrate. In the SmPC, co-administration of omaveloxolone with moderate or strong CYP3A inhibitors is recommended to be avoided and if necessary, a dose reduction is proposed. In the clinical study of omaveloxolone with verapamil, a moderate CYP3A inhibitor and a P-gp inhibitor, only a weak DDI (AUC-ratio: 1.24) was observed. The dose of verapamil in the study (120 mg QD) was lower than recommended and the CYP3A/P-gp DDI is possibly underestimated. Nevertheless, this indicates that the PBPK model overpredicts DDI of omaveloxolone with CYP3A inhibitors. The submitted PBPK platform is not considered qualified for SmPC recommendations in place of clinical DDI studies.

PBPK simulations predict that co-administration of omaveloxolone with a strong or moderate CYP3A4 inducers will lead to a significant reduction in omaveloxolone exposure. The PBPK platform is not considered fully qualified for the purpose and the applicant has therefore committed to perform a DDI study with the moderate CYP3A inducer efavirenz and to submit the final report in Q2 2024.

Pharmacodynamics

Omaveloxolone is a novel, orally bioavailable Nrf2 activator. PD activity (Nrf2 target gene induction) was assessed by analysing serum levels of ferritin, GGT, ALT, AST, and CK, which are regulated by Nrf2. Compared to placebo, dose-related changes in several Nrf2 target genes, including those coding for ferritin, GGT, ALT, and AST were seen at week 4 and 12.

As for dose finding, the dose rationale has been described. Based on non-clinical and clinical evidence, it is concluded that there are no data available suggesting that a higher or lower exposure than the one observed in the pivotal study would produce a greater treatment effect. Therefore, the dose explored in the pivotal study is considered appropriate.

Based on C-QTc evaluation, no indication of a QT prolonging effect of omaveloxolone in HVs was demonstrated. The applicant plans to conduct a thorough QTc study (study 408-C-2201) in healthy subjects in which the exposure will be 5-fold higher (study in fed state) than the observed steady state exposure in FA patients receiving 150 mg once daily. There are no plans for a QTc study in FA patients. If the ongoing thorough QTc study in healthy subjects turns out positive, the applicant proposes to insert further precautions/instructions in the product information. This is acceptable. The results of study 408-C-2201

should be submitted (**REC**). It is unclear whether there is any relationship between FXN genotype and expected biomarker (i.e., ferritin) response.

The applicant has provided both dose-mFARS and exposure-mFARS analyses. Based on the graphical dose-mFARS relationship, no clear difference in effect between placebo and the 150 mg dose group is observed. In the figure of mFARS change from baseline a small effect is seen between treated and placebo patients. No exposure-mFARS relationship was demonstrated.

The exposure-safety analyses for cardiac events showed that C_{max}, the strongest exposure predictor of the incidence of cardiac events, did not have a significant impact on the risk of having a cardiac event. The risk of infections was shown to be significantly associated with the C_{max} exposure with higher levels of C_{max} increasing the risk of infections.

2.6.4. Conclusions on clinical pharmacology

The PK and PD of omaveloxolone were evaluated in *in vitro* studies and clinical pharmacology studies and by modelling and simulation studies. Overall, the clinical pharmacology programme and documentation is considered adequate for the evaluation of the PK and PD of omaveloxolone.

The CHMP recommends the following measures in relation to pharmacology issues:

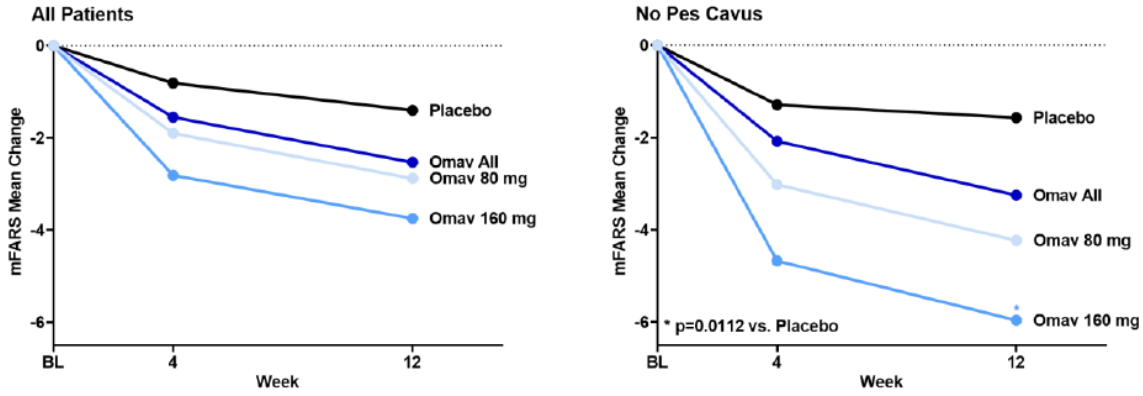
- The applicant should submit the final clinical study report for DDI study with efavirenz by Q2 2024.
- The applicant should submit the final clinical study report for study 408-C-2201 by Q2 2024.
- The applicant should -on basis of the *in vitro* finding that CYP2C19 was induced by omaveloxolone- evaluate the potential for relevant clinical interactions with CYP2C19 substrates according to the DDI guideline and if necessary, perform a clinical DDI study with a sensitive CYP2C19 substrate by June 2026.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

A dose-ranging study was conducted with omaveloxolone in FA (Study 1402 Part 1). Based on the efficacy and safety results from this study and the assessment of PD data for markers of Nrf2 activation (as per the omaveloxolone mechanism of action), a 150-mg dose of omaveloxolone was selected for further development, beginning with Study 1402 Part 2.

Figure 20: Study 1402 Part 1: Changes from Baseline in mFARS scores over time for all patients and patients without pes cavus (Intent-to-Treat Population)



mFARS: modified Friedreich's ataxia rating scale. Omav: Omaveloxolone.

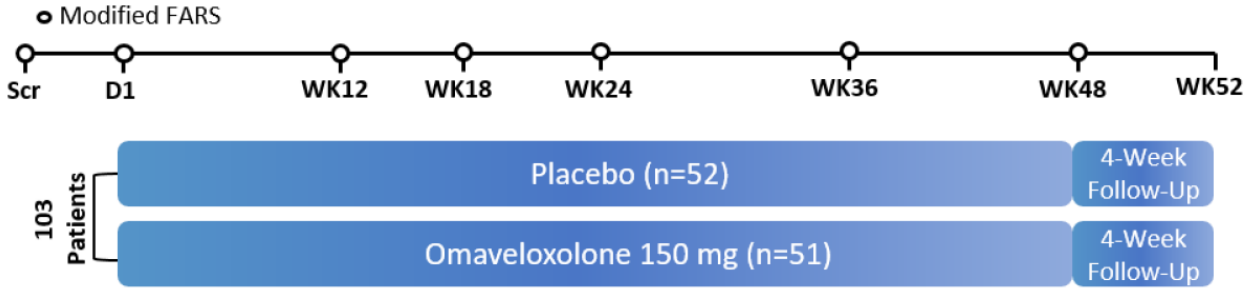
2.6.5.2. Main study(ies)

Study 1402 Part 2: A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia

Methods

Study 1402 Part 2 was a double-blind, randomised, placebo-controlled, parallel-group study to assess the safety and efficacy of omaveloxolone in male and female patients aged 16 to 40 years with genetically confirmed FA.

Figure 21: Study 1402 Part 2 study design



Abbreviations: D=day; FARS=Friedreich's ataxia rating scale; Scr=screening; WK=week Note: Patients self-administered study treatment once daily for 48 weeks, ie, they were off treatment in the 4-week follow-up period

- **Study Participants**

Inclusion criteria:

1. Have genetically confirmed Friedreich's ataxia

2. Have an mFARS score ≥ 20 and ≤ 80. The average of the two mFARS values collected at Screening and Day 1 visits must fall within the allowable range, and they must be within 4.5 points of each other.

3. Be male or female and ≥ 16 years of age and ≤ 40 years of age

4. Have no changes to their exercise regimen within 30 days prior to Study Day 1 and be willing to remain on the same exercise regimen during the study period

5. Have the ability to complete maximal exercise testing

6. Have adequate kidney function defined as an eGFR ≥ 60 mL/min/1.73 m2 using the Modification of Diet in Renal Disease 4-variable formula

7. Have a left ventricular ejection fraction ≥ 40% (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)

8. Be able to swallow capsules

9. Be willing and able to cooperate with all aspects of the protocol

10. Be willing to practice medically acceptable methods of birth control

11. Provide written informed consent for study participation, approved by the appropriate Institutional Review Board.

Exclusion criteria:

1. Have uncontrolled diabetes (HbA1c > 11.0%)

2. Have BNP level > 200 pg/mL

3. Have a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with FA, including but not limited to any of the following:

    a. Clinically significant congenital or acquired valvular disease

    b. Pericardial constriction (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)

    c. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)

    d. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina)

    e. History of hospitalisation 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

4. Have known active fungal, bacterial, and/or viral infection, including human immunodeficiency virus (HIV) or hepatitis virus (B or C)

5. Have known or suspected active drug or alcohol abuse, as per investigator judgment

6. Have clinically significant abnormalities of clinical haematology or biochemistry, including but not limited to elevations greater than 1.5 times the upper limit of normal (ULN) of AST or ALT. Levels above this threshold are allowable if attributable to muscle injury

7. Have any abnormal laboratory test value or clinically significant pre-existing medical condition that, in the opinion of the investigator, would put the patient at risk by study enrolment

8. Have taken any of the following drugs within 7 days prior to Study Day 1 or plan to take any of these drugs during the time of study participation:

    a. Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)

    b. Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)

    c. Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)

9. Have a history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), or has, 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. ALP > 2-fold ULN

d. albumin < lower limit of normal (LLN)

10. Have participated in any other interventional clinical study within 30 days prior to Study Day 1

11. Have a cognitive impairment that may preclude ability to comply with study procedures

12. Be unable to comply with the requirements of the study protocol or be unsuitable for the study for any reason, in the opinion of the investigator

13. Have used antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and vitamin E above the recommended daily allowance, within 14 days prior to Study Day 1, or plan to take any of these supplements during the time of study participation

14. Have previously documented mitochondrial respiratory chain disease

15. Have a history of thromboembolic events within the past 5 years

16. Have taken anticoagulant therapy within 30 days prior to Study Day 1

17. Have scheduled surgical treatment for scoliosis or foot deformity during the study

18. Have had significant suicidal ideation within 1 month prior to Screening Visit as per investigator judgment or any history of suicide attempts

19. Be pregnant or breastfeeding

20. Prior participation in a trial with RTA 408

- **Treatments**

Following randomisation on Day 1, patients self-administered study treatment once daily for 48 weeks, in the morning on an empty stomach (approximately 1 hour before or 2 hours after eating). The study medication was taken as three 50-mg capsules once daily.

Capsules containing either omaveloxolone in the 50-mg strength (omaveloxolone, pregelatinised starch, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate, in white opaque, size #0 capsule shells consisting of hypromellose and titanium dioxide) or the corresponding placebo, were used in this study.

Patients were provided a dosing diary to track all doses administered, including the date and time of each dose.

Reasons for **study treatment discontinuation** could have included: occurrence of an AE or change in medical status that led the Investigator to be concerned about the patient's welfare, protocol violation, administrative reasons (e.g, inability to continue), sponsor termination of the study, voluntary withdrawal, pregnancy during the study and investigator unblinding.

Patients were **permanently discontinued** from the study, if any of the following occurred: ALT or AST >8× ULN ALT or AST >5× ULN for more than 2 weeks, ALT or AST >3× ULN and total bilirubin (TBL) >2× ULN, ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain, or tenderness, fever, rash, and/or eosinophilia (>5%). Patients who were discontinued from study drug in Part 1 or Part 2 had to complete all study visits and undergo all scheduled study assessments, if possible.

Excluded Medications: anticoagulant therapy, with the exception of a daily baby aspirin (up to 81 mg), antioxidant supplements, including but not limited to idebenone, CoQ10, nicotinamide, and dosages

exceeding the recommended daily allowance of vitamin E, herbal preparations, minerals, or over-the-counter medication, sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g, repaglinide, midazolam, sildenafil), moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g, carbamazepine, phenytoin, ciprofloxacin, grapefruit juice), substrates for p-glycoprotein transporter (e.g, ambrisentan, digoxin), any interventional therapy intended to treat the FA disease condition, with the exception of a constant exercise regimen, anti-spasticity agents.

Permitted Medications: antibiotics, except as noted above, daily multivitamin, pain medication, except as noted above, other medications intended to manage concurrent diseases, except as noted above, oral, implantable, or injectable contraceptives.

Patients taking medication chronically were to be maintained on those same doses and dose schedules throughout the study period, as medically feasible. Patients taking medications with intermittent or as-needed schedules were to try to avoid taking the concomitant medication on days when PK samples were collected, as medically feasible.

- **Outcomes/endpoints**

Primary: change from baseline in mFARS to Week 48

The primary endpoint was the change in mFARS score from baseline to Week 48. A higher mFARS score indicates worsened functioning, while a decrease in mFARS indicates improvement. The primary efficacy analysis population (FAS) for Study 1402 Part 2 was based on all patients without pes cavus who had at least 1 post-baseline measurement (whether or not they received study drug). The primary analysis utilised all mFARS values collected through Week 48, irrespective of whether or not a patient was receiving treatment. Patients with pes cavus were also included in Study 1402 Part 2 but were limited by the protocol to not comprise more than 20% of patients enrolled into the study. All efficacy endpoints were also summarised for all randomised patients (those with and without pes cavus; the All-randomised Population (ARP)).

Key secondary: PGIC at Week 48; CGIC at Week 48

The key secondary endpoints were patient global impression of change (PGIC) and clinical global impression of change (CGIC) at Week 48. The PGIC and CGIC are 7-point scales that require the patient and clinician, respectively, to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention (Guy, 1976). Scores less than 4 represent some measure of improvement, scores greater than 4 represent some measure of worsening and a score of 4 represents no change.

Additional secondary and exploratory efficacy endpoints assessed in the FAS in Study 1402 Part 2 included:

- Change in performance on a 9-hole peg test (9-HPT) from baseline at Week 48
- Change in performance on a timed 25-foot walk (T25FW) test from baseline at Week 48
- Frequency of falls over 48 weeks
- Change in peak work during maximal exercise testing from baseline at Week 48
- Change in the FA-ADL score from baseline at Week 48
- Change in raters' assessments of videos of normal walking from baseline at Week 24 and Week 48
- Change in Short-form 36-item Health Survey Questionnaire® (SF-36) Health Survey Update score from baseline at Week 24 and Week 48

- **Sample size**

Up to approximately 172 patients will be enrolled in this study (up to 72 patients in Part 1 and approximately 100 patients in Part 2). The extension will only include qualified patients from Part 1 and Part 2.

- **Randomisation and Blinding (masking)**

The patients were randomised 1:1 to receive 48 weeks of omaveloxolone 150 mg or placebo. Randomisation was stratified by pes cavus status, which was limited to 20% of the total randomised population in Part 2.

To maintain the study double-blind, all study drug kits were packaged with blinded labels. The number and type of bottles in placebo kits matched the omaveloxolone kits at each dose level. Investigators distributed the blinded study drug kits by kit number to patients as assigned by the Interactive Web Response System.

All patients, investigators, site personnel, and laboratories with direct involvement in the conduct of the study or their designees were blinded to treatment assignments, and appropriate measures were taken to ensure the blind was maintained to reduce potential bias. The assessment of the primary outcome (mFARS) was conducted by a neurologist who was blinded to laboratory values in most cases, and several sections of the examination (e.g, upright stability subscore) included timed components that are objective measures and not readily altered by subject effort.

During Part 2 of the study, all sponsor personnel were blinded to treatment assignment. The only people with access to treatment assignments for Part 2 were those individuals who maintained the Interactive Web Response System, the Data and Safety Monitoring Board (DSMB), the unblinded statistical team providing data to and analyzing data for the DSMB, and safety personnel without direct involvement in the conduct of the study who were assigned to report unblinded data to regulatory authorities as required.

- **Statistical methods**

The description of the study population can be found below.

Table 14: Study 1402 Part 2: Summary of analysis populations for efficacy analyses

Analysis Population	Description
Full analysis set	• Primary analysis of efficacy in patients without pes cavus who have at least 1 post-baseline measurement, categorized by their randomized treatment group (whether or not they received study drug) • Implemented as a predictive enrichment strategy
All-randomized population	• All randomized patients, categorized by their randomized treatment group (whether or not they received study drug) • Descriptive analysis of efficacy
Pes cavus population	• All patients with pes cavus categorized by their randomized treatment group (whether or not they received study drug) • Descriptive analysis of efficacy
Per-protocol population	• Patients without pes cavus who received study drug through Week 48 and had no major protocol deviation that could potentially affect the efficacy assessments • Sensitivity analysis exploring the robustness of the primary FAS findings

FAS: Full analysis set

[A] Study 1402 Part 2 Predefined analyses: Estimand (target of estimation)

The estimand of the primary analysis was defined as follows:

- **Population**: Full analysis set (FAS) described above, with exclusion of patients with pes cavus.
- **Primary endpoint**: change from baseline of mFARS score at week 48. Difference between treatment groups in LS means were calculated MMRM model with no imputation.
- **Key secondary endpoints**: PGIC and CGIC at week 48 were analysed using an analysis of covariance (ANCOVA) model with imputation of missing values. Treatment based multiple imputation was used.
- **Other secondary endpoints:** 9-HPT at Week 48, change in timed T25-FWT at Week 48, frequency of falls over 48 weeks, peak work during maximal exercise testing at Week 48, change in FA-ADL at Week 48. Difference between treatment groups were estimated using an MMRM model except for frequency of falls where a Poisson model was used.
- **Intercurrent events** were handled using "treatment policy strategy", ICH E9(R1). I.e patients who discontinued either study treatment or the study itself were still followed up for mFARS assessments.

Two-sided p-values at a significance level of 5% were used. Test method was non-parametric rank sum test (Kruskall Wallis).

A test hierarchy dealing with multiplicity was prespecified in the Statistical analysis plan and is concordant with an overall test probability not to exceed 5%.

[B] Additional analyses:

Study 1402 Extension, delayed start analyses (*post hoc*):

- **Inferiority analysis:** To test whether the effect achieved by the omaveloxolone treated patients at week 48 could not be recovered in the delayed treatment population. This analysis compared the treatment effect at week 48 with the treatment effect at extension week 72 where both treatment groups were treated with omaveloxolone as part of the Open Label extension. The applicant used an MMRM model. Additionally, the applicant compared the annualised rate of change in mFARS score through extension week 144 in the two groups to see if they differed statistically. Another way of investigating the non-inferiority question. Again, an MMRM model was used.
- **Propensity-matched analysis** was designed to evaluate the long-term Efficacy (up to 3 years) of omaveloxolone using external natural history data as a comparator. Matching was done on the covariates: Age, age of FA onset, sex, gait score at baseline and mFARS score at baseline using logistic regression. Matching of sex was exact. Pes cavus status was omitted. The analysis of the primary endpoint, the mFARS score was done using an MMRM model
- **Baseline-controlled analysis** was done to investigate pre-treatment and post-treatment annualised rate of change in mFARS slopes within each patient considered treatment naïve prior to the Open Label Extension. This included patients from dose ranging study 1 and placebo patients from the pivotal study 2. They excluded patients with pes cavus. Paired (two-sided) t-test was used to evaluate the difference.

[C] Sensitivity analyses

Sensitivity analyses were done throughout using alternative populations from the above table. Additionally, multiple imputation which a control-based imputation strategy was done in the primary mFARS (MMRM) analysis to challenge the implicit MAR (missing at random) assumption. Tipping point analysis was also performed to investigate at which level the imputation would cancel the significant findings in the primary mFARS analysis.

The below table shows deviations from the pre-specified statistical analysis plan taken from SAS part 2 version 2 dated 17 September 2019

Version	Revision Description	Date
2.0	• Specified that patients in the primary efficacy analysis population must have at least one post-baseline measurement • Changed analysis of the two key secondary endpoints to analysis of covariance (ANCOVA) and specified how to handle missing responses • Added tipping point and control-based multiple imputation as sensitivity analyses for the primary and key secondary endpoints to assess the impact of missing data • Updated power calculations to account for dropouts in sample size planning • Added "site" as a covariate for analysis of the primary and key secondary endpoints • Added analysis of efficacy using the "All Randomized" and "Pes Cavus" populations for descriptive purposes. Analyses of the "All Randomized" population includes a covariate for "pes cavus" • Added correlation of change in mFARS to other efficacy endpoints at Week 48 • Added categorical summary to quantify the number of patients improved from baseline at Week 48 for all efficacy endpoints • Clarifications throughout	17 September 2019

Results

- **Participant flow**

Figure 22: Disposition of Patients

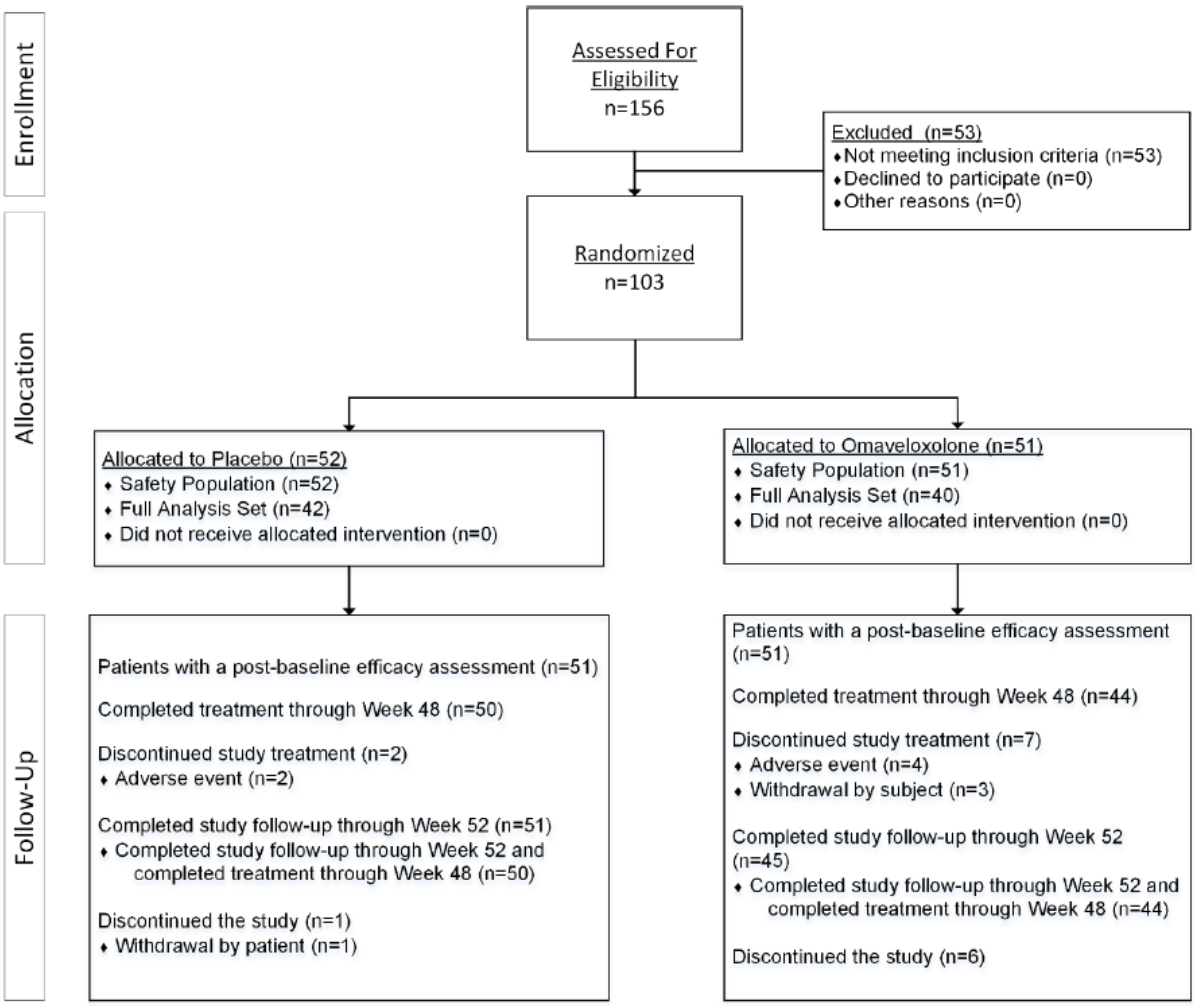


Table 15: Study 1402 Part 2: disposition of patients

	Without Pes Cavus (N = 83)		With Pes Cavus (N = 20)		All Patients (N = 103)	
	Omaveloxolone 150 mg (N = 41) n (%)	Placebo (N = 42) n (%)	Omaveloxolone 150 mg (N = 10) n (%)	Placebo (N = 10) n (%)	Omaveloxolone 150 mg (N = 51) n (%)	Placebo (N = 52) n (%)
Safety population	41 (100%)	42 (100%)	10 (100%)	10 (100%)	51 (100%)	52 (100%)
Full analysis set	40 (97.6%)	42 (100%)	0	0	40 (78.4%)	42 (80.8%)
All-randomized population	41 (100%)	42 (100%)	10 (100%)	10 (100%)	51 (100%)	52 (100%)
Per-protocol population	29 (70.7%)	32 (76.2%)	0	0	29 (56.9%)	32 (61.5%)
Pes cavus population	0	0	10 (100%)	10 (100%)	10 (19.6%)	10 (19.2%)
Completed treatment through Week 48	35 (85.4%)	40 (95.2%)	9 (90.0%)	10 (100%)	44 (86.3%)	50 (96.2%)
Discontinued study treatment	6 (14.6%)	2 (4.8%)	1 (10.0%)	0	7 (13.7%)	2 (3.8%)
Adverse events	3 (7.3%)	2 (4.8%)	1 (10.0%)	0	4 (7.8%)	2 (3.8%)
Withdrawal by patient	3 (7.3%)	0	0	0	3 (5.9%)	0
Completed study follow-up through Week 52	36 (87.8%)	41 (97.6%)	9 (90.0%)	10 (100%)	45 (88.2%)	51 (98.1%)
Completed study follow-up through Week 52 and completed treatment through Week 48	35 (85.4%)	40 (95.2%)	9 (90.0%)	10 (100%)	44 (86.3%)	50 (96.2%)
Completed study follow-up through Week 52 but did not complete treatment through Week 48	1 (2.4%)	1 (2.4%)	0	0	1 (2.0%)	1 (1.9%)
Discontinued study	5 (12.2%)	1 (2.4%)	1 (10.0%)	0	6 (11.8%)	1 (1.9%)
Administrative reasons	2 (4.9%)	0	0	0	2 (3.9%)	0
Withdrawal by patient	3 (7.3%)	1 (2.4%)	1 (10.0%)	0	4 (7.8%)	1 (1.9%)

- **Recruitment**

Date first patient enrolled: 20 October 2017

Date last patient completed: 31 October 2019

A total of 11 investigative sites (7 sites in the United States, 1 site in Australia, 1 site in Austria, 1 site in Italy, and 1 site in the United Kingdom) enrolled at least 1 patient.

- **Conduct of the study**

The DSMB performed quarterly reviews of unblinded data for safety throughout Part 2.

The original protocol, dated 23 July 2014, was amended 8 times. All patients in Part 2 of the study were enrolled under version 9 of the protocol. Amendment 8 (version 09 of the protocol) was dated 17 Aug 2017.

The original statistical analysis plan (SAP) (version 1.0), dated 16 May 2019, was amended twice, ie, version 1.1 dated 04 Jun 2019 and version 2.0 dated 18 Sep 2019. An addendum to version 2.0 of the SAP was finalised on 9 October 2019.

The final analysis plan (which supersedes planned analyses in the protocol) specified that the primary analysis of efficacy is based on the FAS, which included only patients without pes cavus. The protocol indicated that all enrolled patients were included in the Intent-to-Treat Population for analysis of efficacy.

The protocol sample size calculations were based on 100 patients (total planned enrolment) using a 2-sided t-test. With the primary analysis of efficacy specified as being based on only those patients without pes cavus, the final SAP included power calculations for the 80 patients in the stratum without pes cavus the Part 2 portion of the study has approximately 85% power to test the difference between the two treatment groups

with respect to change from baseline in mFARS at Week 48. Power calculations included in this analysis plan used MMRM with an assumption of 5 repeated measurements (Weeks 4, 12, 18, 24, 26, and 48) having compound symmetry covariance structure.

Additionally, the SAP changed the defined order of some efficacy endpoints. The SAP elevated PGIC and CGIC from secondary endpoints in the protocol to key secondary endpoints. Selected protocol-specified exploratory endpoints (9-HPT, 25-foot timed walk test, frequency of falls, and ADL) were elevated to secondary endpoints in the SAP. The protocol did not specify change in raters' assessments of videos of normal walking as an endpoint, but this SAP added it as an exploratory endpoint.

In addition to changes to the planned analyses stated in the protocol, the following changes to the analyses specified in version 2.0 of the SAP were made: 1) for exploratory analyses of efficacy, the number and percentage of patients with an improvement from baseline in 9-HPT, T25-FWT, peak work, and ADL were not summarised and 2) *post hoc* analyses were conducted.

Overall, 37 patients had major protocol deviations; of those, 20 patients were in the omaveloxolone group, and 17 patients were in the placebo group. Overall, the most frequently occurring major protocol deviations were "study procedures deviations."

- **Baseline data**

Table 16: Study 1402 Part 2: Patient demographics by population

	Without Pes Cavus[a] (FAS) (N = 82)		With Pes Cavus[a] (Pes Cavus Population) (N = 20)		All Patients[a] (Safety Population) (N = 103)	
Parameter	**Omaveloxolone 150 mg (N = 40)**	**Placebo (N = 42)**	**Omaveloxolone 150 mg (N = 10)**	**Placebo (N = 10)**	**Omaveloxolone 150 mg (N = 51)[b]**	**Placebo (N = 52)**
Age at Screening (years)						
n	40	42	10	10	51	52
Mean (SD)	24.2 (6.48)	23.6 (7.79)	19.9 (2.56)	26.0 (8.21)	23.4 (6.08)	24.1 (7.85)
Median (Min, Max)	23.0 (16, 39)	21.0 (16, 40)	20.0 (16, 23)	27.0 (16, 38)	22.0 (16, 39)	21.0 (16, 40)
Age group at Screening, n (%)						
<18 years	7 (17.5%)	13 (31.0%)	2 (20.0%)	2 (20.0%)	9 (17.6%)	15 (28.8%)
≥18 years	33 (82.5%)	29 (69.0%)	8 (80.0%)	8 (80.0%)	42 (82.4%)	37 (71.2%)
Sex, n (%)						
Female	24 (60.0%)	14 (33.3%)	7 (70.0%)	3 (30.0%)	31 (60.8%)	17 (32.7%)
Male	16 (40.0%)	28 (66.7%)	3 (30.0%)	7 (70.0%)	20 (39.2%)	35 (67.3%)
Ethnicity, n (%)						
Hispanic or Latino	1 (2.5%)	3 (7.1%)	1 (10.0%)	0	2 (3.9%)	3 (5.8%)
Not Hispanic or Latino	39 (97.5%)	39 (92.9%)	9 (10.0%)	10 (100%)	49 (96.1%)	49 (94.2%)
Race, n (%)						
White	40 (100.0%)	40 (95.2%)	9 (90.0%)	10 (100%)	50 (98.0%)	50 (96.2%)
Other	0	2 (4.8%)	1 (10.0%)	0	1 (2.0%)	2 (3.8%)

Abbreviations: FAS=full analysis set; Max=maximum; Min=minimum

[a] One patient without pes cavus did not have at least 1 post-baseline measurement and thus the total across with pes cavus and without pes cavus is less than the total for the All Patients column.

[b] Of the 51 patients randomized to omaveloxolone, 10 (20%) had pes cavus and 41 (80%) did not (Study 1402 Part 2 CSR Table 14.1.1.3; Table 14.1.1.2).

Source: Study 1402 Part 2 CSR, Table 14.1.2.5; Table 14.1.2.3; Table 14.1.2.2

Table 17: Study 1402 Part 2: Patient demographics by age at baseline (Safety Population)

	<18 Years		≥18 Years	
Parameter	**Omaveloxolone 150 mg (N = 9) n (%)**	**Placebo (N = 15) n (%)**	**Omaveloxolone 150 mg (N = 42) n (%)**	**Placebo (N = 37) n (%)**
Sex				
Male	3 (33.3%)	10 (66.7%)	17 (40.5%)	25 (67.6%)
Female	6 (66.7%)	5 (33.3%)	25 (59.5%)	12 (32.4%)
Ethnicity				
Hispanic or Latino	0	1 (6.7%)	2 (4.8%)	2 (5.4%)
Not Hispanic or Latino	9 (100%)	14 (93.3%)	40 (95.2%)	35 (94.6%)
Race				
White	9 (100%)	15 (100%)	41 (97.6%)	35 (94.6%)
Other	0	0	1 (2.4%)	2 (5.4%)

Note: Percentages are based on the number of patients with data. Age group is based on age at first double-blind treatment.

All patients had genetically confirmed FA. Across treatment groups, the mean age at FA onset was approximately 15 years and ranged from 5 to 36 years, with a mean disease duration of approximately 4.6 years in the Safety population. As per protocol eligibility criteria, in each group no more than 20% of patients had pes cavus. Mean compliance was above 85% for both treatment groups (89.7% for the placebo group and 86.2% for the omaveloxolone group).

Table 18: Study 1402 Part 2: Summary of baseline characteristics

Parameter	Without Pes Cavus (FAS)		All Patients (Safety Population)	
	Omaveloxolone 150 mg (N = 40)	Placebo (N = 42)	Omaveloxolone 150 mg (N = 51)	Placebo (N = 52)
BMI (kg/m^2) [Mean (SD)]	23.649 (5.4282)	22.890 (5.1006)	23.151 (5.1240)	22.838 (4.7544)
mFARS [Mean (SD)]	40.94 (10.393)	38.77 (11.026)	40.84 (10.149)	37.94 (10.767)
Peak work (W/kg) [Mean (SD)]	1.0776 (0.53564)	1.1822 (0.61151)	1.0905 (0.57617)	1.2281 (0.62207)
FA-ADL [Mean (SD)]	10.74 (4.766)	9.87 (4.834)	11.03 (4.486)	9.85 (4.716)
Age at FA onset (years) [Mean (SD)]	15.9 (5.74)	15.1 (5.34)	14.8 (5.67)	15.3 (5.31)
Years since FA onset (years) [Mean (SD)]	4.8 (3.98)	4.7 (4.70)	4.7 (3.78)	4.4 (4.42)
GAA1 Repeat length[a] [Mean (SD)]	739.2 (214.88)	693.8 (277.19)	736.8 (206.80)	676.2 (267.88)
Ambulatory [n (%)]	37 (92.5%)	39 (92.9%)	46 (90.2%)	49 (94.2%)
History of cardiomyopathy [n (%)]	19 (47.5%)	12 (28.6%)	25 (49.0%)	15 (28.8%)
History of scoliosis [n (%)]	29 (72.5%)	32 (76.2%)	39 (76.5%)	37 (71.2%)
History of scoliosis surgery [n (%)]	12 (30.0%)	7 (16.7%)	16 (31.4%)	10 (19.2%)
History of areflexia [n (%)]	36 (90.0%)	41 (97.6%)	47 (92.2%)	51 (98.1%)

Abbreviations: BMI=body mass index; FA=Friedreich's ataxia; FA-ADL=Friedreich's ataxia activities of daily living; FAS=full analysis set; mFARS=modified Friedreich's ataxia rating scale

[a] Not all patients had GAA1 repeat length measurements. For without pes cavus, omaveloxolone n = 31 and placebo n = 36. For all patients, omaveloxolone n = 41 and placebo n = 43.

Table 19: Study 1402 Part 2: Summary of baseline characteristics by baseline age (safety population)

Parameter	Age <18 Years		Age ≥18 Years	
	Omaveloxolone 150 mg (N = 9)	Placebo (N = 15)	Omaveloxolone 150 mg (N = 42)	Placebo (N = 37)
BMI (kg/m^2) [Mean (SD)]	19.600 (2.5612)	20.506 (4.0428)	23.912 (5.2323)	23.783 (4.7416)
mFARS [Mean (SD)]	43.88 (10.519)	39.35 (11.036)	40.19 (10.078)	37.36 (10.756)
Peak work (W/kg) [Mean (SD)]	1.1641 (0.62612)	1.1812 (0.59259)	1.0748 (0.57175)	1.2471 (0.64059)
FA-ADL [Mean (SD)]	11.11 (4.091)	9.73 (5.085)	11.01 (4.612)	9.89 (4.631)
Age at FA onset (years) [Mean (SD)]	10.4 (3.05)	10.0 (3.18)	15.8 (5.69)	17.5 (4.41)
Years since FA onset (years) [Mean (SD)]	3.1 (3.02)	2.7 (2.82)	5.1 (3.87)	5.1 (4.77)
GAA1 repeat length[a] [Mean (SD)]	820.8 (246.72)	772.8 (264.09)	716.5 (194.82)	638.8 (264.04)
Ambulatory [n (%)]	9 (100%)	13 (86.7%)	37 (88.1%)	36 (97.3%)
History of cardiomyopathy [n (%)]	6 (66.7%)	7 (46.7%)	19 (45.2%)	8 (21.6%)
History of scoliosis [n (%)]	9 (100%)	12 (80.0%)	30 (71.4%)	25 (67.6%)
Scoliosis surgery [n (%)]	7 (77.8%)	6 (40.0%)	9 (21.4%)	4 (10.8%)
History of areflexia [n (%)]	9 (100%)	15 (100%)	38 (90.5%)	36 (97.3%)

Abbreviations: BMI=body mass index; FA=Friedreich's ataxia; FA-ADL=Friedreich's ataxia activities of daily living; mFARS=modified Friedreich's ataxia rating scale

[a] Not all patients had GAA1 repeat length measurements. For age <18, omaveloxolone n = 8 and placebo n = 12. For age ≥18 years, omaveloxolone n = 33 and placebo n = 31.

- **Numbers analysed**

Table 20: Analysis populations

Number of:	All Subjects (N = 103)		With Pes Cavus (N = 20)		Without Pes Cavus (N = 83)	
	Placebo (N = 52) n, (%)	Omaveloxolone 150 mg (N = 51) n, (%)	Placebo (N = 10) n, (%)	Omaveloxolone 150 mg (N = 10) n, (%)	Placebo (N = 42) n, (%)	Omaveloxolone 150 mg (N = 41) n, (%)
Safety Population	52 (100)	51 (100)	10 (100)	10 (100)	42 (100)	41 (100)
Full Analysis Set	42 (80.8)	40 (78.4)	0	0	42 (100)	40 (97.6)
All Randomized Population	52 (100)	51 (100)	10 (100)	10 (100)	42 (100)	41 (100)
Per-Protocol Population	32 (61.5)	29 (56.9)	0	0	32 (76.2)	29 (70.7)
Pes Cavus Population	10 (19.2)	10 (19.6)	10 (100)	10 (100)	0	0

- **Outcomes and estimation**

Table 21: Study 1402 Part 2: Pivotal efficacy study key results (Full Analysis Set)

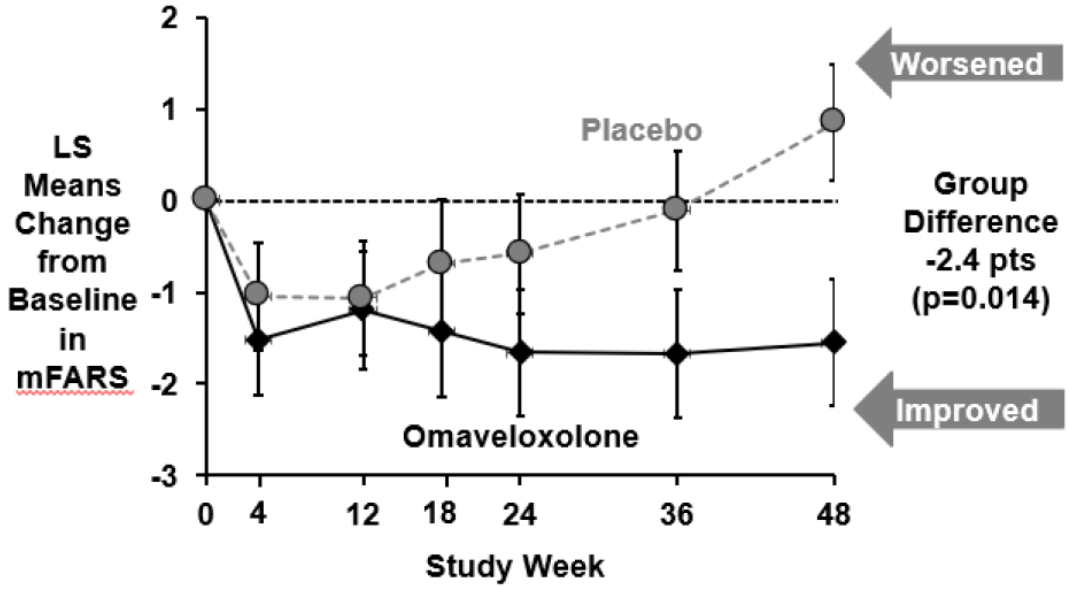
Visit	Statistic	Primary Efficacy Endpoint		Key Secondary Efficacy Endpoints				Secondary Efficacy Endpoint	
		mFARS		PGIC		CGIC		FA-ADL	
		Omav 150 mg (N = 40)	Placebo (N = 42)	Omav 150 mg (N = 40)	Placebo (N = 42)	Omav 150 mg (N = 40)	Placebo (N = 42)	Omav 150 mg (N = 40)	Placebo (N = 42)
Baseline	n	40	42					40	42
	Mean (SD)	40.94 (10.393)	38.77 (11.026)	NA	NA	NA	NA	10.738 (4.7663)	9.869 (4.8339)
	Median	39.15	35.65					11.500	10.000
	Min, Max	24.3, 59.3	19.8, 63.0					2.00, 21.00	1.00, 20.50
Week 48	n	34	41	36	41	36	41	36	41
	Mean (SD)	39.17 (10.019)	39.54 (11.568)	3.8 (1.17)	4.2 (1.18)	3.8 (0.81)	4.0 (0.91)	10.556 (4.7174)	11.073 (4.9982)
	Median	38.10	38.70	4.0	4.0	4.0	4.0	12.000	11.000
	Min, Max	26.0, 56.7	18.3, 64.5	1, 6	1, 6	2, 5	2, 6	3.00, 22.00	0.00,24.00
	LS mean difference (SE)	-2.40[a] (0.956)		-0.43[b] (0.281)		-0.13[b] (0.199)		-1.30[a] (0.629)	
	95% CI	-4.31, -0.50		-0.98, 0.12		-0.52, 0.26		2.56, -0.05	
	p-value	0.0141		0.1251		0.5199		0.0420	

Abbreviations: CGIC=clinical global impression of change; CI=confidence interval; FA=Friedreich's ataxia; FA-ADL=FA activities of daily living; LS=least squares; Max=maximum; mFARS=modified FA rating scale; Min=minimum; NA=not available; Omav=omaveloxolone; PGIC=patient global impression of change

[a] LS means change from baseline is omaveloxolone - placebo

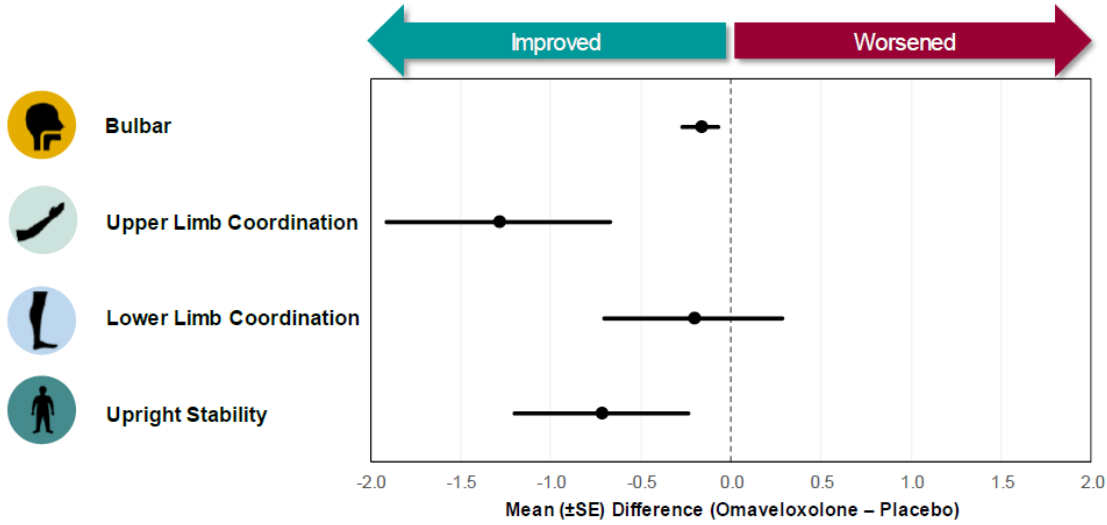
[b] LS mean difference is omaveloxolone - placebo. Comparison of PGIC and CGIC for patients treated with omaveloxolone 150 mg and placebo was estimated using analyses of covariance, with the following fixed factors: site, and treatment. Missing data were imputed using multiple imputation based on the treatment group to which the patient was assigned.

Figure 23: Study 1402 Part 2: Primary efficacy analysis for change in mFARS at week 48 (full analysis set)



Abbreviations: mFARS=modified Friedreich's ataxia rating scale; MMRM=mixed model repeated measures; Omav=omaveloxolone; pts=points
Note: Data plotted were the changes from baseline in mFARS and p-value estimated from MMRM analysis.

Figure 24: Study 1402 Part 2: Analysis of changes in mFARS subsections at week 48 (full analysis set)



Abbreviation: mFARS=modified Friedreich's ataxia rating scale

Table 22: Study 1402 Part 2: Categorical responses of patient global impression of change and clinical global impression of change at week 48 (full analysis set)

Assessment	Response	Omaveloxolone 150 mg (N = 40) n (%)	Placebo (N = 42) n (%)
PGIC	Very much improved (1)	1 (2.8%)	1 (2.4%)
	Much improved (2)	3 (8.3%)	2 (4.9%)
	Minimally improved (3)	12 (33.3%)	8 (19.5%)
	No change (4)	9 (25.0%)	13 (31.7%)
	Minimally worse (5)	9 (25.0%)	12 (29.3%)
	Much worse (6)	2 (5.6%)	5 (12.2%)
	Very much worse (7)	0	0
CGIC	Very much improved (1)	0	0
	Much improved (2)	1 (2.8%)	2 (4.9%)
	Minimally improved (3)	12 (33.3%)	10 (24.4%)
	No change (4)	15 (41.7%)	17 (41.5%)
	Minimally worse (5)	8 (22.2%)	11 (26.8%)
	Much worse (6)	0	1 (2.4%)
	Very much worse (7)	0	0

Abbreviations: CGIC=clinical global impression of change; PGIC=patient global impression of change

Table 23: Secondary efficacy endpoints (full analysis set)

Endpoint at Week 48	LS Mean Change ± SE from Baseline[a]		LS Mean Difference ± SE Between Treatment Groups
	Placebo (n = 42)	Omaveloxolone (n = 40)	
9-HPT (1/sec)[b]	-0.0001 ± 0.0006 (p = 0.82)	-0.0014 ± 0.0007 (p = 0.04)	-0.0013 ± 0.001 (p = 0.18)
25-foot timed walk test (1/sec)[c]	-0.0226 ± 0.0053 (p <0.0001)	-0.0169 ± 0.0056 (p = 0.004)	0.0058 ± 0.0078 (p = 0.46)
Frequency of falls[d] (Median [Min, Max])	8.5 (0, 131)	3.0 (1, 89)	-0.32 ± 0.293 (p = 0.28)
Peak work (watt/kg)	0.09 ± 0.033 (p = 0.006)	0.03 ± 0.035 (p = 0.33)	-0.06 ± 0.049 (p = 0.22)
Activities of Daily Living	1.14 ± 0.421 (p = 0.009)	-0.17 ± 0.450 (p = 0.71)	-1.30 ± 0.629 (p = 0.04)

Abbreviations: 9-HPT=9-hole peg test; LS=least squares; Max=maximum; Min=minimum; MMRM=mixed model for repeated measures; SE=standard error; sec=second.

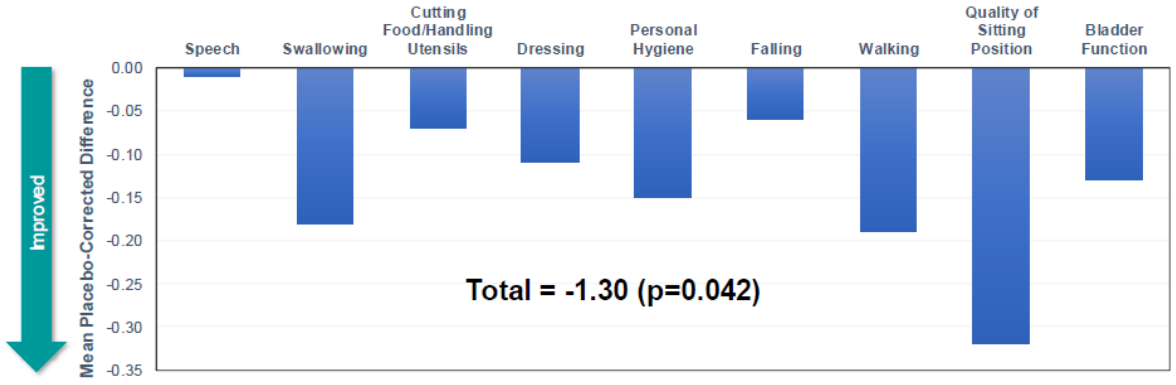
[a] Mean changes and p-values estimated from MMRM analyses for 9-HPT, 25-foot timed walk test, peak work, and Activities of Daily Living; Incidence rate of falls analyzed using a Poisson model

[b] Analysis based on reciprocal of average time, nondominant hand

[c] Analysis based on reciprocal of average walk time

[d] Comparison in the frequency of falls for omaveloxolone patients versus placebo patients was estimated from the Poisson model with the natural logarithm of time on study (days) included as an offset term.

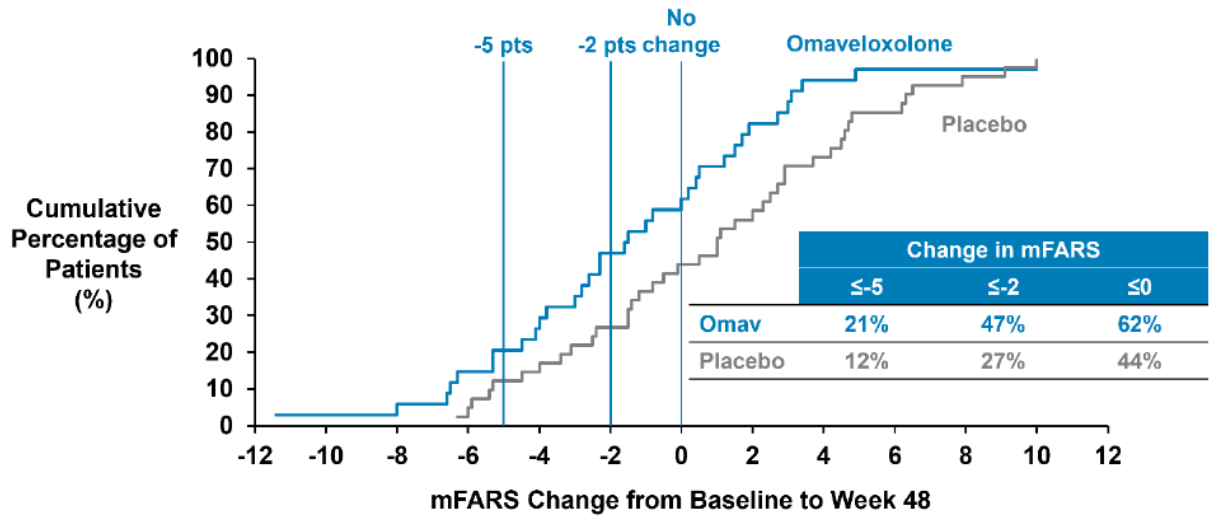
Figure 25: Study 1402 Part 2: MMRM analysis of change from baseline at week 48 mean differences between treatment groups in FA-ADL individual section scores (full analysis set)



- **Ancillary analyses**

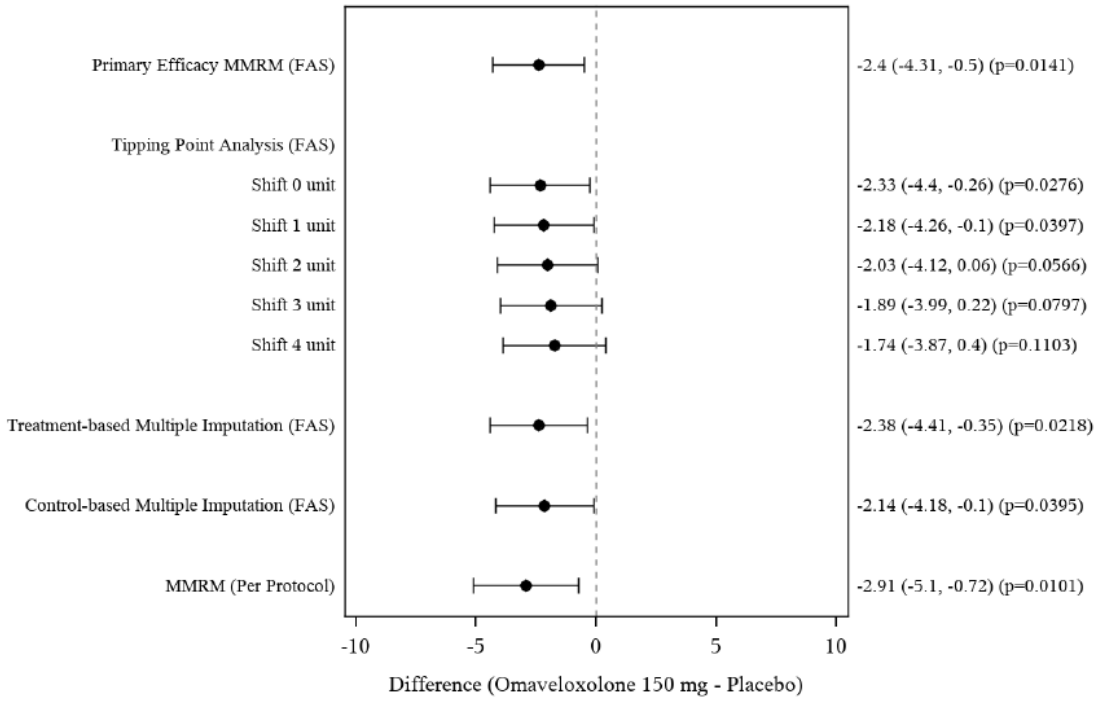
(1) mFARS Sensitivity Analyses

Figure 26: Study 1402 Part 2: Cumulative distribution plot of change from baseline in mFARS scores at week 48 (full analysis set)



Abbreviations: mFARS=modified Friedreich's ataxia rating scale; Omav=omaveloxolone
Source: Study 1402 Part 2 CSR, Figure 14.2.56.2, Table 14.2.4

Figure 27: Analysis of mFARS change from baseline to week 48



The primary analysis of efficacy was based on an MAR assumption. Missing mFARS data were not imputed for the primary analysis of efficacy using an MMRM model. Note: 95% [585/618] of the total mFARS values expected for the trial after baseline were collected. Control-based multiple imputation was performed to

assess the robustness of conclusions based on the MAR assumption for the primary endpoint. Results of the sensitivity analysis using control-based multiple imputation (Figure 27; p = 0.040) upheld the conclusions of the primary analysis.

Additional *post hoc* analyses were performed to evaluate the effect of attrition and whether the timing of omaveloxolone missing data may have contributed to the separation in mFARS scores between the omaveloxolone and placebo groups. The divergence between treatment groups in mFARS change from baseline after Week 12 was driven by a worsening (ie, an increase) in mFARS in the placebo group. The placebo group LS mean change from baseline worsened by 1.91 points from Week 12 to Week 48 (-1.06 to 0.85). In contrast, the omaveloxolone group LS mean change from baseline improved by 0.35 points from Week 12 to Week 48 (-1.20 to -1.55).

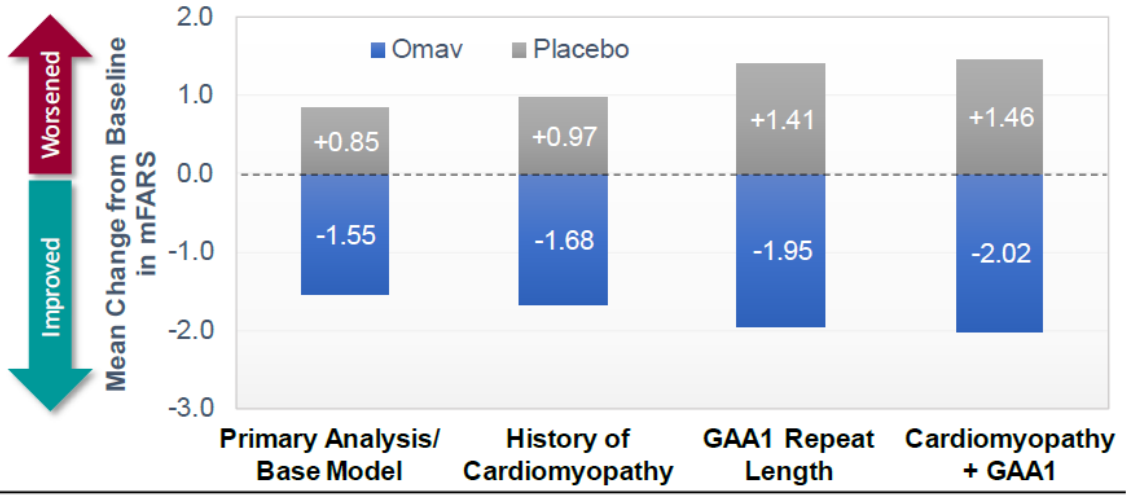
Only one patient in the placebo group had missing data at Week 48 and, in the omaveloxolone group, the trajectory of mFARS scores remained stable during the time period where patients were withdrawing from the study. Patients with missing Week 48 mFARS were generally stable or improved from baseline at their last assessment. Together, these results support that the separation was due to worsening in the placebo group, not due to missing data. Finally, the above pre-specified control-based multiple imputation (ie, jump to reference) is a conservative approach to handling missing data due to the observed profile of mFARS and this analysis maintained statistical significance.

In addition, the tipping point analysis summarised in Figure 27 uses multiple imputation of missing Week 48 data. Multiple imputation for the "Shift 0" analysis is based on observed data from the randomised treatment group and assumes that data were MAR. Various shifts of the imputed data in the omaveloxolone group were explored. The tipping point for the trial, where the treatment effect loses significance, is a shift of +2 points (worsening) in the imputed data for missing omaveloxolone mFARS values at Week 48. The shift required to change the conclusion of the trial is more than twice the magnitude of worsening in the placebo group (+0.85 points).

A *post hoc* analysis using an ANCOVA to assess the effect of treatment group on post-baseline mFARS included the same covariates as the MMRM analysis (ie, baseline mFARS and site). The ANCOVA analysis showed a greater treatment effect favoring omaveloxolone at Week 48, with an improvement in mFARS relative to placebo of -2.83 points (p = 0.0068).

Some baseline characteristics that are consistent with more advanced disease were more prevalent in the patients randomised to omaveloxolone than in patients randomised to placebo. The prespecified model did not account for these imbalances. Although all demographic and baseline disease characteristics were explored in a *post hoc* manner for inclusion as covariates in the repeated measures model, history of cardiomyopathy and GAA1 repeat length provided the best improvements in overall model fit. Accordingly, additional *post hoc* sensitivity analyses were performed to assess the impact of controlling for imbalances in these baseline disease characteristics between the randomised cohorts. Results from these sensitivity analyses are shown in Figure 28. Accounting for a history of cardiomyopathy as a covariate in the model resulted in an improvement in mFARS of -2.65 points at Week 48 for omaveloxolone relative to placebo (p = 0.0064). Although not all randomised patients had baseline GAA1 repeat length data, the inclusion of GAA1 repeat length as a covariate in the longitudinal model for the patients with available data (n = 31 for omaveloxolone and n = 36 for placebo) improved the treatment effect on mFARS with omaveloxolone, resulting in a difference between treatment groups of -3.36 points (p = 0.0017). Inclusion of both covariates (ie, history of cardiomyopathy and GAA1 repeat length) into the longitudinal model further improved the treatment effect with omaveloxolone, with a difference of -3.48 points between treatment groups (p = 0.0012).

Figure 28: Study 1402 Part 2: Analyses of change in mFARS from baseline at week 48 using the primary analysis MMRM methodology with additional baseline covariates (full analysis set)



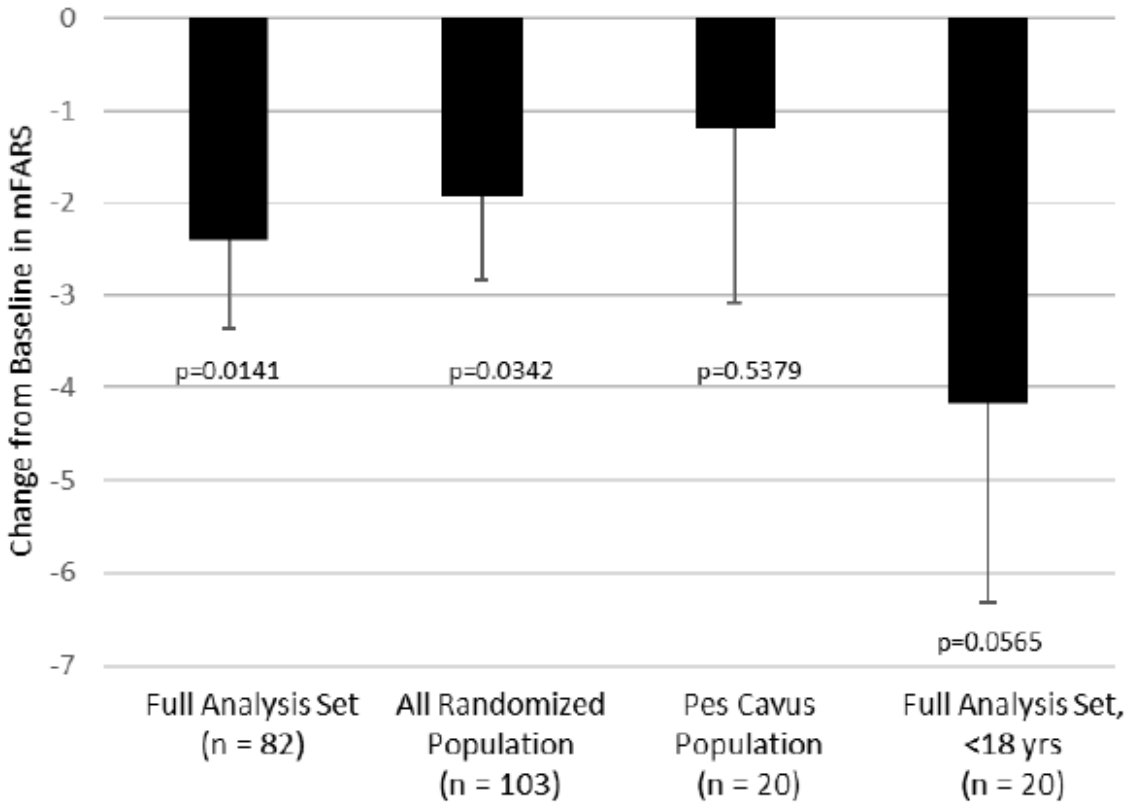
	Primary Analysis/ Base Model	History of Cardiomyopathy	GAA1 Repeat Length	Cardiomyopathy + GAA1
Placebo-Corrected Difference using MMRM	-2.40 (p=0.014)	-2.65 (p=0.0064)	-3.36 (p=0.0017)	-3.48 (p=0.0012)

Abbreviations: mFARS=modified Friedreich's ataxia rating scale; MMRM=mixed model repeated measures; Omav=omaveloxolone

Inclusion of covariates to account for baseline imbalances consistently improved the sensitivity of the analyses (ie, lower SE) and increased the difference between treatments. These analyses suggest that the observed imbalances in baseline disease characteristics that are consistent with more advanced disease biased the results against omaveloxolone. Collectively, these analyses support the conclusion reached from the primary analysis suggesting that the base model yielded a conservative estimate of the treatment effect.

(2) Change from Baseline in the mFARS in Other Analysis Populations

Figure 29: Changes in modified Friedreich's ataxia rating scale at week 48 across analysis populations

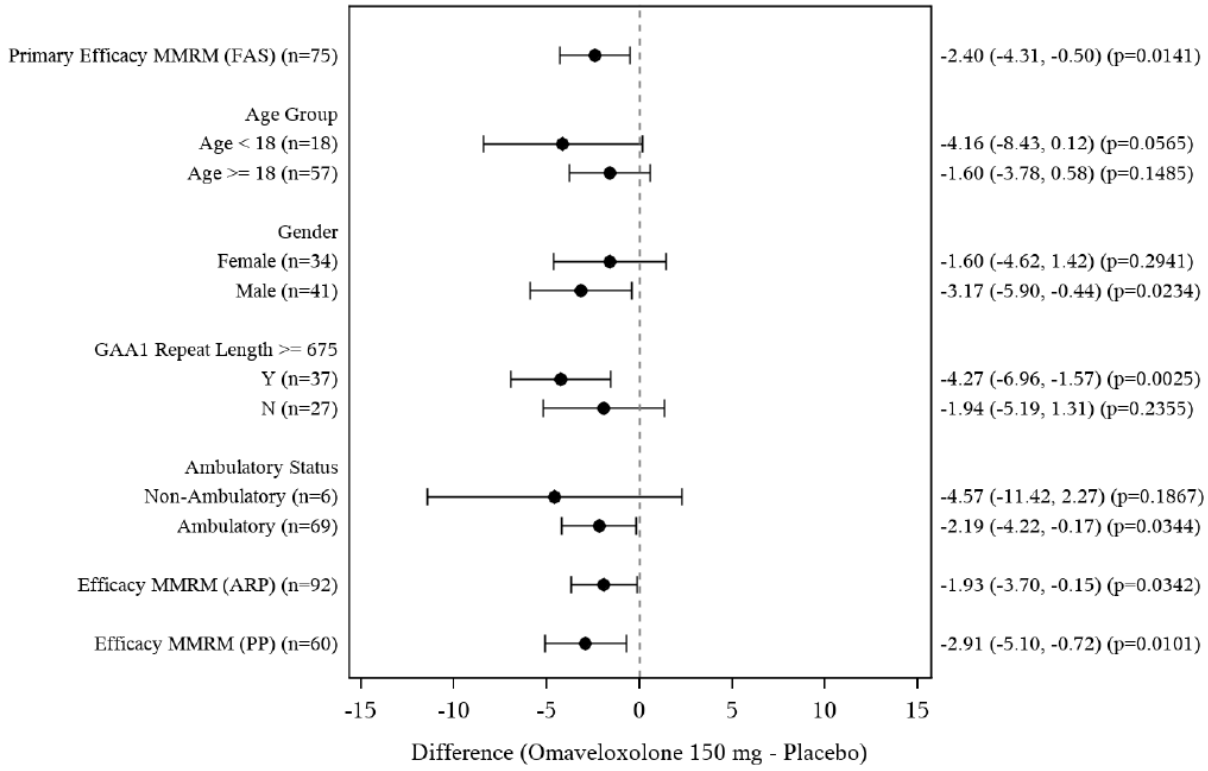


Abbreviation: mFARS=modified Friedreich's ataxia rating scale.

Additionally, in the PP Population, as with the FAS, statistically significant changes in mFARS with omaveloxolone treatment were observed at Week 48.

(3) Subgroup analyses

Figure 30: Study 1402 Part 2: Change in mFARS at week 48 in pre-specified subgroups



Abbreviations: ARP=All Randomized Population; FAS=Full Analysis Set; MMRM=mixed model for repeated measures; PP=Per Protocol.
Note: Data plotted are LS means differences between omaveloxolone and placebo patients estimated from a mixed model repeated measures (MMRM) analysis. The analysis used Visits 4, 12, 18, 24, 36, and 48. The number of patients (n) shown is the number of patients with an mFARS assessment at Week 48.

Some of the numerically greatest improvements in mFARS were observed in the subset of adolescent patients in the FAS (mean ± SE difference = -4.16 ± 2.147 points; n = 20; p = 0.0565) (Figure 31 and Table 24).

Figure 31: Study 1402 Part 2: mFARS over time in patients <18 years (full analysis set)

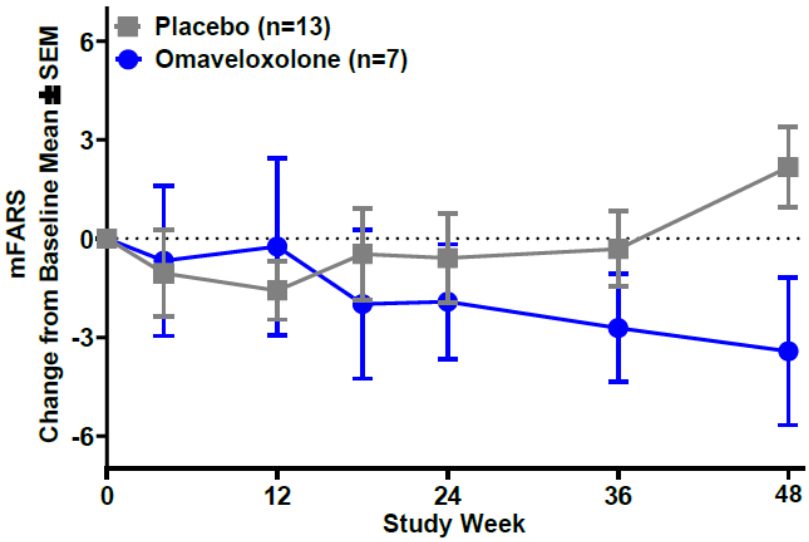


Table 24: Study 1402 Part 2: mFARS results by age subgroups

Subgroups by Baseline Age (Years)	LS Mean Change from Baseline in mFARS (±SE) at Week 48					
	N	Placebo	N	Omaveloxolone	Difference + p-value	
FAS						
<18	13	2.52 (1.175)	7	0.05 (0.783)	-4.16 (2.147)	p=0.0565
≥18	29	0.05 (0.783)	33	-1.55 (0.744)	-1.60 (1.093)	p=0.1485
<25	28	1.39 (0.789)	24	-1.05 (0.911)	-2.43 (1.215)	p=0.0490
≥25	14	-0.10 (1.095)	16	-2.37 (1.142)	-2.27 (1.597)	p=0.1601
ARP						
<18	15	2.18 (1.142)	9	-0.48 (1.612)	-2.66 (1.974)	p=0.1812
≥18	37	0.24 (0.735)	42	-1.18 (0.712)	-1.43 (1.028)	p=0.1688
<25	32	1.01 (0.780)	34	-0.28 (0.811)	-1.28 (1.134)	p=0.2616
≥25	20	0.57 (0.978)	17	-2.81 (1.206)	-3.38 (1.549)	p=0.0321

In Study 1402 Part 2, of the 103 patients randomised a total of 32 patients were enrolled outside the United States (US), with 24 patients from Europe (Austria, Italy, and the United Kingdom) and 8 patients from Australia (Table 25). Across subgroups and treatment arms, omaveloxolone-treated patients in the Europe subgroup had slightly higher mean age, slightly higher age of FA onset, and lower mean baseline mFARS. When the primary endpoint was analysed by subgroups of region relative to placebo, treatment differences (least squares mean difference ± SE) of 0.91±1.9 (p=0.6394) and -2.85±1.14 (p=0.0146) were observed for the Europe and Other (US and Australia) subgroups, respectively, indicating that omaveloxolone was directionally favoured over placebo in both subgroups.

Table 25: Study 1402 Part 2: Patient enrolment by country

Number (%) of Patients Enrolled	All Randomized Patients		Full Analysis Set	
	Omav N=51	Placebo N=52	Omav N=40	Placebo N=42
United States	**36 (70.6)**	**35 (67.3)**	**26 (65.0)**	**28 (66.7)**
Australia	**5 (9.8)**	**3 (5.8)**	**4 (10.0)**	**2 (4.8)**
Europe	**10 (19.6)**	**14 (26.9)**	**10 (25)**	**12 (28.6)**
Austria	3 (5.9)	6 (11.5)	3 (7.5)	6 (14.3)
Italy	2 (3.9)	5 (9.6)	2 (5)	5 (11.9)
United Kingdom	5 (9.8)	3 (5.8)	5 (12.5)	1 (2.4)

Abbreviations: Omav=omaveloxolone

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia (Part 2)			
Study identifier	408-C-1402-PT2 EudraCT 2015-002762-23 NCT02255435		
Design	Study 1402 Part 2 was a randomised, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of omaveloxolone 150 mg in patients with Friedreich's ataxia. Patients enrolled in Part 2 were randomised 1:1 to receive omaveloxolone 150 mg or placebo. Enrolment of patients with pes cavus, a musculoskeletal foot deformity characterised by high arch of the foot that does not flatten with weight-bearing, was limited to 20% of the total randomised population in Part 2. Following randomisation on Day 1, patients self-administered study treatment once daily for 48 weeks. A follow-up visit for safety occurred at Week 52 (4 weeks after last dose).		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		48 weeks of treatment not applicable not applicable
Hypothesis	Superiority		
Treatment groups	Omaveloxolone group		Randomised to omaveloxolone, 48 weeks, 51 patients between 16 and 40 years of age.
	Placebo group		Randomised to placebo, 48 weeks, 52 patients between 16 and 40 years of age.
Endpoints and definitions	Primary endpoint	Week 48	Change in mFARS score at Week 48.
	Key secondary endpoint 1	Week 48	PGIC at Week 48.
	Key secondary endpoint 2	Week 48	CGIC at Week 48

Title: A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia (Part 2)			
Study identifier	408-C-1402-PT2 EudraCT 2015-002762-23 NCT02255435		
	Secondary endpoint	Week 48	Change in FA-ADL score at Week 48
Database lock	Study completed: 31 Oct 2019 (Last patient last visit) Database lock: 12 Nov 2019 Date of study report: 05 Nov 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Population: Full Analysis Set The pre-specified primary analysis of efficacy was analysed in FAS, which included all patients enrolled without pes cavus who had at least 1 post-baseline measurement. Timepoint: Week 48.		
Descriptive statistics and estimate variability	Treatment group	Omaveloxolone group	Placebo Group
	Number of subjects	40	42
	Change in mFARS at Week 48 (LS Mean [SE])	-1.55 (0.689)	0.85 (0.640)
	95% CI	-2.93, -0.18	-0.43, 2.13
Effect estimate per comparison	mFARS	Comparison groups	Omaveloxolone vs Placebo
		LS Mean Difference (SE)	-2.40 (0.956)
		95% CI	-4.31, -0.50
		P-value vs placebo (MMRM)	0.0141
Notes	In Study 1402 Part 2, change from baseline in mFARS scores for patients treated with omaveloxolone was compared with placebo at Week 48 using MMRM analysis, with site and baseline mFARS as covariates and the following fixed factors: treatment group, time, the interaction between treatment and time, the interaction between baseline and time. The analysis included mFARS values collected at Weeks 4, 12, 18, 24, 36, and 48. Week 48 values were available for 34 patients in the omaveloxolone group and 41 patients in the placebo group. Missing data were not imputed. A decrease in mFARS score represents improved function.		
Analysis description	**Key secondary 1 analysis: PGIC (Pre-specified)**		
Analysis population and time point description	Population: Full Analysis Set The FAS included all patients enrolled without pes cavus who had at least 1 post-baseline measurement. Timepoint: Week 48.		
Descriptive statistics and estimate variability	Treatment group	Omaveloxolone group	Placebo Group
	Number of subjects	40	42
	PGIC at Week 48 (LS Mean [SE])	3.90 (0.209)	4.33 (0.210)
	95% CI	3.49, 4.31	3.91, 4.74
Effect estimate per	PGIC	Comparison groups	Omaveloxolone vs Placebo

Title: A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia (Part 2)			
Study identifier	408-C-1402-PT2 EudraCT 2015-002762-23 NCT02255435		
comparison		LS Mean Difference (SE)	-0.43 (0.281)
		95% CI	-0.98, 0.12
		P-value vs placebo (ANCOVA)	0.1251
Notes	PGIC responses at Week 48 for patients treated with omaveloxolone were compared to placebo using ANCOVA, with treatment group and site as covariates. Week 48 values were available for 36 patients in the omaveloxolone group and 41 patients in the placebo group. Missing Week 48 values were imputed using multiple imputation based on the treatment group to which the patient was assigned.		
Analysis description	**Key secondary 2 analysis: CGIC (Pre-specified)**		
Analysis population and time point description	Population: Full Analysis Set The FAS included all patients enrolled without pes cavus who had at least 1 post-baseline measurement. Timepoint: Week 48.		
Descriptive statistics and estimate variability	Treatment group	Omaveloxolone group	Placebo Group
	Number of subjects	40	42
	Change in CGIC at Week 48 (LS Mean [SE])	3.93 (0.149)	4.06 (0.149)
	95% CI	3.64, 4.22	3.76, 4.35
Effect estimate per comparison	CGIC	Comparison groups	Omaveloxolone vs Placebo
		LS Mean Difference (SE)	-0.13 (0.199)
		95% CI	-0.52, 0.26
		P-value vs placebo (ANCOVA)	0.5199
Notes	CGIC responses at Week 48 for patients treated with omaveloxolone were compared to placebo using ANCOVA, with treatment group and site as covariates. Week 48 values were available for 36 patients in the omaveloxolone group and 41 patients in the placebo group. Missing Week 48 values were imputed using multiple imputation based on the treatment group to which the patient was assigned.		
Analysis description	**Secondary analysis: FA-ADL (Pre-specified)**		
Analysis population and time point description	Population: Full Analysis Set The FAS included all patients enrolled without pes cavus who had at least 1 post-baseline measurement. Timepoint: Week 48.		
Descriptive statistics and estimate variability	Treatment group	Omaveloxolone group	Placebo Group
	Number of subjects	40	42
	Change in FA-ADL at Week 48 (LS Mean [SE])	-0.17 (0.450)	1.14 (0.421)
	95% CI	-1.07, 0.73	0.30, 1.98

Title: A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia (Part 2)			
Study identifier	408-C-1402-PT2 EudraCT 2015-002762-23 NCT02255435		
Effect estimate per comparison	FA-ADL	Comparison groups	Omaveloxolone vs Placebo
		LS Mean Difference (SE)	-1.30 (0.629)
		95% CI	-2.56, -0.05
		P-value vs placebo (MMRM)	0.0420
Notes	Change from baseline in FA-ADL for patients treated with omaveloxolone was compared with placebo at Week 48 using MMRM analysis, with baseline FA-ADL, treatment group, visit, the interaction between treatment and visit, the interaction between baseline and visit as covariates. The analysis included FA-ADL values collected at Weeks 24, 36, and 48. Week 48 values were available for 36 patients in the omaveloxolone group and 41 patients in the placebo group. Missing data were not imputed.		

2.6.5.3. Clinical studies in special populations

See clinical pharmacology section.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study(ies)

Table 26: Description of clinical efficacy studies

Study / Study Abbreviation (Status; Data Cutoff / DBL Date)	Study Design / Objectives	Treatment	Number of Patients	Duration	Efficacy Endpoints[a]	Key Efficacy Findings
408-C-1402 / 1402 Extension (Ongoing; DBL 24 Mar 2022)	Open-label, long-term extended access / Long-term safety and tolerability	Omaveloxolone 150 mg, oral, once daily	N = 149 enrolled (Placebo-Omav = 106; Omav-Omav = 43)	Until omaveloxolone is commercially available or until patient withdrawal (whichever occurs first)	None	Not applicable; efficacy data are summarized descriptively

- / 1402 Propensity-matched analysis (-; DBL 24 Mar 2022)	Post hoc comparative analysis versus natural history / Supportive efficacy	Omaveloxolone 150 mg, oral, once daily	272 (Primary Pooled Population; 136 from FA-COMS and 136 from Study 1402 Extension)	Up to 3 years	Primary: change from baseline in mFARS at Year 3 Secondary: change from baseline in mFARS at Year 1 and Year 2	After 3 years, in the largest analysis population, the Primary Pooled Population (n = 272; 136 from FA-COMS and 136 from Study 1402 Extension), matched FA-COMS patients had progressed 6.611 mFARS points whereas patients treated with omaveloxolone in Study 1402 Extension progressed only 3.004 points (difference = -3.607, nominal p = 0.0001); thus, progression in mFARS was slowed by 55% with omaveloxolone treatment relative to propensity-matched natural history controls.
- / 1402 Delayed-start analysis (-; DBL 24 Mar 2022)	Post hoc analysis / Supportive efficacy	Omaveloxolone 150 mg, oral, once daily	N = 82 (FAS)	Up to 124 weeks at Extension Week 72 (model includes data through Extension Week 144)	Primary: placebo-corrected difference in the delayed-start period (Study 1402 Extension Week 72 change from baseline mFARS values) versus the placebo-corrected difference in the placebo-controlled period (Study 1402 Part 2 Week 48 change from baseline mFARS values)	Indication of a persistent effect of omaveloxolone treatment on slowing the progression of FA disease course (difference [LS mean] of Omav-Omav vs. Placebo-Omav placebo-controlled period[b]: -2.17; delayed-start period[c]: -2.91). Patients with FA who received omaveloxolone a year later than the patients randomized to omaveloxolone in the pivotal Study 1402 Part 2 do not recover the same treatment benefit even after 2.5 to 3 years of treatment in Study 1402 Extension.
- / 1402 Baseline-controlled analysis (-; DBL 31 Jul 2020)	Post hoc analysis / Supportive efficacy	Omaveloxolone 150 mg, oral, once daily	N = 70 (Full analysis population) / 34 (Primary analysis population)	48 weeks	Primary: paired difference in annualized rate of change in mFARS score at Week 48 in the treated period relative to the untreated period	Treatment-naïve patients receiving omaveloxolone showed a significantly improved annual rate of change in neurological function, as measured by the paired difference in mFARS slope, by -3.758 points relative to the pre-treatment rate of change (n = 34; p = 0.0022)

Abbreviations: CGIC=clinical global impression of change; DBL=database lock; FA-COMS= Clinical Outcome Measures in Friedreich's Ataxia; FAS=full analysis set; LS=least squares; mFARS=modified Friedreich's ataxia rating scale; Omav-Omav group in Study 1402 Extension=patients initially randomised to omaveloxolone in Study 1402 Part 2; Omav-Omav group in Delayed-start analysis=patients randomised to omaveloxolone in Study 1402 Part 2 who then continued with omaveloxolone treatment in Study 1402 Extension; PD=pharmacodynamic(s); PGIC=patient global impression of change; PK=pharmacokinetic(s); Placebo-Omav group in Study 1402 Extension=patients initially randomised to placebo in Study 1402 Part 2 or patients participating in Study 1402 Part 1; Placebo-Omav in Delayed-start analysis=patients randomised to placebo in Study 1402 Part 2 who then initiated treatment with omaveloxolone in Study 1402 Extension

a Includes primary and key secondary efficacy endpoints for Study 1402 Part 2; primary endpoints for Delayed-start analysis, Propensity-matched analysis, and Baseline-controlled analysis, and primary and secondary endpoints for Study 1402 Part 1.

B Study 1402 Part 2 Week 48 (primary Study 1402 Part 2 efficacy analysis timepoint).

C Study 1402 Extension Week 72 (represents 124 weeks of total follow-up; model included data through Extension Week 144)

Study 1402 Extension

Study 1402 Extension is an ongoing, open-label study which allows qualified patients with FA to continue treatment with omaveloxolone following the completion of Study 1402 Part 1 (had been off treatment for at least 21 months prior to enrolling in Study 1402 Extension) or Study 1402 Part 2. Patients were not unblinded to study treatment in Study 1402 Part 1 or Study 1402 Part 2 upon entering Study 1402 Extension. The patients are receiving omaveloxolone (150 mg) once daily until the drug is available through

commercial channels or until patient withdrawal, whichever occurs first. In addition to safety and tolerability data, several efficacy assessments, including mFARS and FA-ADL, are being collected. The efficacy measures are assessed every 24 weeks on study.

At present the longest duration of treatment is over 3.4 years (median exposure of 2.75 years). A maximum of 172 patients were potentially eligible to be enrolled into this study. A total of 149 patients received omaveloxolone, 136 patients had mFARS assessed after starting treatment in the extension. As of the database lock on 24 March 2022, 123 (82.6%) patients are continuing the study (Table 27). A total of 133 (89.3%) patients were exposed to study drug for greater than 48 weeks in Study 1402 Extension, 125 (83.9%) patients were exposed to study drug for greater than 96 weeks, and 69 (46.3%) patients were exposed to study drug for greater than 144 weeks.

All patients who had enrolled in Study 1402 Part 1 and those patients randomised to placebo in Study 1402 Part 2 were considered treatment-naïve upon enrolment in Study 1402 Extension and were analysed as Placebo-Omav. Study 1402 Part 2 patients randomised to omaveloxolone were analysed as Omav-Omav. The efficacy analyses were performed for all patients who received at least 1 dose of open label omaveloxolone (Safety population) and are summarised separately for patients with and without pes cavus. To align with the Study 1402 Part 2 primary analysis, the primary analyses of efficacy in the Delayed-start analysis and Baseline-controlled analysis were performed using only patients without pes cavus. Efficacy was also examined as a sensitivity analysis in both the Delayed-start analysis and baseline-controlled analysis using populations that included patients with pes cavus. Notably, for the propensity-matched analysis pes cavus status was not a matching criterion or an analysis subgroup as it was not available for all patients in the Clinical Outcome Measures in Friedreich’s Ataxia; FAS=full analysis set (FA-COMS) natural history study, and it was not systematically evaluated in the same manner as in Study 1402 Part 2 and Study 1402 Extension.

Table 27: Study 1402 extension: disposition of patients

	Placebo-Omav (N = 106) n (%)	Omav-Omav (N = 43) n (%)	Overall Omav (N = 149) n (%)
Safety population in Study 1402 Extension			
From Study 1402 Part 1	57 (53.8%)	0	57 (38.3%)
From Study 1402 Part 2	49 (46.2%)	43 (100%)	92 (61.7%)
Continuing treatment	84 (79.2%)	39 (90.7%)	123 (82.6%)
Terminated early from treatment	22 (20.8%)	4 (9.3%)	26 (17.4%)
Reason for terminating treatment			
Withdrawal by patient	13 (12.3%)	2 (4.7%)	15 (10.1%)
Adverse event	8 (7.5%)	2 (4.7%)	10 (6.7%)
Other	1 (0.9%)	0	1 (0.7%)
Terminated early from treatment because of COVID-19			
Yes	0	0	0
No	22 (20.8%)	4 (9.3%)	26 (17.4%)
Terminated early from the study			
Terminated early from the study	22 (20.8%)	4 (9.3%)	26 (17.4%)
Reason for terminating study			
Administrative reasons	1 (0.9%)	0	1 (0.7%)
Withdrawal by patient	13 (12.3%)	2 (4.7%)	15 (10.1%)
Other	8 (7.5%)	2 (4.7%)	10 (6.7%)
Terminated early from the study because of COVID-19			
Yes	0	0	0
No	22 (20.8%)	4 (9.3%)	26 (17.4%)

Abbreviations: Omav-Omav=patients initially randomized to omaveloxolone in Study 1402 Part 2; Overall Omav=all patients combined; Placebo-Omav=patients initially randomized to placebo in Study 1402 Part 2 or patients participating in Study 1402 Part 1

The mean age (SD) at baseline was 26.2 (7.15) years (Table 28). 11 (7.4%) patients were adolescents (<18 years at Study 1402 Extension baseline). Most of the demographic characteristics were comparable between the treatment groups, except that more patients in the Placebo-Omav group were male (55.7%, 59/106 patients) and more patients in the Omav-Omav group were female (62.8%, 27/43 patients).

Table 28: Study 1402 extension: patient demographics (Safety Population)

Parameter	Statistic / Category	Placebo-Omav (N = 106)	Omav-Omav (N = 43)	Overall Omav (N = 149)
Baseline age (years)	Mean (SD)	26.9 (7.39)	24.6 (6.31)	26.2 (7.15)
	Median	26.0	24.0	25.0
	Min, Max	16, 41	16, 40	16, 41
Baseline age group (years, n [%])	<18	7 (6.6%)	4 (9.3%)	11 (7.4%)
	≥18	99 (93.4%)	39 (90.7%)	138 (92.6%)
Sex, n (%)	Female	47 (44.3%)	27 (62.8%)	74 (49.7%)
	Male	59 (55.7%)	16 (37.2%)	75 (50.3%)
Ethnicity, n (%)	Hispanic or Latino	5 (4.7%)	1 (2.3%)	6 (4.0%)
	Not Hispanic or Latino	101 (95.3%)	42 (97.7%)	143 (96.0%)
Race, n (%)	White	103 (97.2%)	42 (97.7%)	145 (97.3%)
	Non-White	3 (2.8%)	1 (2.3%)	4 (2.7%)

Abbreviations: Omav-Omav=patients initially randomized to omaveloxolone in Study 1402 Part 2; Overall Omav=all patients combined; Placebo-Omav=patients initially randomized to placebo in Study 1402 Part 2 or patients participating in Study 1402 Part 1

In the Overall Omav group, the mean (± SD) baseline mFARS was 42.66 (± 12.512) points and the mean (± SD) baseline FA-ADL score was 12.50 (±4.980) points (Table 29). The mean (± SD) age at onset of FA was 15.2 (± 5.30) years and the mean (± SD) years since onset of FA was 11.0 (± 5.35) years. Most patients were without pes cavus (104 [69.8%] patients), and 73 (49.0%) patients had GAA1 repeat length ≥675. Overall baseline characteristics were generally comparable between the Placebo-Omav and Omav-Omav treatment groups.

Table 29: Study 1402 extension: Summary of baseline characteristics (safety population)

Parameter	Placebo-Omav (N = 106)	Omav-Omav (N = 43)	Overall Omav (N = 149)
Weight (kg) [Mean (SD)]	69.066 (15.6670)	67.064 (18.1490)	68.488 (16.3842)
BMI (kg/m^2) [Mean (SD)]	24.049 (4.9939)	23.376 (5.4868)	23.855 (5.1313)
Diastolic blood pressure (mmHg) [Mean (SD)]	76.3 (8.55)	71.4 (7.74)	74.9 (8.59)
Systolic blood pressure (mmHg) [Mean (SD)]	123.2 (12.37)	115.0 (13.49)	120.9 (13.19)
Heart rate (beats/min) [Mean (SD)]	79.7 (11.94)	80.0 (14.27)	79.8 (12.60)
mFARS [Mean (SD)]	43.28 (12.720)	41.12 (11.987)	42.66 (12.512)
FA-ADL [Mean (SD)]	12.70 (4.915)	12.00 (5.162)	12.50 (4.980)
Age at FA onset (years) [Mean (SD)]	15.3 (5.17)	15.0 (5.69)	15.2 (5.30)
Years since FA onset (years) [Mean (SD)]	11.6 (5.50)	9.5 (4.72)	11.0 (5.35)
GAA1 repeat length[a] [Mean (SD)]	721.5 (280.29)	734.1 (217.30)	724.8 (264.18)
GAA1 repeat length ≥675, n (%)	51 (48.1%)	22 (51.2%)	73 (49.0%)
Without pes cavus [n (%)]	70 (66.0%)	34 (79.1%)	104 (69.8%)
Ambulatory [n (%)]	96 (90.6%)	38 (88.4%)	134 (89.9%)
History of cardiomyopathy [n (%)]	33 (31.1%)	20 (46.5%)	53 (35.6%)

Abbreviations: BMI=body mass index; FA=Friedreich's ataxia; FA-ADL=Friedreich's ataxia activities of daily living; mFARS=modified Friedreich's ataxia rating scale; Omav-Omav=patients initially randomized to omaveloxolone in Study 1402 Part 2; Overall Omav=all patients combined; Placebo-Omav=patients initially randomized to placebo in Study 1402 Part 2 or patients participating in Study 1402 Part 1

[a] Not all patients had GAA1 repeat length measurements. For Omav-Omav n = 35, for Placebo-Omav n = 96, and for Overall Omav n = 131.

Results of the mFARS (without prior exercise) change from baseline for all patients and for patients without pes cavus are shown in Table 30.

Table 30: Study 1402 extension: mFARS scale mean change from baseline (safety population)

	All Patients		Without Pes Cavus	
	Placebo-Omav (N = 106)	**Omav-Omav (N = 43)**	**Placebo-Omav (N = 70)**	**Omav-Omav (N = 34)**
Change from Study 1402 Extension Baseline in mFARS				
Week 24				
n	87	36	52	28
Mean (SD)	-1.03 (4.623)	-0.03 (3.970)	-1.32 (4.472)	-0.50 (3.695)
Week 48				
n	71	26	44	20
Mean (SD)	0.13 (4.452)	2.28 (3.743)	-0.53 (5.050)	1.76 (3.839)
Week 72				
n	45	19	28	17
Mean (SD)	1.41 (4.940)	0.18 (6.862)	1.40 (5.222)	-0.33 (7.095)
Week 96				
n	46	24	30	22
Mean (SD)	1.64 (4.533)	1.25 (5.550)	1.54 (4.946)	1.05 (5.761)
Week 120				
n	65	31	44	27
Mean (SD)	2.48 (5.170)	2.18 (5.814)	2.35 (5.244)	1.21 (5.472)
Week 144				
n	54	20	34	17
Mean (SD)	3.37 (4.939)	2.28 (5.896)	3.29 (5.052)	2.10 (6.185)

Abbreviations: mFARS=modified Friedreich's ataxia rating scale; Omav-Omav=patients initially randomized to omaveloxolone in Study 1402 Part 2; Placebo-Omav=patients initially randomized to placebo in Study 1402 Part 2 or patients participating in Study 1402 Part 1

Baseline values for the mean FA-ADL score were similar in both groups (12.698 in the Placebo-Omav group and 12.000 in the Omav-Omav group). Changes from baseline in total ADL score for the Placebo-Omav group at Week 24, Week 48, Week 96, and Week 144 were 0.244, 0.390, 1.405, and 1.873, respectively. Changes from baseline in total ADL score for the Omav-Omav group at Week 24, Week 48, Week 96, and Week 144 were -0.068, 0.212, 1.692, and 1.286, respectively.

Propensity-Matched Analysis

The Propensity-matched analysis was designed to evaluate the long-term efficacy of omaveloxolone in Study 1402 Extension using external natural history data as a comparator (the FA-COMS natural history study).

Methods:

The logistic regression model used for calculating propensity scores included multiple covariates that were considered prognostic for FA progression, including sex, baseline age, age of FA onset, baseline mFARS score, and baseline gait score.

Subsets of Study 1402 Extension patients based on prior treatment status (ie, treatment-naïve, Placebo-Omav; continued treatment, Omav-Omav) were each matched to a set of FA-COMS patients using propensity scores to define additional analysis populations.

The primary endpoint of change from baseline in mFARS at Year 3 was analysed using an MMRM model, which included treatment group, baseline mFARS, visit, and interaction terms for visit-by-baseline and treatment group-by-visit as covariates. Baseline values were defined depending on the first study drug administration in Study 1402 Extension.

The secondary endpoints of the change from baseline in mFARS at Year 1 and Year 2 were analysed using the same MMRM model. Sensitivity analyses were performed using the subsets of additional analysis populations.

For inclusion in each of the study populations, patients must have had (1) baseline mFARS, (2) at least one post-baseline mFARS within 3 years after baseline, and (3) values for all propensity score model covariates (ie, sex, baseline mFARS score, age at baseline, age of FA onset, and baseline gait score). Three study populations were defined:

• Study 1402 Extension population

• Natural History (NH) population

• Sensitivity NH population – the subset of patients from the NH population with the following additional requirements: (1) baseline mFARS score was within the range observed in Study 1402 Extension (mFARS 8 to 74) and (2) age at baseline was within the range observed in Study 1402 Extension (age 16 to 41 years).

Note: For both the NH population and the Sensitivity NH population, these represent the pool of patients available for matching; not all patients were used.

Based on these, then 6 analysis populations were defined:

• The Primary Pooled Population, which included all patients in the Study 1402 Extension population and the corresponding matched natural history patients from the NH population.

• The Primary Placebo-Omaveloxolone (Placebo-Omav) Population, which included all patients in the Study 1402 Extension population who were enrolled in Study 1402 Part 1 or were randomised to placebo in Study 1402 Part 2 and received omaveloxolone in Study 1402 Extension, and the corresponding matched natural history patients from the NH population.

• The Primary Omaveloxolone-Omaveloxolone (Omav-Omav) Population, which included all patients in the Study 1402 Extension population who were randomised to receive omaveloxolone in Study 1402 Part 2 and received omaveloxolone in Study 1402 Extension and the corresponding matched natural history patients from the NH population.

• Then, Sensitivity Pooled, Sensitivity Placebo-Omav, and Sensitivity Omav-Omav populations were defined following similar criteria as outlined above for the primary analysis populations; however, instead of matching to the NH population, Study 1402 Extension patients were matched to patients in the Sensitivity NH population.

The matching and analyses outlined above were repeated for all the primary analysis populations as well as for each of the three sensitivity populations.

<u>Patient population:</u>

For the Propensity-matched analysis, the sample sise is based on the 136 patients from Study 1402 Extension who had an on-treatment post-baseline mFARS assessment and were thus available for matching to 136 patients from the FA-COMS natural history study. The median treatment duration in Study 1402 Extension (exclusive of treatment duration in Study 1402 Part 1 or Part 2) was 2.76 years (144.14 weeks), with a maximum treatment duration of 3.4 years (177.0 weeks) and a minimum treatment duration of 0.5 years (25.0 weeks).

The FA-COMS dataset received from C-Path included 810 patients who consented to have their data shared outside of the core FA-COMS study. Of these 810 patients, 598 patients met the criteria for inclusion in the NH study population, and 278 patients met the criteria for inclusion in the sensitivity NH study population and were included in the pool of patients used to identify potential matches to patients in Study 1402 Extension. The FA-COMS external cohort that was the matched set for the Primary Pooled population Study 1402 Extension patients consisted of 136 patients. These patients had a median follow-up duration in the ongoing FA-COMS natural history study of 2.92 years (152.14 weeks), with a maximum follow-up duration of 3.5 years (182.1 weeks) and a minimum follow-up of 0.6 years (29.1 weeks) (Propensity-matched report 2022, Section 4.1).

Baseline characteristics (Table 31), particularly those used as covariates for determining the propensity scores (mFARS, Gait), were very well-balanced between the groups. The slight differences observed in GAA1 and GAA2 repeat length were not clinically meaningful.

Table 31: Propensity-matched analysis: baseline characteristics (primary pooled population)

Characteristic	Statistic	Matched FA-COMS	Study 1402 Extension
mFARS	n	136	136
	Mean (SD)	41.0 (16.10)	42.2 (12.60)
Gait (Assessment #7 in FARS Section E [Upright Stability])	n	136	136
	Mean (SD)	2.7 (1.69)	2.8 (1.36)
FA-ADL Total Score	n	124	136
	Mean (SD)	11.78 (5.937)	12.51 (4.947)
GAA1 Repeat Length	n	129	119
	Mean (SD)	589.7 (245.50)	720.9 (269.58)
	≥675, n (%)	54 (41.9%)	66 (55.5%)
GAA2 Repeat Length	n	121	116
	Mean (SD)	862.8 (232.38)	727.6 (296.93)

Abbreviations: FA= Friedreich's ataxia; FA-ADL=FA Activities of Daily Living; FA-COMS=Clinical Outcome Measures in FA; FARS=FA rating scale; GAA=guanosine-adenine-adenine; mFARS=modified FA rating scale; SD=standard deviation
Note: Only patients with available information are summarized for each parameter.

Key Results:

After 3 years, in the Pooled Primary Population, matched FA-COMS patients progressed 6.611 mFARS points whereas patients treated with omaveloxolone in Study 1402 Extension progressed only 3.004 points (difference = -3.607 points; nominal p = 0.0001); thus, progression in mFARS was slowed by 55% with omaveloxolone treatment (Table 32, Table 33). It took the omaveloxolone patients 3 years to experience a similar extent of mFARS progression to what the untreated, natural history patients had already experienced at approximately Year 1.3.

Table 32: Change in mFARS over 3 Years (primary pooled population)

	Baseline		mFARS Change from Baseline					
			Year 1		Year 2		Year 3	
	N	Mean (SD)	N	LS Mean (±SE)	N	LS Mean (±SE)	N	LS Mean (±SE)
Study 1402 Extension	136	42.223 (12.6019)	133	0.015 (0.5556)	102	1.179 (0.5949)	77	3.004 (0.6638)
Matched FA-COMS	136	41.030 (16.1017)	108	2.113 (0.5909)	103	4.584 (0.5930)	83	6.611 (0.6459)
Difference[a]	-	-	-	-2.098 (0.8115) p=0.0101	-	-3.405 (0.8401) p< 0.0001	-	-3.607 (0.9263) p=0.0001

Abbreviations: LS=least squares; mFARS=modified Friedreich's ataxia rating scale
[a] Difference is Study 1402 Extension – matched FA-COMS.

Table 33: mFARS change from baseline treatment differences over time (primary populations)

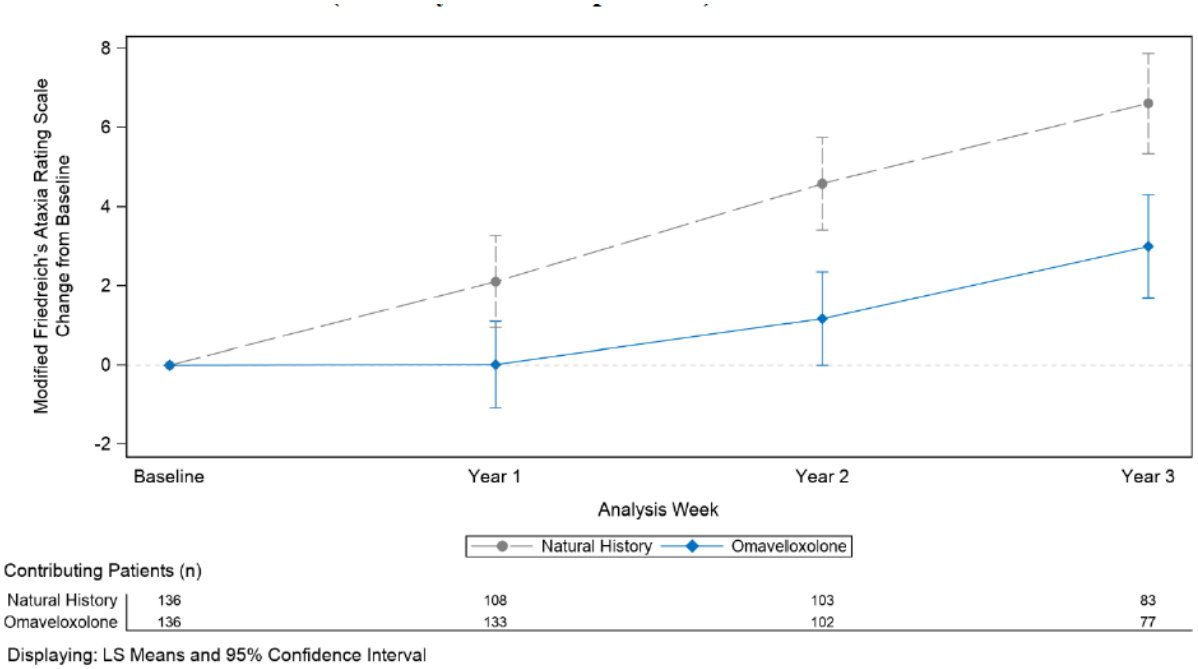
Analysis Population	mFARS Change from Baseline (LS Mean [±SE])		
	Year 1	Year 2	Year 3
Primary Pooled (Match 1) Difference	-2.098 (0.8115) p=0.0101	-3.405 (0.8401) p< 0.0001	-3.607 (0.9263) p=0.0001
Primary Placebo-Omav (Match 2) Difference	-2.754 (0.9358) p=0.0035	-3.055 (0.9655) p=0.0017	-4.087 (1.0453) p=0.0001
Primary Omav-Omav (Match 3) Difference	-1.425 (1.5643) p=0.3641	-2.466 (1.6035) p=0.1265	-3.764 (1.8173) p=0.0400

Abbreviations: LS=least squares; mFARS=modified Friedreich's ataxia rating scale
Note: Each Primary population (Pooled, Placebo-Omav, Omav-Omav) represents a different set of matched patients (Match 1, Match 2, or Match 3).

In all other analysis populations, including the Primary Placebo-Omav Population (n = 190) and Omav-Omav Population (n = 82), the difference between treatment groups in change from baseline at Year 3 consistently favoured omaveloxolone. In the Primary Placebo-Omav Population, progression in mFARS was slowed by 56% in Study 1402 Extension patients. In the Primary Omav-Omav Population, progression in mFARS was slowed by 61% in Study 1402 Extension patients, thus indicating that these patients were continuing to benefit from omaveloxolone treatment.

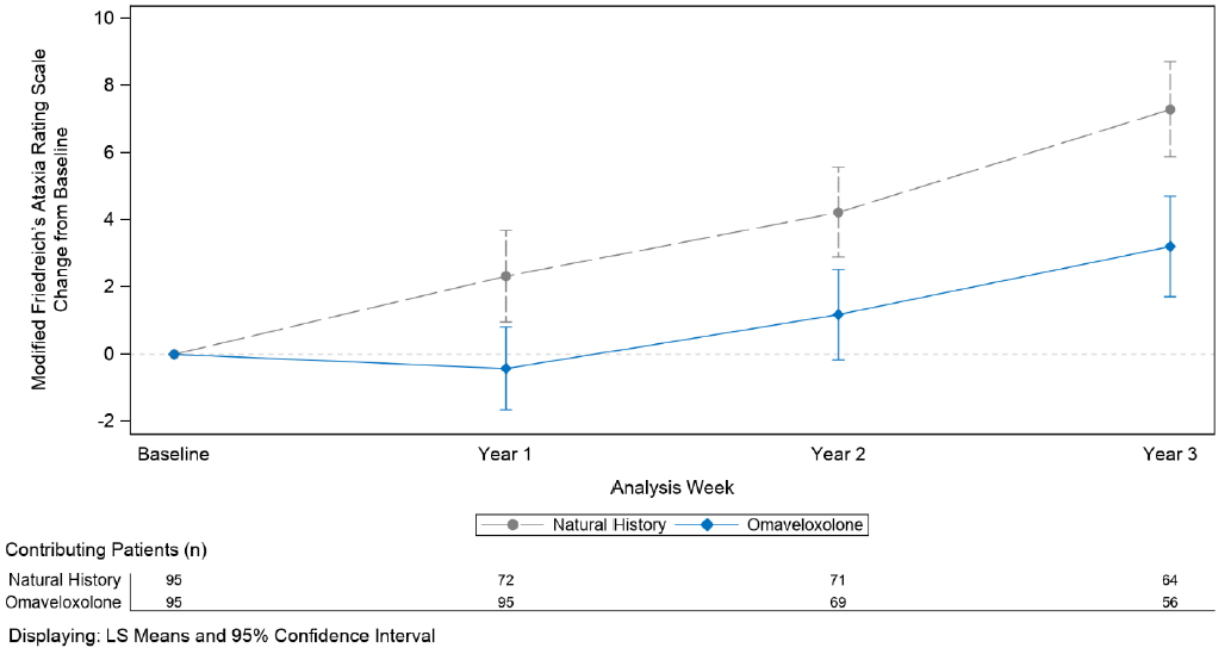
Results of the secondary endpoints, change from baseline in mFARS score at Year 1 and Year 2, favoured omaveloxolone in the Primary Pooled, Primary Placebo-Omav, and Primary Omav-Omav Populations (Table 33). At each year, patients in Study 1402 Extension experienced a smaller change from baseline in mFARS than the matched FA-COMS patients. Distinct trajectories over 3 years show consistent separation between the omaveloxolone and corresponding FA-COMS external control groups (Figure 32, Figure 33 and Figure 34).

Figure 32: Propensity-matched analysis: LS mean change from baseline in mFARS over time (primary pooled population)



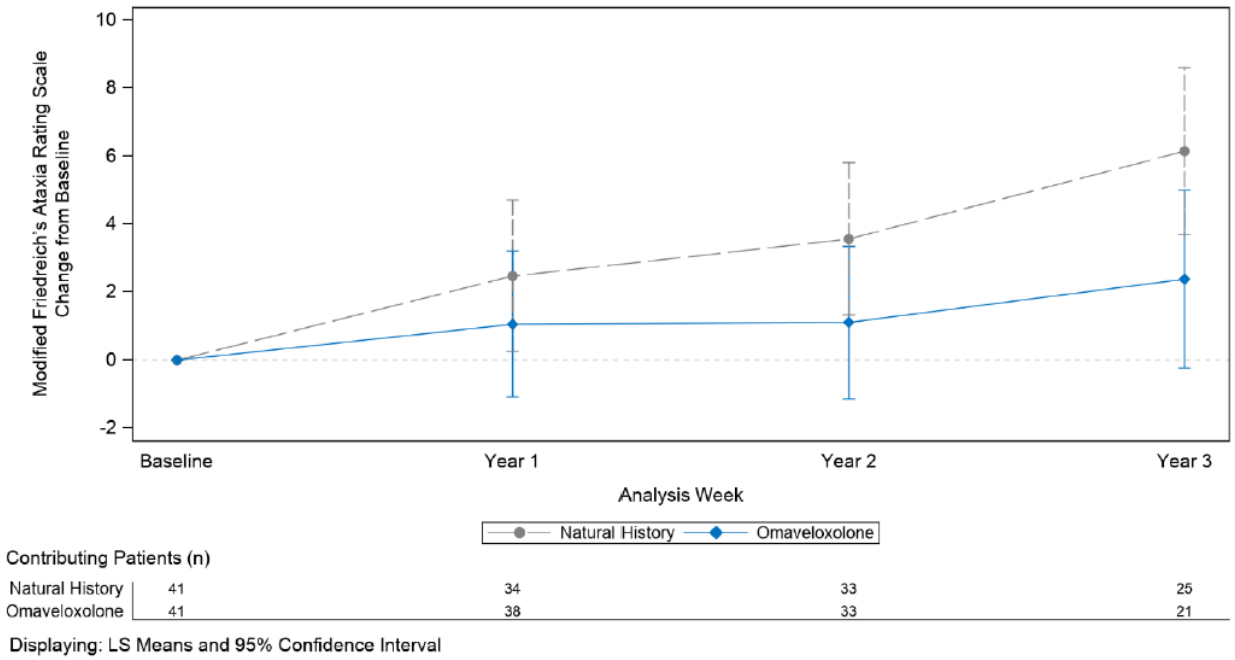
Abbreviations: LS=least squares; FA-COMS=Clinical Outcome Measures in Friedreich's Ataxia; mFARS=modified Friedreich's ataxia rating scale
Note: Natural History (NH) = Matched FA-COMS

Figure 33: LS mean change from baseline in mFARS over time (primary placebo-Omav population)



Note: Natural History (NH) = Matched FA-COMS

Figure 34: LS mean change from baseline in mFARS over time (primary Omav-Omav population)



Note: Natural History (NH) = Matched FA-COMS

In the sensitivity populations, the pool of FA-COMS patients available for matching for each Study 1402 Extension set was further restricted to patients who had a baseline mFARS value and baseline age within the range observed in Study 1402 Extension patients at baseline. At all timepoints, and in all 3 sensitivity populations, results favored omaveloxolone (Study 1402 Extension patients). At Year 3, the 3 sensitivity populations showed a treatment benefit of -2.388, -3.151, and -4.675 mFARS points for the Sensitivity Pooled, Sensitivity Placebo-Omav, and Sensitivity Omav-Omav populations, respectively (Table 34).

Table 34: Baseline-controlled analysis: mFARS change from baseline treatment differences over time (sensitivity populations)

Analysis Population	**mFARS Change from Baseline (LS Mean [±SE])**		
	Year 1	**Year 2**	**Year 3**
Sensitivity Pooled (Match 4) Difference	-1.498 (0.7071) p = 0.0347	-1.572 (0.7434) p = 0.0349	-2.388 (0.8237) p = 0.0039
Sensitivity Placebo-Omav (Match 5) Difference	-2.393 (0.8844) p = 0.0072	-2.086 (0.9195) p = 0.0239	-3.151 (1.0015) p = 0.0018
Sensitivity Omav-Omav (Match 6) Difference	-1.137 (1.3335) p = 0.3955	-3.411 (1.3509) p = 0.0128	-4.675 (1.5502) p = 0.0030

Abbreviations: LS=least squares; mFARS=modified Friedreich's ataxia rating scale; SE=standard error
Note: Each Sensitivity population (Pooled, Placebo-Omav, Omav-Omav) represents a different set of matched patients (Match 4, Match 5, or Match 6).

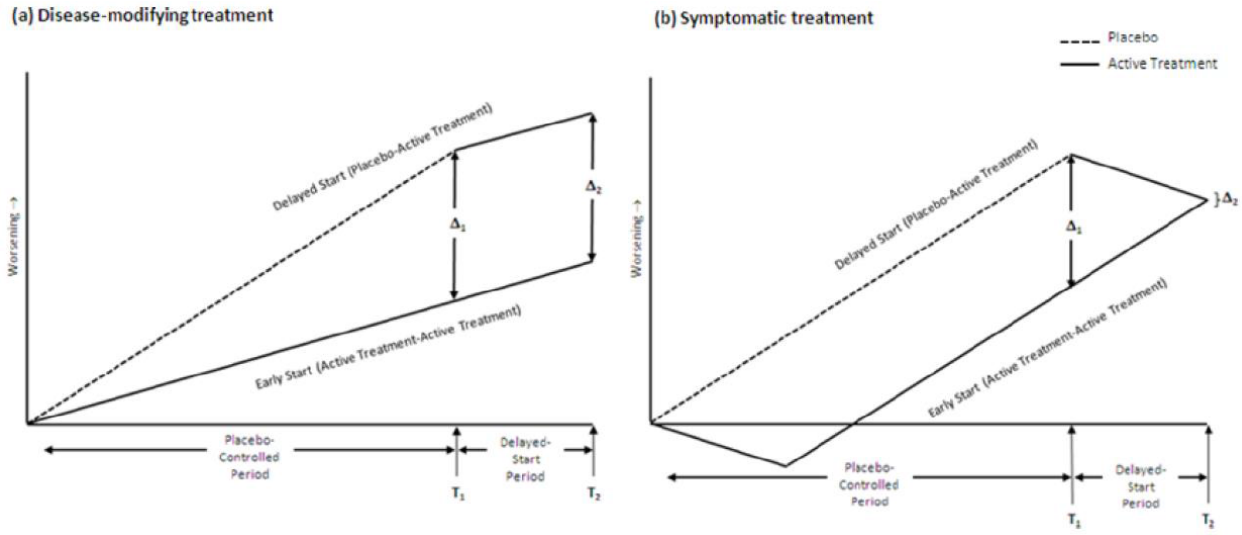
Delayed-Start Analysis

Study Design and Objectives:

This post hoc analysis was designed to assess whether the benefit observed in Study 1402 Part 2 is a persistent effect on FA disease course, and to assess if the neurologic benefit in the Study 1402 Part 2 omaveloxolone group cannot be recovered by patients who start omaveloxolone 1 year later in time (the Study 1402 Part 2 placebo group).

The following analyses were performed: 1) a non-inferiority test, based on the methodology outlined in Liu-Seifert, et al (Liu-Seifert, 2015a; Liu-Seifert, 2015b) (Figure 35), conducted by comparing the difference between treatment groups in mFARS change from baseline at the end of the placebo-controlled period in Study 1402 Part 2 versus the difference at Study 1402 Extension Week 72, and 2) an evaluation of mFARS trajectory over time (slope) in the extension, by treatment group as based on their Study 1402 Part 2 randomised treatment. While the primary delayed-start analysis is based on results at Extension Week 72, additional analyses were then also performed with the end of the delayed-start period set to Extension Week 96, 120, or 144.

Figure 35: Delayed-start analyses schematic

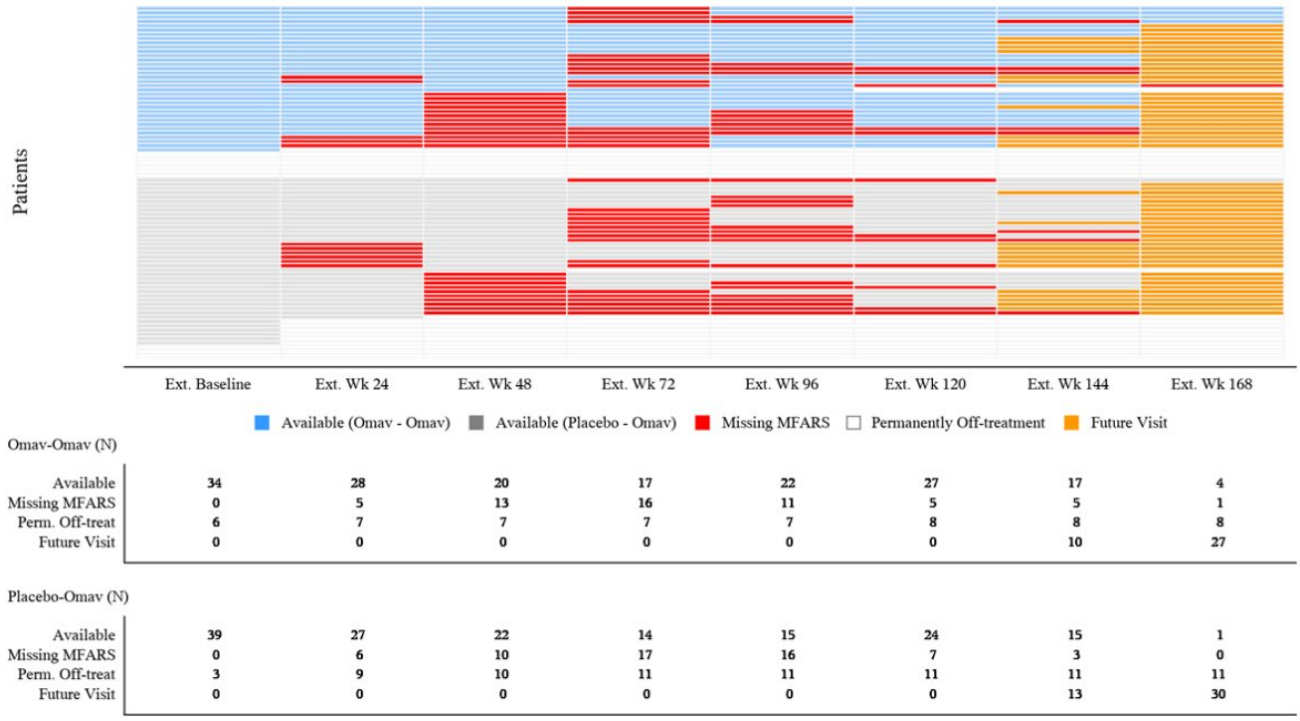


Delayed-start design under conditions of (a) a disease-modifying treatment effect and (b) a symptomatic treatment effect. Δ1 represents the initial treatment effect at the end of the placebo-controlled period (T1) and Δ2 represents the treatment effect at the end of the delayed-start period (T2). The hypothetical results for a symptomatic treatment (b) assume that the time to peak treatment effect is equal to the duration of the delayed-start period.
Source: Liu-Seifert 2015a

Patient Population:

The patient population for the primary analysis in the Delayed-start analysis included 82 patients (Omav-Omav n = 40, Placebo-Omav n = 42) from Study 1402 Part 2 (FAS). Of these, 73 patients enrolled into Study 1402 Extension, including 39 patients who were randomised to placebo in Study 1402 Part 2 (Placebo-Omav group) and 34 patients randomised to omaveloxolone in Study 1402 Part 2 (Omav-Omav group). Within the FAS, 75 patients had mFARS assessments at Week 48, 31 patients had mFARS assessments at Extension Week 72, and 51 patients had mFARS assessments at Study 1402 Extension Week 120. The ARP (all randomised patient) included 103 patients.

Figure 36: Individual mFARS status by extension study visit (data as of March 2022)



Omav-Omav (N)

Available	34	28	20	17	22	27	17	4
Missing MFARS	0	5	13	16	11	5	5	1
Perm. Off-treat	6	7	7	7	7	8	8	8
Future Visit	0	0	0	0	0	0	10	27

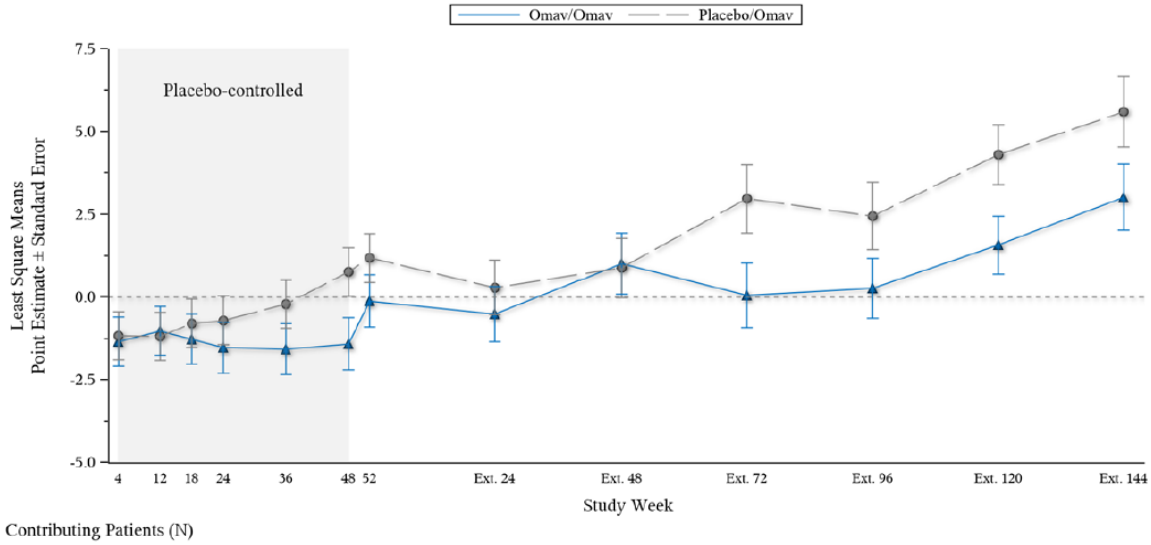
Placebo-Omav (N)

Available	39	27	22	14	15	24	15	1
Missing MFARS	0	6	10	17	16	7	3	0
Perm. Off-treat	3	9	10	11	11	11	11	11
Future Visit	0	0	0	0	0	0	13	30

Abbreviations: mFARS=modified Friedreich's ataxia rating scale

Key Results:

Figure 37: MMRM of change from baseline in mFARS (full analysis set)



Contributing Patients (N)

Placebo/Omav	42	42	41	41	41	41	39	27	22	14	15	24	15
Omav/Omav	40	40	38	36	35	34	34	28	20	17	22	27	17

Abbreviations: Ext=Study 1402 Extension; mFARS=modified Friedreich's ataxia rating scale; MMRM=mixed model repeated measures; Omav=omaveloxolone
Note: MMRM analysis based on data from all visits up to Extension Week 144.

Results of the non-inferiority testing using a single MMRM model, that included data through Study 1402 Extension Week 144 for patients in the FAS, demonstrated that the between-group difference in mFARS observed at the end of Study 1402 Part 2 (Week 48 least squares [LS] mean difference = -2.17 ± 1.089) was preserved at Week 72 of the delayed-start period (Extension Week 72 LS mean difference = -2.91 ± 1.437), within the pre-defined margin of 0.5 × Δ1. Of note, Δ1 is the difference between treatment groups at the end of the placebo-controlled period (Study 1402 Part 2, Week 48 change from baseline mFARS values). The upper limit of the 90% CI for the MMRM difference estimate between Δ1 and Δ2 was less than zero (-0.090), demonstrating significant evidence of non-inferiority and therefore preservation of the between-group mFARS difference.

Table 35: Non-inferiority results – mFARS change from baseline (full analysis set)

Δ_2 Timepoint	Difference[a] (LS Mean ± SE)		Estimate ± SE $\Delta_2 - 0.5 \times \Delta_1$	Upper Limit of 1-sided 90% CI for Estimate
	Placebo-Controlled[b] (Δ_1)	Delayed-Start[c] (Δ_2)		
Extension Week 72	-2.17 ± 1.089 p=0.0471	-2.91 ± 1.437 p=0.0433	-1.826 ± 1.3535	-0.090

Abbreviations: Δ_1= the difference between treatment groups at the end of the placebo-controlled period (Study 1402 Part 2, Week 48 change from baseline mFARS values); Δ_2= the difference between treatment groups in the delayed-start period (Study 1402 Extension, Week 72 change from baseline mFARS values); CI=confidence interval; LS=least squares; mFARS=modified Friedreich's ataxia rating scale; SE=standard error

[a] Difference is omaveloxolone - placebo, based on Study 1402 Part 2 randomized treatment assignment (model includes data through Extension Week 144, as of a March 2022 interim database lock, and represents 196 weeks of total follow-up)

[b] Study 1402 Part 2 Week 48 (primary Study 1402 Part 2 efficacy analysis timepoint)

[c] Study 1402 Extension Week 72 (primary Delayed-start efficacy analysis timepoint)

Similar analyses were performed that evaluated each visit after Extension Week 72 (ie, Extension Weeks 96, 120, and 144) for non-inferiority (Table 36). The numerical difference between treatment groups consistently showed a >2 point separation and was similar for all evaluated visits. Echoing the results at Extension Week 72, the non-inferiority criteria were also met at Extension Week 120.

Table 36: Non-inferiority Results at Study 1402 Extension Weeks 96, 120, and 144 – mFARS Change from Baseline (Full Analysis Set)

Δ_2 Timepoint	Difference[a] (LS Mean ± SE)		Estimate ± SE $\Delta_2 - 0.5 \times \Delta_1$	Upper Limit of 1-sided 90% CI for Estimate
	Placebo-Controlled[b] (Δ_1)	Delayed-Start[c] (Δ_2)		
Extension Week 96	-2.17 ± 1.089 p=0.0471	-2.19 ± 1.375 p=0.1128	-1.10 ± 1.2991	0.567
Extension Week 120	-2.17 ± 1.089 p=0.0471	-2.74 ± 1.264 p=0.037	-1.657 ± 1.2086	-0.106
Extension Week 144	-2.17 ± 1.089 p=0.0471	-2.58 ± 1.468 p=0.0796	-1.496 ± 1.4630	0.382

Abbreviations: Δ_1= the difference between treatment groups at the end of the placebo-controlled period (Study 1402 Part 2, Week 48 change from baseline mFARS values); Δ_2= the difference between treatment groups in the delayed-start period (Study 1402 Extension, Week 96, 120, or Week 144 change from baseline mFARS values); CI=confidence interval; LS=least squares; mFARS=modified Friedreich's ataxia rating scale; SE=standard error

[a] Difference is omaveloxolone - placebo, based on Study 1402 Part 2 randomized treatment assignment (model includes data through Extension Week 144, as of a March 2022 interim database lock, and represents 196 weeks of total follow-up)

[b] Study 1402 Part 2 Week 48 (primary endpoint timepoint for Study 1402 Part 2)

[c] Extension Week 96, 120, or 144 (alternate delayed-start analysis timepoints)

Annualised slopes during the open-label extension showed similar slopes in mFARS for the Omav-Omav and Placebo-Omav groups (difference ± SE = -0.314 ± 0.7118; p = 0.6602). The annual slope (± SE) for each group in Study 1402 Extension (Omav-Omav 0.446 [± 0.6340], Placebo-Omav 0.760 [± 0.2773]) is less than the expected 1 to 2 points per year based on natural history data for the 16-to-40-year age group (Patel, 2016).

When tested in the ARP, no timepoint met the threshold for non-inferiority (Table 37).

Table 37: Non-inferiority results at Study 1402 extension weeks 72, 96, 120, and 144 – mFARS change from baseline (all-randomised population)

Δ_2 Timepoint	Difference[a] (LS Mean ± SE)		Estimate ± SE $\Delta_2 - 0.5 \times \Delta_1$	Upper Limit of 1-sided 90% CI for Estimate
	Placebo-Controlled[b] (Δ_1)	Delayed-Start[c] (Δ_2)		
Extension Week 72	-1.81 ± 1.057 p=0.0878	-2.17 ± 1.382 p=0.1172	-1.264 ± 1.2367	0.357
Extension Week 96	-1.81 ± 1.057 p=0.0878	-1.20 ± 1.326 p=0.3675	-0.291 ± 1.2216	1.276
Extension Week 120	-1.81 ± 1.057 p=0.0878	-1.20 ± 1.220 p=0.3247	-0.298 ± 1.1285	1.150
Extension Week 144	-1.81 ± 1.057 p=0.0878	-2.21 ± 1.367 p=0.1069	-1.305 ± 1.3172	0.386

Abbreviations: Δ_1= the difference between treatment groups at the end of the placebo-controlled period (Study 1402 Part 2, Week 48 change from baseline mFARS values); Δ_2= the difference between treatment groups in the delayed-start period (change from baseline mFARS values); CI=confidence interval; LS=least squares; mFARS=modified Friedreich's ataxia rating scale; SE=standard error

[a] Difference is omaveloxolone - placebo, based on Study 1402 Part 2 randomized treatment assignment (model includes data through Extension Week 144, as of a March 2022 interim database lock, and represents 196 weeks of total follow-up)

[b] Study 1402 Part 2 Week 48 (primary Study 1402 Part 2 efficacy analysis timepoint)

[c] Extension Week 72, 96, 120, or 144 (delayed-start sensitivity analysis timepoint)

Baseline-Controlled Analysis

The results of the Baseline-controlled analysis, which utilised patients as their own control, support the mFARS results of Study 1402 Part 2.

Table 38: Baseline-controlled analysis: Annualised rate of change in mFARS score at week 48 (primary analysis population)

Analysis	Statistics	Combined (Study 1402 Part 1 + Study 1402 Part 2) (N = 34)	Study 1402 Part 2 Analysis Population (N = 14)	Study 1402 Part 1 Analysis Population (N = 20)
Pre-treatment Slope	n	34	14	20
	Mean (SE)	2.283 (0.4878)	2.835 (1.0482)	1.897 (0.3965)
	Median	2.015	2.439	2.015
	(Min, Max)	(-3.26, 11.63)	(-3.26, 11.63)	(-0.84, 5.15)
Treatment Slope	n	34	14	20
	Mean (SE)	-1.474 (0.9627)	-1.788 (1.5630)	-1.255 (1.2490)
	Median	-1.767	-0.123	-2.008
	(Min, Max)	(-10.72, 12.78)	(-10.72, 6.56)	(-9.00, 12.78)
Paired Difference	n	34	14	20
	Mean (SE)	-3.758 (1.1329)	-4.623 (1.8875)	-3.152 (1.4271)
	Median	-3.720	-3.249	-4.598
	(Min, Max)	(-19.02, 9.87)	(-19.02, 5.90)	(-12.60, 9.87)
Paired t-test[a]	95% CL	-6.062, -1.453	-8.701, -0.545	-6.139, -0.165
	p-value	0.0022	0.0293	0.0397

Abbreviations: CL=confidence limits on the paired difference; Max=maximum; mFARS=modified Friedreich's ataxia rating scale; Min=minimum

[a] Two-sided paired t-test on the paired difference: treatment value – pre-treatment value.

Sensitivity analyses were supportive. The All-enrolled population was assessed, which included patients with and without pes cavus (Table 39).

Table 39: Baseline-controlled analysis: Sensitivity analyses of annualised rate of change in mFARS

Sensitivity Analysis	Contributing Data (n)		mFARS Slope, Mean (SE)	
	Pre-treatment	Treatment	Difference[a]	p-value[b]
Multiple imputation[c,d] (Full analysis population) (S1)	52	52	-2.34 (1.044)	0.0253
Linear regression[e] Slope computation analyzed with a paired t-test (Full analysis population) (S2)	52	52	-2.486 (1.1064)	0.0290
Mixed model[e] (Full analysis population; Study 1402 Part 2, placebo + Study 1402 Part 1 patients) (S3)	70	34	-2.89 (1.072)	0.0089
Mixed model and linear regression[e] (Full analysis population; Study 1402 Part 2, placebo + Study 1402 Part 1 patients) (S4)	70	52	-2.83 (1.080)	0.0108
All-enrolled population[d] (S5)	59	59	-2.144 (0.7878)	0.0086

Abbreviation: mFARS=modified Friedreich's ataxia rating scale
[a] Difference = (Treatment – Pre-treatment). Paired differences within patient for S1, S2, and S5.
[b] Based on paired t-test for S1, S2, and S5. Based on mixed model for S3 and S4.
[c] Multiple imputation for missing Study 1402 Extension Week 48 values.
[d] Prespecified analyses.
[e] Post hoc analyses.

Annualised mFARS slopes in the treatment period versus the pre-treatment period were summarised categorically by using categories of either "stable or improved" or "worsened" (Table 40).

Table 40: Baseline-controlled analysis: mFARS responder analysis (primary analysis population)

Status	Baseline-Controlled Analysis		Natural History Study[a]
	Pre-Treatment Period (n = 34)	Treatment Period (n = 34)	(n = 148)
Stable or Improved[b]	8 (23.53%)	21 (61.76%)	45 (30%)
Worsened[c]	26 (76.47%)	13 (38.24%)	103 (70%)

Abbreviation: mFARS=modified Friedreich's ataxia rating scale
[a] Data from patients in the Clinical Outcome Measures in Friedreich's Ataxia natural history study matching baseline age and mFARS requirements defined for Study 1402.
[b] Stable or improved defined as annualized changes from baseline ≤0 points for mFARS scores.
[c] Worsened defined as annualized changes from baseline >0 points for mFARS scores.

2.6.6. Discussion on clinical efficacy

The indication sought for omaveloxolone is the treatment of FA in adults and adolescents aged 16 years and older. The proposed dosage of omaveloxolone is 150 mg administered as three 50-mg capsules once daily (QD) by mouth. The dosing with 3 hard capsules every morning without crushing or chewing, feasibility of use in FA population and in PIP study, handling of missed doses was questioned. The applicant recommended an alternative administration method (the entire contents sprinkled onto 2 tablespoons of apple sauce) which is included in the SmPC, and the Study 408-C-2106 data will be evaluated further (the 90% Cis of the

geometric mean ratios falling entirely within the 80.00% to 125.00% reference interval). The missed doses are not to be replaced.

Phase II Study 408-C-1402 enrolled a total of 172 patients overall (33 adolescent patients) and provides all efficacy and safety data for omaveloxolone with the longest treatment duration of 3.7 years. This study was conducted in 3 parts: Study 1402 Part 1 (dose finding, n=69), Study 1402 Part 2 (pivotal, n=103) and Study 1402 Extension (open-label extension, n=149, interim analysis data cutoff date 24 March 2022).

There are no CHMP guidelines on the clinical development of medicines for the treatment of FA.

Regulatory advice was obtained for paediatric development programme and the applicant received scientific advice (see section 1.6).

The clinical trials were performed in accordance with GCP as claimed by the applicant. However, the conclusion of the GCP inspection raised concerns with regard to the reliability of the data due to unintentional unblinding, the QTcB values reported as QTcF for part 1 and potential inconsistency in selecting EF values. The applicant investigated the quantitative impact of occurrence of side effects on mFARS. The unblinding risk cannot be fully excluded but the impact on the primary endpoint is considered minimal or none.

The fact that the applicant has submitted a single pivotal trial in a treatment area of many previous failures is balanced out with the rarity of the disease and very high unmet medical need. The design is overall acceptable, but some limitations were discussed including the small sample size, modest duration, potential unblinding due to safety profile and possible limitations of the generalizability of the results. Most of these points were also raised during previous regulatory interactions. The primary endpoint (mFARS change from baseline to week 48) was met (in patients without pes cavus) with the support of FA-ADL (nominal significance) but without the formal support of the key secondary endpoints (trends only). The adolescent group showed the highest change in mFARS score, which necessitates immediate kick off of PIP study due to the risk of off-label use. Meanwhile, the off-label use is expected to be monitored through PSUR as usual.

Main discussion points at CHMP evaluation were:

- Robustness of the efficacy results taking totality of the evidence into consideration

- Justification of the proposed inclusion of the pes cavus population in the indication and discussion if the population of patients with pes cavus represents a distinct pathological and clinical phenotype and discuss the extrapolation to patients without pes cavus. The discussion also included the methods to be used for pes cavus classification and that the primary analysis only includes patients without pes cavus.

Design and conduct of clinical studies

Study 1402 Part 1 served as the dose-ranging study with omaveloxolone in FA. Based on the efficacy and safety results from this study and the assessment of PD data for markers of Nrf2 activation (as per the omaveloxolone mechanism of action), a 150-mg dose of omaveloxolone was selected for further development, beginning with Study 1402 Part 2. Improvement of mFARS in subjects with pes cavus was limited and to a lesser degree than those without pes cavus in Part 1. This has led to a major protocol change in Part 2 to limit the primary analysis to the patients without pes cavus.

Study 1402 Part 2 was an international, multicentre, double-blind, randomised, placebo-controlled, registrational, parallel-group phase 2 trial to evaluate the safety and efficacy of omaveloxolone 150mg per day in patients with FA. The trial was conducted at 11 clinical institutions in the United States, Europe, and Australia. The choice of blinded and placebo-controlled design is supported despite some concerns on the study duration of 48 weeks as the mechanism of action of omaveloxolone being likely to stabilise the disease

by slowing deterioration rather than reversing established pathology, hence the efficacy will be determined by the rate of deterioration in the placebo group. This was also pointed out in previous scientific advice provided by CHMP. Extension study data is of limited value here but will be discussed in terms of its support for maintenance of effect in comparison to historical data.

Eligible patients were 16 to 40 years of age with genetically confirmed FA, had baseline mFARS scores between 20 and 80 (and the average of 2 mFARS values collected at Screening and Day 1 visits must have been within 4.5 points of each other), and could complete maximal exercise testing on a recumbent stationary bicycle. Choice of age range and inclusion of genetically confirmed patients are supported. The chosen mFARS score range represents individuals just after the time of presentation at the mildest and several years after loss of ambulation at the most severe but excludes advanced disease.

The applicant was requested to justify the extrapolation to different phenotypes such as LOFA (age > 24 years) and VLOFA (age > 40 years) during the procedure.

(1) In Study 1402 Part 2, the number of patients with LOFA was small (n=2 in each treatment group). Since all enrolled patients were ≤40 years old per protocol, no patients in Study 1402 Part 2 had VLOFA (>40 years). Both LOFA patients in the omaveloxolone group experienced improvements (-4,7 and -6,5 points decrease) from baseline in mFARS score, while both patients in the placebo group experienced worsening (numerical increases) from baseline (0.4 and 2.3 points increase).

(2) To evaluate the potential effect modification of age on the treatment of effect, the applicant analysed subgroups in the FAS based on the median age of FA onset (15 years). In Study 1402 Part 2, patients with age of onset >15 years (n=37) benefited from the treatment (-1.07 (1.377) p=0.4411) although the benefit was larger with patients with age of onset ≤15 years (n=45) (-3.60 (1.313) p=0.0077). The small group sizes are acknowledged.

(3) Further evaluation of the treatment effect by age of onset subgroup was conducted using the propensity-matched analysis Primary Pooled Population (ie, Study 1402 Extension patients [n=136] and their propensity score matched patients from the FA-COMS natural history study [n=136]). In this analysis, 61 Study 1402 Extension patients had age of onset >15 years. Patients with age of onset >15 years were older at study baseline compared to patients with age of onset ≤15 years and had lower baseline mFARS scores. After 3 years, the results showed benefit in omaveloxolone-treated patients with an age of onset >15 years (-3.47 (1.478) p=0.0193) compared to untreated controls and the benefit was similar to patients with an age of onset ≤15 years (-3.33 (1.198) p=0.0057).

Despite a slower progression experienced for patients >15 years of age at disease onset or >24 years, the data from patients with slower progression (demographics, baseline disease characteristics, results) in the clinical programme and the comparison to historical controls allow extrapolation of results to late onset FA population. VLOFA population (>40 years) is rare, and data is not available. The indication wording regarding LOFA and VLOFA is considered justified in an orphan disease setting.

Patients were excluded if they had uncontrolled diabetes, clinically significant cardiac disease, active infections, clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), significant laboratory abnormalities, or interfering medical conditions. Frataxin decrease causes a multisystem impact on the patient, with cardiac disorders and diabetes being the two most troublesome. In the light of the exclusion criteria, extrapolation to the entire FA population was discussed but ultimately it was agreed not to contraindicate the use in these subpopulations but to update the SmPC to include warnings on hyperlipidaemic and increased BNP levels.

The 1:1 randomisation scheme to omaveloxolone or placebo was stratified by pes cavus status. Patients with "severe" pes cavus were included in the study but did not comprise more than 20% of patients enrolled in Study 1402 Part 2 and were not part of the primary analysis. In this study, "severe" pes cavus was systematically defined by the visualisation of a flashlight on the medial aspect of the foot when shown from the lateral aspect. The applicant claims that the patients with severe pes cavus have a musculoskeletal foot deformity which limits their performance on efficacy scales. Nevertheless, a variety of pes cavus severities have been included in the pivotal study on top of 20 severe pes cavus patients. Pes cavus population is variably classified or detected in the literature. No distinct phenotypical or clinical profile could be established from the literature for the severe pes cavus population. This was a relevant point for the agreement on the extrapolation to the FA patients with pes cavus. Further details on the extrapolation on the population with pes cavus can be found in the next subsection of this discussion.

The key efficacy analyses were based on change from baseline to week 48 in mFARS in patients without pes cavus. FARS is a well validated and known scale used by specialists as a series of physical examination assessments to measure impairment level, functional status and disease progression in patients with FA. mFARS is a modified version of this rating scale that is used in clinical trials to assess the efficacy of investigational products for use in FA. This rating scale was developed by Friedreich's Ataxia Research Alliance (FARA) and the physician-researchers in the Collaborative Clinical Research Network in FA, with input from the FDA. The mFARS is an objective physician-assessed examination that evaluates changes in patients' speech, arm/hand function, balance, and ability to stand (scores 0-99, with lower scores indicating better neurological function). Due to significantly high gastrointestinal side effect burden in omaveloxolone arm, potential unblinding can be a concern for such a small size pivotal trial. The side effects or the need for unplanned or additional laboratory testing (e.g, if necessitated by amino transferase increases), and any treatment adjustments (study treatment or concomitant medication) could have caused unblinding. The AEs tended to occur within the first 12 weeks after treatment initiation which is prior to observed divergence of curves in mFARS (starting around week 18). To minimise potential bias, assessment of the primary outcome (mFARS) was conducted by a neurologist who was blinded to laboratory values in almost all cases (% not known from the dossier), and several sections of the examination (e.g, upright stability subscore) included timed components that are objective measures and not readily altered by subject effort. Upon request, a new sensitivity analysis showed a similar magnitude of change from baseline in mFARS for omaveloxolone-treated patients, irrespective of whether they experienced gastrointestinal AEs or aminotransferase increases. The potential impact of unblinding on primary analysis is considered negligible.

The primary endpoint is considered acceptable as it is commonly used in recent clinical trials, and data from a longitudinal cohort up to 5 years support its correlation with measures of disease progression (including disease duration, ataxia staging, loss of ambulation, and FA-ADL scores), and seems to be a good choice with a (short) pivotal study period of 48 weeks. The ongoing natural history study (FA-COMS), organised by FARA, has enrolled more than 1,000 patients with FA to date and is collecting robust longitudinal natural history data, with a follow-up as long as 19 years in some patients. Patel (2016) reported that FARS and mFARS scores increase over time (indicating a decrease in neurologic function), with an average increase of 1 to 2 points per year in the 16-to-40-year age group. The mean worsening during the first year for the cohort aged 16 to 40 years was 1.04 points (SD=5.31) and for the overall cohort was 1.91 points (SD=6.34). It should be noted that FA is a disease of substantial day to day variability, not all of which is minimised in natural history studies, so the 2-points difference chosen as cut off for sample size calculations is considered a more appropriate choice. Although concerns were raised on the choice of mFARS instead of FARS as primary endpoint, the previous scientific advice concluded that the study design and sample size calculations were acceptable with the condition that "compelling results are expected, and it therefore may be wise to recruit

more patients (if possible) to try and avoid a p-value close to 5%" and "the need to have the data from the primary endpoint to be supported by functional and QOL endpoints."

Key secondary outcome measures included the PGIC, CGIC, and secondary outcome measures included 9-HPT, T25-FW, frequency of falls, peak work during maximal exercise testing, and FA-ADL scores (using FA-validated ADL questionnaire), all evaluated at week 48 as change from baseline. Of note, the FA-ADL scale is a well-established fit-for-purpose assessment by patients of their FA-specific activities of daily living and is considered of most importance among all key/secondary endpoints to support the primary endpoint by demonstrating that the change in mFARS is also based on decreased functional worsening. In the natural history cohort from Patel et al, the mean worsening of FA-ADL scores during the first year was 0.43 points (SD=3.2) which is the best measure to refer to in the absence of an established minimally clinical important difference for FA-ADL.

In general, the statistical methods and analyses are acceptable and well chosen. The applicant included sensitivity analyses to test the MAR assumption on missingness. Tipping point analysis were also included. These sensitivity analyses are considered acceptable.

Study 1402 Extension

Study 1402 Extension is an ongoing, open-label study with the primary objective to provide continuing treatment with omaveloxolone, until the drug is available through commercial channels or until patient withdrawal. All patients from Study 1402 Part 1 had been off treatment for at least 21 months prior to enrolling in Study 1402 Extension. Patients were not unblinded to study treatment in Study 1402 Part 1 or Study 1402 Part 2 upon entering Study 1402 Extension. At present the longest duration of treatment is over 3.4 years (median exposure of 2.75 years; as of data cut of date for interim analysis). In addition to safety and tolerability data, several efficacy assessments, including mFARS and FA-ADL, are being collected (every 24 weeks). Additional *post hoc* analyses include:

• Propensity-matched analysis which was designed to evaluate the long-term Efficacy (up to 3 years) of omaveloxolone using external natural history data as a comparator. Matching was done on the covariates: Age, age of FA onset, sex, gait score at baseline and mFARS score at baseline using logistic regression. Matching of sex was exact. Pes cavus status was omitted as a matching criterion or an analysis subgroup as it was not available for all patients in the FA-COMS natural history study, and it was not systematically evaluated in the same manner as in Study 1402 Part 2 and Study 1402 Extension. The analysis of the primary endpoint, the mFARS score was done using an MMRM model.

• Delayed start analyses: To test whether the effect achieved by the omaveloxolone treated patients at week 48 could not be recovered in the delayed treatment population. This analysis compared the treatment effect at week 48 with the treatment effect at extension week 72 where both treatment groups were treated with omaveloxolone as part of the Open Label extension. The applicant used an MMRM model. Additionally, the applicant compared the annualised rate of change in mFARS score through extension week 144 in the two groups to see if they differed statistically. Another way of investigating the non-inferiority question. Again, an MMRM model was used.

• Baseline-controlled analysis was done to investigate pre-treatment and post-treatment annualised rate of change in mFARS slopes within each patient considered treatment naïve prior to the Open Label Extension (Placebo-Omav). This included patients from dose ranging study 1 and placebo patients from the pivotal study 2. They excluded patients with pes cavus. Paired (two-sided) t-test was used to evaluate the difference.

The extension study design is inclusive, and the statistical methods and analyses are well chosen. Efficacy data collected in the extension period is of limited value due to open-label design but considered supportive for maintenance of effect in comparison to historical data. External comparisons to natural history data should always be evaluated with caution due to well-known limitations. The propensity score matched analysis required the participants have specific availability of some data. In particular, for inclusion in each of the study populations, patients must have had (1) baseline mFARS, (2) at least one post-baseline mFARS within 3 years after baseline, and (3) values for all propensity score model covariates (ie, sex, baseline mFARS score, age at baseline, age of FA onset, and baseline gait score). Additionally, the subset of patients from the NH population should have the following additional requirements: (1) baseline mFARS score was within the range observed in Study 1402 Extension (mFARS 8 to 74) and (2) age at baseline was within the range observed in Study 1402 Extension (age 16 to 41 years). The selection of the eligible participants based on the availability of data raised concerns about selection bias. The propensity matching is considered acceptable, and covariates chosen (sex, baseline age, age of FA onset, baseline mFARS score, and baseline gait score) are suitable. Overall, due to the rarity of the disease and very high unmet medical need, the propensity score matching analysis is considered suitable to support the positive findings in the trial.

Efficacy data and additional analyses

Study 1402 Part 2 (Pivotal study)

Participants: Between Aug 2017 and Oct 2018, 156 patients were screened and a total of 103 patients were randomised into Study 1402 Part 2; 51 patients to omaveloxolone (10 with pes cavus and 41 without pes cavus) and 52 patients to placebo (10 with pes cavus and 42 without pes cavus). A total of 44 (86.3%) omaveloxolone-treated patients and 50 (96.2%) placebo-treated patients completed treatment through Week 48; of these, respectively, 41 and 34 patients had mFARS assessed at Week 48. There is higher discontinuation rate in active arm compared to placebo arm.

Overall, patients were between the ages of 16 and 40 years, and the mean age was 24.1 and 23.4 years for the placebo and omaveloxolone groups, respectively. A total of 24 paediatric patients (age 16 or 17 years) were randomised into the study. The distribution of the entire randomised patient population by sex was 53% (55/103 patients) male and 47% (48/103) female, with a higher proportion of patients randomised to the omaveloxolone treatment group being female (31/51 [61%] patients). There was a marked difference in female patients in the active arm in all analysis populations. Sex is not a known factor to influence disease progression as measured by FARS.

In addition to sex, age distribution was also different for all randomised patients, patients without pes cavus, and patients with pes cavus. There were almost double amount of adolescents in placebo arm compared to omaveloxolone arm in FAS population (13 versus 7) and ARP (15 versus 9). Age can predict mFARS progression unless balanced between groups or the results are controlled by age at onset. Inclusion of baseline age as a covariate in the MMRM model showed no impact on the mFARS results in the FAS and ARP. A new subgroup analysis using the 25 years cutoff shows more balanced baseline characteristics and a treatment effect in each subgroup in the FAS that is similar to the overall treatment effect.

In the FAS, the mean age at FA onset ranged from 15.1 years to 15.9 years, with a mean disease duration of 4.7 to 4.8 years. While the distribution of many baseline characteristics was similar between treatment groups, some surprisingly large imbalances occurred despite randomisation. The omaveloxolone cohort had characteristics consistent with slightly more advanced disease: higher mFARS scores (mean 40.9 points vs 38.8 points), longer GAA1 repeat lengths (mean 739.2 vs 693.8), and, most importantly, a greater

proportion of patients with a history of cardiomyopathy (48% versus 29%) compared to placebo patients. In medical history, DM was only present in omaveloxolone population (5% versus 0). Patients with pes cavus had a shorter GAA1 repeat length also, specifically in the placebo cohort (mean 585.6 vs 736.6 in omaveloxolone cohort). Longer GAA1 repeat lengths are known to be associated with earlier disease onset, faster progression, and higher occurrence of cardiomyopathy and diabetes mellitus. However, repeat length is not as efficient at predicting differences within groups of patients with similar ages of onset. This imbalance is not expected to create bias in favour of treatment arm over placebo in ARP or FAS (without pes cavus) populations in terms of efficacy. Age at onset, time since onset, patients who are ambulatory or with scoliosis are considered to be balanced between arms in the FAS population (without pes cavus). This is reassuring as age of onset could also be seen as an index of overall disease severity. Short mean time since onset could have impact on the safety profile though, as longer disease duration is associated with higher disease and concomitant disease burden.

Baseline characteristics between arms in adolescent or adult subgroups are not balanced either. Higher mFARS, FA-ADL, GAA1 repeat length, cardiomyopathy or scoliosis history were observed with active arm in adolescents which do not favour this arm over placebo. However, ambulation was worse in the placebo arm. The overall number of non-ambulatory patients across adolescents and adults was 6. To address the potential impact of worse ambulation in the placebo adolescent subgroup on the primary endpoint, an exploratory analysis of mFARS mixed models repeated measures was conducted in adolescents and adults with ambulatory status as a covariate. The omaveloxolone arm was numerically favoured over the placebo arm with LS mean difference ± SE of -3.99±2.163 and -1.62±1.098 in both adolescent and adult subgroups, respectively, when ambulatory status was included as a covariate for the analysis of mFARS (compared to -4.16±2.147 and -1.6±1.093 in adolescent and adult subgroups using the base model). Thus, imbalances in non-ambulatory patients did not impact the mFARS results of the primary endpoint in adolescent and adult subgroups.

The study met its primary efficacy endpoint: omaveloxolone significantly improved mFARS relative to placebo (mean difference of -2.40, p = 0.014) after 48 weeks of treatment in patients without pes cavus (n = 82, FAS). The restriction to patients without pes cavus is not in accordance with the ITT principle. However, it is noted that sensitivity analyses are done on a number of populations, especially on all randomised population (ARP) with covariate adjustment for pes cavus. The pivotal results regarding changes in mFARS seems robust to these sensitivity analyses.

The key secondary endpoints did not formally contribute to evidence for efficacy. Likewise, omaveloxolone did not significantly improve the other secondary endpoints compared to placebo, except for FA-ADL. Nevertheless, all secondary endpoints numerically favoured omaveloxolone (mean difference of -0.43, p = 0.1251 for PGIC; and -0.13, p = 0.5199 for CGIC). Omaveloxolone improved FA-ADL scores relative to baseline relative to placebo at week 48 (mean ± SE difference between treatment groups: -1.30 ± 0.629; p = 0.0420). All sections of the FA-ADL score numerically improved with omaveloxolone. Thus, concurrent with the neurological improvements evidenced by improved mFARS scores, omaveloxolone-treated patients experienced functional improvements representing sparing of functional loss.

Within the mFARS assessment, omaveloxolone improved each component (bulbar, upper limb coordination, lower limb coordination, and upright stability) relative to placebo, although the greatest effects were on the upright stability which predicts important clinical milestones in FA (e.g, loss of ambulation). Upright stability scores in placebo patients consistently worsened over time, with no observed placebo effect.

Prespecified sensitivity analyses of the primary endpoint in ARP (n = 103), including those with pes cavus, confirmed the primary analysis in the FAS population, with a difference between omaveloxolone and placebo

groups of −1.93 (95% CI = −3.7 to −0.15) points (n = 103, p = 0.034). The least difference observed between study arms (out of 4 defined populations, FAS, ARP, PCP, PP) was the "severe" pes cavus population (PCP; -1.19 points difference; n = 20; p = 0.5379), however due to the size of the subgroup in an orphan disease area, statistically significant results are not expected, directional support is considered satisfactory as with other subgroups. Nevertheless, a variety of pes cavus severities have been included in the pivotal study. Pes cavus population is variably classified or detected in the literature. No distinct phenotypical or clinical profile could be established from the literature for the severe pes cavus population. Baseline characteristics or safety data did not show any major differences according to pes cavus severity. Consequently, no reason for a different pharmacodynamic effect could be thought of in the severe pes cavus population. Insignificant differences in effect size in different subgroups are considered due to small sample size, although an impact of foot structure on performance cannot be excluded. All above considered, extrapolation to the FA population with pes cavus is considered acceptable.

The point estimates for the improvements in mFARS were consistently favouring omaveloxolone treatment across subgroups. However, the variability was higher for adults (n=57) or females (n=34) or patients with GAA repeat length below 675 (n=27) or non-ambulatory patients (n=6). Results of the additional analysis requested by the Agency showed no impact on the primary endpoint when categorical age (<18; ≥18), sex, and GAA1 repeat length were all included as covariates in the primary analysis. When all characteristics were included in the analysis, the Week 48 mFARS difference was -3.54 with a p-value of 0.0014. Similarly, no impact on the primary endpoint was observed when categorical age (<18; ≥18), sex, or GAA1 repeat length were included individually as covariates in the primary analysis.

The greatest improvement in mFARS occurred in patients <18 years of age; placebo-treated adolescent patients worsened by +2.17 points at Week 48, while omaveloxolone-treated adolescent patients improved by -3.42 points at Week 48, resulting in a placebo-corrected improvement of -4.16 points (n = 20; p = 0.0565). This is not surprising as the youngest age group shows the highest mean yearly changes in mFARS score, which decreases with age in natural history cohorts. The middle-aged groups and older groups show less substantial change over a 2-year assessment given the variance in baseline phenotypes in older subjects and the influence of ceiling effects in both the disease biology and standard outcome measures.

Study 1402 Extension

A maximum of 172 patients were potentially eligible to be enrolled into this study. A total of 149 patients received omaveloxolone, 136 patients had mFARS assessed after starting treatment in the extension. A total of 11 patients were adolescents. As of the database lock on 24 March 2022, 123 (82.6%) patients are continuing the study. A total of 133 (89.3%) patients were exposed to study drug for greater than 48 weeks in Study 1402 Extension, 125 (83.9%) patients were exposed to study drug for greater than 96 weeks, and 69 (46.3%) patients were exposed to study drug for greater than 144 weeks.

The extension study shows a 2-3 points increase in mean mFARS up to week 144 which is actually in line with the range in the natural history cohort findings, maybe just on the slower end. Due to small numbers of patients in the groups, a variability of 1-2 points were also observed in mean mFARS scores between two consecutive visits. At Week 120, mean mFARS increased from Study 1402 Extension baseline in the Placebo-Omav group for all patients (mean mFARS change from baseline ± SD was 2.48 ± 5.803; n=65) and for patients without pes cavus (2.35 ± 5.769; n=44); in the Omav-Omav group, it increased for all patients (2.18 ± 5.814; n=31) and for patients without pes cavus (1.21 ± 5.472; n=27).

FA-ADL scores also change a littler slower in the beginning but catch up with the reported change in natural history data over time (1.3 points over 144 weeks). Changes from baseline in total ADL score for the

Placebo-Omav group at Week 24, Week 48, Week 96, and Week 144 were 0.244, 0.390, 1.405, and 1.873, respectively. Changes from baseline in total ADL score for the Omav-Omav group at Week 24, Week 48, Week 96, and Week 144 were -0.068, 0.212, 1.692, and 1.286, respectively.

While the extension study alone does not demonstrate a strong evidence for maintenance of efficacy given all the biases of open-label design and small numbers, it is considered sufficient for a MAA.

The propensity matched analysis confirms what has already been found in the pivotal study after 1 year and expands the observation period so an assessment after 3 years can be done. After 3 years, in the Primary Pooled Population, matched FA-COMS patients had progressed 6.611 mFARS points, whereas patients treated with omaveloxolone in Study 1402 Extension progressed only 3.004 points (difference = -3.607, nominal p = 0.0001).

In the Primary Placebo-Omav Population, an improvement from baseline at Year 1 in the Study 1402 Extension patients considered treatment naïve is similar to the omaveloxolone arm in Study 1402 Part 1 and Study 1402 Part 2, in which an improvement from baseline was also observed upon initiation of treatment with active drug, and results in a slightly larger difference compared to matched FA-COMS patients at Year 1 (-2.754 mFARS points; nominal p=0.0035) than in the Primary Pooled Population. As a cross study comparison, this Year 1 treatment difference is similar in magnitude to the Study 1402 Part 2 treatment difference in the primary analysis population at Week 48 (-2.40 mFARS points).

The Primary Omav-Omav Population did not experience an improvement from baseline, likely because they were in their second year of treatment with active drug.

It is noted that this analysis does not adjust for pes cavus, as pes cavus is evaluated differently in this study and in FA-COMS, and it still seems to slow disease progression.

Of note, there were concerns regarding propensity matching (DOI: 10.1017/pan.2019.11) and precautions to the results should be taken accordingly. The applicant was asked to validate the propensity control group by comparing them to the randomised control group after 1 year. Upon request, the applicant effectively conducts a comparison of initial characteristics between control groups managed through propensity control and those managed through randomisation. They discuss and investigate the differences observed in mFARS change from baseline after one year. Additionally, the applicant strengthens the comparison by conducting extra evaluations and analyses. Ultimately, they address general concerns related to propensity matching. These have strengthened the overall efficacy conclusion as the control groups are shown to be similar after 1 year.

The non-inferiority analysis supports that the treatment effect, in FA patients without pes cavus, at extension week 72 (where both groups were treated with Omaveloxolone) preserved more than 50% of the treatment effect from week 48 (where the controls were still treated with placebo). This gives evidence of a persistent effect of Omaveloxolone that cannot be recovered by delayed treatment.

This analysis is well thought but should be taken with precaution as the sensitivity analysis using the ARP set fails to show similar conclusions as the analysis done on the FAS set. Additionally, the numbers are low due to attrition (n=31 at extension week 72). Similarly, the comparison of slopes fails to show statistically significant differences although there’s a numerical trend.

The baseline analysis confirms what have been found in the pivotal study where each treatment naïve patient act as their own control. The difference between pre-treatment and post treatment slopes seems a bit numerically large (Difference=-3.8, n = 34; p = 0.0022). However, it does validate the results from the pivotal study, where the difference between treatment groups is -2.4 (n = 82; p = 0.0141).

2.6.7. Conclusions on the clinical efficacy

Efficacy of omaveloxolone 150 mg/day has been demonstrated against placebo in FA population with and without pes cavus in a single pivotal study. Maintenance of efficacy is supported by the ongoing extension study and its comparison to an external natural history cohort. The applicant is expected to commit to PIP study timelines (to be completed by Jan 2026) and they are encouraged to finalise the study protocol as soon as possible through interactions with PDCO and SAWP.

2.6.8. Clinical safety

Omaveloxolone is a novel, potent, orally bioavailable Nrf2 activator. It selectively and reversibly binds to Keap1, resulting in the activation of Nrf2, a transcription factor that modulates the expression of genes involved in regulating mitochondrial function, oxidative stress, and inflammation.

The pivotal submission is composed of data from 2 randomised, placebo-controlled, double-blind portions of Study 1402 in patients with FA (Studies 1402 Part 1 and Part 2), and data from Study 1402 Extension, which is open-label and informs long-term safety.

2.6.8.1. Patient exposure

Table 41: Overview of the omaveloxolone development programme (oral administration)

Study Number, Phase	Design	Population	Treatment Period	Treatments	Number Patients/ Subjects	Data Cutoff (LPLO)
Patients with Friedreich's ataxia						
408-C-1402 Part 2, Phase 2	Randomized, double-blind, placebo-controlled, parallel-group study	Patients with FA	48 weeks	Placebo, Omav 150 mg	N=103 Placebo; n=52 150 mg; n=51	31 Oct 2019
408-C-1402 Extension, Phase 2	Long-term safety/tolerability of omaveloxolone	Patients with FA who completed Part 1 or Part 2	Until omaveloxolone is available through commercial channels or until patient withdraws	Omav 150 mg	N=149 (as of 24 Mar 2022)	Ongoing
408-C-1402 Part 1, Phase 2	Randomized, double-blind, placebo-controlled, dose-ranging	Patients with FA	12 weeks	Placebo, Omav 2.5/5, 10, 20, 40, 80, 160, and 300 mg Fixed dose (dose-escalation in Cohort 1)	N=69 Placebo; n=17 2.5/5 mg; n=6 10 mg; n=6 20 mg; n=6 40 mg; n=6 80 mg; n=6 160 mg; n=12 300 mg; n=10	13 Jun 2017
Patients with Mitochondrial Myopathy						
408-C-1403, Phase 2	Randomized, double-blind, placebo-controlled, dose-ranging	Patients with mitochondrial myopathy	12 weeks	Placebo, Omav 2.5/5, 10, 20, 40, 80, and 160 mg	N=53 Placebo n=13 2.5/5 mg; n=6 10 mg; n=6 20 mg; n=6 40 mg; n=6 80 mg; n=6 160 mg; n=10	30 Nov 2017

Study Number, Phase	Design	Population	Treatment Period	Treatments	Number Patients/ Subjects	Data Cutoff (LPLO)
Clinical Pharmacology/Pharmacokinetics Studies						
408-C-1703; Phase 1	Open-label, food effect, dose proportionality	Healthy subjects	Part 1: single dose on Day 1 of each of the two in-clinic periods (Day -1 to Day 6) Part 2: single dose on Day 1 of in-clinic period (Day -1 to Day 6)	Omav 50, 100, and 150 mg	N=34 50 mg; n=10 100 mg; n=8 150 mg; n=16	20 Nov 2018
408-C-1804; Phase 1	Single-dose, open-label, non-randomized, parallel-group	Patients with mild, moderate, or severe hepatic impairment/matched healthy normal subjects	single dose on Day 1 of in-clinic period (Day -1 to Day 6)	Omav 150 mg	N=32 normal; n=12 mild; n=8 moderate; n=7 severe; n=5	30 Jan 2020
408-C-1805; Phase 1	Open-label, non-randomized, single-dose AME study	Healthy male subjects	single dose on Day 1 of in-clinic period (Day -1 up to Day 23)	150 mg ^{14}C-omaveloxolone	N=8	31 May 2019
408-C-1806; Phase 1	Open-label, fixed-sequence, drug-drug interaction study	Healthy subjects	Part 1: ~9 weeks total duration of study with Omav treatment on Days 12 to 27 Parts 2, 3 and 4: 8 weeks total duration of study with Omav treatment on Days 1 and 13	Omav 150 mg	Part 1: n=16 Part 2: n=15 Part 3: n=15 Part 4: n=15	28 Aug 2019
Patients with Advanced Solid Tumors						
408-C-1303; Phase 1	Open-label, multicenter, dose escalation	Patients with stage IIIB/IV NSCLC or stage IIIB/IV melanoma	12 cycles of treatment, 28 days per cycle.	Omav 2.5, 5, 10, and 15 mg	N=11 2.5 mg; n=3 5 mg; n=3 10 mg; n=3 15 mg; n=2	02 Jul 2015
408-C-1401; Phase 1b/2	Open-label, multicenter, dose escalation	Patients with stage III/IV melanoma	168 weeks in combination with ipilimumab, 169 weeks in combination with nivolumab	Omav 5 and 10 mg	N=41 omaveloxolone/ ipilimumab; n=12 omaveloxolone/ nivolumab n=29	23 Jul 2018

Abbreviations: AME=absorption, metabolism, and excretion; FA=Friedreich's ataxia; LPLO=last patient's last observation; NSCLC=non-small cell lung cancer; Omav=omaveloxolone.
Source: Study 1402 Part 2 CSR; Study 1402 Extension Interim CSR 2022; Study 1402 Part 1 CSR; 408-C-1403 CSR; 408-C-1703 CSR; 408-C-1804 CSR; 408-C-1805 CSR; 408-C-1806 CSR; 408-C-1303 CSR; 408-C-1401 CSR

The pivotal and supportive clinical studies for the proposed indication of omaveloxolone for the treatment of FA in this SCS are:

- **Study 1402 Part 2:** a completed, double-blind, randomised, placebo-controlled study in patients with FA to assess the efficacy and safety of omaveloxolone 150 mg compared with placebo. A total of 103 patients (including 24 adolescents) were randomised into Study 1402 Part 2 (51 to omaveloxolone and 52 to placebo). Eligible patients were 16 to 40 years of age and had baseline modified FA Rating Scale (mFARS) scores ≥20 and ≤80. Patients were randomised 1:1 to omaveloxolone 150 mg or placebo and were treated over a 48-week treatment period. Per protocol, randomisation was also stratified by pes cavus status (presence or absence), with enrolment of patients with pes cavus limited to no more than 20% of the study population based on efficacy findings from Study 1402 Part 1.

- **Study 1402 Extension:** an ongoing, open-label study to assess the long-term safety of 150 mg omaveloxolone in patients with FA who previously completed Study 1402 Part 1 or Study 1402 Part 2. Eligible patients are 16 to 40 years of age and had baseline mFARS scores ≥20 and ≤80. At the time of the interim database lock (24 March 2022), 149 patients (including 11 adolescents) were enrolled, with a median omaveloxolone treatment duration in the Extension of approximately 2.7 years (1006 days; range 18 to 1239 days).
- **Study 1402 Part 1:** a completed, dose-ranging, randomised, double-blind, placebo-controlled study in 69 patients (including 9 adolescents) with FA. Patients were randomised 3:1 to omaveloxolone at the cohort-specific dose (n=6) or placebo (n=2). Eight dose levels were evaluated: 2.5/5, 10, 20, 40, 80, 160, and 300 mg during a 12- week treatment period to allow for adequate dose ranging for selection of the dose of omaveloxolone to be used in Study 1402 Part 2. A total of 69 patients were randomised (52 to omaveloxolone and 17 to placebo). Eligible patients were 16 to 40 years of age and had baseline mFARS scores ≥10 and ≤80.

Table 42: Enrolment for pivotal and supportive clinical studies in Friedreich's ataxia.

Study	Treatment	Number of Patients Enrolled
Study 1402 Part 2	Placebo	52
	Omav 150 mg	51
	Total Patients	**103**
Study 1402 Extension[a]	From Part 1:	57
	Randomized to Placebo	13
	Randomized to Omav	44
	From Part 2:	92
	Randomized to Placebo	49
	Randomized to Omav	43
	Total Patients	**149**
Study 1402 Part 1	Placebo	17
	All Omav	52
	Total Patients	**69**
	2.5/5 mg[b]	6
	10 mg	6
	20 mg	6
	40 mg	6
	80 mg	6
	160 mg	12
	300 mg	10

Abbreviations: All Omav=all omaveloxolone doses in the study combined; Omav=omaveloxolone.

[a] All patients enrolled in Study 1402 Extension were previously enrolled in and completed either Study 1402 Part 1 or Study 1402 Part 2.

[b] Patients received 2.5 mg Omav for 2 weeks then dose-escalated to 5 mg for the remainder of the treatment phase of the trial.

Safety Analysis Sets

For the evaluation of omaveloxolone safety in this submission, 6 analysis sets were generated and are described below. Analysis Set A forms the basis of all safety conclusions, with data from the other analysis sets providing supporting information. The analysis sets are as follows:

- **Primary Placebo-Controlled Analysis Set A (hereafter referred to as "Analysis Set A") (103 patients: 51 omaveloxolone and 52 placebo)**: Includes data from Study 1402 Part 2 in patients with FA. This analysis set is considered the primary analysis set for the proposed labeling, as it provides a placebo comparison and the proposed marketed dose and formulation of omaveloxolone. Summaries include placebo and omaveloxolone 150 mg.
- **Placebo-Controlled Integrated FA Analysis Set B (hereafter referred to as "Analysis Set B") (132 patients: 63 omaveloxolone and 69 placebo):** Includes data from Study 1402 Part 1 and Study 1402 Part 2 in 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 include placebo and omaveloxolone doses of 150/160 mg pooled. This analysis set was assessed to confirm the safety profile of Analysis Set A.
- **FA Overall Omaveloxolone Exposure Integrated Analysis Set C (hereafter referred to as "Analysis Set C") (165 patients: all omaveloxolone):** 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, Study 1402 Part 2, and Study 1402 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 characterise patients treated with any omaveloxolone dose for any duration. This analysis set was assessed to confirm the safety profile of Analysis Set A.
- **Long-Term Safety Study 1402 Subgroup Set D (Analysis Set D) (51 patients: 51 omaveloxolone):** Includes all omaveloxolone-treated patients (no placebo-treated patients) who enrolled in Study 1402 Part 2 and were randomised to omaveloxolone. Patients who completed Study 1402 Part 1 and patients who were randomised to placebo in Study 1402 Part 2 are not included in this subgroup. The results summarise the entire patient exposure on omaveloxolone in Study 1402 Part 2 and Study 1402 Extension. This analysis set was assessed to confirm the long-term safety of omaveloxolone 150 mg QD.
- **FA Exposure Analysis Set E (hereafter referred to as "Analysis Set E") (137 patients: all omaveloxolone):** Includes patients with ≥48 weeks of exposure to omaveloxolone 150 mg, ≥96 weeks of exposure to omaveloxolone 150 mg, and ≥144 weeks of exposure to omaveloxolone 150 mg. The results summarise the patient exposure on omaveloxolone in Study 1402 Part 2 and the Study 1402 Extension.
- **Placebo-Controlled Integrated All Analysis Set X (hereafter referred to as "Analysis Set X") (155 patients: 73 omaveloxolone and 82 placebo):** Includes data from Study 1402 Part 1 and Study 1402 Part 2 in patients with FA and from Study 408-C-1403 in patients with mitochondrial myopathy randomised to 150/160 mg or placebo. The purpose of this analysis set was to summarise safety findings from all placebo-controlled studies at the 150-/160-mg dose.

Overall Extent of Exposure

Table 43 presents the number of individuals exposed to the capsule formulation of omaveloxolone during the clinical development programme. Additionally, omaveloxolone exposure with the oral capsule formulation occurred in 2 studies in oncology (Studies 408-C-1303 and 408-C-1401) and 4 clinical pharmacology studies in healthy volunteers (Studies 408-C-1703; 408-C-1804; 408-C-1805; and 408-C-1806).

Table 43: Total exposure to capsule formulation of omaveloxolone

Safety Data for Capsule Formulation of Omaveloxolone n=412			
Clinical Trial Group	**Studies Included**	**Omaveloxolone (n=392)**	**Placebo (n=82)**
Placebo-controlled studies conducted in patients with FA	Study 1402 Part 2	51[a]	52
	Study 1402 Part 1	52[a]	17
Open-label studies conducted in patients with FA	Study 1402 Extension	87[b]	62
Placebo-controlled studies conducted in patients with mitochondrial myopathies	408-C-1403	40	13
Open-label studies conducted in patients with oncologic indications	408-C-1303	11	0
	408-C-1401	41	0
Clinical pharmacology studies conducted in healthy volunteers	408-C-1703	34	0
	408-C-1804	32	0
	408-C-1805	8	0
	408-C-1806	61	0

Abbreviation: FA=Friedreich's ataxia.
[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.

Table 44: Exposure in analysis sets A and C (all patients)

Analysis Set	N	Duration of Study Drug Exposure			Study Drug Compliance	
		Median Exposure (Years)	>0.92 Patient Years (>48 Weeks) n (%) of Patients[a]	>1.84 Patient Years (>96 Weeks) n (%) of Patients[a]	80% to <90% n (%) of Patients	≥90% n (%) of Patients
Analysis Set A: Primary Placebo-Controlled Analysis						
Omaveloxolone 150 mg	51	0.92	20 (40.0%)	0	3 (6.0%)	46 (92.0%)
Placebo	52	0.92	27 (51.9%)	0	1 (1.9%)	51 (98.1%)
Analysis Set C: FA Overall Omaveloxolone Exposure Integrated Analysis						
Omaveloxolone[b]						
5 to 20 mg	18	0.23	0	0	0	18 (100%)
40 to 80 mg	12	0.23	0	0	2 (16.7%)	10 (83.3%)
150/160 mg	167	2.77	137 (82.0%)	125 (74.9%)	37 (22.2%)	102 (61.1%)
300 mg	10	0.23	0	0	1 (10.0%)	9 (90.0%)
Combined	207	2.72	137 (66.2%)	125 (60.4%)	40 (19.3%)	139 (67.1%)

Abbreviation: FA=Friedreich's ataxia.
[a] Percentages are based on the number of non-missing observations.
[b] For patients who started omaveloxolone in Study 1402 Part 1 and entered Study 1402 Extension, exposure and compliance were 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 and compliance were calculated across both studies when entering Study 1402 Extension.

As shown in Table 45 total of 22 adolescent patients were exposed to omaveloxolone capsule formulation at doses ranging from 10 mg to 300 mg (Analysis Set C).

Table 45: Adolescent exposure in analysis sets A and C (all patients)

Analysis Set	N	Duration of Study Drug Exposure			Study Drug Compliance	
		Median Exposure (Years)	>0.92 Patient Years (>48 Weeks) n (%) of Patients[a]	>1.84 Patient Years (>96 Weeks) n (%) of Patients[a]	80% to <90% n (%) of Patients	≥90% n (%) of Patients
Analysis Set A: Primary Placebo-Controlled Analysis						
Omaveloxolone 150 mg	9	0.92	4 (44.4%)	0	0	8 (88.9%)
Placebo	15	0.92	7 (46.7%)	0	0	15 (100%)
Analysis Set C: FA Overall Omaveloxolone Exposure Integrated Analysis						
Omaveloxolone[b]						
5 to 20 mg	1	0.23	0	0	0	1 (100%)
40 to 80 mg	1	0.23	0	0	0	1 (100%)
150/160 mg	18	2.77	14 (77.8%)	12 (66.7%)	8 (44.4%)	8 (44.4%)
300 mg	2	0.23	0	0	0	2 (100%)
Combined	22	2.44	14 (63.6%)	12 (54.5%)	8 (36.4%)	12 (54.5%)

Abbreviation: FA=Friedreich's ataxia.
[a] Percentages are based on the number of non-missing observations.
[b] For patients who started omaveloxolone in Study 1402 Part 1 and entered Study 1402 Extension, exposure and compliance were 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 and compliance were calculated across both studies when entering Study 1402 Extension.

2.6.8.2. Adverse events

Table 46: Overall Summary of treatment-emergent adverse events (analysis set A)

	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Patients who had a TEAE	51 (100%)	52 (100%)
Patients who had a TEAE related to study drug	37 (72.5%)	19 (36.5%)
Patients who had a TEAE with action taken of study drug discontinuation	4 (7.8%)	2 (3.8%)
Patients who had a TEAE with action taken of study drug interrupted	9 (17.6%)	1 (1.9%)
Patients who had a serious TEAE	5 (9.8%)	3 (5.8%)
Patients who had a serious TEAE related to study drug	1 (2.0%)	0
Patients who had a TEAE with severity of:		
Mild	22 (43.1%)	34 (65.4%)
Moderate	24 (47.1%)	18 (34.6%)
Severe	5 (9.8%)	0
Patients who had a TEAE related to study drug with severity of:		
Mild	20 (39.2%)	15 (28.8%)
Moderate	17 (33.3%)	4 (7.7%)
Severe	0	0
Patients who had a fatal TEAE	0	0

Abbreviation: TEAE=treatment-emergent adverse event.
For counts by severity, patients with multiple events were counted only once at the highest severity.

Table 47: Overall summary of treatment-emergent adverse events in adolescent patients (analysis set A)

	Omaveloxolone 150 mg (N=9)	Placebo (N=15)
Patients who had a TEAE	9 (100%)	15 (100%)
Patients who had a TEAE related to study drug	6 (66.7%)	10 (66.7%)
Patients who had a TEAE with action taken of study drug discontinuation	0	0
Patients who had a TEAE with action taken of study drug interrupted	0	0
Patients who had a serious TEAE	0	0
Patients who had a serious TEAE related to study drug	0	0
Patients who had a TEAE with severity of:		
Mild	4 (44.4%)	11 (73.3%)
Moderate	3 (33.3%)	4 (26.7%)
Severe	2 (22.2%)	0
Patients who had a TEAE related to study drug with severity of:		
Mild	3 (33.3%)	9 (60.0%)
Moderate	3 (33.3%)	1 (6.7%)
Severe	0	0
Patients who had a fatal TEAE	0	0

Abbreviation: TEAE=treatment-emergent adverse event.
For counts by severity, patients with multiple events were counted only once at the highest severity.
Age group was based on age at first double-blind treatment.

Table 48: Overview of treatment-emergent adverse events (Friedreich's ataxia overall omaveloxolone exposure integrated analysis set C)

	Omaveloxolone 5-20 mg (N=18)	Omaveloxolone 40-80 mg (N=12)	Omaveloxolone 150/160 mg (N=159)	Omaveloxolone 300 mg (N=10)	Omaveloxolone All Treated (N=165)
Patients who had a TEAE	16 (88.9%)	12 (100%)	156 (98.1%)	10 (100%)	162 (98.2%)
Patients who had a TEAE related to study drug	4 (22.2%)	5 (41.7%)	102 (64.2%)	4 (40.0%)	107 (64.8%)
Patients who had a TEAE with action taken of study drug interrupted	0	0	39 (24.5%)	0	39 (23.6%)
Patients who had a TEAE with action taken of study drug discontinued	0	1 (8.3%)	14 (8.8%)	0	15 (9.1%)
Patients who had a serious TEAE	0	0	18 (11.3%)	0	18 (10.9%)
Patients who had a serious TEAE related to study drug	0	0	1 (0.6%)	0	1 (0.6%)
Patients who had a TEAE with severity of:					
Mild	11 (61.1%)	5 (41.7%)	50 (31.4%)	4 (40.0%)	46 (27.9%)
Moderate	5 (27.8%)	7 (58.3%)	85 (53.5%)	6 (60.0%)	95 (57.6%)
Severe	0	0	21 (13.2%)	0	21 (12.7%)
Patients who had a TEAE related to study drug with severity of:					
Mild	3 (16.7%)	3 (25.0%)	64 (40.3%)	3 (30.0%)	66 (40.0%)
Moderate	1 (5.6%)	2 (16.7%)	37 (23.3%)	1 (10.0%)	40 (24.2%)
Severe	0	0	1 (0.6%)	0	1 (0.6%)
Patients who had a fatal TEAE	0	0	0	0	0

Abbreviation: TEAE=treatment-emergent adverse event.
For counts by severity, patients with multiple events are counted only once at the highest severity.
Some patients may be represented in multiple columns if they changed dose level when entering Study 1402 Extension.
Each column reflects number of unique patients. Events are counted within the treatment group at the start of the event.

Common Treatment-Emergent Adverse Events

Analysis Set A

A common treatment-emergent adverse event (TEAE) was defined as an event that occurred in ≥2% of omaveloxolone-treated patients and at a greater incidence than in placebo-treated patients. Common TEAEs for Analysis Set A are presented in Table 49.

Table 49: Summary of treatment-emergent adverse events with an incidence of ≥2% and excess in the omaveloxolone treatment group over the placebo group (primary placebo-controlled analysis set A).

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Number (%) of Patients Reporting Selected[a] TEAEs	**50 (98.0%)**	**40 (76.9%)**
Gastrointestinal disorders	**31 (60.8%)**	**19 (36.5%)**
Nausea	17 (33.3%)	7 (13.5%)
Diarrhoea	10 (19.6%)	5 (9.6%)
Vomiting	8 (15.7%)	6 (11.5%)
Abdominal pain upper	5 (9.8%)	1 (1.9%)
Abdominal pain	4 (7.8%)	1 (1.9%)
Abdominal discomfort	3 (5.9%)	1 (1.9%)
Dyspepsia	2 (3.9%)	1 (1.9%)
Abdominal distension	2 (3.9%)	0
Constipation	2 (3.9%)	0
Gastrooesophageal reflux disease	2 (3.9%)	0
Injury, poisoning and procedural complications	**26 (51.0%)**	**18 (34.6%)**
Skin abrasion	13 (25.5%)	11 (21.2%)
Skin laceration	8 (15.7%)	8 (15.4%)
Limb injury	4 (7.8%)	1 (1.9%)
Muscle strain	3 (5.9%)	1 (1.9%)
Concussion	2 (3.9%)	1 (1.9%)
Foot fracture	2 (3.9%)	0
Nervous system disorders	**20 (39.2%)**	**13 (25.0%)**
Headache	19 (37.3%)	13 (25.0%)
Dyskinesia	2 (3.9%)	0
Somnolence	2 (3.9%)	0
Musculoskeletal and connective tissue disorders	**18 (35.3%)**	**10 (19.2%)**
Back pain	7 (13.7%)	4 (7.7%)

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Muscle spasms	7 (13.7%)	3 (5.8%)
Myalgia	2 (3.9%)	2 (3.8%)
Musculoskeletal chest pain	2 (3.9%)	1 (1.9%)
Joint swelling	2 (3.9%)	0
Pain in jaw	2 (3.9%)	0
Investigations	**22 (43.1%)**	**2 (3.8%)**
Alanine aminotransferase increased	19 (37.3%)	1 (1.9%)
Aspartate aminotransferase increased	11 (21.6%)	1 (1.9%)
Blood creatine phosphokinase increased	3 (5.9%)	2 (3.8%)
Gamma-glutamyltransferase increased	3 (5.9%)	0
VLDL increased	2 (3.9%)	0
Respiratory, thoracic and mediastinal disorders	**15 (29.4%)**	**9 (17.3%)**
Oropharyngeal pain	9 (17.6%)	3 (5.8%)
Cough	4 (7.8%)	4 (7.7%)
Epistaxis	2 (3.9%)	2 (3.8%)
Rhinorrhoea	2 (3.9%)	0
General disorders and administration site conditions	**11 (21.6%)**	**8 (15.4%)**
Fatigue	11 (21.6%)	7 (13.5%)
Non-cardiac chest pain	2 (3.9%)	1 (1.9%)
Infections and infestations	**14 (27.5%)**	**4 (7.7%)**
Influenza	7 (13.7%)	2 (3.8%)
Gastroenteritis viral	3 (5.9%)	1 (1.9%)
Urinary tract infection	4 (7.8%)	0
Viral upper respiratory tract infection	2 (3.9%)	1 (1.9%)
Conjunctivitis	2 (3.9%)	0
Metabolism and nutrition disorders	**7 (13.7%)**	**2 (3.8%)**
Decreased appetite	6 (11.8%)	2 (3.8%)
Hypertriglyceridaemia	2 (3.9%)	0
Skin and subcutaneous tissue disorders	**6 (11.8%)**	**2 (3.8%)**
Hyperhidrosis	2 (3.9%)	1 (1.9%)
Rash	2 (3.9%)	1 (1.9%)
Rash macular	2 (3.9%)	0
Psychiatric disorders	**3 (5.9%)**	**3 (5.8%)**
Insomnia	3 (5.9%)	3 (5.8%)
Reproductive system and breast disorders	**5 (9.8%)**	**0**
Dysmenorrhoea	3 (5.9%)	0
Ovarian cyst	2 (3.9%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event; VLDL=very-low density lipoprotein.

[a] Selected events are TEAEs that occurred in ≥2% of patients in the omaveloxolone group and had a higher incidence in the omaveloxolone group than in the placebo group based on the Primary Placebo-Controlled Analysis Set A population.

Adolescents

Common TEAEs by age group occurring in ≥10% of patients in the omaveloxolone treatment group and with a difference in incidence of ≥2% between omaveloxolone-treated and placebo-treated patients by age are shown in Table 50.

Table 50: Summary of treatment-emergent adverse events with an incidence of ≥10% of patients in the omaveloxolone treatment group and with a difference in incidence of ≥2% between treated and placebo by age group (analysis set A).

System Organ Class / Preferred Term	Age Group			
	<18 Years		≥18 Years	
	Omaveloxolone (N=9)	Placebo (N=15)	Omaveloxolone (N=42)	Placebo (N=37)
Number (%) of Patients Reporting Selected[a] TEAEs	7 (77.8%)	14 (93.3%)	38 (90.5%)	22 (59.5%)
Gastrointestinal disorders	**3 (33.3%)**	**6 (40.0%)**	**20 (47.6%)**	**10 (27.0%)**
Nausea	2 (22.2%)	2 (13.3%)	15 (35.7%)	5 (13.5%)
Diarrhoea	1 (11.1%)	2 (13.3%)	9 (21.4%)	3 (8.1%)
Vomiting	2 (22.2%)	3 (20.0%)	6 (14.3%)	3 (8.1%)
Nervous system disorders	**0**	**6 (40.0%)**	**19 (45.2%)**	**7 (18.9%)**
Headache	0	6 (40.0%)	19 (45.2%)	7 (18.9%)
Investigations	**0**	**0**	**19 (45.2%)**	**1 (2.7%)**
Alanine aminotransferase increased	0	0	19 (45.2%)	1 (2.7%)
Aspartate aminotransferase increased	0	0	11 (26.2%)	1 (2.7%)
Musculoskeletal and connective tissue disorders	**1 (11.1%)**	**3 (20.0%)**	**12 (28.6%)**	**4 (10.8%)**
Back pain	1 (11.1%)	2 (13.3%)	6 (14.3%)	2 (5.4%)

System Organ Class / Preferred Term	Age Group			
	<18 Years		≥18 Years	
	Omaveloxolone (N=9)	Placebo (N=15)	Omaveloxolone (N=42)	Placebo (N=37)
Muscle spasms	0	1 (6.7%)	7 (16.7%)	2 (5.4%)
Injury, poisoning and procedural complications	**4 (44.4%)**	**4 (26.7%)**	**9 (21.4%)**	**7 (18.9%)**
Skin abrasion	4 (44.4%)	4 (26.7%)	9 (21.4%)	7 (18.9%)
General disorders and administration site conditions	**2 (22.2%)**	**1 (6.7%)**	**9 (21.4%)**	**6 (16.2%)**
Fatigue	2 (22.2%)	1 (6.7%)	9 (21.4%)	6 (16.2%)
Respiratory, thoracic and mediastinal disorders	**2 (22.2%)**	**2 (13.3%)**	**7 (16.7%)**	**1 (2.7%)**
Oropharyngeal pain	2 (22.2%)	2 (13.3%)	7 (16.7%)	1 (2.7%)
Infections and infestations	**0**	**0**	**7 (16.7%)**	**2 (5.4%)**
Influenza	0	0	7 (16.7%)	2 (5.4%)
Metabolism and nutrition disorders	**1 (11.1%)**	**0**	**5 (11.9%)**	**2 (5.4%)**
Decreased appetite	1 (11.1%)	0	5 (11.9%)	2 (5.4%)

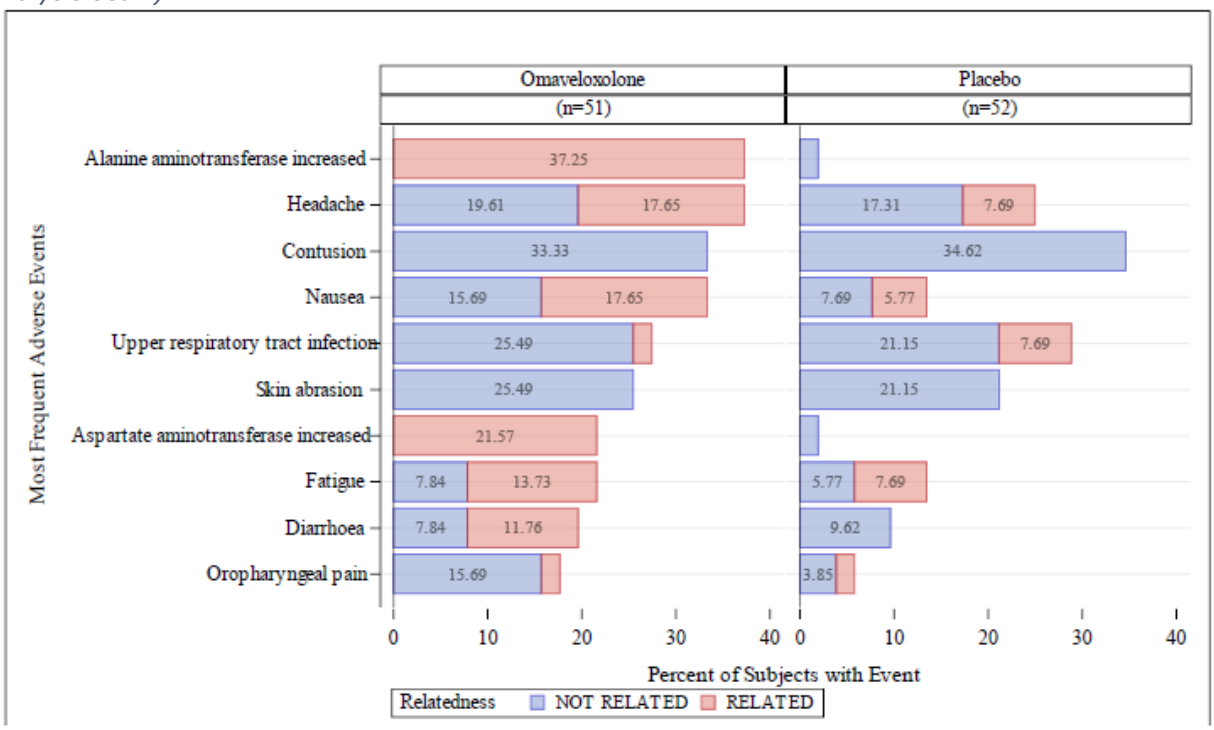
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
[a] Selected events are treatment-emergent events that occurred in ≥10% of patients in the omaveloxolone group and had ≥2% higher incidence in the omaveloxolone group than placebo group, based on the Primary Placebo-controlled Analysis Set A population.
Adverse event terms were mapped according to MedDRA v 21.1.
Age group is based on age at first double-blind treatment.

Treatment-Emergent Adverse Events by Relationship to Study Drug

A frequency plot of the most common TEAEs and relatedness to study drug reported in Analysis Set A is shown in Related TEAEs such as ALT increased, and AST increased are hypothesised to be related due to the pharmacological effect of omaveloxolone.

Figure 38. Related TEAEs such as ALT increased, and AST increased are hypothesised to be related due to the pharmacological effect of omaveloxolone.

Figure 38: Frequency plot of common adverse events by preferred term and relationship to study drug (analysis set A)



Abbreviation: TEAE=treatment-emergent adverse event.
If a patient had both related and non-related occurrences of an event, they are counted only once as related.
Values of <0.01 are rounded to 0.01.
Drug-related TEAEs are those events reported as related, unknown, possibly, probably, or definitely related. Events are considered unrelated if reported as not related or unlikely related.
Numbers within bars represent the percentage of patients with event. See ISS Table 7.1.1 and ISS Table 7.2.1 for details. Some percentages may not display due to space constraints. Blank boxes denote 1 patient-reported event.

Treatment-Emergent Adverse Events by Severity

A summary of TEAEs by severity is presented in Table 51 (only page 1 is shown).

Table 51: Summary of treatment-emergent adverse events by maximum severity (primary placebo-controlled analysis set A)

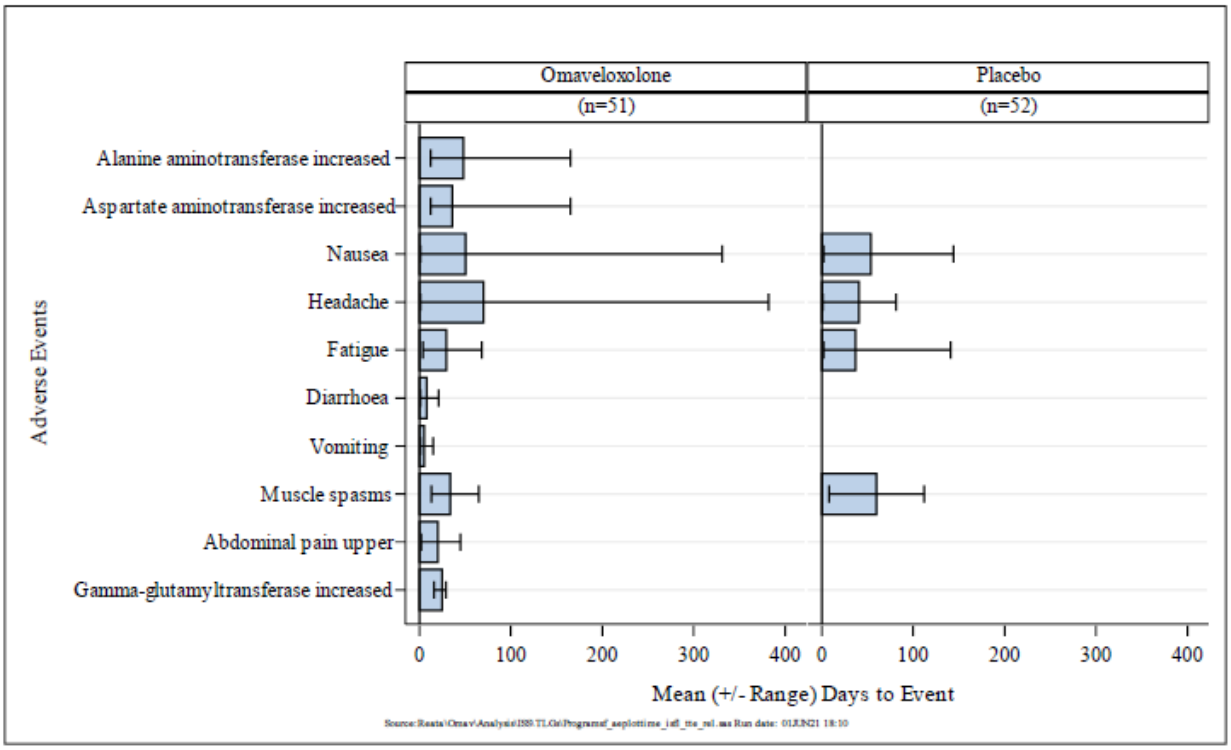
System Organ Class / Preferred Term	Omaveloxolone 150 mg (N=51)			Placebo (N=52)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Number (%) of Patients Reporting TEAEs	22 (43.1%)	24 (47.1%)	5 (9.8%)	34 (65.4%)	18 (34.6%)	0
Infections and infestations	24 (47.1%)	10 (19.6%)	0	26 (50.0%)	4 (7.7%)	0
Upper respiratory tract infection	13 (25.5%)	1 (2.0%)	0	12 (23.1%)	3 (5.8%)	0
Nasopharyngitis	6 (11.8%)	1 (2.0%)	0	11 (21.2%)	0	0
Influenza	3 (5.9%)	4 (7.8%)	0	2 (3.8%)	0	0
Gastroenteritis viral	2 (3.9%)	1 (2.0%)	0	0	1 (1.9%)	0
Urinary tract infection	4 (7.8%)	0	0	0	0	0
Sinusitis	0	1 (2.0%)	0	2 (3.8%)	0	0
Viral upper respiratory tract infection	1 (2.0%)	1 (2.0%)	0	1 (1.9%)	0	0
Conjunctivitis	2 (3.9%)	0	0	0	0	0
Pharyngitis streptococcal	0	1 (2.0%)	0	1 (1.9%)	0	0
Respiratory tract infection viral	0	0	0	2 (3.8%)	0	0
Rhinitis	0	0	0	2 (3.8%)	0	0
Viral infection	0	0	0	1 (1.9%)	1 (1.9%)	0
Bronchitis	1 (2.0%)	0	0	0	0	0

Note: Patients are counted once at the worst severity per system organ class and preferred term.
Note: TEAE = treatment-emergent adverse event. Adverse event terms were mapped according to MedDRA v21.1.

Treatment-Emergent Adverse Events by Time to Onset

The time to onset of the common TEAEs related to study drug in omaveloxolone-treated and placebo-treated patients is shown in Figure 39 for Analysis Set A.

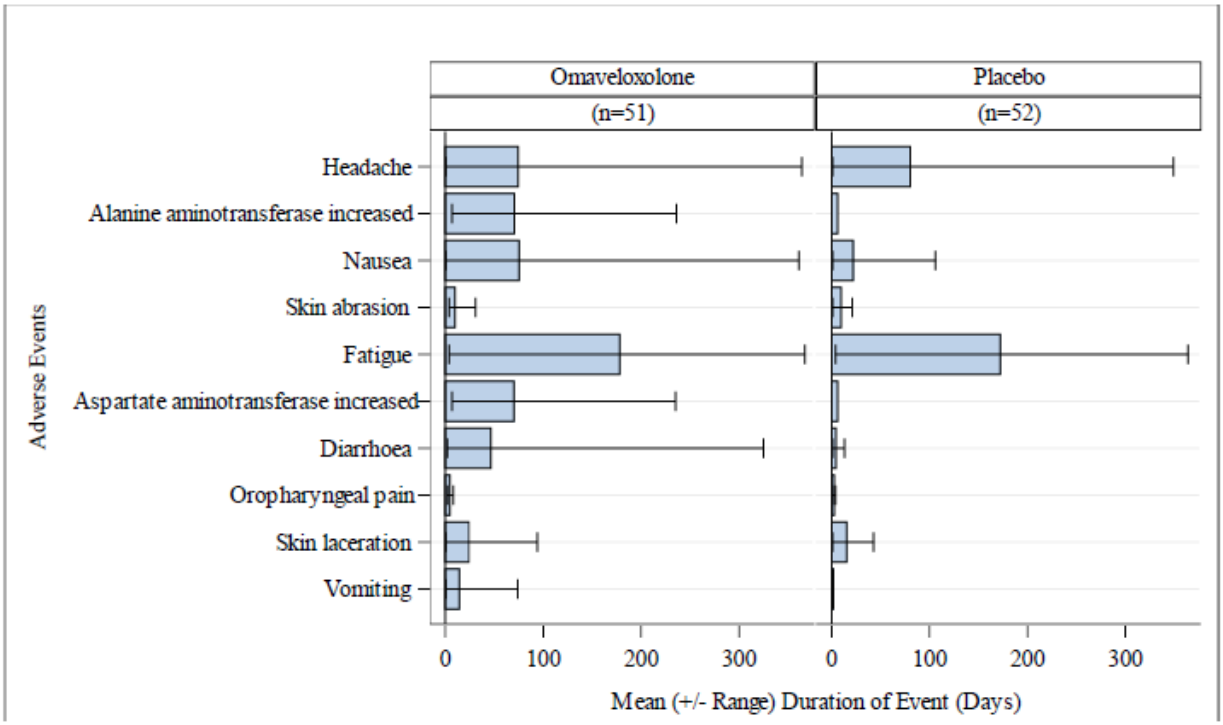
Figure 39: Plot of time to first onset of treatment-emergent adverse events related to study drug (primary placebo-controlled analysis set A)



Abbreviation: TEAE=treatment-emergent adverse event.
Events shown are the 10 most frequent events experienced by omaveloxolone patients who met the selection criteria in the current population, shown in order of frequency among all omaveloxolone patients in the current population. Minimum and maximum times are shown only for events that occurred in more than 1 patient. Events with the same frequency are sorted by average time to onset (lowest first).
Drug-related TEAEs are those events reported as related, unknown, possibly, probably, or definitely related. Events were considered unrelated if reported as not related or unlikely related.

A plot of duration AEs with incidence ⩾2% and excess in omaveloxolone for Analysis Set A is shown in Figure 40.

Figure 40: Plot of duration of adverse events with incidence ≥ 2% and excess in omaveloxolone (analysis set A)



Abbreviation: AE=adverse event.
Selected events are treatment-emergent events that occurred in ≥2% of patients in the omaveloxolone group and had a higher incidence in the omaveloxolone group than placebo group, based on the Primary Placebo-controlled Analysis Set A population.
Events shown are the 10 most frequent events meeting the selection criteria in the omaveloxolone population, shown in order of frequency in the omaveloxolone group. Minimum and maximum time are shown only for events that occurred in more than 1 patient.
Events with the same frequency are sorted by average duration (highest first).
When no AE end date was present, the end date was imputed as double-blind treatment date +30 days, last contact date in the double-blind study, start date of Study 1402 Extension dosing, or death date, whichever came first.

Analysis Set C

A summary of common TEAEs occurring in ≥10% of patients in omaveloxolone-treated patients and with a difference in incidence of ≥2% between omaveloxolone-treated patients and placebo-treated patients identified in Analysis Set A are presented for Analysis Set C in Table 52.

Table 52: Summary of treatment-emergent adverse events occurring in ≥ 10% of patients in the omaveloxolone treatment group and with a difference in incidence of ≥ 2% in the omaveloxolone treatment group over the placebo group in analysis set A (Friedreich's ataxia overall omaveloxolone exposure integrated analysis set C)

System Organ Class Preferred Term	Omaveloxolone				
	5-20 mg (N=18)	40-80 mg (N=12)	150/160 mg (N=159)	300 mg (N=10)	All Treated (N=165)
Number (%) of Patients Reporting Selected[a] TEAEs	**7 (38.9%)**	**6 (50.0%)**	**128 (80.5%)**	**4 (40.0%)**	**132 (80.0%)**
Gastrointestinal disorders	**2 (11.1%)**	**1 (8.3%)**	**60 (37.7%)**	**2 (20.0%)**	**62 (37.6%)**
Nausea	1 (5.6%)	1 (8.3%)	38 (23.9%)	2 (20.0%)	42 (25.5%)
Diarrheoa	1 (5.6%)	1 (8.3%)	30 (18.9%)	1 (10.0%)	32 (19.4%)
Vomiting	1 (5.6%)	0	19 (11.9%)	1 (10.0%)	20 (12.1%)
Nervous system disorders	**1 (5.6%)**	**2 (16.7%)**	**48 (30.2%)**	**2 (20.0%)**	**51 (30.9%)**
Headache	1 (5.6%)	2 (16.7%)	48 (30.2%)	2 (20.0%)	51 (30.9%)
Investigations	**1 (5.6%)**	**1 (8.3%)**	**45 (28.3%)**	**2 (20.0%)**	**47 (28.5%)**
Alanine aminotransferase increased	1 (5.6%)	1 (8.3%)	45 (28.3%)	2 (20.0%)	47 (28.5%)
Aspartate aminotransferase increased	1 (5.6%)	1 (8.3%)	22 (13.8%)	2 (20.0%)	25 (15.2%)
Musculoskeletal and connective tissue disorders	**2 (11.1%)**	**1 (8.3%)**	**40 (25.2%)**	**0**	**43 (26.1%)**
Muscle spasms	1 (5.6%)	0	24 (15.1%)	0	25 (15.2%)
Back pain	1 (5.6%)	1 (8.3%)	20 (12.6%)	0	22 (13.3%)
General disorders and administration site conditions	**3 (16.7%)**	**2 (16.7%)**	**31 (19.5%)**	**0**	**36 (21.8%)**
Fatigue	3 (16.7%)	2 (16.7%)	31 (19.5%)	0	36 (21.8%)
Injury, poisoning and procedural complications	**1 (5.6%)**	**1 (8.3%)**	**29 (18.2%)**	**0**	**31 (18.8%)**
Skin abrasion	1 (5.6%)	1 (8.3%)	29 (18.2%)	0	31 (18.8%)
Infections and infestations	**0**	**0**	**15 (9.4%)**	**0**	**15 (9.1%)**
Influenza	0	0	15 (9.4%)	0	15 (9.1%)
Respiratory, thoracic and mediastinal disorders	**0**	**1 (8.3%)**	**11 (6.9%)**	**0**	**12 (7.3%)**
Oropharyngeal pain	0	1 (8.3%)	11 (6.9%)	0	12 (7.3%)
Metabolism and nutrition disorders	**0**	**0**	**9 (5.7%)**	**0**	**9 (5.5%)**
Decreased appetite	0	0	9 (5.7%)	0	9 (5.5%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
[a] Selected events are TEAEs that occurred in ≥10% of patients in the omaveloxolone group and had a ≥2% higher incidence in the omaveloxolone group than in the placebo group based on the Primary Placebo-Controlled Analysis Set A population.
Adverse event terms were mapped according to MedDRA v_21.1.
Some patients may be represented in multiple columns if they changed dose levels when entering Study 1402 Extension. Each column reflects the number of unique patients. Events were counted within the treatment group at the start of the event.

Treatment-Emergent Adverse Events by Severity

A summary of TEAEs by severity is presented in Table 53 (only page 1 is shown).

Table 53: Summary of treatment-emergent adverse events by maximum severity (FA overall omaveloxolone exposure integrated analysis set C)

System Organ Class / Preferred Term	Omaveloxolone (N=165)		
	Mild	Moderate	Severe
Number (%) of Patients Reporting TEAEs	46 (27.9%)	95 (57.6%)	21 (12.7%)
Infections and infestations	77 (46.7%)	30 (18.2%)	4 (2.4%)
Upper respiratory tract infection	43 (26.1%)	8 (4.8%)	0
Corona virus infection	21 (12.7%)	5 (3.0%)	2 (1.2%)
Nasopharyngitis	25 (15.2%)	3 (1.8%)	0
Influenza	8 (4.8%)	6 (3.6%)	1 (0.6%)
Urinary tract infection	12 (7.3%)	2 (1.2%)	0
Gastroenteritis viral	6 (3.6%)	1 (0.6%)	0
Sinusitis	5 (3.0%)	1 (0.6%)	0
Bronchitis	4 (2.4%)	0	0
Rhinitis	4 (2.4%)	0	0
Viral upper respiratory tract infection	1 (0.6%)	3 (1.8%)	0
Viral infection	3 (1.8%)	0	0
Chlamydial infection	2 (1.2%)	0	0
Conjunctivitis	2 (1.2%)	0	0

Note: Patients are counted once at the worst severity per system organ class and preferred term.
Note: TEAE = treatment-emergent adverse event. Adverse event terms were mapped according to MedDRA v21.1.

Adverse Drug Reactions

The TEAE safety data that met at least 1 of the screening criteria were evaluated for inclusion as an adverse drug reaction (ADR) because of potential clinical significance (i.e., clinically relevant and/or presence of biologic plausibility). The molecule/cohort-specific core safety information screening criteria used in the assessment of these clinical trial safety data in Analysis Set A were as follows:

Commonly occurring ADRs:

- Events that occurred at a rate of ≥5% in the active treatment group (ie, omaveloxolone Analysis Set A) and with a difference of ≥5% versus the frequency in the placebo group

Less common ADRs:

- Serious, low-frequency AEs may have been included if there was sufficient reason to suspect that the drug may have caused the event. Rationale may include but was not limited to the following:
  - timing of onset or termination with respect to drug use
  - plausibility considering the drug's known pharmacology
  - occurrence at a frequency above that expected in the treated population
  - occurrence of an event typical of drug-induced ADRs Table 54 presents TEAEs that met the above screening criteria.

Table 54: Summary of adverse drug reactions observed with omaveloxone treatment in patients with Friedreich's ataxia (analysis set A)

System Organ Class	Preferred Term[a]	Frequency Category[b]
Gastrointestinal disorders	Nausea	Very common
	Diarrhoea	Very common
	Abdominal pain upper	Common
	Abdominal pain	Common
General disorders and administration site conditions	Fatigue	Very common
Injury, poisoning and procedural complications	Limb injury	Common
Infections and infestations	Influenza	Very common
	Urinary tract infection	Common
Investigations	ALT increased	Very common
	AST increased	Very common
	GGT increased	Common
Metabolism and nutritional disorders	Decreased appetite	Very common
Musculoskeletal and connective tissue disorders	Back pain	Very common
	Muscle spasms	Very common
Nervous system disorders	Headache	Very common
Reproductive system and breast disorders	Dysmenorrhoea	Common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Very common

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in the FA studies. Across the entire omaveloxolone development program, 7 deaths were reported, all in oncology studies in patients with stage 4 cancer; 6 deaths were in studies using the capsule formulation (1 death in Study 408-C-1303 and 5 deaths in Study 408-C-1401 [all primarily due to disease progression]), and 1 death was reported in a study using the lotion formulation (Study 408-C-1306). Although all patients were receiving omaveloxolone, none of the deaths were assessed as related to study treatment.

Serious Adverse Events

In Analysis Set A, 5 (9.8%) omaveloxolone-treated patients, and 3 (5.8%) placebo-treated patients reported serious TEAEs (

Table 55).

Table 55: Summary of serious treatment-emergent adverse events by system organ class and preferred term (primary placebo-controlled analysis set A).

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Number (%) of Patients Reporting Serious TEAEs	**5 (9.8%)**	**3 (5.8%)**
Cardiac disorders	**3 (5.9%)**	**1 (1.9%)**
Atrial fibrillation	1 (2.0%)	1 (1.9%)
Palpitations	1 (2.0%)	0
Sinus tachycardia	1 (2.0%)	0
Ventricular tachycardia	1 (2.0%)	0
Injury, poisoning and procedural complications	**1 (2.0%)**	**1 (1.9%)**
Ankle fracture	0	1 (1.9%)
Craniocerebral injury	1 (2.0%)	0
Blood and lymphatic system disorders	**1 (2.0%)**	**0**
Anaemia	1 (2.0%)	0
General disorders and administration site conditions	**1 (2.0%)**	**0**
Non-cardiac chest pain	1 (2.0%)	0
Hepatobiliary disorders	**0**	**1 (1.9%)**
Gallbladder disorder	0	1 (1.9%)
Infections and infestations	**1 (2.0%)**	**0**
Laryngitis	1 (2.0%)	0
Viral upper respiratory tract infection	1 (2.0%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Adverse event terms were mapped according to MedDRA v_21.1.

In Analysis Set C, the frequency of serious TEAEs reported in omaveloxolone-treated patients was similar to Analysis Set A (11.3% in the 150/160 mg dose [N=159]; 10.9% overall).

Safety Topics of Interest

Safety topics of interest were selected based on standard drug registration topics or due to potential clinical significance during the omaveloxolone development programme. Based on the pharmacological properties of omaveloxolone, the following were closely monitored during the development programme:

A. Hepatic safety was evaluated because of observed transient aminotransferase elevations in omaveloxolone clinical trials.

B. Weight changes were evaluated since the target of omaveloxolone, Nrf2, affects cellular metabolism.

C. Infections and infestations were evaluated because of the anti-inflammatory effects associated with Nrf2 activation that could possibly lead to a decreased immune response.

D. Cardiovascular safety was evaluated because cardiomyopathy is common in patients with FA.

[A] Hepatic Safety

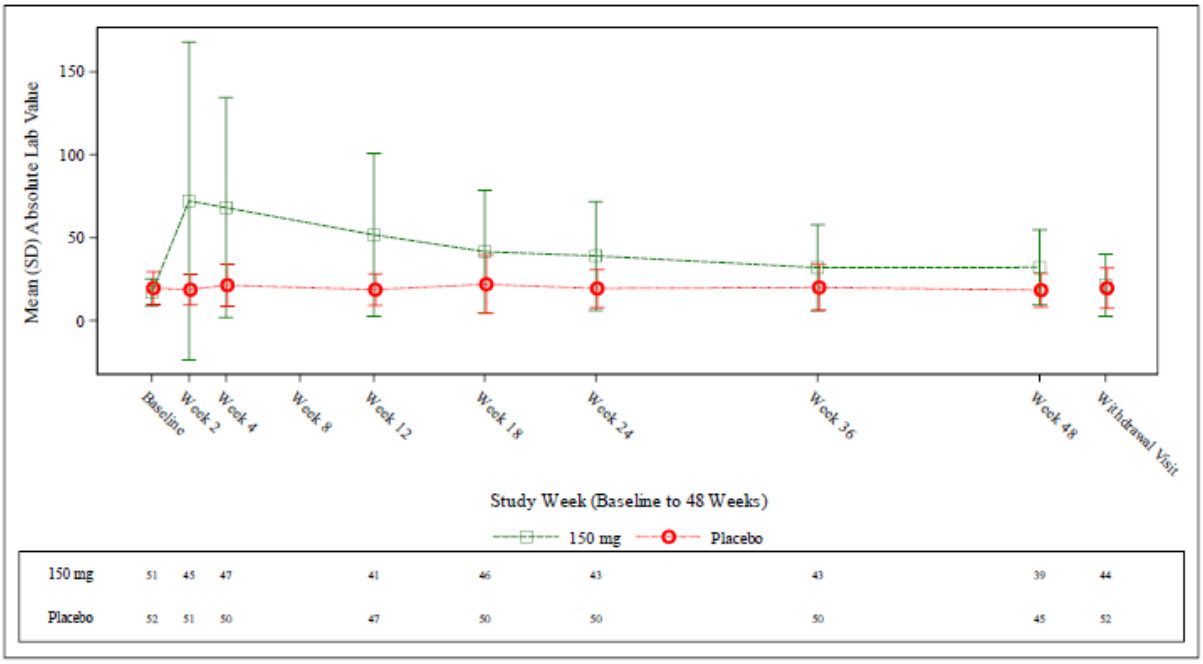
Analysis Set A

Alanine Aminotransferase

As shown in Figure 41, in omaveloxolone-treated patients, peak elevations in serum ALT were observed at Week 2, with values decreasing toward baseline values through Week 48. In contrast, serum ALT

concentrations in placebo-treated patients remained unchanged throughout the 48-week treatment period, with mean serum ALT concentrations remaining below 25 U/L. Increases in ALT during omaveloxolone treatment appeared reversible, with mean serum ALT concentrations declining toward baseline values within 4 weeks following drug withdrawal.

Figure 41: Mean absolute alanine aminotransferase levels (U/L) baseline to week 48 (primary placebo-controlled analysis set A)

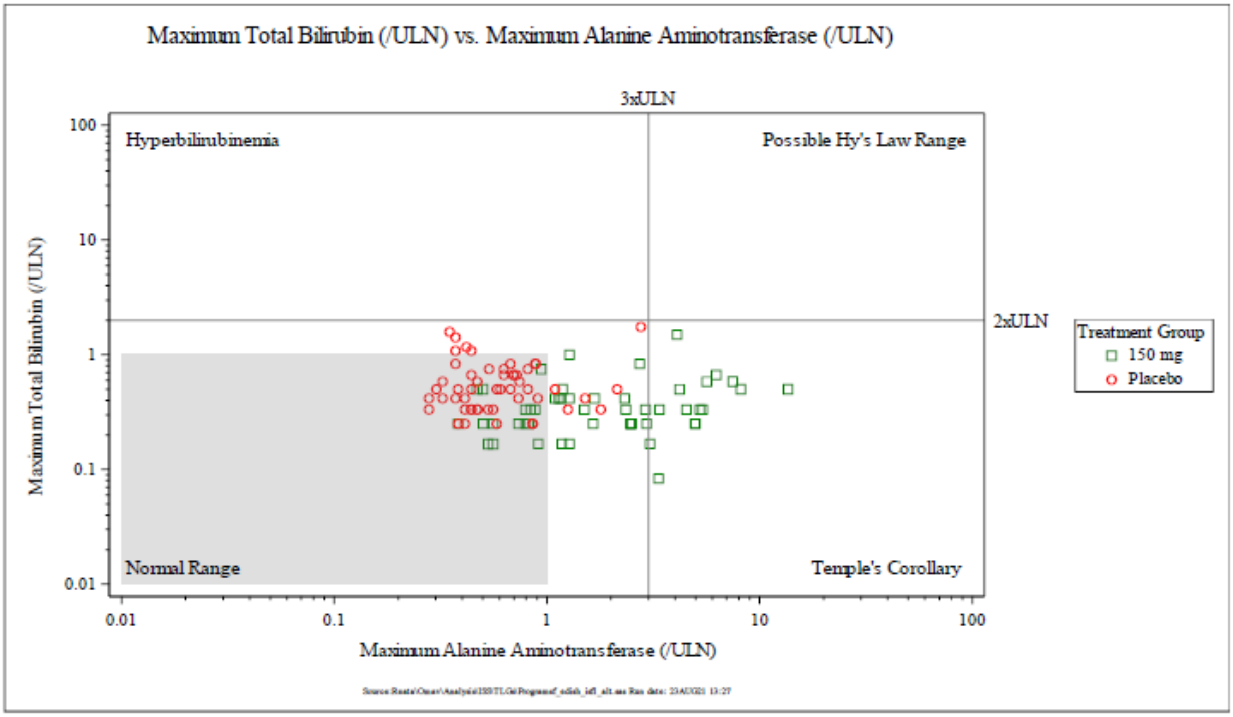


Abbreviation: lab=laboratory.
Timepoints with a single observation are not shown.

One omaveloxolone-treated patient had ALT values ≥10× ULN. The patient discontinued study drug due to protocol-specified criteria.

Increases in ALT were asymptomatic and not associated with increases in total bilirubin. As shown in Figure 47 (eDISH plot), none of the omaveloxolone-treated patients had maximum ALT or total bilirubin values that met potential Hys law criteria (ie, ALT ≥3× ULN and total bilirubin >2× ULN).

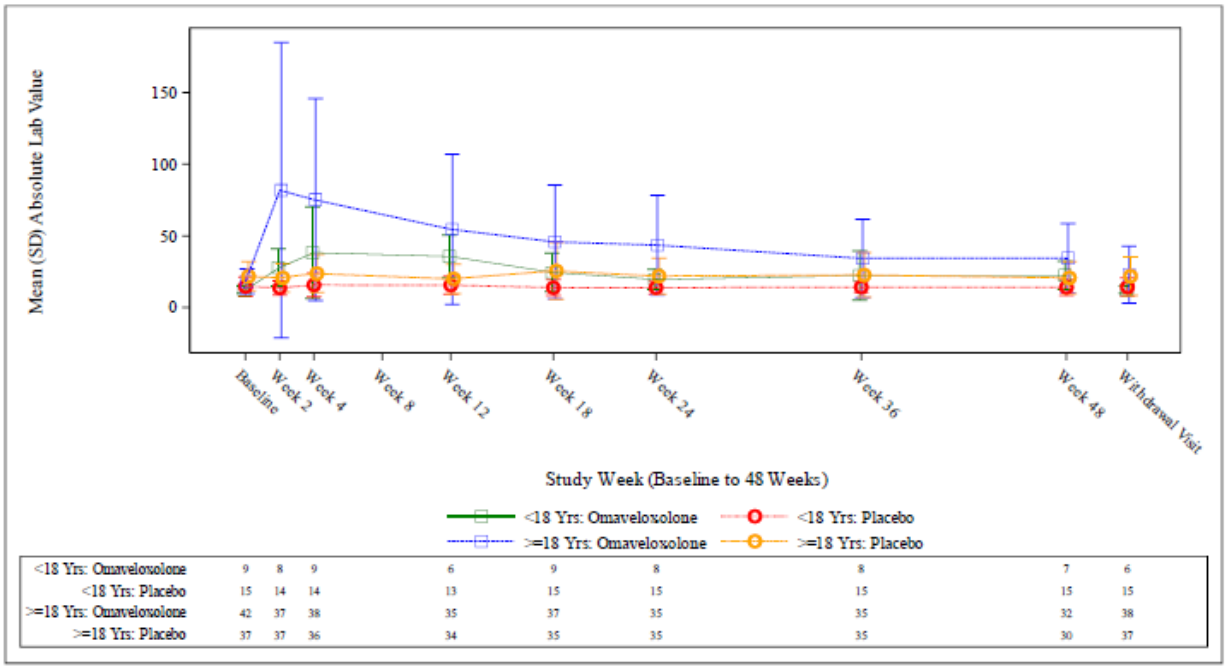
Figure 42: Maximum total bilirubin versus maximum alanine aminotransferase (primary placebo-controlled analysis set A)



Abbreviation: ULN=upper limit of normal.
Values shown are the maximum postreatment values per patient in the double-blind period. Values for each parameter do not necessarily occur concurrently.

As shown in Figure 43, adolescent patients had similar transient increases in ALT, but the magnitude of increases was less than that observed in the adult population.

Figure 43: Mean absolute alanine aminotransferase levels (U/L) by age group, baseline to week 48 (primary placebo-controlled analysis set A)

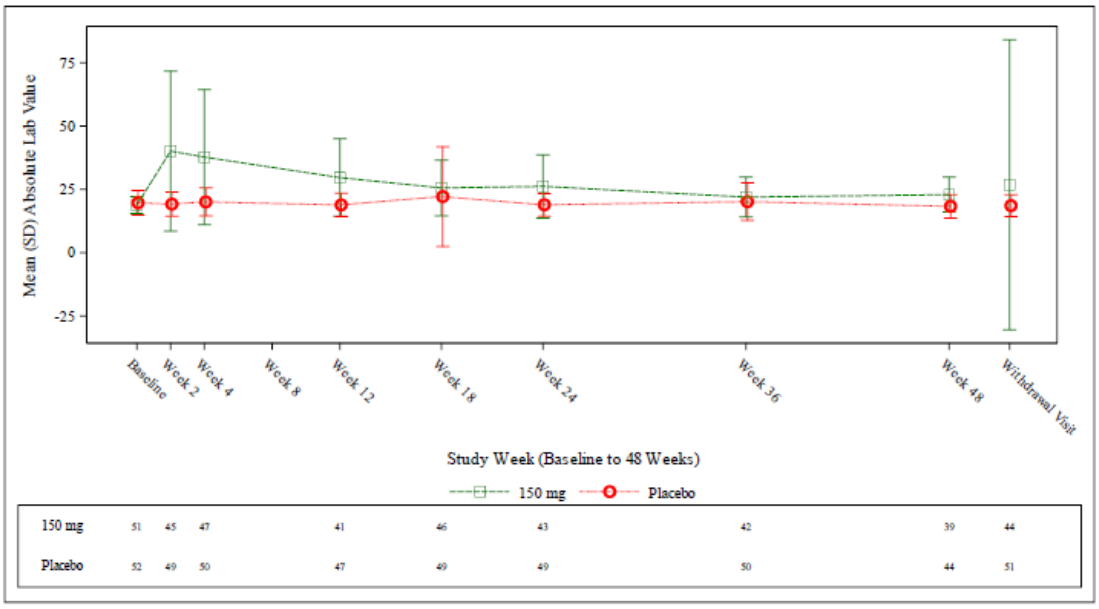


Abbreviations: Lab=laboratory; Yrs=years.
Age group was based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Aspartate aminotransferase

In omaveloxolone-treated patients, peak elevations in serum AST were observed at Week 2, with values decreasing toward baseline values through Week 48. In contrast, serum AST concentrations in placebo-treated patients remained unchanged throughout the 48-week treatment period, with mean serum AST concentrations remaining below 25 U/L (Figure 49). Increases in AST with omaveloxolone treatment appeared reversible, with mean serum AST concentrations near-baseline values within 4 weeks following drug withdrawal.

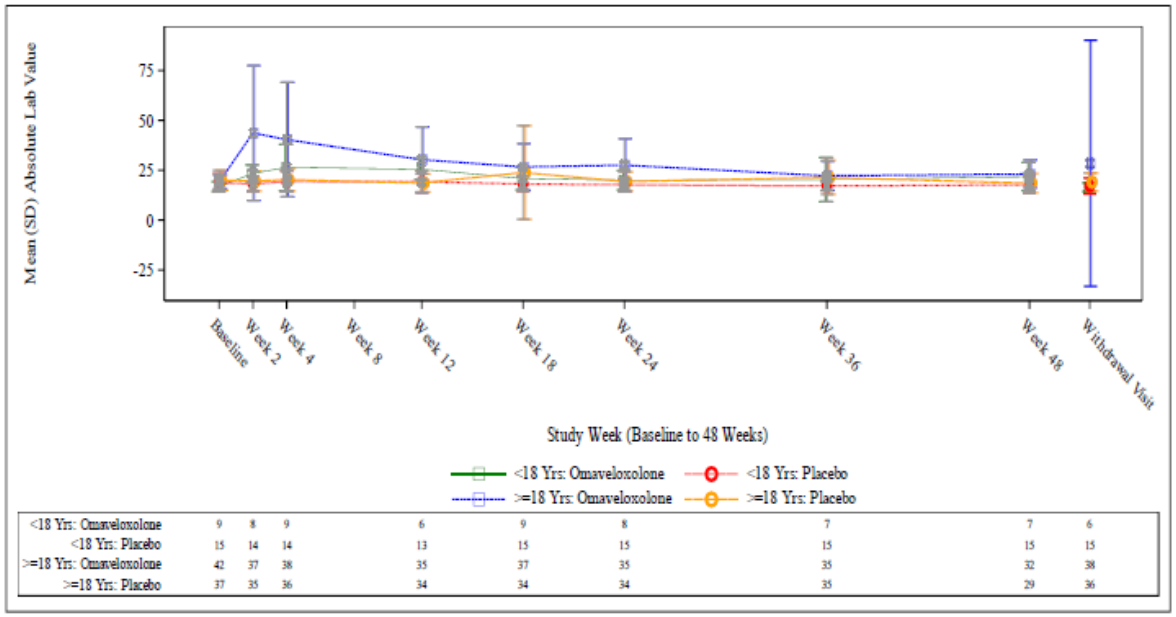
Figure 44: Mean absolute aspartate aminotransferase levels (U/L) baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

As shown in Figure 45, adolescent patients also had transient increases in AST, but the magnitude of increases was smaller than that observed in the adult population.

Figure 45: Mean absolute aspartate aminotransferase levels (U/L) by age group, baseline to week 48 (primary placebo-controlled analysis set A)

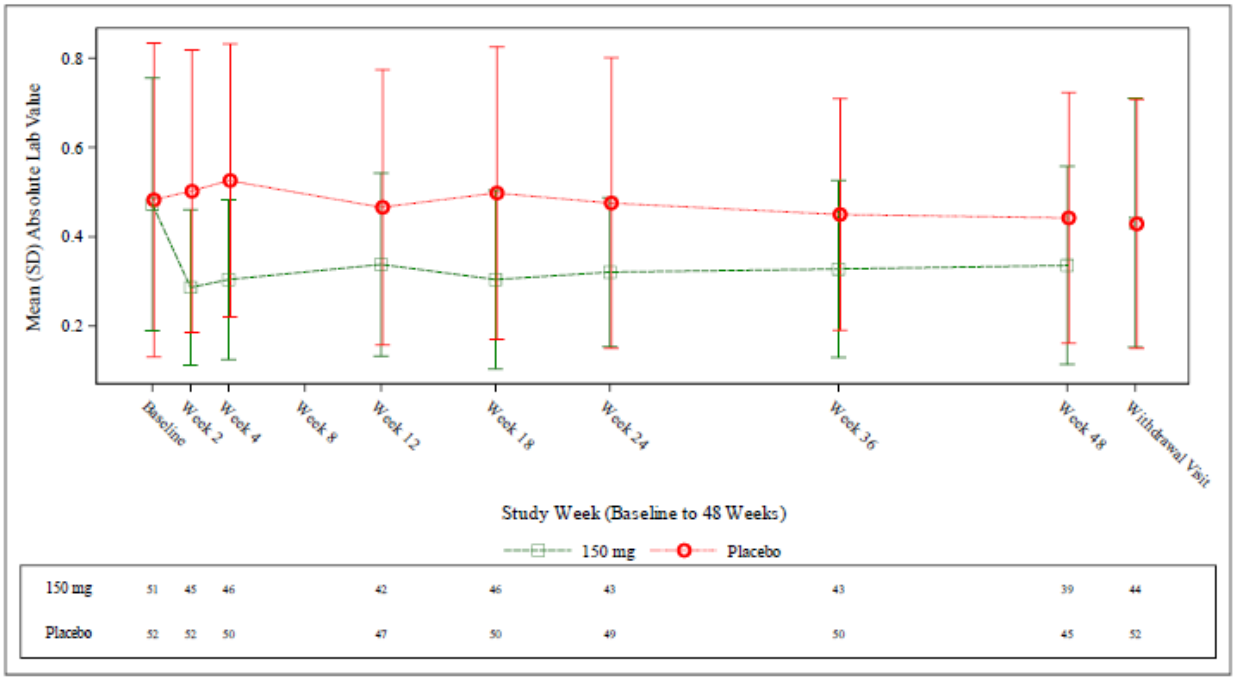


Abbreviations: Lab=laboratory; Yrs=years.
Age group was based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Total bilirubin

In omaveloxolone-treated patients, mean decreases from baseline in total bilirubin were observed (Figure 46). The modest decreases in total bilirubin were apparent within the first few weeks after treatment initiation, remained lower than baseline values through Week 48, and returned to baseline after drug withdrawal. In contrast, mean serum total bilirubin in placebo-treated patients remained unchanged throughout the 48-week treatment period.

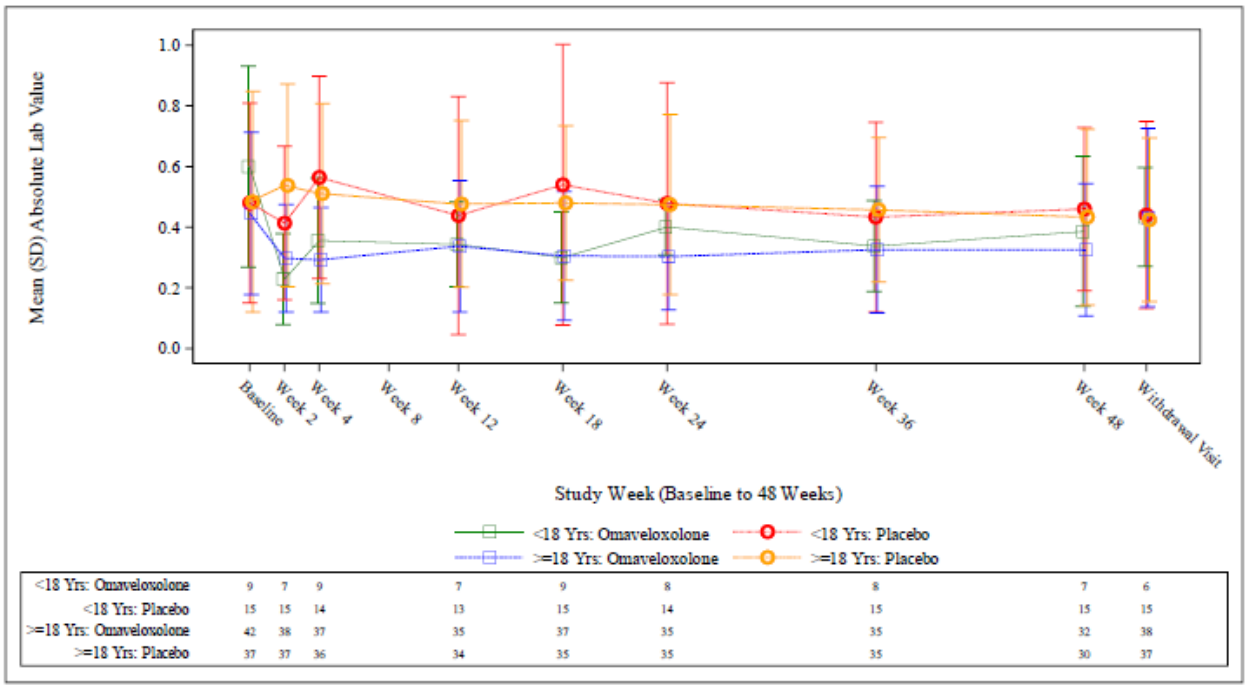
Figure 46: Mean absolute bilirubin levels (mg/dL) baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

As shown in Figure 47, adolescent patients treated with omaveloxolone also had similar decreases in total bilirubin but to a smaller extent than the adult population and had mean total bilirubin values that were similar to placebo-treated adolescent patients at Week 48.

Figure 47: Mean absolute bilirubin levels (mg/dL) by age group, baseline to week 48 (primary placebo-controlled analysis set A)



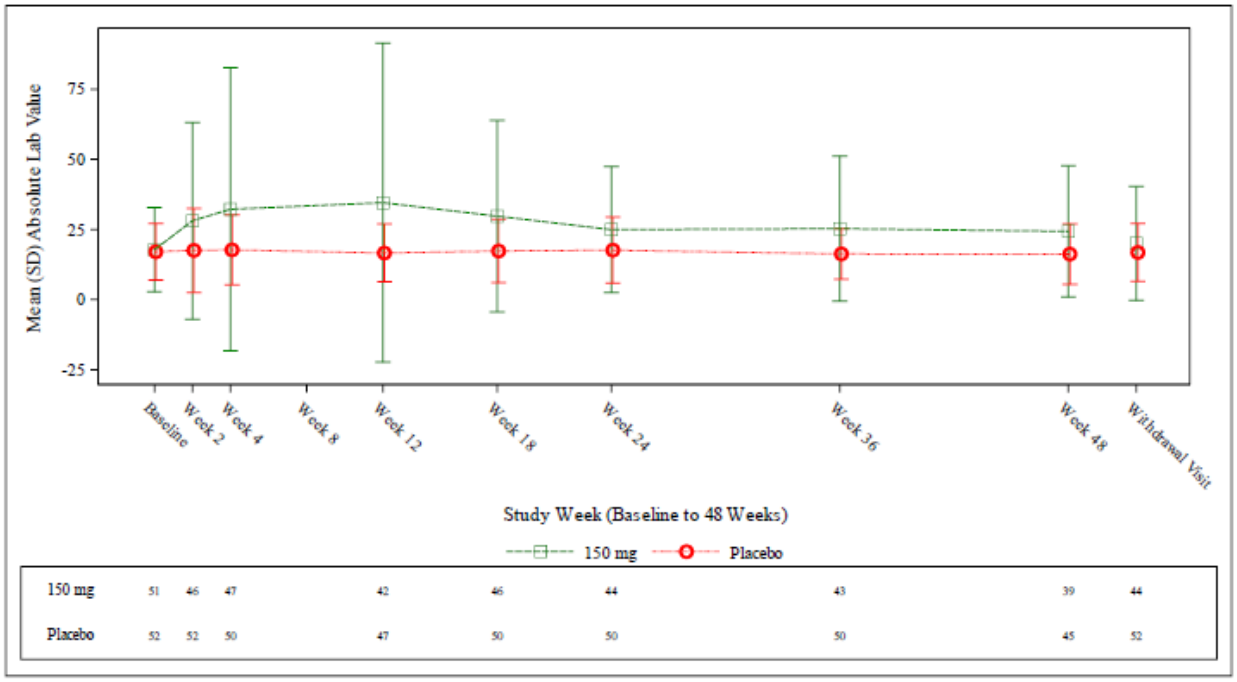
<18 Yrs: Omaveloxolone	9	7	9	7	9	8	8	7	6
<18 Yrs: Placebo	15	15	14	13	15	14	15	15	15
>=18 Yrs: Omaveloxolone	42	38	37	35	37	35	35	32	38
>=18 Yrs: Placebo	37	37	36	34	35	35	35	30	37

Abbreviation: Lab=laboratory; Yrs=years.
Age group was based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Gamma-glutamyl transferase

In omaveloxolone-treated patients, mean elevations in serum GGT were observed beginning at Week 2 that remained between 25 and 35 U/L throughout Week 48 of therapy. In contrast, mean serum GGT concentrations in placebo-treated patients did not vary throughout the 48-week treatment period (16 and 17 U/L), with mean serum GGT concentrations remaining below 25 U/L. Mean GGT values returned to baseline within 4 weeks following drug withdrawal.

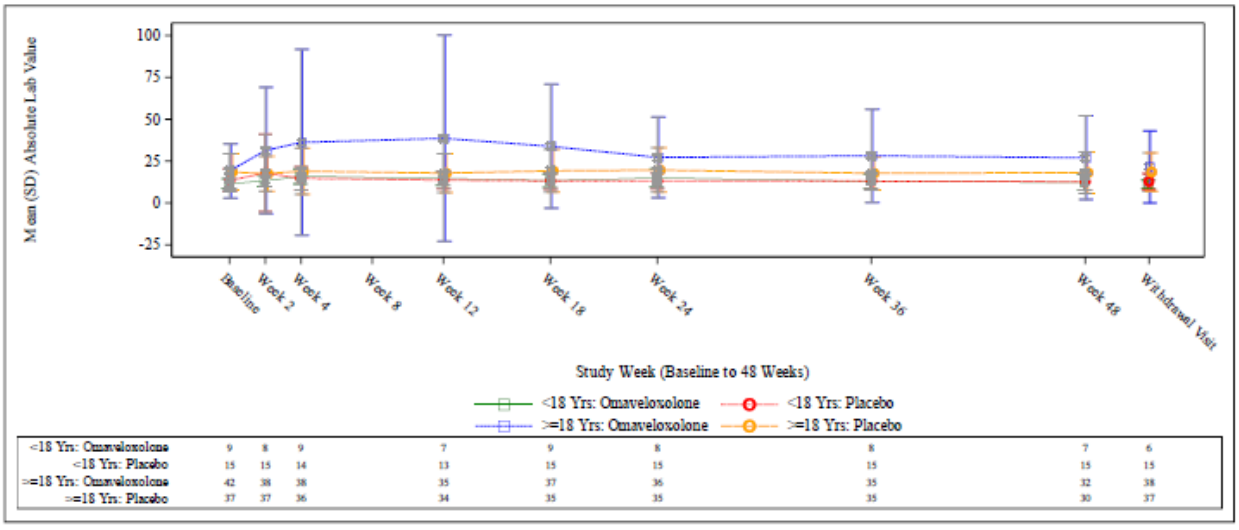
Figure 48: Mean gamma glutamyl transferase levels (U/L) baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

As shown in Figure 49, adolescent patients had slight increases in GGT due to omaveloxolone treatment, but to a smaller extent than the adult population. Only 1 omaveloxolone-treated adolescent patient had an increase in GGT > ULN.

Figure 49: Mean gamma glutamyl transferase levels (U/L) by age group, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviations: Lab=laboratory; Yrs=years.
Age group is based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Treatment-emergent adverse events related to hepatic safety in analysis set A

Table 56 summarises the TEAEs related to hepatic safety by system organ class (SOC) and preferred term (PT) in Analysis Set A.

Table 56: Summary of hepatic treatment-emergent adverse events by systemic organ class and preferred term (primary placebo-controlled analysis set A)

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Investigations		
Alanine aminotransferase increased	19 (37.3%)	1 (1.9%)
Aspartate aminotransferase increased	11 (21.6%)	1 (1.9%)
Gamma-glutamyltransferase increased	3 (5.9%)	0
Hepatobiliary disorders		
Cholelithiasis	1 (2.0%)	0
Gallbladder disorder	0	1 (1.9%)
Hepatic steatosis	1 (2.0%)	0

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities.
Adverse event terms were mapped according to MedDRA v_21.1.

Analysis Set C

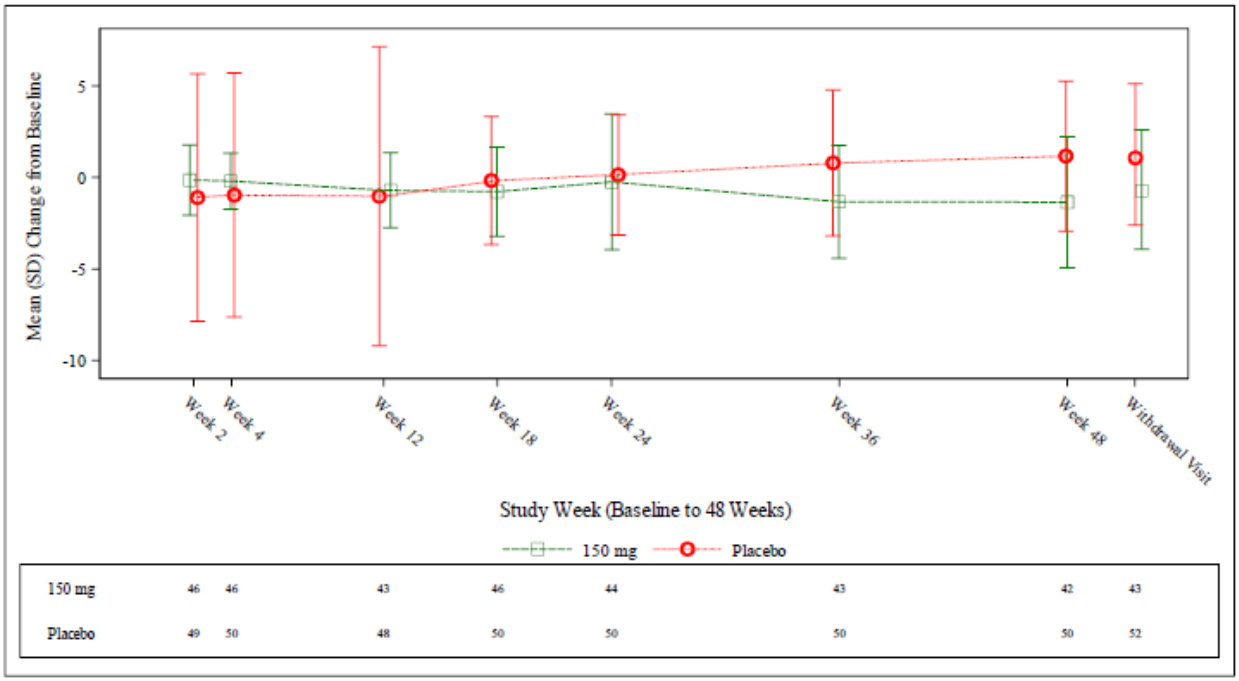
Similar safety profile is observed in Analysis Set C.

[B] Evaluation of Weight

Results of Weight Evaluation in Analysis Set A

Mean changes from baseline in weight in Analysis Set A are shown in Figure 50. Omaveloxolone-treated patients had a small mean decrease in weight relative to baseline at Week 48.

Figure 50: Mean change from baseline to week 48 in weight (kg) (primary placebo-controlled analysis set A)

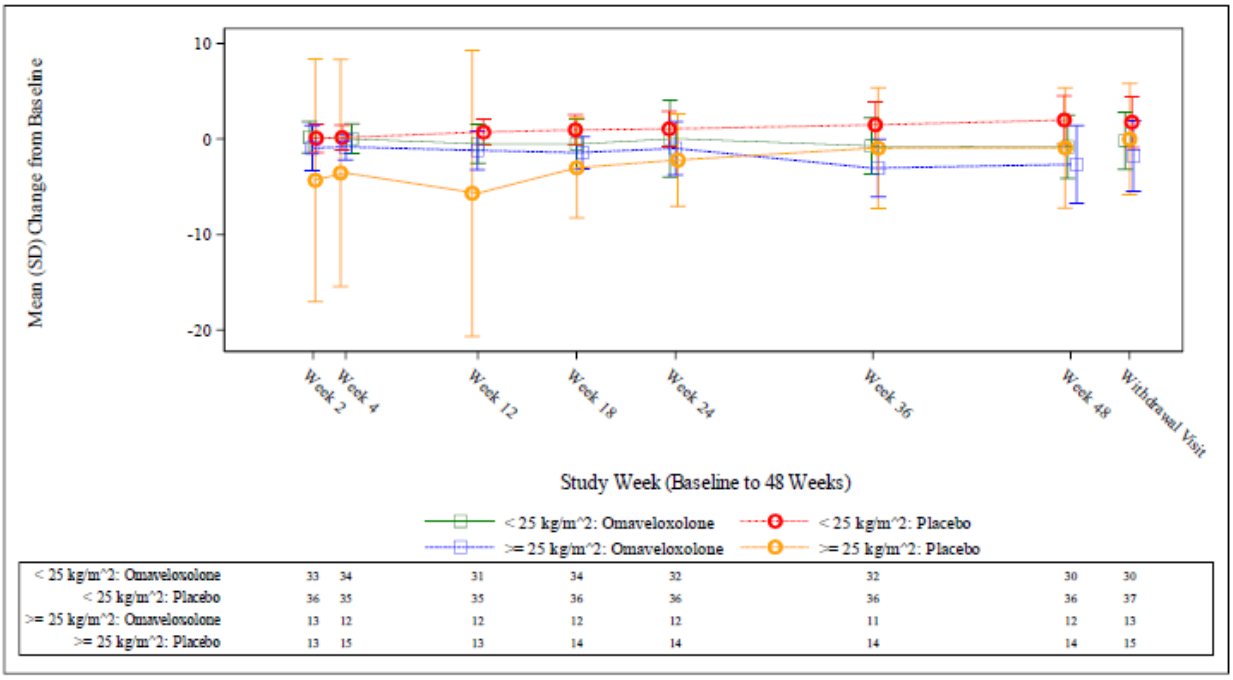


Analysis Set A Subgroups

Baseline Body Mass Index

Additional analysis of weight change by baseline BMI subgroups shows that the mean decreases in weight over 48 weeks were more pronounced in omaveloxolone-treated patients who were overweight at baseline (BMI ≥25 kg/m2) (Figure 51).

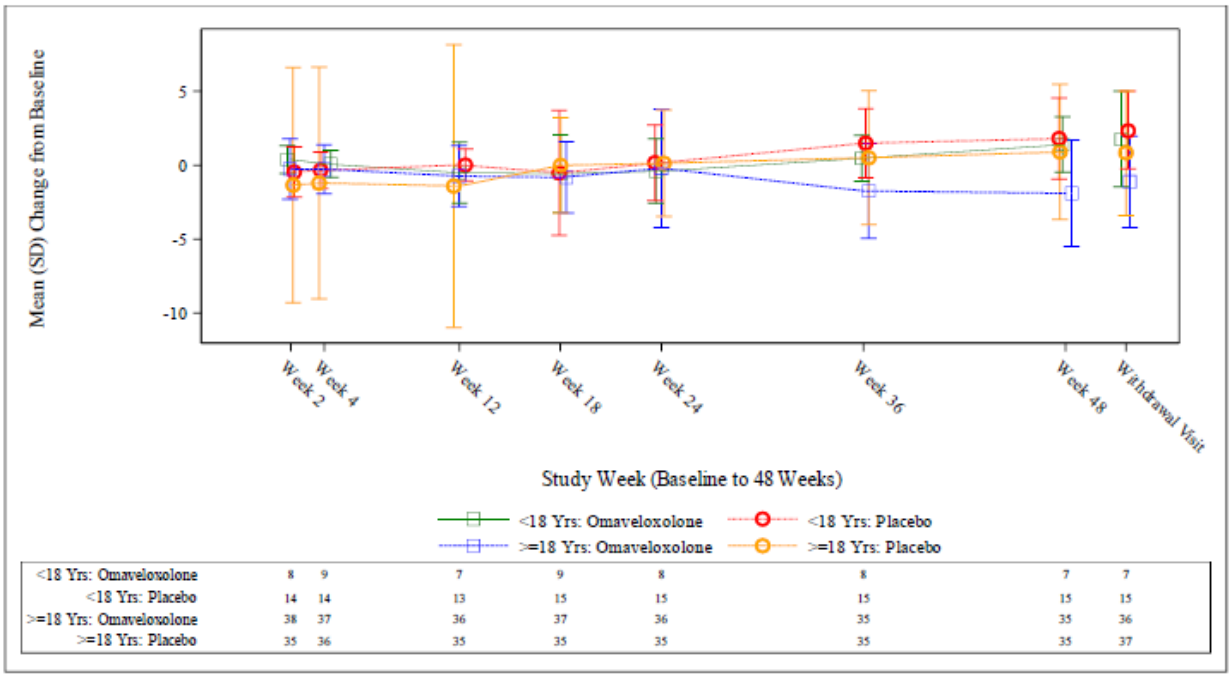
Figure 51: Mean change from baseline to week 48 in weight (kg) by baseline body mass index (primary placebo-controlled analysis set A)



Age

Analysis by age subgroup showed that the mean decreases in weight were not observed among adolescent patients over the 48-week treatment period (Figure 52). The mean changes in weight for adolescent patients treated with omaveloxolone were similar to that of adolescent patients treated with placebo.

Figure 52: Mean Change from baseline to week 48 in weight (kg) by baseline age (primary placebo-controlled analysis set A)

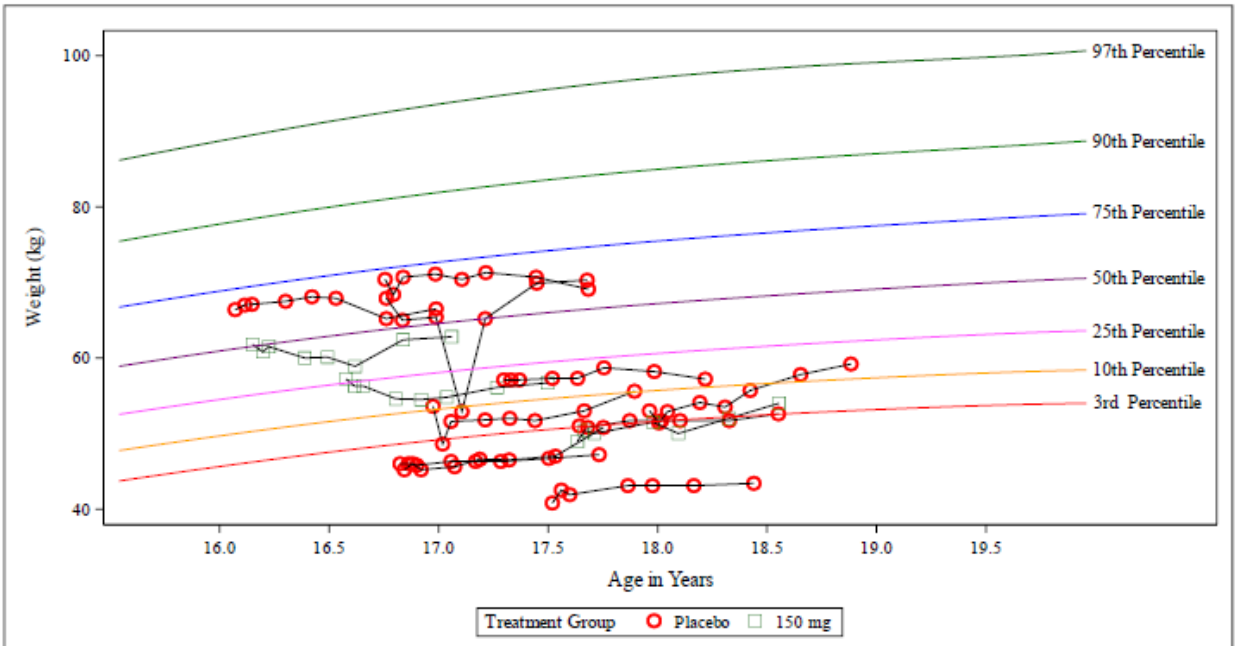


Age group is based on age at first Double-blind treatment.

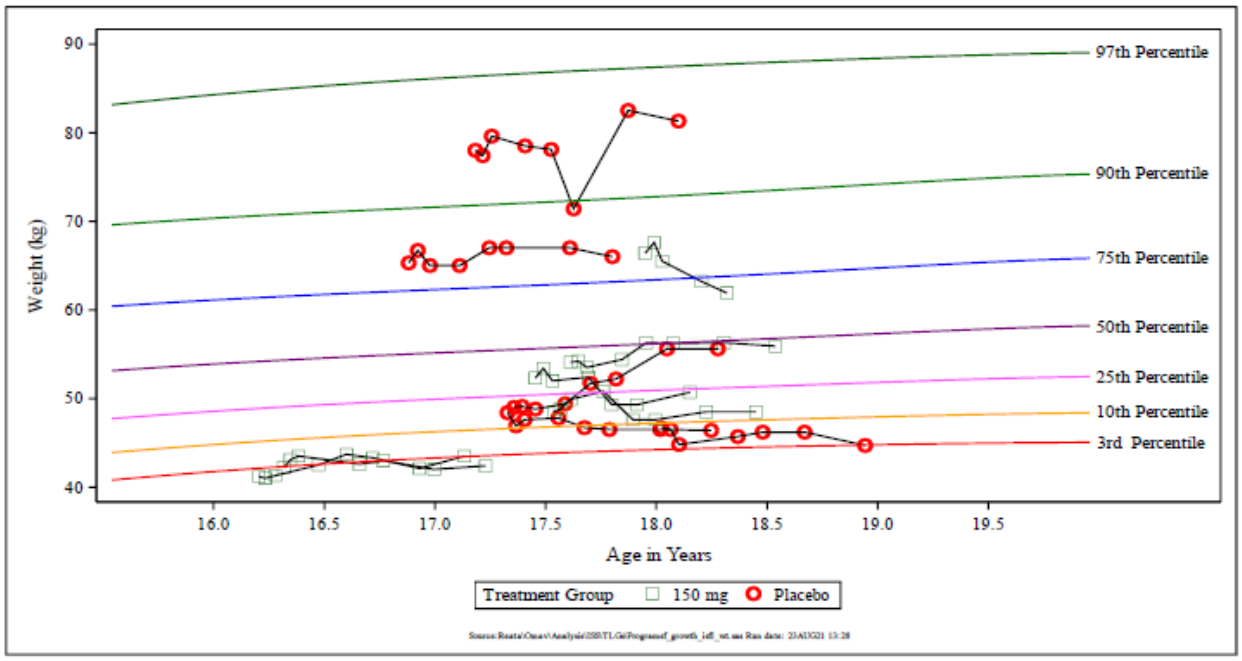
In addition, adolescent patients generally continued along their growth curves for weight during treatment with omaveloxolone (Figure 53), and no patient declined 2 standard deviations in weight along the normal growth curves.

Figure 53: Scatter plot of weight (kg) for adolescent patients (primary placebo-controlled analysis set A)

Male Adolescent Patients



Female Adolescent Patients

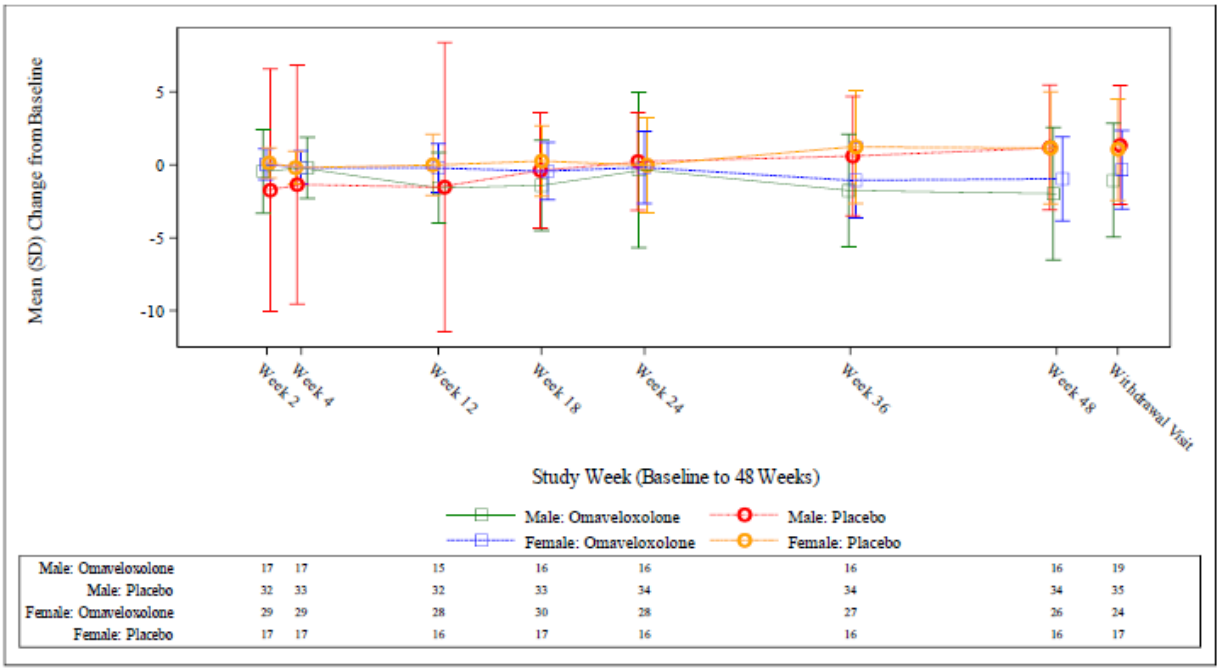


Reference lines for percentiles are taken from Centers for Disease Control and Prevention National Center for Health Statistics: https://www.cdc.gov/growthcharts/percentile_data_files.htm
Adolescent was defined as age <18 years, based on age at first treatment in the double-blind study. Figure shows all double-blind data through age 20.

Sex

Analysis of weight change from baseline by sex is shown in Figure 54.

Figure 54: Mean Change from baseline to week 48 in weight (kg) by baseline sex (primary placebo-controlled analysis set A)



Analysis Set C

Similar safety profile is observed in Analysis Set C.

[C] Evaluation of Infections and Infestations

Preferred terms within the Infections and infestations SOC were assessed as TEAEs of interest based on standard drug registration topics and due to the hypothetical concern, that the anti-inflammatory effects associated with Nrf2 activation may lead to a decreased innate immune response.

Treatment-Emergent Infections and Infestations in Analysis Set A

TEAEs in the Infections and infestations SOC for Analysis Set A are presented in Table 57.

Table 57: Summary of infections and infestations treatment-emergent adverse events (primary placebo-controlled analysis set A)

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Infections and infestations	**34 (66.7%)**	**30 (57.7%)**
Upper respiratory tract infection	14 (27.5%)	15 (28.8%)
Nasopharyngitis	7 (13.7%)	11 (21.2%)
Influenza	7 (13.7%)	2 (3.8%)
Urinary tract infection	4 (7.8%)	0
Gastroenteritis viral	3 (5.9%)	1 (1.9%)
Viral upper respiratory tract infection	2 (3.9%)	1 (1.9%)
Conjunctivitis	2 (3.9%)	0
Sinusitis	1 (2.0%)	2 (3.8%)
Pharyngitis streptococcal	1 (2.0%)	1 (1.9%)
Bronchitis	1 (2.0%)	0
Furuncle	1 (2.0%)	0

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Hordeolum	1 (2.0%)	0
Laryngitis	1 (2.0%)	0
Lower respiratory tract infection	1 (2.0%)	0
Nail bed infection	1 (2.0%)	0
Oral herpes	1 (2.0%)	0
Pilonidal cyst	1 (2.0%)	0
Pneumonia	1 (2.0%)	0
Rash pustular	1 (2.0%)	0
Respiratory tract infection	1 (2.0%)	0
Tinea pedis	1 (2.0%)	0
Tonsillitis	1 (2.0%)	0
Respiratory tract infection viral	0	2 (3.8%)
Rhinitis	0	2 (3.8%)
Viral infection	0	2 (3.8%)
Cellulitis	0	1 (1.9%)
Cystitis	0	1 (1.9%)
Ear infection	0	1 (1.9%)
Gastroenteritis	0	1 (1.9%)
Otitis externa	0	1 (1.9%)
Pharyngitis	0	1 (1.9%)

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities
Adverse event terms were mapped according to MedDRA v 21.1. Patients were counted only once for each preferred term.

Two serious adverse event (SAEs) in the Infections and infestations SOC were reported in Analysis Set A, 1 event of laryngitis and 1 event of viral upper respiratory tract infection that were experienced in the same patient and were considered to be unlikely related to study drug and the study drug was not change after any of the SAEs.

No patients in either treatment group discontinued because of to TEAEs in the Infections and infestations SOC.

Treatment-Emergent Infections and Infestations for Analysis Set C

Table 58: Summary of infections and infestations treatment-emergent adverse events in > 2 patients (Friedreich Ataxia Overall Omaveloxolone Exposure integrated analysis set C)

System Organ Class Preferred Term	Omaveloxolone 150/160 mg (N=159)	Omaveloxolone All Treated (N=165)
Infections and infestations	**100 (62.9%)**	**111 (67.3%)**
Upper respiratory tract infection	35 (22.0%)	51 (30.9%)
Corona virus infection	28 (17.6%)	28 (17.0%)
Nasopharyngitis	23 (14.5%)	28 (17.0%)
Influenza	15 (9.4%)	15 (9.1%)
Urinary tract infection	13 (8.2%)	14 (8.5%)
Gastroenteritis viral	6 (3.8%)	7 (4.2%)
Sinusitis	6 (3.8%)	6 (3.6%)
Bronchitis	4 (2.5%)	4 (2.4%)
Rhinitis	3 (1.9%)	4 (2.4%)
Viral upper respiratory tract infection	3 (1.9%)	4 (2.4%)
Viral infection	3 (1.9%)	3 (1.8%)

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities
Adverse event terms were mapped according to MedDRA v21.1.
Some patients may be represented in multiple columns if they changed dose level when entering Study 1402 Extension. Each column reflects number of unique patients. Events were counted within the treatment group at the start of the event.

A majority of the TEAEs were considered mild to moderate in severity for omaveloxolone-treated patients. There were 4 severe TEAEs in the Infections and infestations SOC.

[D] Evaluation of Cardiovascular Safety

Cardiovascular safety was evaluated as cardiomyopathy is the most common comorbid condition for patients with FA. In these patients, heart failure and arrhythmia are the top causes of death. In an early study with another NrF2 activator, bardoxolone methyl, congestive heart failure was observed. However, that study population was patients with type 2 diabetes mellitus and advanced chronic kidney disease (Stage 4 CKD). The risk factors for heart failure in that study were identified and used as population selection criteria to mitigate cardiovascular risk in patients our subsequent studies with NrF2 activators. Elevated baseline BNP and prior hospitalisation for heart failure are among the major risk factors identified for the events (Chin, 2014). Patients with FA who had mild to moderate cardiomyopathy were allowed in Study 1402 Part 1, Study 1402 Part 2, and Study 1402 Extension; signs and symptoms of heart failure were closely monitored during the studies.

Lipid changes were evaluated because of observed LDL increases and high-density lipoprotein (HDL) decreases in omaveloxolone treated patients from baseline and relative to placebo. The observed lipid changes with omaveloxolone may be explained by Nrf2-dependent regulation of cholesterol synthesis. Genetic and pharmacologic activation of Nrf2 has been shown to increase serum cholesterol in animal models (Zhang, 2012). Mechanistically, Nrf2 influences several factors that may impact cholesterol synthesis including fatty acid oxidation, NADPH production, and redox balance.

Cardiovascular Safety Evaluation in Analysis Set A

Blood Pressure

Mean changes from baseline to Week 48 in SBP are shown in Figure 55, and mean changes from baseline to Week 48 in DBP are shown in Figure 56.

Figure 55: Mean Change from baseline to week 48 in systolic blood pressure (mmHg) (primary placebo-controlled analysis set A)

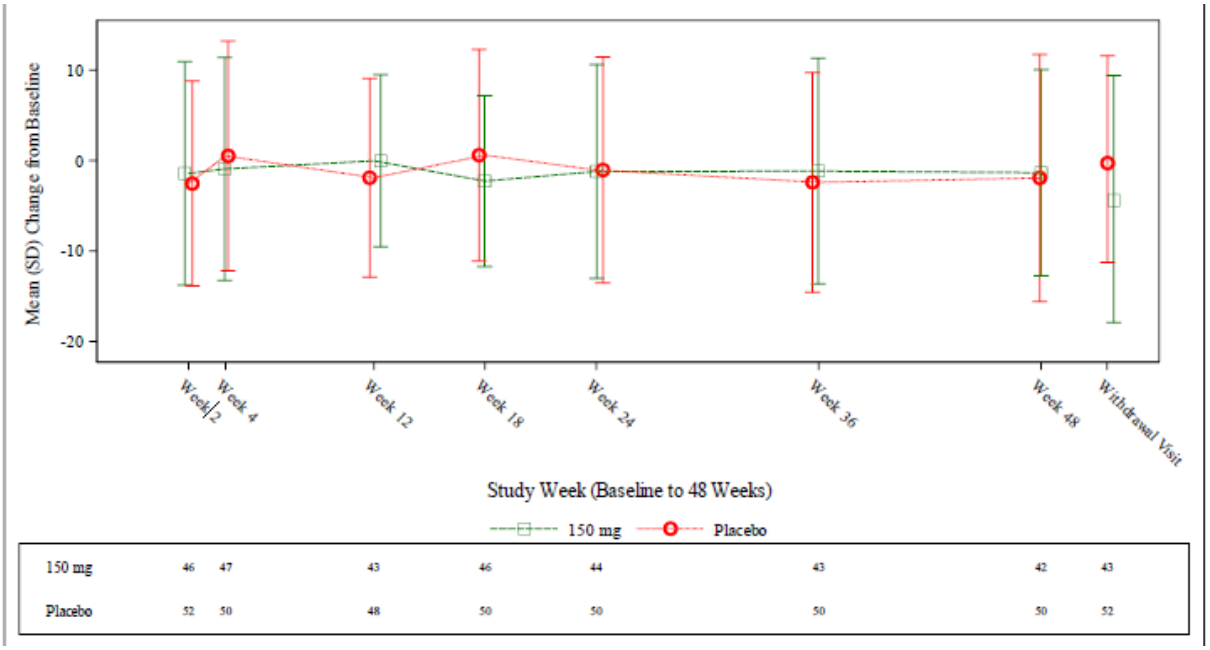


Figure 56: Mean Change from baseline to week 48 in diastolic blood pressure (mmHg) (primary placebo-controlled analysis set A)

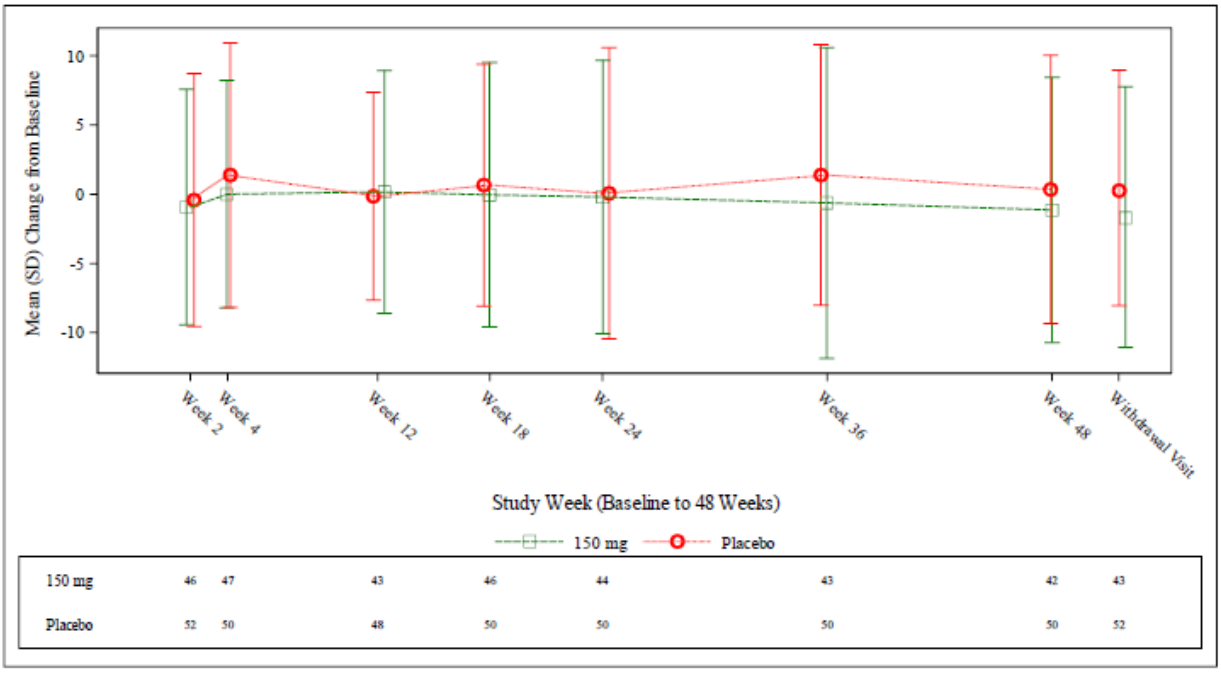


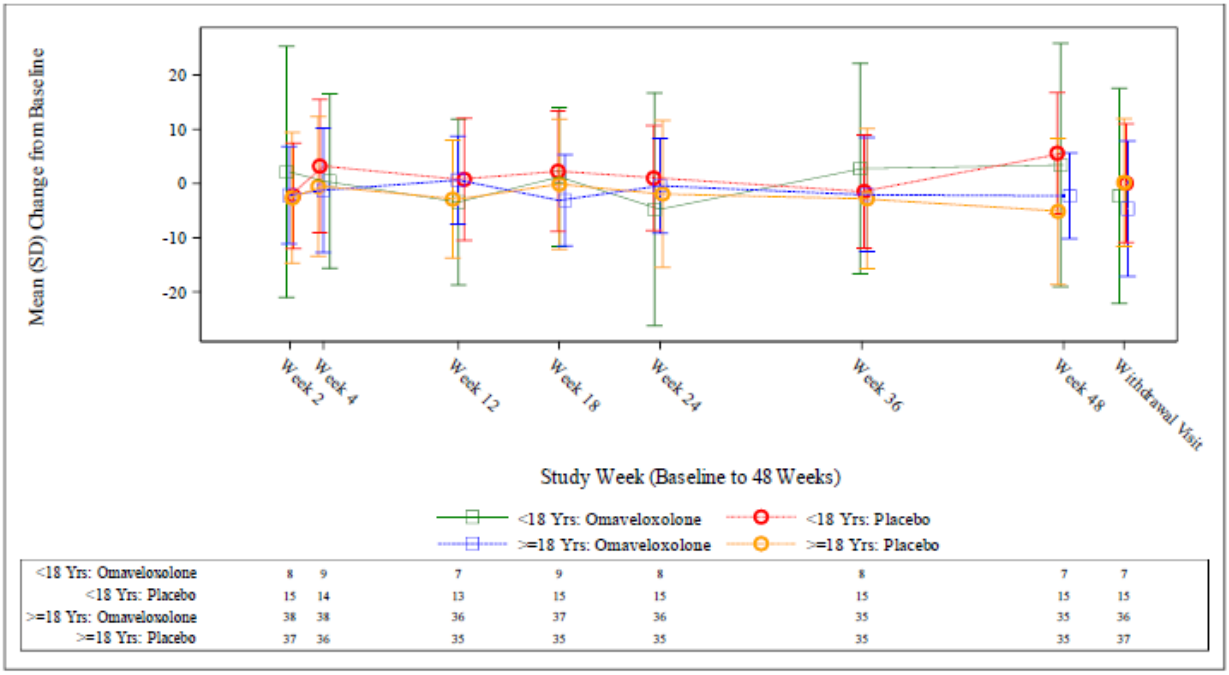
Table 59: Summary of categorical shifts for on-treatment systolic and diastolic blood pressure values (primary placebo-controlled analysis set A)

Parameter/Baseline Category	Number (%) of Patients - Maximum On-Treatment Category				
	Omaveloxolone (N=51)				
Systolic Blood Pressure	**<90 mmHg**	**≥90 mmHg- 120 mmHg**	**>120 mmHg- 140 mmHg**	**>140 mmHg- 160 mmHg**	**>160 mmHg**
<90 mmHg	0	0	0	0	0
≥90 mmHg to 120 mmHg	0	15 (29.4%)	16 (31.4%)	1 (2.0%)	0
>120 mmHg to 140 mmHg	0	0	11 (21.6%)	5 (9.8%)	0
>140 mmHg to 160 mmHg	0	0	1 (2.0%)	1 (2.0%)	0
>160 mmHg	0	0	0	0	0
Diastolic Blood Pressure	**<50 mmHg**	**≥50 mmHg- 80 mmHg**	**>80 mmHg- 90 mmHg**	**>90 mmHg- 100 mmHg**	**>100 mmHg**
<50 mmHg	0	0	0	0	0
≥50 mmHg to 80 mmHg	0	23 (45.1%)	15 (29.4%)	1 (2.0%)	0
>80 mmHg to 90 mmHg	0	3 (5.9%)	5 (9.8%)	1 (2.0%)	0
>90 mmHg to 100 mmHg	0	0	1 (2.0%)	1 (2.0%)	0
>100 mmHg	0	0	0	0	0
	Placebo (N=52)				
Systolic Blood Pressure	**<90 mmHg**	**≥90 mmHg- 120 mmHg**	**>120 mmHg- 140 mmHg**	**>140 mmHg- 160 mmHg**	**>160 mmHg**
<90 mmHg	0	0	0	0	0
≥90 mmHg to 120 mmHg	0	9 (17.3%)	16 (30.8%)	1 (1.9%)	0
>120 mmHg to 140 mmHg	0	2 (3.8%)	9 (17.3%)	11 (21.2%)	1 (1.9%)
>140 mmHg to 160 mmHg	0	0	0	2 (3.8%)	1 (1.9%)
>160 mmHg	0	0	0	0	0
Diastolic Blood Pressure	**<50 mmHg**	**≥50 mmHg- 80 mmHg**	**>80 mmHg- 90 mmHg**	**>90 mmHg- 100 mmHg**	**>100 mmHg**
<50 mmHg	0	0	0	0	0
≥50 mmHg to 80 mmHg	0	18 (34.6%)	17 (32.7%)	4 (7.7%)	1 (1.9%)
>80 mmHg to 90 mmHg	0	0	3 (5.8%)	6 (11.5%)	1 (1.9%)
>90 mmHg to 100 mmHg	0	0	1 (1.9%)	0	0
>100 mmHg	0	0	1 (1.9%)	0	0

Percentages are based on the number of expected observations per parameter per treatment group.
Patients with missing values for on-treatment systolic and diastolic blood pressure results are not presented in above table. See source for details.

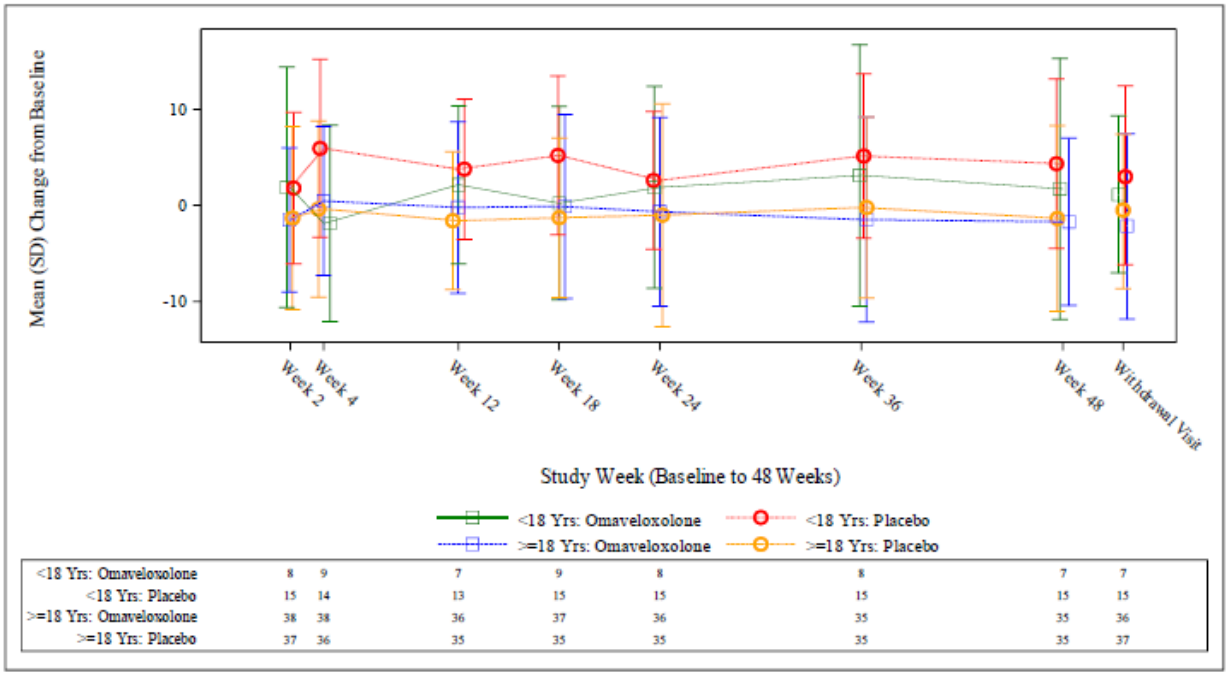
As shown in Figure 57 and Figure 58, on average, omaveloxolone-treated adolescent patients had modest increases from baseline in SBP and DBP at Week 48 relative to baseline, although the results were similar to placebo-treated adolescent patients.

Figure 57: Mean Change from baseline to week 48 in systolic blood pressure (mmHg) by age group (primary placebo-controlled analysis set A)



Age group is based on age at first double-blind treatment.

Figure 58: Mean Change from baseline to week 48 in diastolic blood pressure (mmHg) by age group (primary placebo-controlled analysis set A)

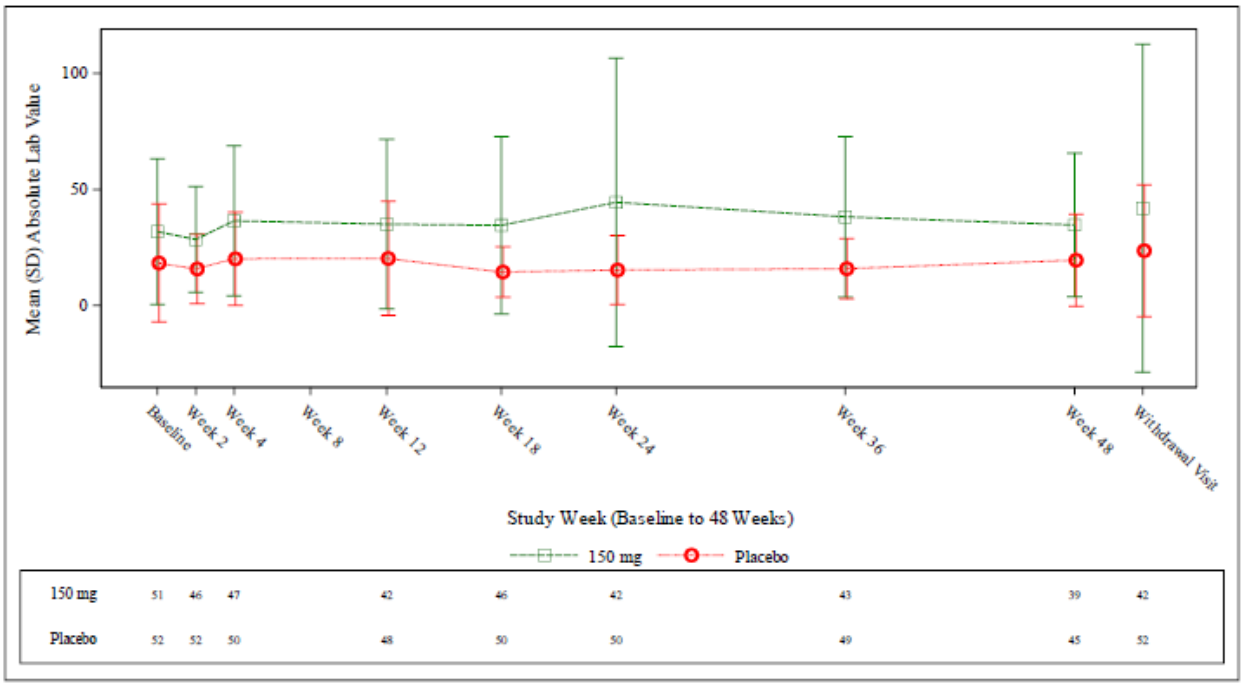


Age group is based on age at first double-blind treatment.

Brain Natriuretic Peptide

Small increases in BNP were observed with omaveloxolone treatment relative to placebo (Figure 59).

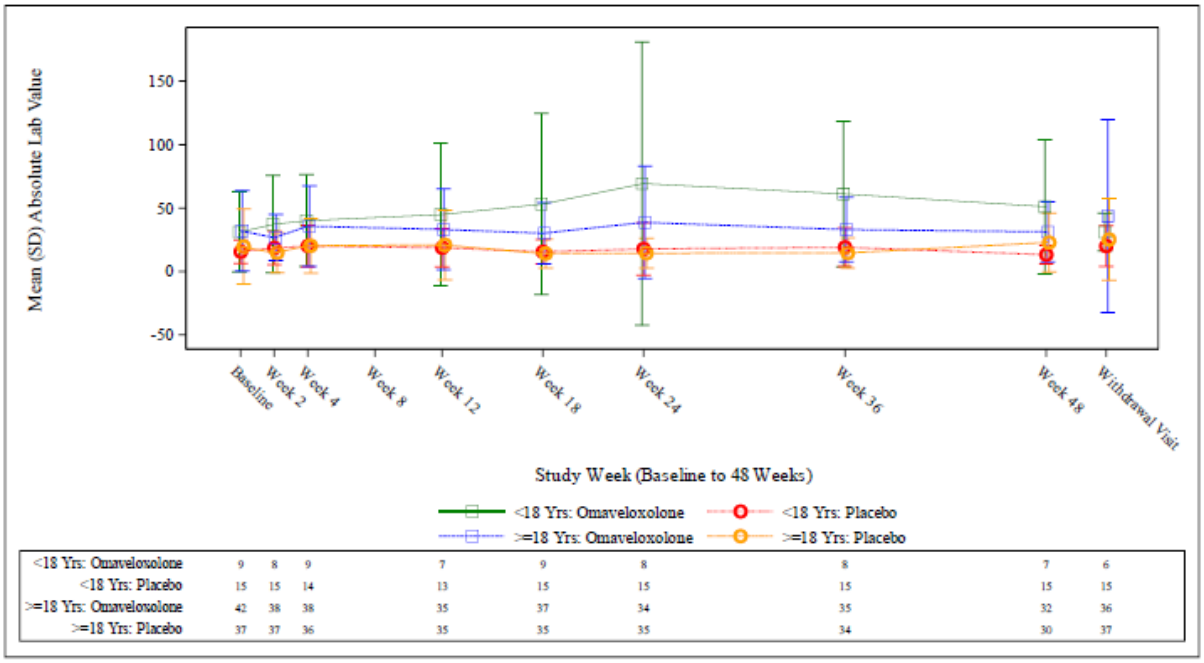
Figure 59: Mean absolute brain natriuretic peptide values (pg/ml) over time, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

Similarly, as shown in Figure 60, small numerical increases from baseline in BNP were also noted in omaveloxolone-treated adolescent patients at Week 48.

Figure 60: Mean absolute brain natriuretic peptide values (pg/ml) over time by age, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Age group was based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Serum Lipids

As shown in Table 60, omaveloxolone-treated patients had a higher incidence of total cholesterol and low-density lipoprotein (LDL) cholesterol values above the ULN. There was 1 TEAE of hypercholesterolemia reported in an omaveloxolone-treated patient.

Table 60: Treatment-emergent abnormal cholesterol values (primary placebo-controlled analysis set A)

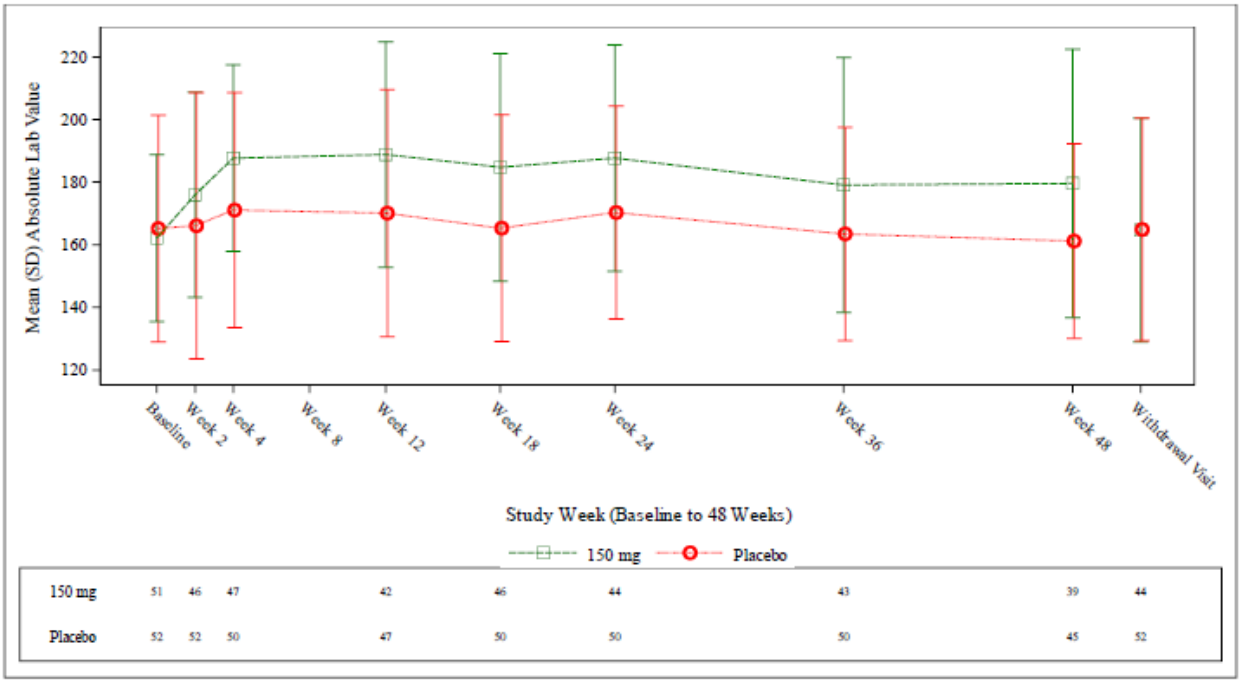
Laboratory Parameter	Abnormality Category	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Cholesterol (mg/dL)	Patients with normal baseline and at least 1 on-treatment value	45	44
	≥1 on-treatment low	3 (6.7%)	5 (11.4%)
	≥1 on-treatment high	15 (33.3%)	3 (6.8%)
	≥240 mg/dL	9 (20.0%)	3 (6.8%)
HDL cholesterol (mg/dL)	Patients with normal baseline and at least 1 on-treatment value	50	47
	≥1 on-treatment low	3 (6.0%)	2 (4.3%)
	≥1 on-treatment high	2 (4.0%)	7 (14.9%)
	<40 mg/dL	19 (38.0%)	14 (29.8%)
	≥60 mg/dL	12 (24.0%)	21 (44.7%)
LDL cholesterol (mg/dL)	Patients with normal baseline and at least 1 on-treatment value	42	44
	≥1 on-treatment low	4 (9.5%)	13 (29.5%)
	≥1 on-treatment high	8 (19.0%)	4 (9.1%)
	≥190 mg/dL	2 (4.8%)	1 (2.3%)
VLDL cholesterol (mg/dL)	Patients with normal baseline and at least 1 on-treatment value	43	46
	≥1 on-treatment low	0	0
	≥1 on-treatment high	16 (37.2%)	14 (30.4%)

Abbreviations: HDL=high-density lipoprotein; LDL=low-density lipoprotein; VLDL=very-low-density lipoprotein.
Percentages are based on the number of patients with normal baseline and at least 1 on-treatment observation. Normal reference ranges are listed in ISS Listing 16.16. Additional abnormality cutoffs for cholesterol ≥240 mg/dL, HDL cholesterol <40 mg/dL, HDL cholesterol ≥60 mg/dL, and LDL cholesterol ≥190 mg/dL are summarized.

Total Cholesterol

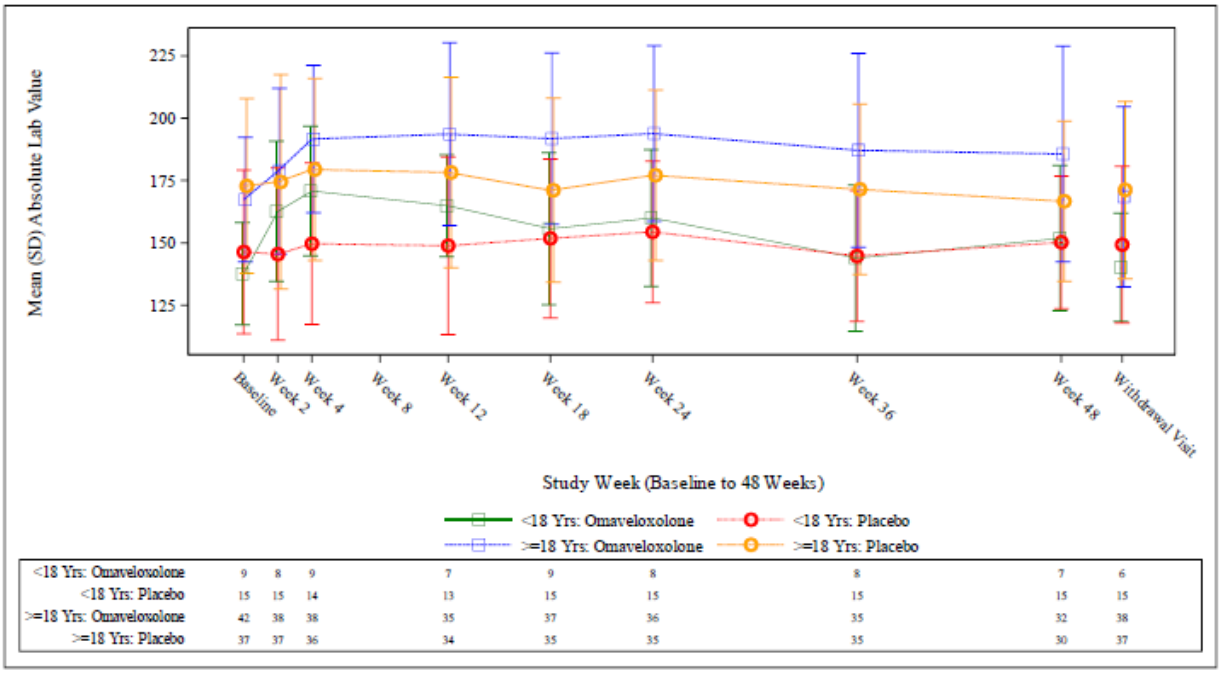
Mean absolute total cholesterol values over the 48-week treatment interval for Analysis Set A are shown in Figure 61. Adolescent patients had lower total cholesterol levels at baseline and throughout the study compared with adult patients, regardless of treatment and omaveloxolone-treated adolescent patients showed lower increases in total cholesterol at Week 48 than omaveloxolone-treated adult patients (Figure 62).

Figure 61: Mean absolute total cholesterol over time, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

Figure 62: Mean absolute total cholesterol over time by age group, baseline to week 48 (primary placebo-controlled analysis set A)

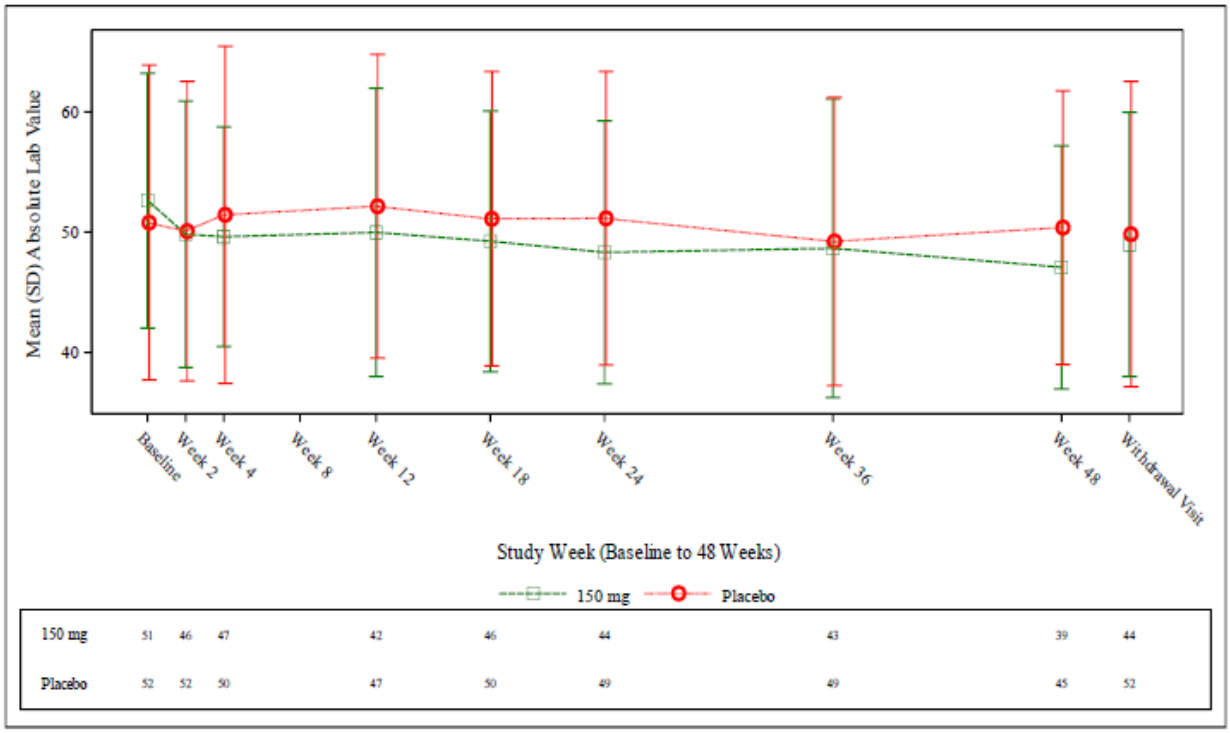


Abbreviation: Lab=laboratory.
Age group was based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

High-Density Lipoprotein Cholesterol

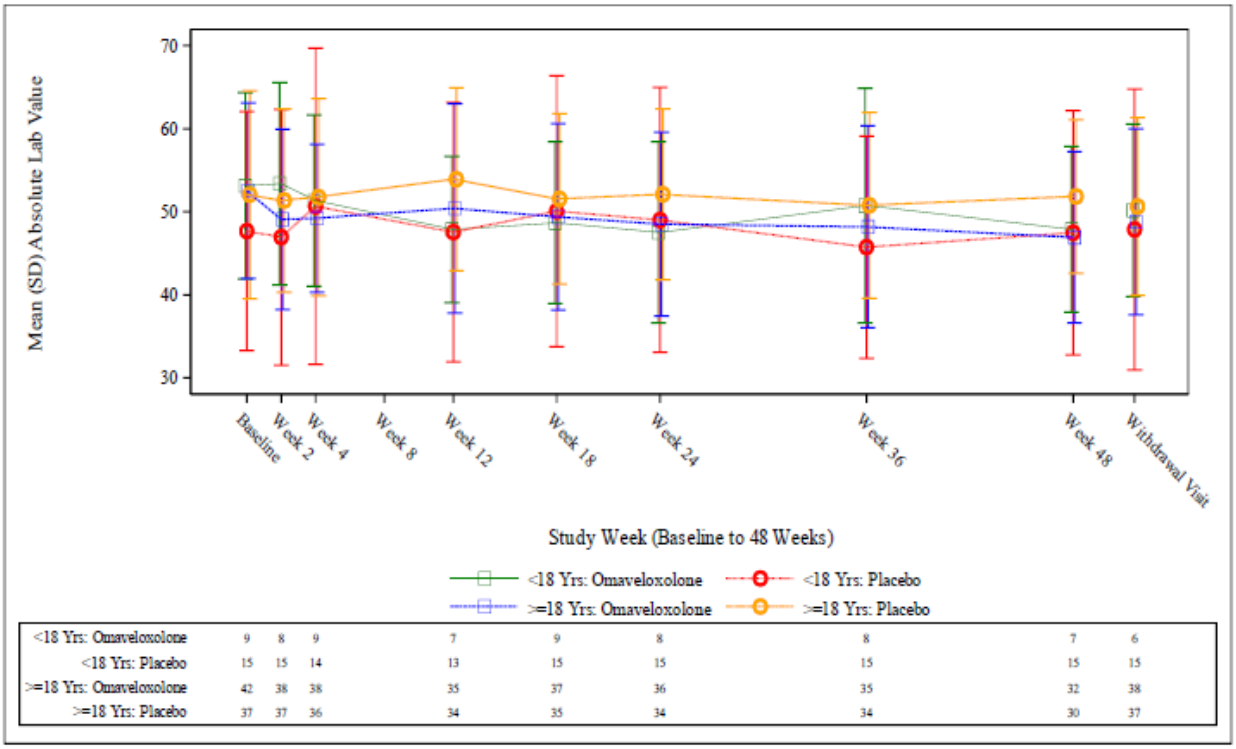
Mean HDL cholesterol values over the 48-week treatment interval for Analysis Set A are shown in Figure 63. Omaveloxolone-treated adolescent patients also showed reductions in HDL cholesterol at Week 48 that were similar to omaveloxolone-treated adult patients (Figure 64).

Figure 63: Mean absolute high-density lipoprotein cholesterol values over time, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

Figure 64: Mean absolute high-density lipoprotein cholesterol values over time by age group, baseline to week 48 (primary placebo-controlled analysis set A)

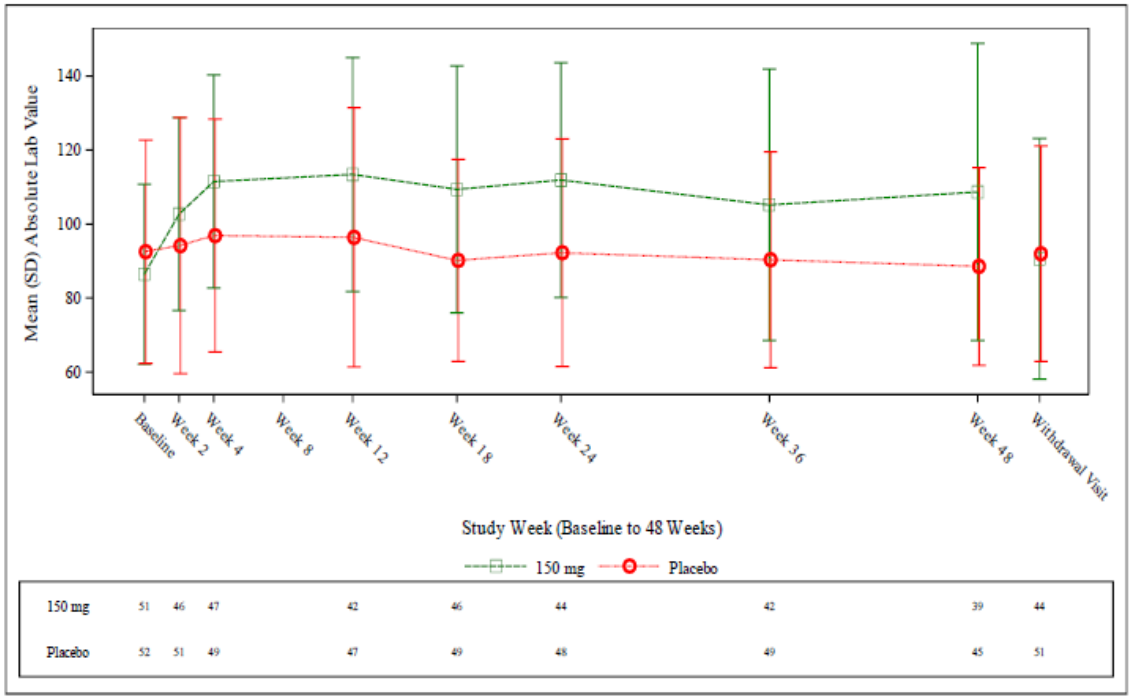


Abbreviation: Lab=laboratory.
Age group was based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Low-Density Lipoprotein Cholesterol

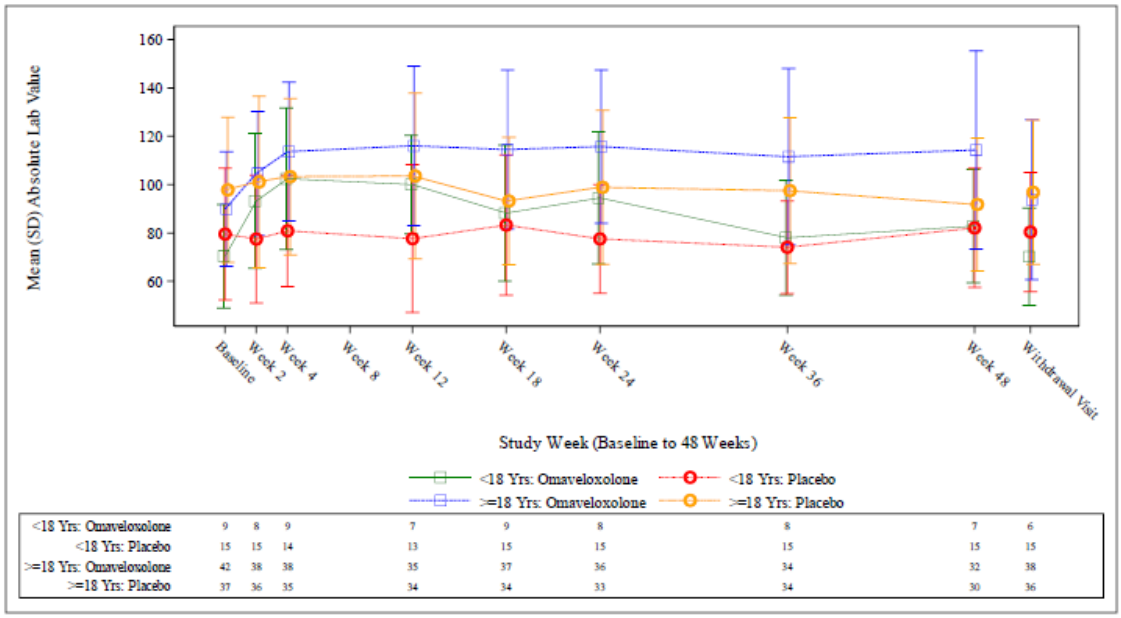
Mean LDL cholesterol values over the 48-week treatment interval for Analysis Set A are shown in Figure 65. Omaveloxolone-treated adolescent patients showed lower increases in LDL cholesterol at Week 48 than omaveloxolone-treated adult patients (Figure 66).

Figure 65: Mean absolute low-density lipoprotein cholesterol values over time, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

Figure 66: Mean absolute low-density lipoprotein cholesterol values over time by age group, baseline to week 48 (primary placebo-controlled analysis set A)



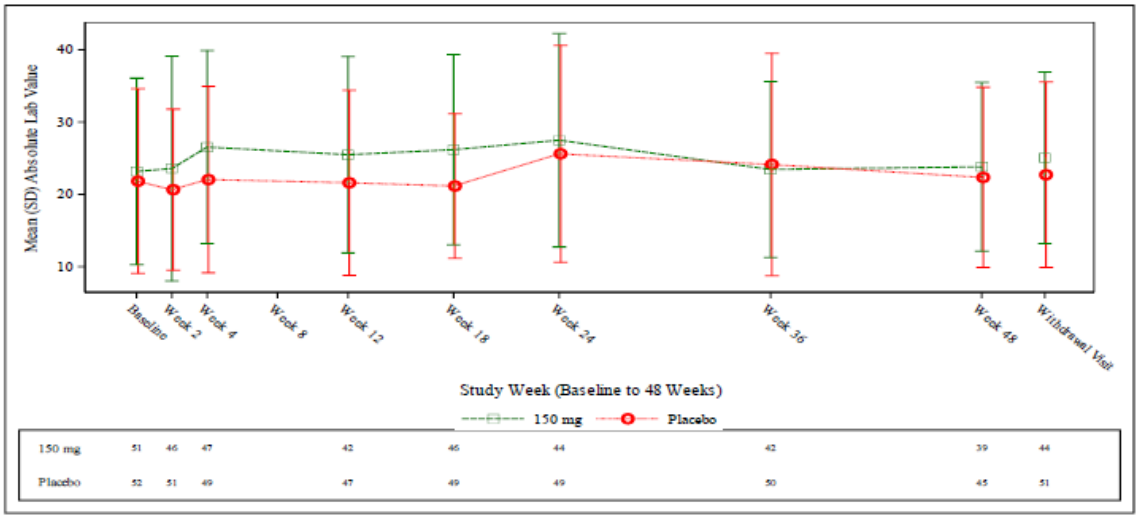
Abbreviation: Lab=laboratory.
Age group is based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Very Low-Density Lipoprotein Cholesterol

Mean very-LDL (VLDL) cholesterol values over the 48-week treatment interval for Analysis Set A are shown in Figure 67.

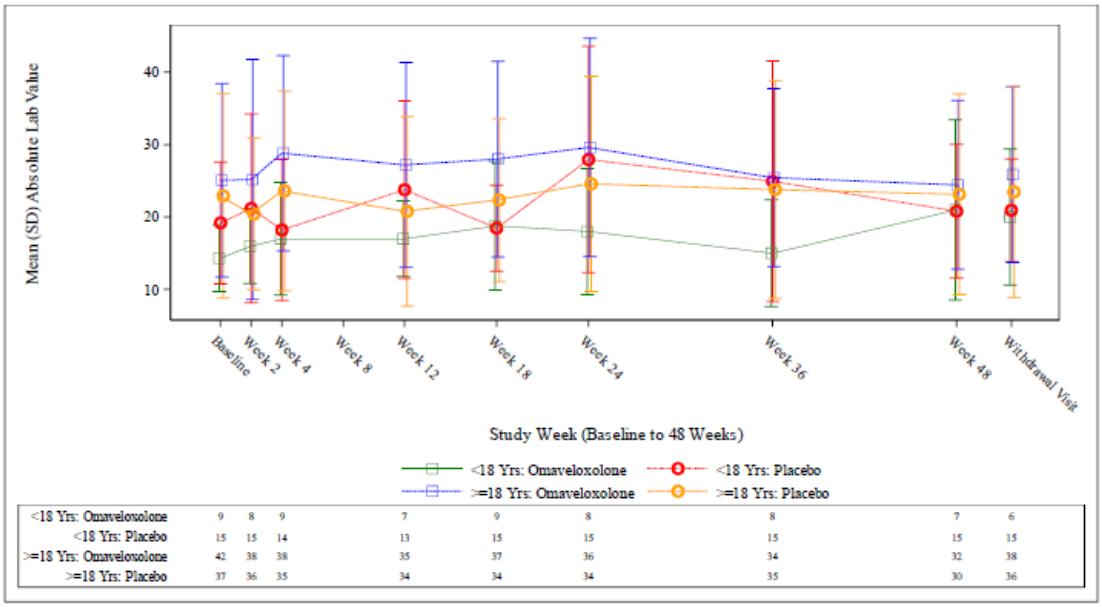
Omaveloxolone-treated adolescent patients showed similar results in VLDL cholesterol at Week 48 as omaveloxolone-treated adult patients (Figure 68).

Figure 67: Mean absolute very-low-density lipoprotein cholesterol values over time, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

Figure 68: Mean absolute very-low-density lipoprotein cholesterol values over time by age group, baseline to week 48 (primary placebo-controlled analysis set A)



Abbreviation: Lab=laboratory.
Age group is based on age at first double-blind treatment.
Timepoints with a single observation are not shown.

Electrocardiograms

Table 61: Mean change from baseline to week 48 in electrocardiogram parameters (primary placebo-controlled analysis set A)

Parameter	Omaveloxolone 150 mg (N=43)	Placebo (N=50)
PR interval (ms)		
Mean change	3.0	1.3
SD	11.48	10.68
Median	3.0	3.0
Min, Max	-15, 58	-30, 20
≤200 ms, n (%)	42 (97.7%)	50 (100%)
>200 ms, n (%)	1 (2.3%)	0
RR interval (ms)		
Mean change	-10.6	-6.7
SD	110.94	120.53
Median	-27.0	-14.0
Min, Max	-203, 234	-250, 339
Ventricular heart rate (bpm)		
Mean change	0.7	1.0
SD	10.22	11.81
Median	3.0	1.0
Min, Max	-19, 19	-27, 35
QRS duration (ms)		
Mean change	-0.2	-0.4
SD	5.19	6.38
Median	0.0	0.0
Min, Max	-9, 21	-14, 14
≤100 ms, n (%)	35 (81.4%)	43 (86.0%)
>100 to 120 ms, n (%)	7 (16.3%)	6 (12.0%)
>120 ms, n (%)	1 (2.3%)	1 (2.0%)
QT interval (ms)		
Mean change	-0.2	0.8
SD	25.38	25.60
Median	-4.0	-0.5
Min, Max	-44, 49	68, 54
≤440 ms, n (%)	42 (97.7%)	49 (98.0%)
>440 ms, n (%)	1 (2.3%)	1 (2.0%)
QTcF interval (ms)		
Mean change	1.1	2.4
SD	18.73	18.45
Median	2.0	0.0
Min, Max	-51, 48	-45, 60

Parameter	Omaveloxolone 150 mg (N=43)	Placebo (N=50)
≤450 ms, n (%)	40 (93.0%)	50 (100%)
>450 to 480 ms, n (%)	3 (7.0%)	0
>30 ms increase from baseline, n (%)	3 (7.0%)	3 (6.0%)
QTcB interval (ms)		
Mean change	1.8	3.1
SD	21.11	21.52
Median	3.0	0.5
Min, Max	-55, 59	-50, 69
≤450 ms, n (%)	37 (86.0%)	47 (94.0%)
>450 to 480 ms, n (%)	5 (11.6%)	3 (6.0%)
>480 to 500 ms, n (%)	1 (2.3%)	0

Abbreviations: Max=maximum; Min=minimum; PR=P wave onset to QRS complex onset; QTc=corrected QT interval; QTcB=QTc interval with Bazett correction; QTcF=corrected QT by Fridericia's formula; RR=time elapsed between 2 successive R-waves.

Echocardiograms

Table 62: Mean change from baseline to week 48 in echocardiogram parameters (primary placebo-controlled analysis set A)

Parameter	Omaveloxolone 150 mg	Placebo
Left ventricular ejection fraction (%)	**n=43**	**n=50**
Mean change	-0.2	2.0
SD	5.15	6.53
Median	0.0	2.0
Min, Max	-16, 9	-12, 16
Left ventricular end-diastolic internal dimension (cm)	**n=43**	**n=50**
Mean change	0.05	0.02
SD	0.382	0.340
Median	0.10	0.00
Min, Max	-1.0, 0.8	-0.9, 0.9
Left ventricular end-systolic internal dimension (cm)	**n=41**	**n=47**
Mean change	0.05	0.02
SD	0.470	0.474
Median	0.00	0.00
Min, Max	-1.2, 1.2	-1.6, 1.0
Left ventricular end-diastolic septal thickness (cm)	**n=43**	**n=50**
Mean change	-0.01	0.00
SD	0.205	0.212
Median	0.00	0.00
Min, Max	-0.6, 0.5	-0.6, 0.4
Left ventricular end-diastolic posterior thickness (cm)	**n=43**	**n=50**

Parameter	Omaveloxolone 150 mg	Placebo
Mean change	-0.03	-0.02
SD	0.265	0.200
Median	-0.10	0.00
Min, Max	-0.4, 1.0	-0.5, 0.5
Right ventricular wall thickness in diastole (cm)	**n=33**	**n=39**
Mean change	-0.05	-0.01
SD	0.236	0.573
Median	0.00	0.00
Min, Max	-1.1, 0.2	-2.5, 1.7

Abbreviations: Max=maximum; Min=minimum

Treatment-Emergent Adverse Events Related to Cardiovascular Safety in Analysis Set A

TEAEs related to cardiovascular safety in Analysis Set A are presented in Table 63. Preferred terms that are both in the Cardiac disorders SOC and SMQ are summarised under the Cardiac disorders SOC so that individual events are counted only once.

Table 63: Summary of cardiovascular treatment-emergent adverse events (primary placebo-controlled analysis set A)

SOC/SMQ Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Cardiac disorders SOC	**5 (9.8%)**	**7 (13.5%)**
Palpitations	1 (2.0%)	2 (3.8%)
Angina pectoris	1 (2.0%)	1 (1.9%)
Atrial fibrillation	1 (2.0%)	1 (1.9%)
Ventricular extrasystoles	0	2 (3.8%)
Atrioventricular block first degree	1 (2.0%)	0
Cardiomyopathy	1 (2.0%)	0
Left ventricular hypertrophy	0	1 (1.9%)
Sinus tachycardia	1 (2.0%)	0
Tachycardia	0	1 (1.9%)
Ventricular tachycardia	1 (2.0%)	0
Vascular disorders SOC	**0**	**3 (5.8%)**
Haematoma	0	3 (5.8%)
Cardiac arrhythmias (SMQ)	**5 (9.8%)**	**5 (9.6%)**
Palpitations	1 (2.0%)	2 (3.8%)
Atrial fibrillation	1 (2.0%)	1 (1.9%)
Ventricular extrasystoles	0	2 (3.8%)
Atrioventricular block first degree	1 (2.0%)	0

SOC/SMQ Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Sinus tachycardia	1 (2.0%)	0
Syncope	1 (2.0%)	0
Tachycardia	0	1 (1.9%)
Ventricular tachycardia	1 (2.0%)	0
Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) (SMQ)	**4 (7.8%)**	**3 (5.8%)**
Atrial fibrillation	1 (2.0%)	1 (1.9%)
Ventricular extrasystoles	0	2 (3.8%)
Atrioventricular block first degree	1 (2.0%)	0
Sinus tachycardia	1 (2.0%)	0
Ventricular tachycardia	1 (2.0%)	0
Ischaemic heart disease (SMQ)	**4 (7.8%)**	**3 (5.8%)**
Blood creatine phosphokinase increased	3 (5.9%)	2 (3.8%)
Angina pectoris	1 (2.0%)	1 (1.9%)
Tachyarrhythmias (including supraventricular and ventricular tachyarrhythmias) (SMQ)	**3 (5.9%)**	**3 (5.8%)**
Atrial fibrillation	1 (2.0%)	1 (1.9%)
Ventricular extrasystoles	0	2 (3.8%)
Sinus tachycardia	1 (2.0%)	0
Ventricular tachycardia	1 (2.0%)	0
Myocardial infarction (SMQ)	**3 (5.9%)**	**2 (3.8%)**
Blood creatine phosphokinase increased	3 (5.9%)	2 (3.8%)
Arrhythmia related investigations, signs and symptoms (SMQ)	**2 (3.9%)**	**2 (3.8%)**
Palpitations	1 (2.0%)	2 (3.8%)
Syncope	1 (2.0%)	0
Tachycardia	0	1 (1.9%)
Cardiac failure (SMQ)	**3 (5.9%)**	**1 (1.9%)**
N-terminal prohormone brain natriuretic peptide increased	1 (2.0%)	0
Oedema peripheral	1 (2.0%)	0
Peripheral swelling	1 (2.0%)	0
Pulmonary congestion	0	1 (1.9%)
Cardiomyopathy (SMQ)	**2 (3.9%)**	**2 (3.8%)**
Palpitations	1 (2.0%)	2 (3.8%)
Cardiomyopathy	1 (2.0%)	0
Syncope	1 (2.0%)	0
Other ischaemic heart disease (SMQ)	**1 (2.0%)**	**1 (1.9%)**
Angina pectoris	1 (2.0%)	1 (1.9%)
Pulmonary hypertension (SMQ)	**1 (2.0%)**	**1 (1.9%)**

SOC/SMQ Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Dyspnoea exertional	1 (2.0%)	0
Heart sounds abnormal	0	1 (1.9%)
Torsade de pointes/QT prolongation (SMQ)	**2 (3.9%)**	**0**
Syncope	1 (2.0%)	0
Ventricular tachycardia	1 (2.0%)	0
Central nervous system vascular disorders (SMQ)	**1 (2.0%)**	**0**
Dysarthria	1 (2.0%)	0
Torsade de pointes, shock-associated conditions (SMQ)	**1 (2.0%)**	**0**
Ventricular tachycardia	1 (2.0%)	0
Blood pressure events – Hypertension (SMQ)	**1 (2.0%)**	**1 (1.9%)**
Blood pressure abnormal	0	1 (1.9%)
Blood pressure increased	1 (2.0%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SMQ=standardized MedDRA Query; SOC=system organ class.

Analysis Set C

The profile of blood pressure, BNP and ECGs over time was similar to the changes shown above for the overall Analysis Set A population.

The incidence of total cholesterol above the ULN was lower compared to Analysis Set A (25.5% vs. 33.3%) and the incidence of LDL cholesterol values above the ULN was higher in Analysis Set C compared to Analysis Set A (25.9% vs. 19.9%).

With regard to echocardiograms, treatment with omaveloxolone did not result in meaningful changes in echocardiogram parameters relative to baseline or compared with Analysis Set A. However, cases of Left ventricle dilated at Week 48 (1 (2.3%), Left ventricular hypertrophy at Week 48 (11 (25,6%)) and Right ventricle enlargement at Week 48 (2 (4.7%)) were reported that was not provided for Analysis Set A in the integrated summary of safety.

With regard to TEAEs related to cardiovascular safety the incidence of palpitations was higher than in Analysis Set A (3.8% vs. 2.0%).

Treatment-Emergent Adverse Events Related to Depression, Suicide, and Self-Injury

Depression occurs in 9% to 36% of the FA patient population (Nieto, 2018). The percentage of patients enrolled in Study 1402 with a medical history of depression is consistent with this estimate. Although reports describing suicidality in patients with FA are limited, it is possible that these patients are at a greater risk for suicide given that depression is a risk factor linked with more than half of the suicide cases.

In Study 1402 Part 2, fewer omaveloxolone-treated patients reported psychiatric disorder TEAEs, despite 1 of the omaveloxolone patients reporting suicidal ideation. In Study 1402 Extension, 4 patients reported a TEAE related to suicide. All 5 patients had a medical history of depression. The annualised rate of suicide attempts observed in Study 1402 Extension (0.56%; data on file) is comparable to the rate in the general US population (0.6% for suicide attempts) (Ivey-Stephenson, 2022).

2.6.8.4. Laboratory findings

Haematology

In Analysis Set A, small decreases in erythrocytes, haematocrit and haemoglobin were observed in omaveloxolone-treated patients at Week 48 compared with placebo treated patients. No omaveloxolone-treated patients had haematology laboratory abnormalities reported as TEAEs.

Clinical Chemistry

Albumin, CK, serum creatinine, eGFR, ferritin, magnesium, potassium, uric acid, BUN, and bicarbonate are discussed separately. These parameters were examined in greater detail due to either observed differences from placebo or expected differences based on pharmacology of the drug. In addition, clinical chemistry parameters related to hepatic safety and cardiovascular safety are provided in section 3.3.7.3. No clinically significant changes were seen for total protein, glucose, lactate dehydrogenase, calcium, chloride or sodium at week 48 compared to baseline, nor for haemoglobin A1c at week 12 compared to baseline.

A summary of Analysis Set A patients with ≥1 on-treatment abnormal values (low or high) for albumin, CK, ferritin, magnesium, uric acid, BUN, phosphate, potassium, and bicarbonate is shown in Table 64.

Table 64: Patients with ≥1 On-treatment abnormal (low or high) value for selected clinical chemistry parameters (primary placebo-controlled analysis set A)

Laboratory Parameter (unit; normal range)	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Albumin (g/dL; 3.3-4.9)		
Patients with normal baseline and at least 1 on-treatment value	44	38
≥1 on-treatment low	0	0
≥1 on-treatment high	10 (22.7%)	14 (36.8%)
Bicarbonate (mEq/L; 17.0-30.6)		
Patients with normal baseline and at least 1 on-treatment value	50	52
≥1 on-treatment low	3 (6.0%)	0
≥1 on-treatment high	0	0
Creatine kinase (U/L; 18-169)		
Patients with normal baseline and at least 1 on-treatment value	49	46
≥1 on-treatment low	0	0
≥1 on-treatment high	4 (8.2%)	7 (15.2%)
Ferritin (ng/mL; 11-306.8)		
Patients with normal baseline and at least 1 on-treatment value	31	29
≥1 on-treatment low	0	2 (6.9%)
≥1 on-treatment high	1 (3.2%)	0
Magnesium (mg/dL; 1.5-3.1)		
Patients with normal baseline and at least 1 on-treatment value	50	52
≥1 on-treatment low	0	0
≥1 on-treatment high	1 (2.0%)	3 (5.8%)
Phosphate (mg/dL; 2.2-5.1)		
Patients with normal baseline and at least 1 on-treatment value	50	52
≥1 on-treatment low	3 (6.0%)	2 (3.8%)
≥1 on-treatment high	1 (2.0%)	1 (1.9%)
Potassium (mEq/L; 3.4-5.4)		
Patients with normal baseline and at least 1 on-treatment value	49	52
≥1 on-treatment low	0	1 (1.9%)
≥1 on-treatment high	0	1 (1.9%)

Laboratory Parameter (unit; normal range)	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Blood urea nitrogen (mg/dL; 4-24)		
Patients with normal baseline and at least 1 on-treatment value	50	52
≥1 on-treatment low	0	0
≥1 on-treatment high	2 (4.0%)	1 (1.9%)
Uric acid (mg/dL; 2.1-7.2)		
Patients with normal baseline and at least 1 on-treatment value	49	52
≥1 on-treatment low	1 (2.0%)	0
≥1 on-treatment high	0	2 (3.8%)

Percentages are based on the number of patients with normal baseline and at least 1 on-treatment observation. Normal ranges are listed, where there is an age difference, the range is listed for patients over 18 years of age and, where there is a sex difference, the range is listed for females.

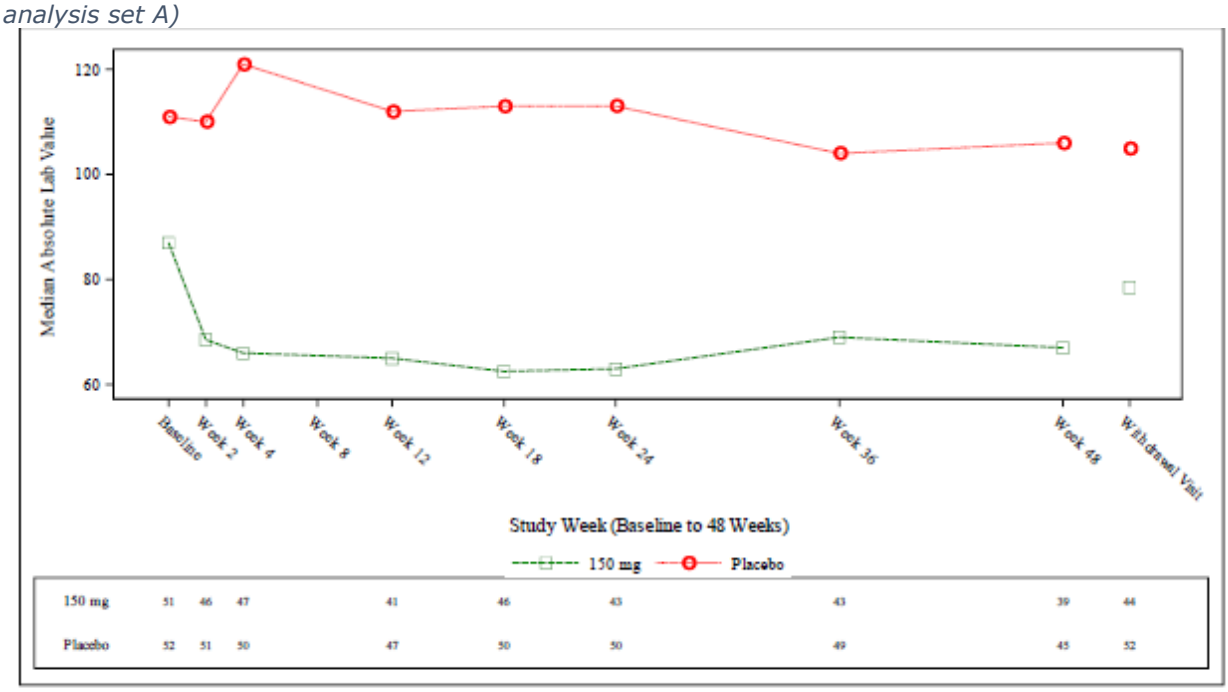
Albumin

Baseline Albumin levels were lower in the omaveloxolone treatment group compared to placebo. There were no clinically significant changes throughout the week 48 and no patients reported low albumin values across treatment groups.

Creatine Kinase

Median changes from baseline in CK by analysis visit for Analysis Set A are shown in Figure 69.

Figure 69: Median absolute creatinine kinase (U/L) values, baseline to week 48 (primary placebo-controlled analysis set A)

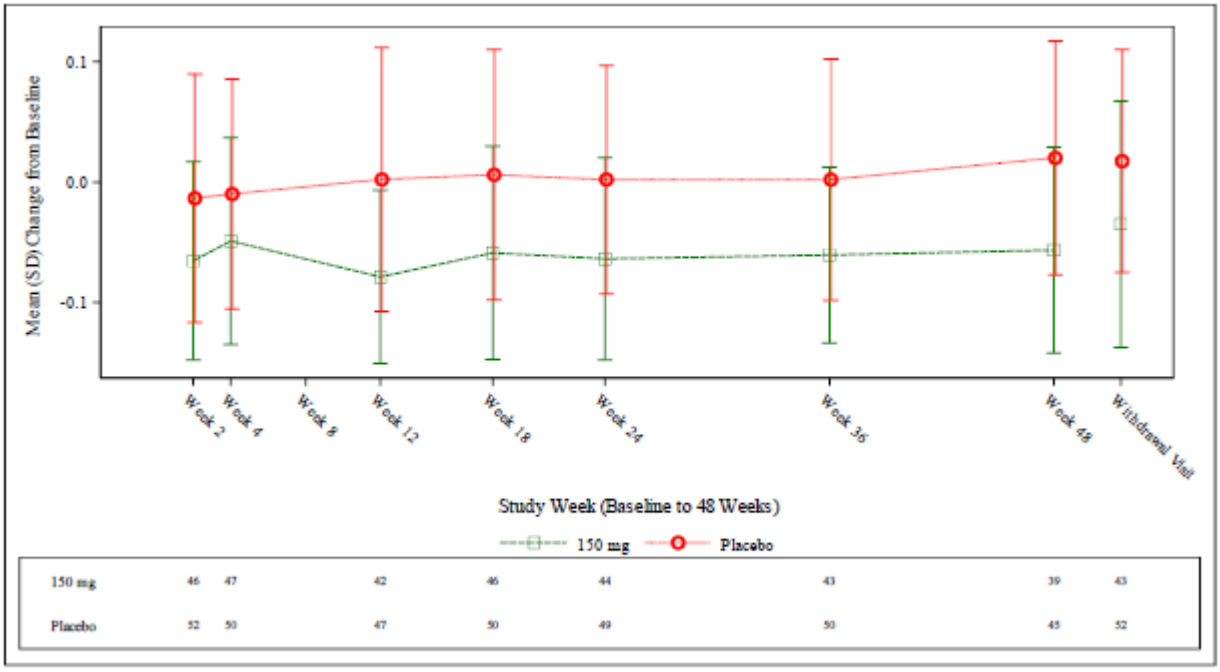


Abbreviation: Lab=laboratory.
Timepoints with a single observation are not shown.

Serum Creatinine and Estimated Glomerular Filtration Rate

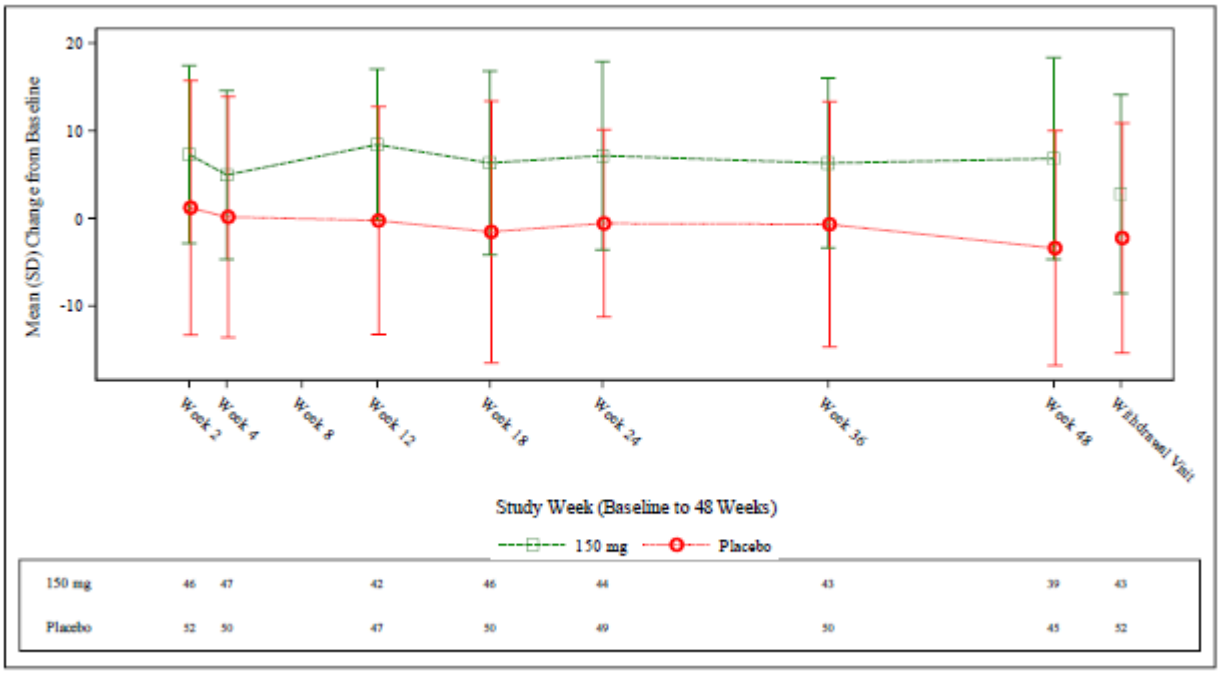
Omaveloxolone-treated patients showed mean decreases from baseline to Week 48 in serum creatinine and mean increases in eGFR; the decreases in serum creatinine were greater than those seen in placebo-treated patients and omaveloxolone-treated patients had larger increases in eGFR (Figure 70, Figure 71).

Figure 70: Median change from baseline to week 48 in serum creatinine (mg/dL) values (primary placebo-controlled analysis set A)



Timepoints with a single observation are not shown.

Figure 71: Median change from baseline to week 48 in estimated glomerular filtration rate (ml/min/1.73m^2) (primary placebo-controlled analysis set A)

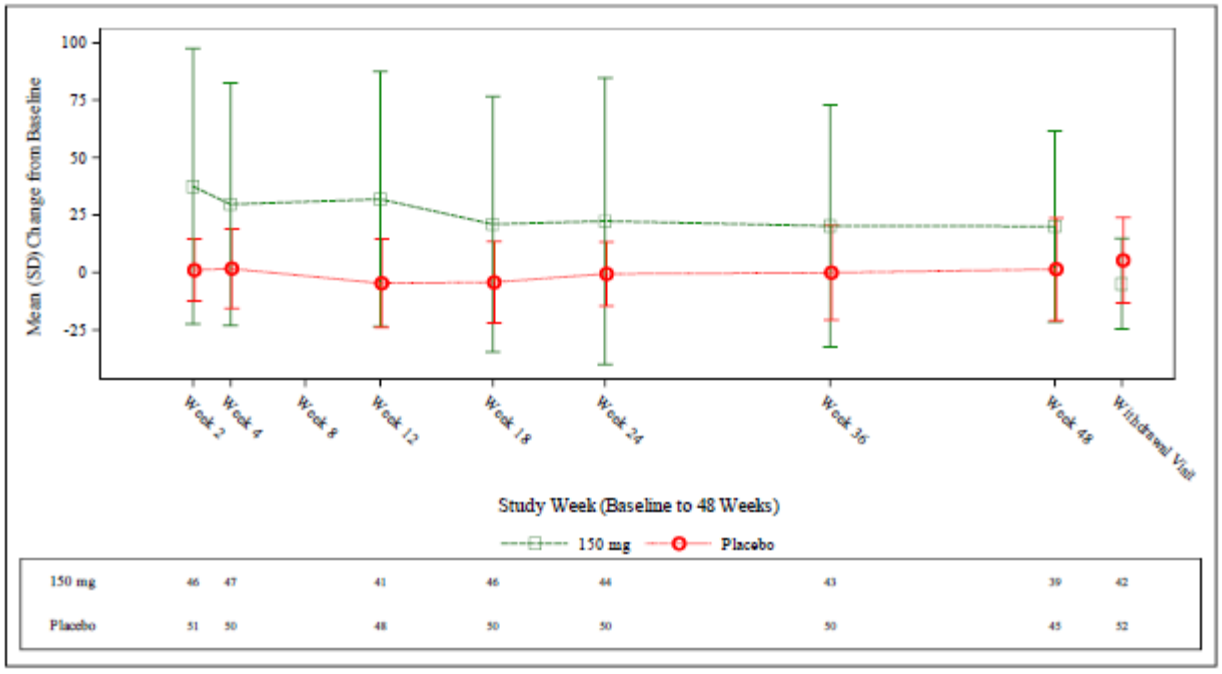


Timepoints with a single observation are not shown.

Ferritin

Mean change from baseline to Week 48 in ferritin for Analysis Set A is shown in Figure 72.

Figure 72: Median change from baseline to week 48 in ferritin (ng/ml) (primary placebo-controlled analysis set A)



Timepoints with a single observation are not shown.

Magnesium

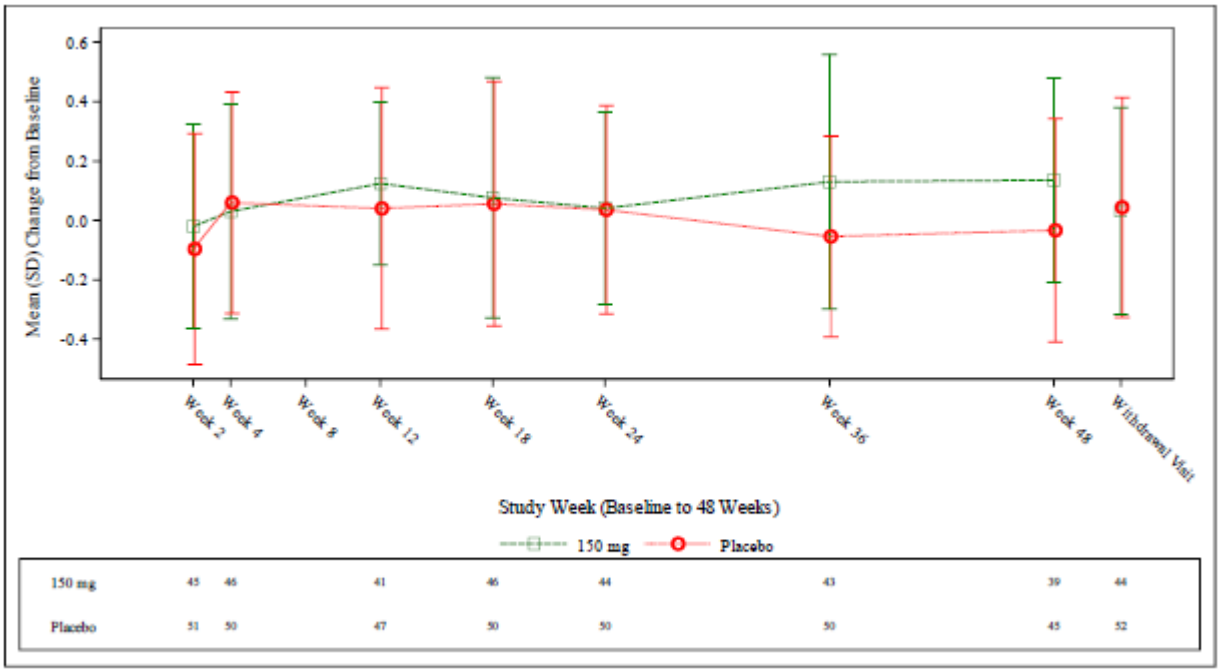
A small decrease in magnesium were observed in the omaveloxolone treated patients, however, no patients reported magnesium values below the lower limit of normal in Analysis Set A. Omaveloxolone-treated patients had a mean change from baseline of -0.02 ± 0.100 mg/dL at Week 48 versus a mean change from baseline of -0.01 ± 0.135 mg/dL in placebo-treated patients. Mean serum magnesium levels returned to baseline after withdrawal of drug. The same pattern was observed in Analysis Set C.

Within Analysis Set A, the correlation analysis of changes from baseline at Week 48 in serum magnesium and QTcF suggested that decreases in serum magnesium were not associated with changes in QTcF for omaveloxolone treated patients (Pearson correlation=0.272; p=0.0811; n=42). However, 3 (7.0%) omaveloxolone treated patients had QTcF interval >450 to 480 ms vs. 0 in the placebo group.

Potassium

Omaveloxolone-treated patients had a mean change from baseline of 0.14 ± 0.344 mEq/L at Week 48 versus a mean change from baseline of -0.03 ± 0.375 mEq/L in placebo-treated patients. No omaveloxolone-treated patients had ≥1 on-treatment high potassium values. Omaveloxolone-treated patients in Analysis Set C had a mean change from baseline of 0.15 ± 0.345 mEq/L at Week 48, 0.11 ± 0.344 mEq/L at Week 96, and 0.13 ± 0.346 mEq/L at Week 144, which shows that the change remained stable. Mean change from baseline in potassium from baseline to Week 48 for Analysis Set A is shown in Figure 73.

Figure 73: Median change from baseline to week 48 in potassium (mEq/L) (primary placebo-controlled analysis set A)

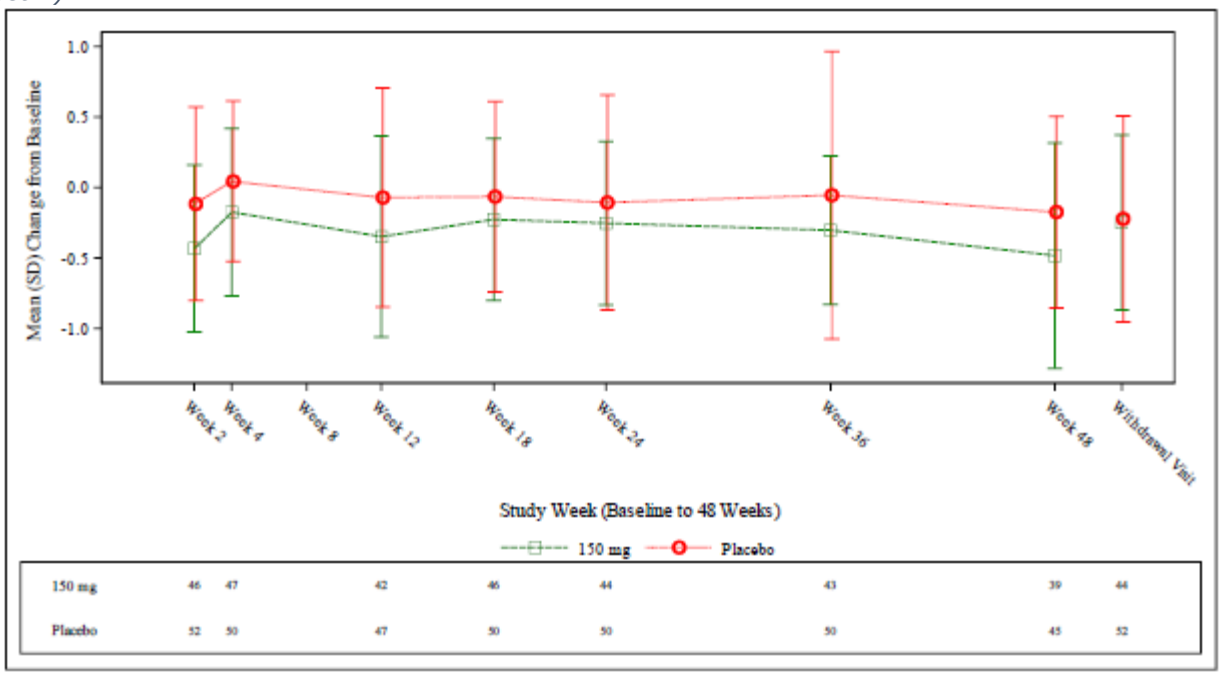


Timepoints with a single observation are not shown.

Uric Acid, Blood Urea Nitrogen, and Bicarbonate

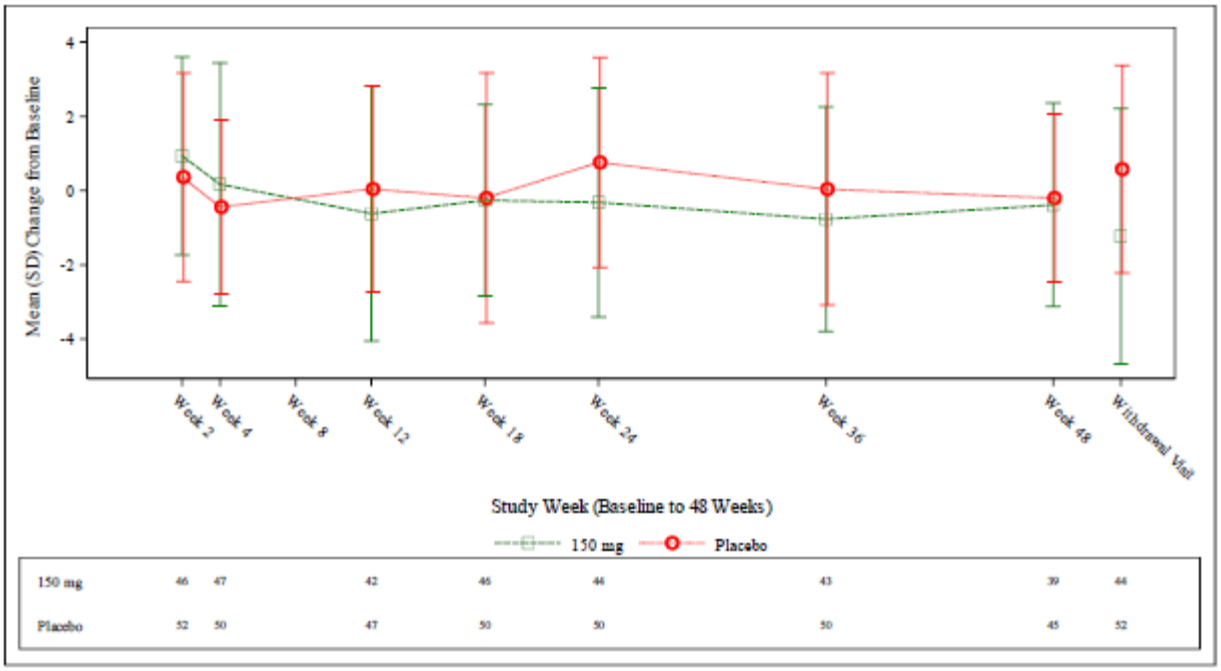
Mean decreases in uric acid (Figure 74), BUN (Figure 75), and bicarbonate (Figure 76) were observed relative to baseline in omaveloxolone-treated patients in Analysis Set A.

Figure 74: Median change from baseline to week 48 in uric acid (mg/dL) (primary placebo-controlled analysis set A)



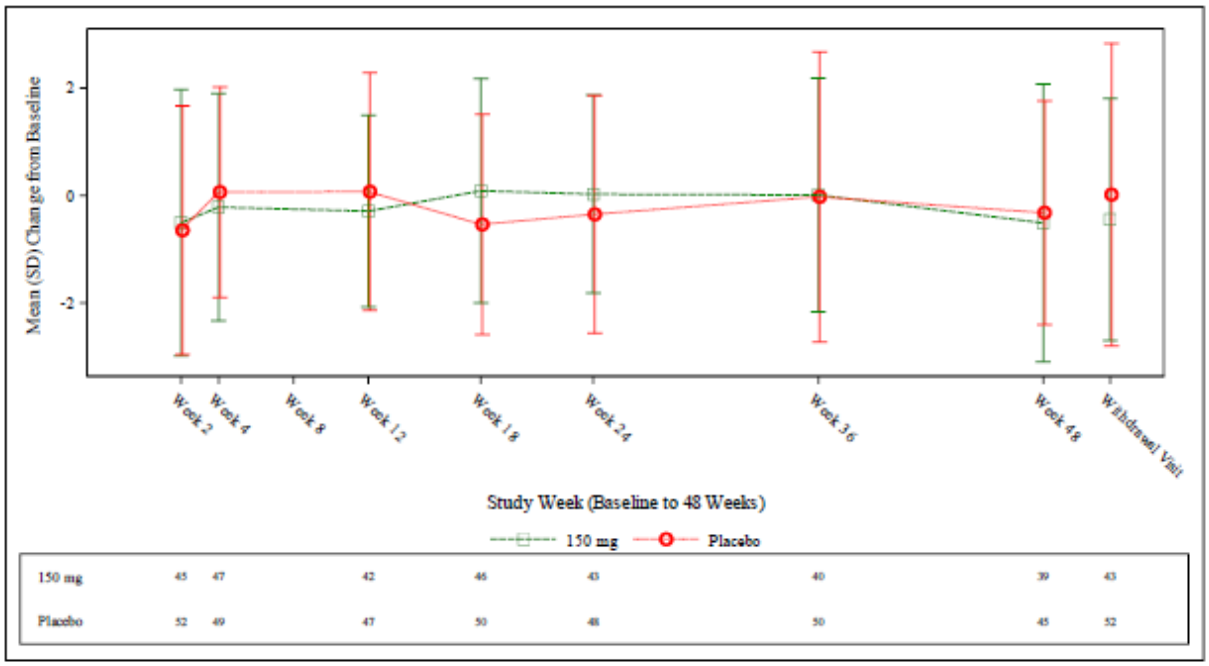
Timepoints with a single observation are not shown.

Figure 75: Median change from baseline to week 48 in blood urea nitrogen (mg/dL) (primary placebo-controlled analysis set A)



Timepoints with a single observation are not shown.

Figure 76: Median change from baseline to week 48 in bicarbonate (mEq/L) (primary placebo-controlled analysis set A)

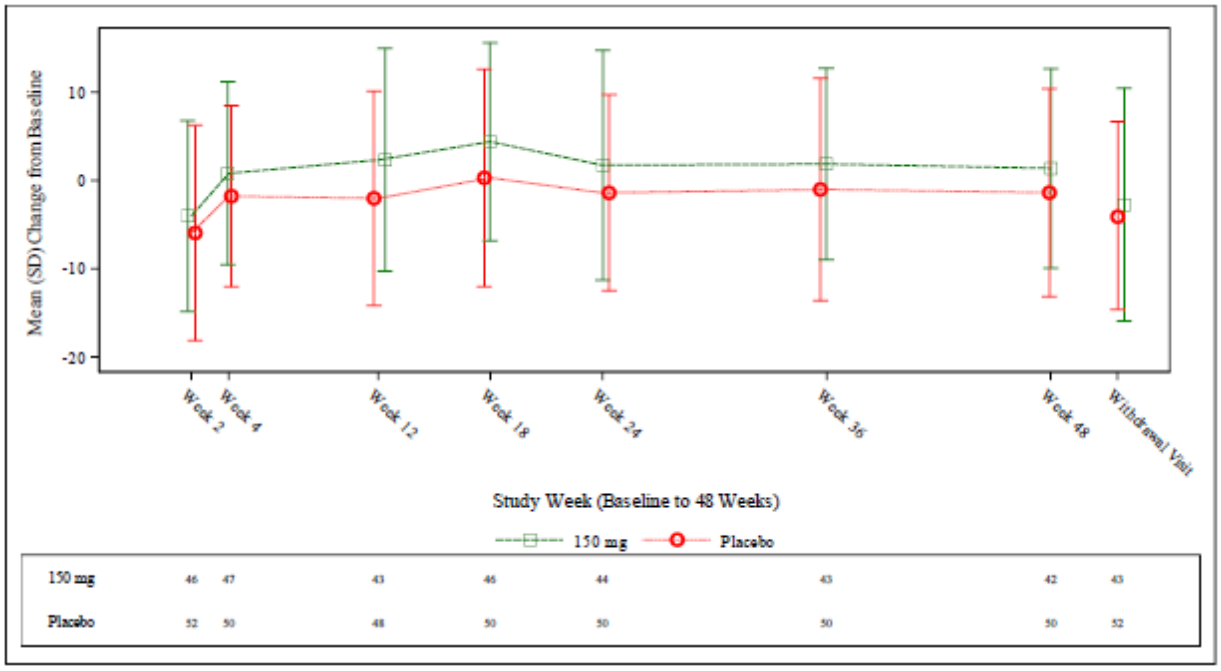


Timepoints with a single observation are not shown.

Vital signs

An evaluation of blood pressure in Analysis Set A is provided in relation to cardiovascular safety and was a safety topic of interest for this submission. Mean change in pulse rate is provided in Figure 77 for Analysis Set A. A small increase in pulse were seen in omaveloxolone treated patients with mean changes from baseline ranging from -4.0 to 4.4 bpm for omaveloxolone-treated patients and -5.9 to 0.3 bpm for placebo-treated patients.

Figure 77: Median change from baseline to week 48 in pulse rate (beats/minute) (primary placebo-controlled analysis set A)



2.6.8.5. Safety in special populations

Age

Overall, the same percentage of adolescent patients (<18 years of age) experienced a TEAE compared with adults ≥18 years of age in both treatment groups (omaveloxolone, 100% versus placebo, 100.0%; and 100.0% of both adolescent and adult patients). Compared with adult patients treated with omaveloxolone, adolescent omaveloxolone-treated patients experienced a higher percentage of TEAEs in the following SOCs: Infections and infestations (77.8% versus 64.3%), General disorders and administration site conditions (55.6% versus 31.0%), Respiratory, thoracic and mediastinal disorders (44.4% versus 35.7%), Cardiac disorders (11.1% versus 9.5%), Immune system disorders (11.1% versus 0%), Surgical and medical procedures (11.1% versus 0%), and Congenital, familial and genetic disorders (11.1% versus 0%). However, due to the small number of adolescent patients (n=9), no individual PT in these SOCs was reported with a notably different frequency in adolescent and adult patients.

Compared with adolescent patients treated with omaveloxolone, adult omaveloxolone-treated patients experienced a higher percentage of TEAEs in the following SOCs: Injury, poisoning and procedural complications (64.3% versus 55.6%), Gastrointestinal disorders (69.0% versus 55.6%), Nervous system disorders (57.1% versus 22.2%), Musculoskeletal and connective tissue disorders (47.6% versus 44.4%), Investigations (57.1% versus 33.3%), Skin and subcutaneous tissue disorders (33.3% versus 22.2%), Psychiatric disorders (11.9% versus 11.1%), Metabolism and nutrition disorders (16.7% versus 11.1%), Renal and urinary disorders (7.1% versus 0%), Reproductive system and breast disorders (16.7% versus 0%), Eye disorders (4.8% versus 0%), Hepatobiliary disorders (4.8% versus 0%), and Blood and lymphatic system disorders (4.8% versus 0%). A higher percentage of adults had a TEAE of ALT increased (45.2% versus 0% of adolescent patients) and AST increased (26.2% versus 0% of adolescent patients).

Due to the small number of adolescent patients, results should be interpreted with caution.

Sex

In Analysis Set A, a slightly higher percentage of patients in the omaveloxolone treatment group were female (60.8%), and a slightly higher percentage of patients in the placebo group were male (67.3%). Overall, the incidence of TEAEs by sex was not meaningfully different across treatment groups, because 100% of patients reported a TEAE.

Compared with female patients treated with omaveloxolone, omaveloxolone-treated male patients experienced a higher percentage of TEAEs in the following SOCs: Investigations (65.0% versus 45.2%), Psychiatric disorders (15.0% versus 9.7%), Eye disorders (5.0% versus 3.2%), Hepatobiliary disorders (10.0% versus 0%), Immune system disorders (5.0% versus 0%), Blood and lymphatic system disorders (5.0% versus 3.2%), Surgical and medical procedures (5.0% versus 0%), and Congenital, familial and genetic disorders (5.0% versus 0%). A higher percentage of male patients had TEAEs of ALT increased (50.0% versus 29.0% of female patients), which contributed to the difference in the Investigations SOC.

Compared with male patients treated with omaveloxolone, omaveloxolone-treated female patients experienced a higher percentage of TEAEs in the following SOCs: Infections and infestations (67.7% versus 65.0%), Injury, poisoning and procedural complications (74.2% versus 45.0%), Gastrointestinal disorders (67.7% versus 65.0%), Nervous system disorders (61.3% versus 35.0%), Musculoskeletal and connective tissue disorders (54.8% versus 35.0%), General disorders and administration site conditions (41.9% versus 25.0%), Respiratory, thoracic and mediastinal disorders (45.2% versus 25.0%), Skin and subcutaneous tissue disorders (35.5% versus 25.0%), Cardiac disorders (12.9% versus 5.0%), Metabolism and nutrition disorders (19.4% versus 10.0%), Renal and urinary disorders (6.5% versus 5.0%), Reproductive system and breast disorders (22.6% versus 0%), and Ear and labyrinth disorders (6.5% versus 0%). A higher percentage of female patients reported a medical history of reproductive system and breast disorders (38.7% versus 0% of male patients) which likely contributed to the imbalance in TEAEs in the Reproductive system and breast disorders SOC.

Geographic region

In Analysis Set A, the majority of patients in both treatment groups were recruited in the US (omaveloxolone, 70.6%; placebo, 67.3%).

Overall, the incidence of TEAEs by geographic region was not meaningfully different across treatment groups, because 100% of patients reported a TEAE.

Slight differences in some SOCs and PTs were noted (e.g, Infections and infestations and Investigations); however, due to the small number of patients in the "other" geographic regions, results should be interpreted with caution.

Ethnicity and Race

In Analysis Set A, the majority of patients in both treatment groups were not Hispanic or Latino (omaveloxolone, 96.1%; placebo, 94.2%). FA most commonly affects individuals of Caucasian descent and is rare in populations from Southeast Asia and Africa (Delatycki, 2012).

On the basis of molecular studies, the estimated incidence of FA in Caucasians is about 1 in 29 000, with a carrier frequency of 1 in 85 (Cossée, 1997).

Because there were only 2 omaveloxolone-treated patients and 3 placebo-treated patients who were Hispanic or Latino, results should be interpreted with caution and are not discussed in this section.

In Analysis Set A, the majority of patients in both treatment groups were white (omaveloxolone, 98.0%; placebo, 96.2%). There was only 1 omaveloxolone-treated patient and 2 placebo-treated patients who were not white; therefore, TEAE results should be interpreted with caution and are not discussed in this section.

Pes Cavus Status

In Analysis Set A, the majority of patients in both treatment groups did not have pes cavus (omaveloxolone, 80.4%; placebo, 80.8%). There were only 10 omaveloxolone-treated patients and 10 placebo-treated patients who did have pes cavus; therefore, TEAE results should be interpreted with caution.

Overall, the incidence of TEAEs by pes cavus status was not meaningfully different across treatment groups, because 100% of patients reported a TEAE.

Compared with omaveloxolone-treated patients without pes cavus, omaveloxolone-treated patients with pes cavus experienced a higher percentage of TEAEs in the following SOCs: Nervous system disorders (80.0% versus 43.9%), Musculoskeletal and connective tissue disorders (60.0% versus 43.9%), General disorders and administration site conditions (40.0% versus 34.1%), Respiratory, thoracic and mediastinal disorders (40.0% versus 36.6%), Renal and urinary disorders (20.0% versus 2.4%), Reproductive system and breast disorders (20.0% versus 12.2%), Ear and labyrinth disorders (10.0% versus 2.4%), and Immune system disorders (10.0% versus 0%).

Compared with omaveloxolone-treated patients with pes cavus, omaveloxolone-treated patients without pes cavus experienced a higher percentage of TEAEs in the following SOCs: Infections and infestations (75.6% versus 30.0%), Injury, poisoning and procedural complications (65.9% versus 50.0%), Gastrointestinal disorders (68.3% versus 60.0%), Investigations (53.7% versus 50.0%), Skin and subcutaneous tissue disorders (31.7% versus 30.0%), Psychiatric disorders (12.2% versus 10.0%), Cardiac disorders (12.2% versus 0%), Metabolism and nutrition disorders (19.5% versus 0%), Eye disorders (4.9% versus 0%), Hepatobiliary disorders (4.9% versus 0%), Blood and lymphatic system disorders (4.9% versus 0%), Surgical and medical procedures (2.4% versus 0%), and Congenital, familial and genetic disorders (2.4% versus 0%). However, there was no individual PT with a notably different incidence in patients with pes cavus compared with patients without pes cavus.

Use in Pregnancy and Lactation

Effects of omaveloxolone on human fetal development are not known, and pregnant and lactating women were excluded from entering the clinical studies. To manage any potential risks, women and men with reproductive potential were required to use a reliable method of birth control during the clinical studies. Pregnancy and breastfeeding were criteria for permanent discontinuation in all omaveloxolone studies.

As of 24 March 2022, in the Reata safety database, no women who were exposed to omaveloxolone became pregnant during any omaveloxolone study. Additionally, there were no pregnancies in partners of male patients exposed to omaveloxolone during their participation in a study.

There is no human data on the use of omaveloxolone in pregnant women or in women exposed via a male partner treated with omaveloxolone. Omaveloxolone has been investigated in a fertility toxicity study in rats, embryo-fetal developmental toxicity studies in rats and rabbits, and in a pre- and postnatal developmental toxicity study in rats. In the fertility study in rats, omaveloxolone produced no adverse effects on male or female reproductive or fertility indices at the highest administered dose (ie, 10 mg/kg/day) but increased pre- and post-implantation loss and resorptions (early and late), decreased the number of implantation sites and viable embryos observed, and set the NOAEL at 3 mg/kg/day. In the rat embryo-fetal toxicity study, no developmental toxicities were observed at the highest administered dose of 10 mg/kg/day. In the rabbit

embryo-fetal toxicity study, early deliveries and abortions were associated with maternal toxicity, including decreased gestational body weight and food consumption; a NOAEL of 3 mg/kg/day was determined. The developmental NOAEL in the rabbit was determined at 10 mg/kg/day, and no fetal malformations were noted. In the PPND toxicity study in rats, the maternal NOAEL was the highest dose evaluated (10 mg/kg/day), whereas the NOAEL for reproductive function was 3 mg/kg/day due to increased stillborn pup and decreased pup survivals. In the F1 generation, the NOAEL was 3 mg/kg/day due to decreased mean body weights and reduced number of corpus lutea and implantation sites, and no effects on behavioural function or other developmental findings were observed. Significant omaveloxolone concentrations were found in the milk, thus exposing the newborn rats through weaning. Malformations were not observed in animals exposed intrauterine to omaveloxolone during pregnancy. AEs on the offspring were associated with maternal toxicity, observed as decreased maternal gestational body weight. Collectively, the reproductive and developmental toxicity studies showed that omaveloxolone was not associated with any direct effects on the fetus, with only adverse effects generally associated with readily apparent (ie, decreased body weight and poor overall condition) maternal tolerability issues. Rats generally exhibited a more favourable tolerability profile compared to rabbits, as the NOAELs in rats correlated with clinical safety multiples (based on $AUC_{0\text{-}24}$) that were at least 2.0-fold, whereas rabbits had a NOAEL associated with exposures below those observed in patients with FA at the MHRD of 150 mg.

Overdose

No cases of overdose have been observed in the omaveloxolone development programme. Available data in the integrated summary of safety for repeated dosing at 150 mg does not indicate any safety concerns with this dose. The information available from Study 1402 Part 1 in doses up to 300 mg (up to 12 weeks) have been used without safety concerns.

Drug Abuse

Multiple nonclinical studies were reviewed to assess the potential for drug abuse liability. Omaveloxolone (200 and 2000 nM) was tested *in vitro* in a panel of receptors, ion channels, transporters, and enzymes that included multiple CNS targets (SafetyScreen44™ panel) (Study RTA-P-18007) and in a GLP CNS safety pharmacology study in rats (Study RTA408-P-1115). 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 500- times, respectively, C_{max} in patients with FA administered the MHRD dose of 150 mg.

Note that in the SafetyScreen44™ study, results for benzodiazepine and serotonin 2A 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 serotonin 2A. 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} after a single 30-mg/kg oral dose in rats corresponds to approximately 20 times the maximal steady-state plasma omaveloxolone concentration in patients with FA administered the MHRD of 150 mg.

Further, in clinical trials with omaveloxolone, no psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) were reported.

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

Withdrawal and Rebound

No clinical trials were conducted looking specifically for a withdrawal and rebound effect for the safety of omaveloxolone, and there was no evidence in the clinical trials.

Effects on the Ability to Drive or Operate Machinery or Impairment of Mental Ability

There are no known effects on the ability to drive and use machines associated with the use of omaveloxolone. Through the clinical studies of omaveloxolone to date, there have been no reports in clinical trial participants that omaveloxolone affects the ability to drive or operate machinery or impairs mental ability.

2.6.8.6. Immunological events

Not applicable.

2.6.8.7. Safety related to drug-drug interactions and other interactions

It is currently unclear whether there are any safety issues due to DDI. Post-authorisation studies should be submitted and clarify this.

2.6.8.8. Discontinuation due to adverse events

Table 65: Summary of treatment-emergent adverse events leading to study drug discontinuation (primary placebo-controlled analysis set A)

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Number (%) of Patients Reporting TEAEs Resulting in Study Drug Discontinuation	**4 (7.8%)**	**2 (3.8%)**
Cardiac disorders	**1 (2.0%)**	**1 (1.9%)**
Atrial fibrillation	0	1 (1.9%)
Ventricular tachycardia	1 (2.0%)	0
Skin and subcutaneous tissue disorders	**1 (2.0%)**	**1 (1.9%)**
Erythrosis	0	1 (1.9%)
Rosacea	1 (2.0%)	0
Investigations	**1 (2.0%)**	**0**
Alanine aminotransferase increased	1 (2.0%)	0
Aspartate aminotransferase increased	1 (2.0%)	0
Musculoskeletal and connective tissue disorders	**1 (2.0%)**	**0**
Muscle spasms	1 (2.0%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Adverse event terms were mapped according to MedDRA v 21.1.

Table 66: Summary of treatment-emergent adverse events leading to study drug discontinuation (Friedrich ataxia overall omaveloxolone exposure integrated analysis set C)

System Organ Class Preferred Term	Omaveloxolone				
	5-20 mg (N=18)	40-80 mg (N=12)	150-160 mg (N=159)	300 mg (N=10)	All Treated (N=165)
Number (%) of Patients Reporting TEAEs Resulting in Study Drug Discontinuation	**0**	**1 (8.3%)**	**14 (8.8%)**	**0**	**15 (9.1%)**
Investigations	**0**	**0**	**5 (3.1%)**	**0**	**5 (3.0%)**
Alanine aminotransferase increased	0	0	5 (3.1%)	0	5 (3.0%)
Aspartate aminotransferase increased	0	0	2 (1.3%)	0	2 (1.2%)
Skin and subcutaneous tissue disorders	**0**	**1 (8.3%)**	**2 (1.3%)**	**0**	**3 (1.8%)**
Alopecia	0	0	1 (0.6%)	0	1 (0.6%)
Rash generalised	0	1 (8.3%)	0	0	1 (0.6%)
Rosacea	0	0	1 (0.6%)	0	1 (0.6%)
General disorders and administration site conditions	**0**	**0**	**2 (1.3%)**	**0**	**2 (1.2%)**
Fatigue	0	0	2 (1.3%)	0	2 (1.2%)
Cardiac disorders	**0**	**0**	**1 (0.6%)**	**0**	**1 (0.6%)**
Ventricular tachycardia	0	0	1 (0.6%)	0	1 (0.6%)
Gastrointestinal disorders	**0**	**0**	**2 (1.3%)**	**0**	**2 (1.2%)**
Abdominal pain upper	0	0	1 (0.6%)	0	1 (0.6%)
Constipation	0	0	1 (0.6%)	0	1 (0.6%)
Frequent bowel movements	0	0	1 (0.6%)	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (0.6%)**	**0**	**1 (0.6%)**
Muscle spasms	0	0	1 (0.6%)	0	1 (0.6%)
Psychiatric disorders	**0**	**0**	**1 (0.6%)**	**0**	**1 (0.6%)**
Bipolar disorder	0	0	1 (0.6%)	0	1 (0.6%)
Reproductive system and breast disorders	**0**	**0**	**1 (0.6%)**	**0**	**1 (0.6%)**
Menstruation irregular	0	0	1 (0.6%)	0	1 (0.6%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Adverse event terms were mapped according to MedDRA v_21.1.
Some patients may be represented in multiple columns if they changed dose levels when entering Study 1402 Extension.
Each column reflects the number of unique patients. Events were counted within the treatment group at the start of the event.

Table 67: Summary of treatment-emergent adverse events leading to study drug interruption (primary placebo-controlled analysis set A)

System Organ Class Preferred Term	Omaveloxolone 150 mg (N=51)	Placebo (N=52)
Number (%) of Patients Reporting TEAEs Resulting in Study Drug Interruption	**9 (17.6%)**	**1 (1.9%)**
Investigations	**6 (11.8%)**	**0**
Alanine aminotransferase increased	6 (11.8%)	0
Aspartate aminotransferase increased	3 (5.9%)	0
Gamma-glutamyltransferase increased	2 (3.9%)	0
Gastrointestinal disorders	**2 (3.9%)**	**0**
Diarrhoea	1 (2.0%)	0
Nausea	1 (2.0%)	0
Cardiac disorders	**1 (2.0%)**	**0**
Palpitations	1 (2.0%)	0
Sinus tachycardia	1 (2.0%)	0
General disorders and administration site conditions	**1 (2.0%)**	**0**
Non-cardiac chest pain	1 (2.0%)	0
Musculoskeletal and connective tissue disorders	**1 (2.0%)**	**0**
Muscle spasms	1 (2.0%)	0
Nervous system disorders	**1 (2.0%)**	**0**
Somnolence	1 (2.0%)	0
Skin and subcutaneous tissue disorders	**0**	**1 (1.9%)**
Rash erythematous	0	1 (1.9%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Adverse event terms were mapped according to MedDRA v 21.1.

Results for all omaveloxolone-treated patients in Analysis Set C (N=165) showed 39 (23.6%) patients reporting a TEAE resulting in study drug interruption, with 18 (10.9%) patients having events related to study drug (Table 68).

Table 68: Summary of treatment-emergent adverse events leading to study drug interruption (Friedrich ataxia overall omaveloxolone exposure integrated analysis set C)

System Organ Class / Preferred Term	Omaveloxolone 5-20 mg (N=18)	Omaveloxolone 40-80 mg (N=12)	Omaveloxolone 150-160 mg (N=159)	Omaveloxolone 300 mg (N=10)	Omaveloxolone All Treated (N=165)
Number (%) of Patients Reporting TEAEs Resulting in Study Drug Interruption	0	0	39 (24.5%)	0	39 (23.6%)
Infections and infestations	0	0	21 (13.2%)	0	21 (12.7%)
Corona virus infection	0	0	17 (10.7%)	0	17 (10.3%)
Influenza	0	0	2 (1.3%)	0	2 (1.2%)
Gastroenteritis viral	0	0	1 (0.6%)	0	1 (0.6%)
Pneumonia viral	0	0	1 (0.6%)	0	1 (0.6%)
Sepsis	0	0	1 (0.6%)	0	1 (0.6%)
Tonsillitis	0	0	1 (0.6%)	0	1 (0.6%)
Viral upper respiratory tract infection	0	0	1 (0.6%)	0	1 (0.6%)
Investigations	0	0	13 (8.2%)	0	13 (7.9%)
Alanine aminotransferase increased	0	0	12 (7.5%)	0	12 (7.3%)
Aspartate aminotransferase increased	0	0	6 (3.8%)	0	6 (3.6%)
Gamma-glutamyltransferase increased	0	0	3 (1.9%)	0	3 (1.8%)
Liver function test increased	0	0	1 (0.6%)	0	1 (0.6%)
Gastrointestinal disorders	0	0	5 (3.1%)	0	5 (3.0%)
Nausea	0	0	2 (1.3%)	0	2 (1.2%)
Vomiting	0	0	2 (1.3%)	0	2 (1.2%)
Constipation	0	0	1 (0.6%)	0	1 (0.6%)
Diarrhoea	0	0	1 (0.6%)	0	1 (0.6%)
Toothache	0	0	1 (0.6%)	0	1 (0.6%)
Cardiac disorders	0	0	3 (1.9%)	0	3 (1.8%)
Atrial fibrillation	0	0	1 (0.6%)	0	1 (0.6%)
Myocarditis	0	0	1 (0.6%)	0	1 (0.6%)
Palpitations	0	0	1 (0.6%)	0	1 (0.6%)
Sinus tachycardia	0	0	1 (0.6%)	0	1 (0.6%)
General disorders and administration site conditions	0	0	2 (1.3%)	0	2 (1.2%)
Non-cardiac chest pain	0	0	1 (0.6%)	0	1 (0.6%)
Pyrexia	0	0	1 (0.6%)	0	1 (0.6%)
Nervous system disorders	0	0	2 (1.3%)	0	2 (1.2%)
Headache	0	0	1 (0.6%)	0	1 (0.6%)
Somnolence	0	0	1 (0.6%)	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.6%)	0	1 (0.6%)
Muscle spasms	0	0	1 (0.6%)	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.6%)	0	1 (0.6%)
Oropharyngeal pain	0	0	1 (0.6%)	0	1 (0.6%)
Vascular disorders	0	0	1 (0.6%)	0	1 (0.6%)
Deep vein thrombosis	0	0	1 (0.6%)	0	1 (0.6%)

Note: TEAE = treatment-emergent adverse event. Adverse event terms were mapped according to MedDRA v21.1.
Note: Some patients may be represented in multiple columns if they changed dose level when entering the Study 1402 Extension. Each column reflects number of unique patients. Events are counted within the treatment group at the start of the event.
Source: ADSL, ADAE, ADAE2

2.6.8.9. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Safety data

The clinical safety database is based on 2 randomised, placebo-controlled, double-blind portions of phase 2 Study 1402 in patients with FA (Studies 1402 Part 1 and Part 2), and data from Study 1402 Extension, which is an open-label study. Further, the safety of omaveloxolone have been investigated in 1 phase 2 study in patients with mitochondrial myopathy (study 1403), 4 phase 1 studies in healthy subjects or patients with hepatic impairment (study 1703, 1804, 1805 and 1806) and 2 studies in patients with advanced solid tumours (study 1303 (phase 1) and 1401 (phase 1b/2)).

The data have been pooled into 6 analysis sets as explained in the patient exposure section.

In the assessment, the placebo-controlled study 1402 Part 2 (Analysis Set A) will be used as the main clinical safety database, Analysis Set C will be used for overall exposure and long-term safety. The remaining analysis sets are considered supportive and will be included where considered relevant.

In the FA clinical trials patients with cardiac disease were excluded from the studies except for mild to moderate cardiomyopathy associated with FA. Further, patients with uncontrolled diabetes were excluded from the studies.

With respect to the adolescent population which is to be included in the indication, based on the SmPC, the safety and efficacy of omaveloxolone in children and adolescents aged less than 16 years have not yet been established as no data are available. The applicant provided age data on the adolescent population as requested. In Study 1402 Part 1, 9 adolescent patients aged 16 or 17 were enrolled (16 years N = 3, 17 years N = 6) and in study 1402 Part 2, 24 adolescents aged 16 or 17 years were enrolled (16 years N = 11, 17 years N = 13). In Study 1402 Extension, 11 adolescent patients aged 16 or 17 were enrolled (16 years N = 3, 17 years N = 8). The information regarding adolescents in the SmPC is considered adequate.

In the RMP the applicant describes a randomised trial with bardoxolone in patients with Type 2 diabetes associated with advanced chronic kidney disease (BEACON study). In this trial, heart failure events were reported in 96/1088 (8.8%) patients randomised to bardoxolone, a structural analogue of omaveloxolone with a similar mechanism of action, versus 55/1097 (5.0%) patients randomised to placebo. The risk factors for heart failure in that study were identified and used as population selection criteria to mitigate cardiovascular risk in patients the subsequent studies with NrF2 activators. The applicant discussed the similarities between Nrf2 activators and omaveloxolone with regard to the chemical structure and safety profile. Omaveloxolone and bardoxolone methyl are Nrf2 activators in the same chemical series of semi-synthetic triterpenoid compounds and share a common pharmacophore. Although they exhibit differences in their structural and chemical properties, available nonclinical data suggest that the pharmacology and safety profiles of omaveloxolone and other Nrf2 activators are similar. Safety results from bardoxolone methyl studies in type 2 diabetes mellitus patients indicate an increased risk of heart failure presenting with fluid overload and increased blood pressure only in patients with advanced Stage 4 CKD, along with underlying cardiac diastolic dysfunction occurring as a consequence of fluid overload. These effects were not observed in patients with less severe CKD. Baseline BNP >200 pg/mL and previous hospitalisation for heart failure were identified as the only factors associated with adjudicated heart failure events. Among patients with previous hospitalisation for heart failure or BNP >200 pg/mL, treatment with bardoxolone methyl increased the risk of heart failure by 60%. Conversely, among patients with no previous heart failure hospitalisations or a baseline BNP level <200 pg/mL, the risk of heart failure was relatively low and similar (2.0%) in the bardoxolone methyl and placebo groups. Based on the totality of evidence, the excess heart failure events observed in

BEACON were likely due to the combination of Stage 4 CKD in patients with underlying diastolic dysfunction. Therefore, the potential for these clinical features in an FA population was evaluated.

Based on the provided evidence, it is acknowledged that the patient population in the BEACON study of bardoxolone methyl was different from the FA population. In the BEACON study all the patients suffered with type 2 diabetes mellitus together with Stage 4 chronic kidney disease. These patients were in increased risk of heart failure based on fluid overload and increased heart pressure. Compared to that, the cause of cardiac dysfunction in the FA patient population is myocardial fibrosis. That means that morphology of end stage heart failure in those two populations is different. The FA patient population has a low likelihood of advanced CKD (Stage 4 and 5) and cardiac diastolic dysfunction. Further, there has been no safety signal for heart failure presenting with fluid overload and increased BP in clinical trials of omaveloxolone in FA, including in patients with mild to moderate cardiomyopathy. Therefore, it is accepted not to include a contraindication in the SmPC. However, as stated by the applicant Approximately 2% of the FA population had T2DM and either Stage 4 or 5 CKD and therefore, it is agreed to updated section 4.4 of the SmPC regarding increases in BNP with warnings regarding fluid overload and congestive heart failure in patients with Stage 4 CKD. The SmPC has been revised with important warnings to give patients for whom there is currently no available treatment the chance to make an informed decision and undergo treatment. This more frequent monitoring of selected patients with a higher risk could lead to the early detection of a possible risk of developing heart failure, and the treatment would thus be adjusted early enough. Therefore, the SmPC updates is considered sufficient to prevent any worsening of the condition of high-risk patients.

The applicant is not proposing sections in the SmPC with warnings regarding thromboembolic, diabetes or renal events in the SmPC. This is accepted based on the data provided and since lipid abnormalities and increased BNP is described in section 4.4 and further it is stated that diabetes mellitus is common in patients with FA and that more frequent monitoring of patients with a recent hospitalisation for fluid overload due to underlying cardiomyopathy, diabetic stage IV chronic kidney disease, or other etiologies, is strongly recommended.

To further investigate the potential risk, the applicant plans to conduct an observational, multinational, post-marketing registry of omaveloxolone-treated patients with FA, which will continue to monitor and characterise any congestive heart failure events. This is acknowledged.

Exposure

Overall, in the omaveloxolone clinical programme, a total of 392 patients have been exposed to omaveloxolone.

Analysis Set A: In Study 1402 Part 2, 51 study participants received at least 1 dose omaveloxolone and 20 study participants received omaveloxolone for more than 48 weeks. The median patient years exposure was 0.92. 9 adolescents were exposed to omaveloxolone in Study 1402 Part 2, the median exposure was 0.92 years.

Analysis Set C: In total, 165 study participants received omaveloxolone at any dose and 159 patients in received omaveloxolone at doses of 150 mg and/or 160 mg. 167 exposure measurements occurred among the 159 patients who received omaveloxolone at doses of 150 mg and/or 160 mg. In total, 137 study participants received omaveloxolone for at least 48 weeks and 125 study participants received omaveloxolone for at least 96 weeks. The median patient years exposure was 2.77.

18 adolescents were exposed to omaveloxolone 150/160 mg in analysis Set C, the median exposure was 2.77 years. This is considered acceptable for representing the safety of the adolescents. In the following assessment this subgroup will be evaluated separately where considered relevant.

Overall, the safety database consisting of a total of 167 FA patients treated with omaveloxolone 150/160 mg is considered small and hardly fulfils the requirements of ICH E1 Population exposure; the extent of population exposure to ensure clinical safety. However, it is recognised that FA is a rare condition. Long-term exposure met the requirements with a total of 137 patients treated with omaveloxolone for at least 48 weeks and a total of 125 patients treated with omaveloxolone for at least 96 weeks. However, the restricted population with limited experience with cardiac disease and diabetes mellitus is of concern. Long-term safety has been included in the safety specification as missing information and congestive heart failure has been included as an important potential risk. An observational, post-marketing registry of omaveloxolone in Patients with FA is planned. The applicant provided a safety update from Study 1402 Extension as requested with the cut-off date 11 May 2023. Overall, based on the updated safety data, no new signals have been observed.

Demographics for Analysis Set A were well-balanced between the omaveloxolone-treated and placebo-treated patients except for sex and cardiomyopathy. 53% patients were male and 47% were female, with a higher proportion of patients in the omaveloxolone treatment group being female (61%) compared to the placebo group (33%). 49.0% had a history of cardiomyopathy in the omaveloxolone-treatment group compared to 28.8% in the placebo group. In the Cardiac Disorder SOC, 12 TEAEs were reported in 3 patients with a history of cardiomyopathy in the omaveloxolone treatment group while 2 TEAEs were reported in 2 patients with a history of cardiomyopathy in the placebo group. Eight out of the 12 TEAEs in the omaveloxolone treatment group occurred in 1 patient. Although an imbalance is noted, review of the TEAEs showed no impact on the safety evaluation.

The age range for exposure to omaveloxolone in Analysis Set A were from 16-39 year of age.

In general, baseline characteristics in patients aged <18 years were similar to those of the overall study population and similar across treatment groups. Omaveloxolone-treated adolescent patients had a higher reported incidence of history of cardiomyopathy (66.7%) compared with placebo-treated adolescent patients (46.7%), like adults. Further, omaveloxolone-treated adolescent patients had a higher incidence of history of scoliosis (100%) and scoliosis surgery (77.8%) compared with placebo (80.0% and 40.0%, respectively). No clinically relevant differences were noted between TEAEs that occurred in adolescent patients with and without scoliosis.

86.3% of omaveloxolone-treated patients completed treatment in the double-blind treatment phase of Study 1402 Part 2 (48 weeks) compared with 96.2% of placebo-treated patients.

Adverse events

Analysis Set A: At least 1 TEAE occurred in all omaveloxolone-treated patients and placebo-treated patients. TEAEs related to study drug were higher in the omaveloxolone treatment group (72.5%) compared to placebo (36.5%). The proportion of patients who interrupted study drug administration because of a TEAE was greater in the omaveloxolone group (17.6%) than the placebo group (1.9%). Discontinuations due to TEAEs were reported in 7.8% in the omaveloxolone treatment group and 3.8% in the placebo group. TEAEs were mostly mild or moderate in severity in both treatment groups (90.2% omaveloxolone; 100% placebo). 5 patients had severe TEAEs (9.8%) in the omaveloxolone treatment group and none in the placebo group. No patients had a severe TEAE that was assessed by the investigator as related to study drug. Serious TEAEs

were reported in 9.8% in the omaveloxolone treatment group and 3.8% in the placebo group. No deaths were reported in Analysis Set A.

The overall patterns of TEAEs in the adolescent population were similar to the adult population in Analysis Set A.

Analysis Set C: Overall, at least 1 TEAE occurred in 98.2% of omaveloxolone treated patients. The overall pattern of TEAEs in analysis set C were comparable to Analysis Set A. However, the percentage of patients who discontinued study drug due to TEAEs (9.1%) and interrupted omaveloxolone use (23.6%) due to TEAEs, was greater than that of the omaveloxolone-treated patients in Analysis Set A (7.8% and 17.6%, respectively). No deaths were reported in Analysis Set C.

Overall, the patterns of TEAEs were comparable between adults and adolescents in Analysis Set A and the incidence of TEAEs did not increase with long-tern administration except for interruptions and discontinuations due to TEAEs.

Common TEAEs

Analysis Set A: The most frequent TEAEs were reported in the SOC of gastrointestinal disorders (60.8% in the omaveloxolone treatment group and 36.5% in the placebo group). Nausea was the most frequent PT within the SOC (33.3% and 13.5%, respectively) followed by Diarrhoea (19.6% and 9.6%, respectively) and vomiting (15.7% and 11.5%, respectively). Abdominal pain upper (9.8% vs. 1.9%) and abdominal pain (7.8% vs. 1.9%) were also reported more frequently in the omaveloxolone treatment group. All the PT's except for vomiting is included in the ADR table in the SmPC.

Vomiting has been added to the ADR table in section 4.8 of the SmPC and under "Description of selected adverse reactions" under the subsection "Gastrointestinal disorders", since 4 cases were possible related and 1 probably related in the omaveloxolone vs. 0 in the placebo group in Study 1402 and therefore a causal relationship to omaveloxolone is considered possible.

In the SOC Injury, poisoning and procedural complications (51.0% in the omaveloxolone treatment group and 34.6% in the placebo group), PTs were overall balanced between the omaveloxolone treatment group and placebo treatment group except for limp injury (7.8% vs. 1.9%), muscle strain (5.9% vs. 1.9%) and skin abrasion (25.5% vs. 21.2%). Skin abrasion and limp injury were not considered related to study drug in any of the events.

Muscle strain is not included in the ADR table in the SmPC since all events in the omaveloxolone-treated patients were nonserious, mild in severity, and assessed by the investigator as unrelated to study medication. Time to onset ranged from Study Day 120 to Study Day 146. For the patient in the placebo group, the event was mild, assessed as unrelated by the investigator, and with onset at Study Day 146. Thus, addition of muscle strain to the ADR table of the SmPC is not considered to be required at this time.

Within the SOC of nervous system disorders (39.2% and 19.2%, respectively), headache was the most common PT and reported more frequently in the omaveloxolone treatment group (37.3% vs. 25.0%). Headache is included in the ADR table in the SmPC. Dyskinesia and somnolence were reported in 2 (3.9%) patients in the omaveloxolone treatment group and 0 in the placebo group. The applicant presented details on the two cases of somnolence. Since the two events were both mild in severity and one of the patients had a relevant medical history of anxiety, depression and fatigue and concomitant medication of fluoxetine 60 mg, it is agreed not to change the SmPC section 4.7 due to these observations.

Within the SOC Musculoskeletal and connective tissue disorders (35.3% vs. 19.2%) Back pain was the most frequent reported PT (13.7% vs. 7.7%) followed by muscle spasms (13.7% vs. 5.8%). Both PT are included in the ADR table in the SmPC. Joint swelling and pain in jaw were both reported in 2 (3.9%) patients in the omaveloxolone treatment group and in 0 in the placebo group. For the 2 omaveloxolone-treated patients who experienced joint swelling, both events were reported to have been a consequence of a fall (swollen knee in one patient and swollen elbow in another). The 2 patients who experienced pain in jaw both reported left jaw pain. As these TEAE occurred at a very low incidence, the events is not considered to be included in the SmPC as an ADR at this time.

Within the SOC Investigations (43.1% vs. 3.8%) ALT increased (37.3% vs. 1.9%), AST increased (21.6% vs. 1.9%), GGT increased (5.9% vs. 0%) and VLDL increased (3.9% vs. 0%) were reported more frequent in the omaveloxolone treatment group compared to the placebo group. ALT, AST, GGT and VLDL increased are all included in the ADR table of the SmPC.

In the SOC Respiratory, thoracic and mediastinal disorders (29.4% vs. 17.3%) Oropharyngeal pain (17.6% vs. 5.8%) and Rhinorrhoea (3.9% vs. 0%) were reported more frequent in the omaveloxolone treatment group compared to the placebo group. Oropharyngeal pain is included in the ADR table in the SmPC. Rhinorrhoea was not assessed to be related to the study drug by the investigator.

Fatigue (21.6% vs. 13.5%) were the most common PT within the SOC General disorders and administration site conditions (21.6% vs. 15.4%) and is included in the ADR table in the SmPC.

In the SOC Infections and infestations (27.5% vs. 7.7%), influenza was the most frequently reported PT in the omaveloxolone treatment group (13.7% vs. 3.8%) followed by urinary tract infection (7.8% vs. 0%) and Gastroenteritis viral (5.9% vs. 1.9%). Further, conjunctivitis was reported more frequently in the omaveloxolone treatment group compared to the placebo group (3.9% vs. 0%). Influenza and urinary tract infection are included in the ADR table in the SmPC. Because gastroenteritis and conjunctivitis occurred at a very low incidence and were considered either unlikely nor unrelated by the investigator, the TEAEs are not required to be included in the SmPC as ADRs.

Decreased appetite (11.8% vs. 3.8%) and Hypertriglyceridemia (3.9% vs. 0%) were reported more frequent in the omaveloxolone treatment group compared to the placebo group within the SOC Metabolism and nutrition disorders (13.7% vs. 3.8%). Decreased appetite and hypertriglyceridemia are included in the ADR table in the SmPC.

Rash macular (3.9% vs. 0%) was reported more frequently in the omaveloxolone treatment group compared to the placebo group in the SOC Skin and subcutaneous tissue disorders (11.8% vs. 3.8%). The TEAEs of rash macular were considered mild in severity, unrelated and unlikely related to study drug and therefore not considered to be included in the ADR table in the SmPC section 4.8.

In the SOC Reproductive system and breast disorders Dysmenorrhoea and Ovarian cyst were only reported in the omaveloxolone treatment group. The difference could be driven by the fact that there were more females in the omaveloxolone group. Dysmenorrhoea is included in the ADR table of the SmPC.

The majority of the most common TEAEs in either group were mild to moderate in severity. Five (9.8%) omaveloxolone-treated patients experienced 6 severe TEAEs (Contusion, Skin laceration, Migraine, Blood creatine phosphokinase increased, Suicidal ideation and Hydrocele). Two severe TEAEs were in adolescent patients (hydrocele in 1 patient and contusion and skin laceration in 1 patient). No severe event occurred in more than 1 patient and none of the severe events were considered related to study drug.

For most of the TEAEs there was a tendency of earlier onset in the omaveloxolone treatment group. Nausea (75.3 vs. 22.0 days) and diarrhoea (46.7 vs. 4.4 days) had a longer mean duration in the omaveloxolone treatment group compared to placebo. However, most TEAEs resolved within 2 months of the event start date.

In general, common TEAEs were reported at a similar proportion in omaveloxolone-treated adolescent and adult patients, with the exception of headache (0% of adolescent patients versus 45.2% of adult patients), ALT increased (0% of adolescent patients versus 45.2% of adult patients), AST increased (0% of adolescent patients versus 26.2% of adult patients), influenza (0% of adolescent patients versus 16.7% of adult patients), and muscle spasms (0% of adolescent patients versus 16.7% of adult patients).

The TEAEs reported during the study drug withdrawal period were well balanced between omaveloxolone-treated (29.4%) patients and placebo-treated (28.8%) patients. No new imbalances were observed.

Analysis Set C: In the table with summary of common TEAEs occurring in ≥10% of patients in omaveloxolone-treated patients and with a difference in incidence of ≥2% between omaveloxolone-treated patients and placebo-treated patients identified in Analysis Set A. All the above mentioned TEAEs were represented, which support the safety observations in Analysis A.

The majority of the most common TEAEs in either group were mild to moderate in severity. 21 (12.7%) omaveloxolone-treated patients experienced severe TEAEs. 4 (2.4%) experienced severe TEAEs within the SOC Infections and infestations (2 corona virus infection, 1 influenza and 1 gastroenteritis). Further, 1 additional omaveloxolone-treated patient reported a severe event of ALT increased, 1 additional omaveloxolone-treated patient reported a severe suicide attempt and 1 severe TEAE of acute left ventricular failure were also reported. Hepatic safety, Suicide and Cardiac safety is further assessed in the relevant sections.

The safety screening criteria used for evaluation of inclusion and an ADR is considered acceptable. The applicant has clarified that all available safety data were reviewed to determine the ADRs in section 4.8 of the SmPC.

According to the report body of studies, "related TEAEs" include both probably and possibly related events. The applicant provided tabulated summaries of TEAEs by relationship with a study drug, outlining the TEAEs possibly or probably related to study drug ("related") and unrelated to study drug. Based on the notes below the tables, events collected with relationship other than unrelated or unlikely related are considered related. A description of definitions which were followed within assessment was provided in study protocols which is accepted. Nevertheless, the applicant provided the overall summary tabulations of TEAEs indicating the concrete relationship category (e.g., definite, probable, possible, unlikely, unrelated) as reported by investigator.

Based on the overall summary of treatment-emergent adverse events (Analysis Set A) (see Table 9 in the submitted Summary of Clinical Safety), a total of 37 patients (72.5%) had a TEAE related to study drug compared to 19 patients (36.5 %) from the placebo group. The applicant provided the events related to study drug in Analysis Set A as assessed by the investigator as requested. No further concerns arose.

Serious adverse events and Deaths, other significant events

Deaths

No deaths were reported in the FA studies. Overall, 7 deaths were reported across the entire omaveloxolone development programme. All were in oncology studies in patients with stage 4 cancer. All deaths were in

omaveloxolone treated patients. 5 of the events were assessed as related to disease progression, 1 to worsening of dehydration and 1 due to injury after an accident. None of the deaths were assessed as related to the treatment. This is acknowledged.

Serious Adverse Events

Analysis Set A: Serious TEAEs were reported in 5 (9.8%) omaveloxolone-treated patients, and 3 (5.8%) placebo-treated patients. Within the SOC Cardiac disorders 3 (5.9%) omaveloxolone treated patients and 1 (1.9%) placebo treated patients experienced serious TEAEs.

A young adult patient had serious events of recurrent palpitations, noncardiac chest pain and sinus tachycardia that were all considered by the investigator to be possibly related to study drug. Although the Investigator considered these events possibly related to study drug, the applicant considered the events as unlikely related to study drug. Confounding factors included the natural history of underlying disease (ventricular wall thickening consistent with FA), recent viral upper respiratory tract infection and dehydration due to fluid restriction. Thus, the applicant does not consider the addition of these events to the SmPC section 4.8 to be required at this time. This is endorsed.

The other serious events were not considered related to study treatment and no adolescent patients had serious TEAEs.

Analysis Set C: The frequency of serious TEAEs reported in omaveloxolone-treated patients was similar to Analysis Set A (11.3% in the 150/160 mg dose). The applicant provided a summary of serious adverse events by PT and SOC for Analysis Set C as requested. No further concerns arose.

Safety Topics of Interest

[A] Hepatic Safety

Analysis Set A: A peak of mean absolute ALT and AST levels were observed at week 2 in the omaveloxolone treatment group with a subsequent decrease in values through week 48 toward baseline. More omaveloxolone-treated patients with normal baseline values had increases in ALT above the ULN while taking study drug than placebo-treated patients.

Only 29.4% omaveloxolone-treated patients had maximum ALT values ≤ ULN at some point during the treatment period. However, 76.5% of the omaveloxolone-treated patients had maximum ALT values ≤ ULN after the 4-week withdrawal period. Maximum AST values ≤ ULN were observed in 43.1% of omaveloxolone-treated patients and 84.3% had AST values ≤ ULN after the 4-week withdrawal period. One omaveloxolone-treated patient had ALT values ≥10× ULN. Further, one patient in Study 1402 Extension had a reversible AST elevation ≥10×ULN.

Adolescent patients had similar transient increases in ALT and AST, but the magnitude of increases was less than that observed in the adult population.

Mean decreases from baseline in total bilirubin were observed in the omaveloxolone treatment group. The decreases in total bilirubin were seen through Week 48 and returned to baseline after drug withdrawal. None omaveloxolone-treated patient exceeded 2× ULN. Adolescent patients treated with omaveloxolone had similar decreases in total bilirubin.

None of the omaveloxolone-treated patients had maximum ALT, AST or total bilirubin values that met potential Hy's law criteria.

Mean elevations in serum GGT were observed beginning at Week 2 that remained between 25 and 35 U/L throughout Week 48 of therapy. Mean GGT values returned to baseline within 4 weeks following drug withdrawal.

Two of 51 (3.9%) omaveloxolone-treated patients had maximum GGT values ≥5× ULN at some point during the treatment period. These 2 patients both had transient GGT elevations with no reported TEAEs, and the GGT values subsequently returned to <5× ULN without any additional measures or changes in dose. After the 4-week off-treatment follow-up period, the GGT values for both patients returned to baseline levels.

Adolescent patients had a slight increase in GGT due to omaveloxolone treatment, but to a smaller extent than the adult population.

In the Hepatobiliary disorders SOC, one TEAE of Cholelithiasis and one TEAE of Hepatic steatosis were reported in the omaveloxolone treatment group. Both TEAEs were mild in severity. The TEAE of Hepatic steatosis was considered to be possibly related to study drug by the investigator.

In the Investigations SOC, increases in ALT occurred in 37.3%, increases in AST in 21.6% and increases GGT in 5.9%.

Analysis Set C: The increase in ALT and AST were similar in Analysis Set C with a peak in week 2 and a decline through week 48. When looking at the mean absolute ALT and AST levels to week 168, there is a peak again in week 72 and subsequently a decline again. The peak observed at Week 72 in the Placebo - Omav group is from data collected in only 5 patients due to Covid 19 affecting 67 patients (45.0%) at week 72. Since the second apparent peak at Week 72 for both ALT and AST is derived from data from a very small number of patients, no meaningful conclusions can be drawn. This is acknowledged. However, the applicant states that out of these 5 patients, 3 of them experienced elevated ALT values and 2 experienced elevated AST values for most visits throughout the study. The applicant has updated the SmPC subsection "Aminotransferase elevations" accordingly.

Three omaveloxolone-treated patients treated with the 150 mg dose had ALT elevations ≥10× ULN and one patient AST elevations ≥10× ULN.

The decrease in bilirubin and the increase in GGT in Analysis Set A were similar in Analysis Set C.

Compared with the results in Analysis Set A, increases in ALT, AST, and GGT reported as TEAEs occurred at a lower frequency in Analysis Set C (28.3%, 13.8% and 3.8%, respectively). 3 TEAEs of Cholelithiasis and 1 TEAE of Hepatic steatosis were reported in the omaveloxolone treatment group. The events of Cholelithiasis were assessed as not related by the investigator.

There were no SAEs related to hepatic safety in patients treated with omaveloxolone. Five patients discontinued omaveloxolone treatment due to hepatic safety. Discontinuations due to elevations in transaminases and liver enzymes were not associated with concomitant elevations in bilirubin.

Overall, increase in AST, ALT and GGT is very common in the omaveloxolone treated patients. The increases in ALT and AST were not associated with increase in bilirubin and were reversible when discontinuation omaveloxolone. The applicant suggest that the increase in ALT, AST, and GGT could be due to pharmacological induction of enzymes without causing underlying injury. In the SmPC section 4.4 and 4.8, the applicant has described that maximal values of aminotransferase elevations typically occurred within first 12 weeks of treatment. Further, it is stated in section 4.4. that "ALT, AST, and bilirubin should be monitored prior to initiation of Skyclarys, monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated." The applicant considers the proposed guidance in the SmPC to be adequate and does not

consider further risk mitigation measures to be required for the increases in ALT and AST. This is acknowledged.

Patients with liver enzyme, bilirubin, albumin abnormalities or with history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis) were not treated in the pivotal study. The applicant recommends avoiding use of omaveloxolone for patients with severe hepatic impairment (Child-Pugh Class C), a modified dose of 100 mg Skyclarys once daily with close monitoring for adverse reactions for patients with moderate hepatic impairment (Child-Pugh Class B), and 150 mg Skyclarys once daily for patients with mild hepatic impairment (Child-Pugh Class A).

Regardless of conflicting evidence in the literature on susceptibilities to DILI in pre-existing chronic liver disease patients, the US Drug Induced Liver Injury Network showed that DILI in patients with pre-existing liver disease was associated with a significantly higher frequency of adverse outcomes, including mortality. The applicant has added in section 5.1 of the SmPC that patients with liver enzyme, bilirubin, albumin abnormalities or with history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis) were not treated in the pivotal study. The applicant will follow DILI as an important potential risk in the RMP.

Patients with significant abnormalities of clinical haematology or biochemistry, including but not limited to elevations greater than 1.5 times the ULN of AST or ALT were not allowed in the studies, unless it was attributable to muscle injury. The applicant clarified that per the above stated exclusion criterion, 3 subjects in Study 1402 Part 1 and 1 subject in Study 1402 Part 2 were excluded and not dosed. No patients met this exclusion criterion in Study 1402 Extension. No patients were enrolled in any part of Study 1402 on the basis of having an elevation attributable to muscle injury.

Drug induced liver injury is included in the safety specification in the RMP as an important potential risk and a precaution is included in the SmPC section 4.4. This is endorsed.

[B] Evaluation of Weight

Analysis Set A: A mean decrease of 1.35 ± 3.585 kg in weight relative to baseline was observed with omaveloxolone treatment over 48 weeks, while it increased 1.17 ± 4.108 kg for placebo-treated patients. Mean decreases in weight in omaveloxolone-treated patients were more pronounced in patients with higher baseline BMI (≥25 kg/m2) compared to patients with baseline BMI <25 kg/m2.

Adolescent patients treated with omaveloxolone had mean changes in weight that were comparable to adolescent patients treated with placebo. Further, it is reassuring that adolescent patients generally continued along their growth curves for weight during treatment with omaveloxolone.

Males treated with omaveloxolone had higher decreases from baseline in weight. However, a greater proportion of omaveloxolone-treated male patients had baseline BMI ≥25 kg/m2 (35.0% versus 22.6% of female patients), which may contribute to the differences between weight over time for males compared to females.

Analysis Set C: The overall changes in weight seen in Analysis Set C and in the subgroups was consistent with Analysis Set A.

A warning has been included in the SmPC section 4.4. This is endorsed. TEAEs of Weight decreased was reported in 1 (2.0%) omaveloxolone-treated patient verses 1 (1.9%) in the placebo group in Analysis Set A. Since a causal relationship is described with regard to weight decreased, it has been included in the ADR table.

[C] Evaluation of Infections and Infestations

Analysis Set A: Overall, 66.7% of the omaveloxolone treated patients reported TEAEs within the SOC infections and infestations compared to 57.7% of the placebo treated patients. None of the Infections and infestations TEAEs were considered severe. 1 patient had 2 SAEs within the SOC of infections and infestations. The SAEs were considered to be unlikely related to study drug, and no changes to study drug were made.

Upper respiratory tract infection and nasopharyngitis were reported more often in the placebo group comparted to the omaveloxolone treatment group. Influenza was the most frequently reported PT in the omaveloxolone treatment group that were reported more often in the omaveloxolone treatment group (13.7% vs. 3.8%) followed by urinary tract infection (7.8% vs. 0%) and Gastroenteritis viral (5.9% vs. 1.9%). Further, conjunctivitis was reported more frequently in the omaveloxolone treatment group compared to the placebo group (3.9% vs. 0%).

Analysis Set C: Overall, 67.3% of the omaveloxolone treated patients reported TEAEs within the SOC infections and infestations. Upper respiratory and Corona virus infections were reported more frequently compared to Analysis Set A. Otherwise the pattern was comparable to Analysis Set A.

The higher risk of influenza and the unknown long-term effect of omaveloxolone is a concern in FA patients, since they may develop dysphagia and aspiration pneumonia. However, no TEAEs of Aspiration pneumonia or Dysphagia occurred in any trial in Friedreich's ataxia. The applicant proposes to monitor for infections via routine pharmacovigilance. In addition, all adverse events, both serious and non-serious, experienced by patients enrolled in the Long-Term Safety Registry 408-C-2301, will be collected and analysed annually. Thus, the applicant will be able to monitor for infection-related adverse events. This is considered acceptable.

Infections and infestations were evaluated because of the anti-inflammatory effects associated with Nrf2 activation that could possibly lead to a decreased immune response. No meaningful differences in immune cells (e.g, white blood cell, lymphocytes, monocytes, neutrophils, eosinophils, basophils) counts were seen between omaveloxolone- and placebo-treated patients. This is acknowledged.

The mean time to onset of a reported TEAE in the Infections and infestations system organ class for omaveloxolone-treated patients was similar to that for placebo treated patients, 106.5 (±16.50) vs 105.3 (±20.93) days, respectively, indicating that administration of omaveloxolone did not compromise the immune response.

In summary, the applicant does not consider infections to be an important potential risk for omaveloxolone. Influenza and Urinary tract infection are adverse drug reactions in section 4.8 of the SmPC. The applicant will monitor infections via routine pharmacovigilance in the post marketing setting. This is acknowledged.

Patients with known active fungal, bacterial, and/or viral infections were excluded from the studies. The reason the applicant excluded patients with active infection was due to their acutely ill health status and the concern that the subjects may not be compliant with continuation of medication and study procedures. The reason for exclusion criteria is acknowledged.

[D] Evaluation of Cardiovascular Safety

Analysis Set A

Blood pressure: With regard to blood pressure, no mean changes from baseline in SBP or DBP were observed at Week 48 in patients in the omaveloxolone or placebo group. The number and proportion of patients with maximum SBP values that exceeded 140 mmHg was lower in the omaveloxolone-treated patients compared

to placebo-treated patient. None omaveloxolone-treated patients had SBP values that exceeded 160 mmHg vs. 2 (3.8%) placebo-treated patients and fewer omaveloxolone treated patients had DBP values that exceeded 90 mmHg than placebo-treated patients (5.9% vs 23.1%, respectively). In the adolescent patients, a modest increase from baseline in SBP and DBP were seen in both omaveloxolone, and placebo treated patients at Week 48 relative to baseline.

BNP: Small mean increases in BNP were observed with omaveloxolone treatment relative to placebo and 2 (3.9%) patients had BNP values that exceeded 200 pg/mL. Small numerical increases from baseline in BNP were also seen in omaveloxolone-treated adolescent patients at Week 48. The applicant hypothesised that the profile and magnitude of BNP increases observed with omaveloxolone treatment are due to improvements in metabolic parameters, this is further assessed in the non-clinical part of the assessment. However, due to the observations of congestive heart failure in a study with another NrF2 activator (bardoxolone methyl) and the cardiovascular risk in FA patients this was raised as a major concern. Elevated baseline BNP and prior hospitalisation for heart failure were among the major risk factors identified for the events in the study. As a consequence, patient with significant heart disease were excluded from the FA studies. Relevant warnings have been included in the SmPC section 4.4.

BNP increase is described in 4.4 and 4.8 under "Description of selected adverse reactions" and included in the ADR table.

Serum Lipids: Omaveloxolone-treated patients had a higher incidence of total cholesterol (33.3% vs. 6.8%) and LDL (19.0% vs. 9.1%) values above the ULN and a higher incidence of low HDL (6.0% vs 4.3) values under the ULN compared to placebo. There was 1 TEAE of hypercholesterolemia reported in an omaveloxolone-treated patient.

Total Cholesterol: Patients treated with omaveloxolone showed increases in total cholesterol of approximately 20 mg/dL within the first 2 weeks of treatment that remained high but returned to baseline after withdrawal of drug. Adolescent patients had lower total cholesterol levels at baseline and also had increases in total cholesterol after two weeks that slightly decreased until Week 48.

HDL cholesterol: Patients treated with omaveloxolone showed a reduction in HDL cholesterol of 5.4 mg/dL during the treatment period. Adolescent patients treated with omaveloxolone also showed reductions in HDL cholesterol at Week 48 that were similar to omaveloxolone-treated adult patients.

LDL cholesterol: Patients treated with omaveloxolone showed increases in LDL cholesterol of approximately 20 mg/dL within the first 2 weeks of treatment that remained high but returned to baseline after withdrawal of drug. The same increase was seen in adolescent patients.

VLDL cholesterol: A small increase in mean VLDL cholesterol was seen until week 24 in omaveloxolone-treated patients. VLDL values above the ULN were reported in 37.2% of omaveloxolone-treated patients compared with 30.4% of placebo-treated patients. The same pattern was seen in the adolescent patients but to a smaller extend.

The applicant suggest that the changes in lipids are related to the PD activation of Nrf2. The changes seen were reversible after withdrawal of the drug. The applicant provided literature showing that the increase in serum cholesterol observed in animal models and in the clinic may be due to higher levels of acetyl-CoA from fatty acid oxidation, higher levels of NADPH, and lower levels of reactive oxygen species that occur as a consequence of Nrf2 activation. Therefore, by suppressing oxidative stress, Nrf2 activation may reduce the formation of oxidised-LDL despite increasing total cholesterol levels. Further, despite the potential to increase

cholesterol levels, pharmacological Nrf2 activation has been shown to be protective in models of atherosclerosis.

During Study 1402 Part 2, the mean LDL value over the 48-week treatment in the omaveloxolone group was 108.7 mg/dL, and the mean increase in LDL from baseline in the omaveloxolone group was 23.5 mg/dL at 48 weeks. 1/51 (1.9%) patients in the omaveloxolone group had persistent elevated LDL ≥160 mg/dL. Persistently elevated LDL>=160 mg/dL is recognised as an ASCVD risk enhancer. A warning regarding lipids is included in the SmPC section 4.4 with a recommendation to monitor lipids prior and during treatment. This is considered relevant.

No patients in either the omaveloxolone or placebo group received treatment for hypercholesterolemia during Study 1402 Part 2. As of 11 May 2023, no ASCVD treatment-emergent adverse events including lipid elevations were reported in Study 1402 Part 2 or the Extension.

Overall, it is agreed with the applicant that the changes in lipids seen in the studies, is not giving a clinically relevant risk of atherosclerosis in FA patients and therefore, it should not be included in the RMP.

Electrocardiograms: Omaveloxolone-treated patients did not show meaningful changes in ECG parameters relative to baseline or compared with placebo-treated patients for PR interval, RR interval, ventricular heart rate or QRS duration. However, 3 (7.0%) omaveloxolone treated patients had QTcF interval >450 to 480 ms vs. 0 in the placebo group. Further, 5 (11.6%) omaveloxolone treated vs. 3 (6.0%) placebo treated patients had QTcB interval >450 to 480 ms and 1 (2.3%) vs. 0 had QTcB interval >480 to 500 ms. All patients had magnesium levels within the normal range at Week 48 when the prolongations of QT interval were observed. Moreover, the patients mentioned above had magnesium levels within the normal range throughout the study except 1 where a mild increase in magnesium level was observed which normalised before Week 48. This indicates that low magnesium is not the cause of the slight prolongation of the QT interval.

The applicant states that any effect of omaveloxolone on the baseline-corrected QT interval by Fridericia's formula (ΔQTcF) was ruled out in healthy subjects receiving the therapeutic omaveloxolone dose (150 mg once daily [fasted]) and in clinical worst case exposure scenarios (150 mg single dose [fed] and 150 mg once daily [fed]). The applicant plans to conduct a thorough QTc study in healthy subjects in which the exposure will be 5-fold higher (study in fed state) than the observed steady state exposure in FA patients receiving 150 mg once daily. An ongoing through QTc study is ongoing in health volunteers. If the study turns out positive, the applicant proposes to insert further precautions/instructions in the product information. This is acceptable. The results of study 408-C-2201 should be submitted (**REC**).

Echocardiograms: Treatment with omaveloxolone did not result in meaningful changes in echocardiogram parameters relative to baseline or compared with placebo-treated patients.

TEAEs related to cardiovascular safety: Overall, the number of patients reporting TEAEs in the Cardiac disorders SOC was similar for omaveloxolone-treated and placebo-treated patients. Overall, the number of patients reporting TEAEs in the Cardiovascular SMQs were well balanced between omaveloxolone treated patients and placebo treated patients. However, evaluation of the Cardiac failure SMQ showed slightly more patients who reported TEAEs in the omaveloxolone group compared with the placebo group (3 (5.9%) patients vs. 1 (1.9%) patient, respectively).

Three omaveloxolone-treated patients reported SAEs within the Cardiac disorders SOC; 1 patient experienced 1 SAE of atrial fibrillation, 1 patient experienced SAEs of recurrent palpitations, worsening sinus tachycardia and noncardiac chest pain and 1 patient experienced the SAE of ventricular tachycardia. The patient experienced SAEs of recurrent palpitations, worsening sinus tachycardia and noncardiac chest pain were

assessed as possibly related by the investigator. However, the applicant considered the events as unexpected and unlikely related to study drug due to confounding factors (ventricular wall thickening consistent with Friedreich's ataxia observed on MRI, recent viral upper respiratory tract infection and dehydration due to fluid restriction. The other cardiac SAEs were assessed as not related to study drug by the investigator.

Analysis Set C

The profile of blood pressure over time was similar to the changes described above for the overall Analysis Set A population (data not included here).

In Analysis Set C, the profile of BNP over time was similar to that observed in Analysis Set A for the overall population and adolescent population. Slight increases in BNP were observed with omaveloxolone treatment. There were 5 patients (3.0%) who had a TEAE reported of BNP increased. None of these 5 had any BNP result over 200 ng/mL. BNP values that exceeded 200 pg/mL at any time while on study treatment were seen in 7 patients, cardiac AEs were reported for 2 of the 7 patients (data not included here). The applicant provided the narratives for the patients with BNP values that exceeded 200 pg/mL and had cardiac AEs and discussed if the events could be treatment related. The events were not considered to be related to omaveloxolone.

The incidence of total cholesterol above the ULN was lower compared to Analysis Set A (25.5% vs. 33.3%) and the incidence of LDL cholesterol values above the ULN was higher in Analysis Set C compared to Analysis Set A (25.9% vs. 19.9%) (data not included here). There were 5 patients with TEAEs of hypercholesterolemia or lipids increased reported in omaveloxolone-treated patients. The mean change from baseline in total cholesterol at Weeks 48, 96, and 144 was 19.4, 40.6, and 28.9 mg/dL, respectively. Like in Analysis set A the change was reversible after withdrawal of the treatment. The Change in HDL, LDL and VLDL cholesterol were similar to the changes seen in Analysis Set A.

With regard to the ECGs, omaveloxolone-treated patients did not show meaningful changes in ECG parameters relative to either baseline, similar to Analysis Set A, except for the mentioned events of QTc prolongations seen in Analysis Set A.

With regard to echocardiograms, treatment with omaveloxolone did not result in meaningful changes in echocardiogram parameters relative to baseline or compared with Analysis Set A. However, cases of Left ventricle dilated at Week 48 (1 (2.3%), Left ventricular hypertrophy at Week 48 (11 (25,6%)) and Right ventricle enlargement at Week 48 (2 (4.7%)) were reported that was not provided for Analysis Set A in the integrated summary of safety. The applicant provided data on these patients. Left ventricular hypertrophy was reported in 11 omaveloxolone treated patients at Week 48. Ten of these patients had left ventricular hypertrophy at baseline. It is agreed with the applicant that the echocardiogram changes appear as unlikely related to omaveloxolone but likely related to the underlying disease, based on the limited number of cases and the slight decrease of ejection fraction at week 48.

With regard to TEAEs related to cardiovascular safety the incidence of palpitations was higher than in Analysis Set A (3.8% vs. 2.0%). However, in Analysis Set A, TEAEs of palpitations occurred less frequently (n=1, 2%) in the omaveloxolone group when compared to the placebo group (n=2, 3.8%). The 1 patient in the omaveloxolone group who experienced palpitations had a medical history of tachycardia with atenolol as treatment and therefore there is not considered to be an association between palpitations and omaveloxolone use and QTc prolongation.

In the Cardiac failure SMQ the incidence of TEAEs were higher in Analysis Set C (8.2%) compared to Analysis Set A (5.9%).

Overall, increase in BNP were seen in both Analyses Set A and C, which is of concern due to the cardiac findings from another NrF2 activator and the cardiac comorbidities in FA patients. Further, Cardiac failure SMQ showed slightly more patients who reported TEAEs in the omaveloxolone group compared with the placebo group and the incidence were higher in Analysis Set C.

Increase in total cholesterol and LDL cholesterol is of concern since the treatment is intended for long-term use and the overall risk of atherosclerotic cardiovascular disease in FA patients treated with omaveloxolone is unknown.

Treatment-Emergent Adverse Events Related to Depression, Suicide, and Self-Injury

In Analysis Set A, 15 (29.4%) Omaveloxolone-treated patients and 10 (19.2%) Placebo treated patients had a prior history of depression. In Study 1402 Part 2, 1 of the omaveloxolone treated patients reported suicidal ideation and in Study 1402 Extension, 4 patients reported a TEAE related to suicide. All 5 patients had a medical history of depression.

Based on the risk factor of depression in all 5 cases, omaveloxolone is not considered related to the suicide attempts.

Laboratory findings

Haematology

In Analysis Set A, small decreases in erythrocytes, haematocrit and haemoglobin were observed in omaveloxolone-treated patients at Week 48. None of the decreases were clinically significant. Overall, no clinically meaningful changes in haematology parameters were noted in Analysis Set A, including leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes and platelets. No omaveloxolone-treated patients had haematology laboratory abnormalities reported as TEAEs.

Clinical Chemistry

No clinically significant changes were seen for total protein, glucose, lactate dehydrogenase, calcium, chloride or sodium at week 48 compared to baseline, nor for haemoglobin A1c at week 12 compared to baseline.

Albumin

Baseline Albumin levels were lower in the omaveloxolone treatment group compared to placebo. There were no clinically significant changes throughout the week 48 and no patients reported low albumin values across treatment groups.

Creatine Kinase

An initial decrease in median CK levels was observed in the omaveloxolone treatment group that were generally maintained through Week 48. Omaveloxolone-treated patients had a median baseline of 87.0 U/L and a median change from baseline of -17.0 U/L at Week 48 versus a baseline of 111.0 U/L and a median change from baseline of -2.0 U/L in placebo-treated patients. Median CK values showed a change from baseline of -12.5 U/L after stopping study drug. A higher percentage of placebo-treated patients had ≥1 on-treatment high CK values compared with omaveloxolone-treated patients (15.2% versus 8.2%, respectively). The applicant suggest that the results may indicate a decreased muscle inflammation and turnover in the omaveloxolone treated patients.

Serum Creatinine and Estimated Glomerular Filtration Rate

Omaveloxolone-treated patients showed mean decreases from baseline to Week 48 in serum creatinine and mean increases in eGFR. The decreases in serum creatinine were greater than those seen in placebo-treated patients and omaveloxolone-treated patients had larger increases in eGFR. In Analysis Set A, omaveloxolone-treated patients had a mean change from baseline in serum creatinine of -0.056 ± 0.0852 mg/dL at Week 48 versus 0.020 ± 0.0968 mg/dL in placebo-treated patients and omaveloxolone-treated patients had a mean change from baseline in eGFR of 6.83 ± 11.515 mL/min/1.73m2 at Week 48 versus -3.39 ± 13.392 mL/min/1.73m2 in placebo-treated patients.

In Analysis Set C the same pattern was seen. The applicant discussed the mechanism of these findings also in light of the opposite non-clinical findings of tubular degeneration/regeneration in rat kidneys accompanied by proteinuria following treatment with omaveloxolone.

Tubular degeneration/regeneration with proteinuria has been observed in the rat. However, in both oral and dermal dosing studies in rat, the renal changes did not appear to have a negative functional impact, based on the lack of concurrent changes in blood urea nitrogen or serum creatinine levels, and they were also not associated with signs of chronic inflammation or fibrosis even after up to 6 months of daily oral administration. The available data indicate that rats are more sensitive than other species to the effects of omaveloxolone in the kidney, as well as other organs. The applicant implemented urinalysis and microscopy assessments, including semi-quantitative urine protein, and a kidney function marker, defined as an estimated glomerular filtration rate (eGFR) in the Study 1402, due to the non-clinical findings. Based on urine protein dipstick test, there were no notable increases in urine protein observed at Week 48 compared to screening in the omaveloxolone group.

Ferritin

Omaveloxolone-treated patients had increased values of ferritin. 1 (3.2%) omaveloxolone-treated patient had ≥1 on-treatment high ferritin values compared to 0 placebo treated patients. Omaveloxolone treated patients had a mean (±SD) change from baseline of 20.09 ± 41.570 ng/mL at Week 48 versus a mean (±SD) change from baseline of 1.38 ± 22.225 ng/mL in placebo-treated patients. Similarly, omaveloxolone-treated patients in Analysis Set C had a mean (±SD) baseline value of 55.01 ± 51.924 ng/mL and mean (±SD) change from baseline in ferritin at Extension Weeks 48, 96, and 144 of 19.32 ± 40.667 ng/mL, 28.16 ± 17.364, and 24.92 ± 49.93, respectively. The values returned to near-baseline values in omaveloxolone-treated patients at the withdrawal visit. The applicant suggest that since Nrf2 induces the expression of the genes that encode the components of the ferritin complex, increases in ferritin likely reflect activation of Nrf2. There were no imbalances in adverse events or serious adverse events that would be reflective of pathological conditions associated with elevated serum ferritin levels. It is agreed with the applicant that the increases in serum ferritin likely reflect Nrf2 activation and are indicative of the pharmacodynamic activity of omaveloxolone and not inflammation.

Magnesium

A small decrease in magnesium were observed in the omaveloxolone treated patients, however, no patients reported magnesium values below the lower limit of normal in Analysis Set A. Omaveloxolone-treated patients had a mean change from baseline of -0.02 ± 0.100 mg/dL at Week 48 versus a mean change from baseline of -0.01 ± 0.135 mg/dL in placebo-treated patients. Mean serum magnesium levels returned to baseline after withdrawal of drug. The same pattern was observed in Analysis Set C.

Within Analysis Set A, the correlation analysis of changes from baseline at Week 48 in serum magnesium and QTcF suggested that decreases in serum magnesium were not associated with changes in QTcF for omaveloxolone treated patients (Pearson correlation=0.272; p=0.0811; n=42). However, 3 (7.0%) omaveloxolone treated patients had QTcF interval >450 to 480 ms vs. 0 in the placebo group.

Potassium

Omaveloxolone-treated patients had a mean change from baseline of 0.14 ± 0.344 mEq/L at Week 48 versus a mean change from baseline of -0.03 ± 0.375 mEq/L in placebo-treated patients. No omaveloxolone-treated patients had ≥1 on-treatment high potassium values. Omaveloxolone-treated patients in Analysis Set C had a mean change from baseline of 0.15 ± 0.345 mEq/L at Week 48, 0.11 ± 0.344 mEq/L at Week 96, and 0.13 ± 0.346 mEq/L at Week 144, which shows that the change remained stable. Small increases in change from baseline in potassium levels were seen compared to placebo and also in the open-label extension study. In addition, small but sustained increases in pulse were seen as well. There is not a plausible mechanistic explanation for the observed small increases in potassium levels or the small increases in pulse. Nonclinical toxicity studies in rats have shown variable effects on potassium levels and there were no changes in potassium levels in any of the toxicity studies conducted in monkeys. Mean potassium levels remained within the normal range in Study 408-C-1402 Part 2 and Study 408-C-1402 Extension. However, 9 individual patients experienced potassium elevations above the ULN. The applicant provided data on these 9 participants. Potassium elevations above the ULN were transient and there was no clear trend regarding the timing of the elevations. No meaningful increases in pulse occurred at the same time as the potassium elevations >ULN and no cardiac AEs were reported in any of the 9 patients with potassium levels >ULN study.

Uric Acid, Blood Urea Nitrogen, and Bicarbonate

Mean decreases in uric acid, BUN and bicarbonate were observed in omaveloxolone-treated patients in Analysis Set A. In omaveloxolone treated patients a mean change from baseline uric acid of -0.48 ± 0.800 mg/dL at Week 48 versus a mean change from baseline of -0.17 ± 0.679 mg/dL in placebo-treated patients. A mean change from baseline BUN of -0.38 ± 2.740 mg/dL at Week 48 in omaveloxolone treated patients versus a mean change from baseline of -0.20 ± 2.262 mg/dL in placebo-treated patients was observed.

Omaveloxolone-treated patients in Analysis Set A had a mean change from baseline bicarbonate of -0.51 ± 2.585 mEq/L at Week 48 versus a mean change from baseline of -0.32 ± 2.082 mEq/L in placebo-treated patients. 3 (6.0%) patients in the omaveloxolone group had abnormal low bicarbonate versus 0 in the placebo group. The observed decreases in uric acid, bicarbonate, and BUN were mild and no associations with increases in ALT and AST were observed. The applicant suggest the decreased uric acid, BUS and bicarbonate are due to increased kidney function. This is acknowledged.

Vital signs

A small increase in pulse were seen in omaveloxolone treated patients with mean changes from baseline ranging from -4.0 to 4.4 bpm for omaveloxolone-treated patients and -5.9 to 0.3 bpm for placebo-treated patients. An OC have been raised on this issue in relation to increased potassium.

Weight loss is discussed above and the observations of weight loss was similar for BMI.

Blood pressure were evaluated in relation to cardiovascular safety.

Safety in special populations

Age

Overall, the same percentage of adolescent patients experienced a TEAE compared with adults ≥18 years of age in both treatment groups (100%). The applicant provided an overall overview of the incidence of the different TEAEs categories in adolescents and adults. TEAEs related to study drug were more frequent in the adults compared to adolescents (65.1% vs. 45.5% in Analysis Set C) and likely were TEAE with study drug discontinuation reported more frequent in adults compared to adolescents (9.4% vs. 4.5%). Due to the small number of adolescent patients (n=22), results should be interpreted with caution.

Adolescent omaveloxolone-treated patients experienced a higher percentage of TEAEs in the following SOCs: Infections and infestations (77.8% versus 64.3%), General disorders and administration site conditions (55.6% versus 31.0%), Respiratory, thoracic and mediastinal disorders (44.4% versus 35.7%), Cardiac disorders (11.1% versus 9.5%), Immune system disorders (11.1% versus 0%), Surgical and medical procedures (11.1% versus 0%), and Congenital, familial and genetic disorders (11.1% versus 0 %). The higher frequency of cardiac disorders, congenital, familial and genetic disorders, surgical and medical procedures and immune system disorders could be due to a higher frequency of cardiac disorders, familial and genetic disorders, scoliosis and immune system disorders in their medical history reported at baseline in the adolescent population compared to the adult population. Due to the small number of adolescent patients (n=9), results should be interpreted with caution.

Sex

The overall incidence of TEAEs was equal between males and female patients (100%). The applicant provided an overall overview of the incidence of different TEAEs categories in the males and females. In Analysis Set A, more TEAEs related to study drug were reported in females in both the placebo and omaveloxolone treatment group compared to male patients. However, in Analysis set C, TEAEs related to study drug were similar for male and female patients (65.5% vs. 64.2%). TEAEs with Study Drug Discontinuation were reported more frequent in male patients compared to female patients (10.7% vs. 7.4%) in Analysis set C.

Male patients experienced a higher percentage of TEAEs compared to females in the following SOCs: Investigations (65.0% versus 45.2%), Psychiatric disorders (15.0% versus 9.7%), Eye disorders (5.0% versus 3.2%), Hepatobiliary disorders (10.0% versus 0%), Immune system disorders (5.0% versus 0%), Blood and lymphatic system disorders (5.0% versus 3.2%), Surgical and medical procedures (5.0% versus 0%), and Congenital, familial and genetic disorders (5.0% versus 0%). A higher percentage of male patients had TEAEs of ALT increased (50.0% versus 29.0% of female patients).

Female patients experienced a higher percentage of TEAEs compared to males in the following SOCs: Injury, poisoning and procedural complications (74.2% versus 45.0%), Nervous system disorders (61.3% versus 35.0%), Musculoskeletal and connective tissue disorders (54.8% versus 35.0%), General disorders and administration site conditions (41.9% versus 25.0%), Respiratory, thoracic and mediastinal disorders (45.2% versus 25.0%), Skin and subcutaneous tissue disorders (35.5% versus 25.0%), Cardiac disorders (12.9% versus 5.0%), Metabolism and nutrition disorders (19.4% versus 10.0%), Renal and urinary disorders (6.5% versus 5.0%), Reproductive system and breast disorders (22.6% versus 0%), and Ear and labyrinth disorders (6.5% versus 0%). The higher frequency of Reproductive system and breast disorders could be due to a higher frequency of females reporting medical history of reproductive system and breast disorders (38.7% versus 0% of male patients).

For most of the SOCs there did not seem to be any differences or pattern of events that were clinically meaningful. In SOCs of Investigations, General disorders and administration site conditions, and Metabolism and nutrition disorders there appeared to be individual PTs (alanine aminotransferase increased, Aspartate aminotransferase increased, Fatigue, and Decreased appetite) that were imbalanced between sex; these events were non-serious and mild to moderate in severity.

Geographic region

The majority of patients in both treatment groups were recruited in the United States (70.6% omaveloxolone-treated, 67.3% placebo-treated). In Analysis Set C more TEAEs related to study drug were reported in the other countries compared to the US (71.1% vs. 63.3%). More infections and infestations were reported in the other countries compared to United states (80.0% vs. 61.1%) in Analysis A. However, due to small numbers in the other countries' category (n=15), cautions should be taken with interpretation.

Ethnicity and Race

The majority of patients in both treatment groups were not Hispanic or Latino (omaveloxolone, 96.1%; placebo, 94.2%) and white (omaveloxolone, 98.0%; placebo, 96.2%). Because there were only 2 omaveloxolone-treated patients who were Hispanic or Latino and 1 omaveloxolone-treated patient who were not white, no conclusions can be drawn.

Pes Cavus Status

The majority of patients in both treatment groups did not have pes cavus (omaveloxolone, 80.4%; placebo, 80.8%). An overall overview of the incidence of different TEAEs categories in the patient with and without pes cavus was provided. The safety profile did not show any differences between patients with severe pes cavus compared to patients without severe pes cavus.

Compared with omaveloxolone-treated patients without pes cavus, omaveloxolone-treated patients with pes cavus experienced a higher percentage of TEAEs in the following SOCs: Nervous system disorders (80.0% versus 43.9%), Musculoskeletal and connective tissue disorders (60.0% versus 43.9%), General disorders and administration site conditions (40.0% versus 34.1%), Respiratory, thoracic and mediastinal disorders (40.0% versus 36.6%), Renal and urinary disorders (20.0% versus 2.4%), Reproductive system and breast disorders (20.0% versus 12.2%), Ear and labyrinth disorders (10.0% versus 2.4%), and Immune system disorders (10.0% versus 0%).

Compared with omaveloxolone-treated patients with pes cavus, omaveloxolone-treated patients without pes cavus experienced a higher percentage of TEAEs in the following SOCs: Infections and infestations (75.6% versus 30.0%), Injury, poisoning and procedural complications (65.9% versus 50.0%), Gastrointestinal disorders (68.3% versus 60.0%), Psychiatric disorders (12.2% versus 10.0%), Cardiac disorders (12.2% versus 0%), Metabolism and nutrition disorders (19.5% versus 0%), Eye disorders (4.9% versus 0%), Hepatobiliary disorders (4.9% versus 0%), Blood and lymphatic system disorders (4.9% versus 0%), Surgical and medical procedures (2.4% versus 0%), and Congenital, familial and genetic disorders (2.4% versus 0%).

Since only 10 omaveloxolone treated patients had pes cavus the results should be interpretated with caution.

Weight and diabetes mellitus

Two patients with diabetes mellitus were enrolled but no clear imbalance in adverse events was observed.

Data was analysed for patients in the omaveloxolone or placebo group with body mass index (BMI) < 25 kg/m2 and BMI ≥ 25 kg/m2.

Overall, there was a numerical imbalance between patients with BMI < 25 kg/m2 and BMI ≥ 25 kg/m2 treated with omaveloxolone for some individual preferred terms. However, given the small number of patients (N=14 for BMI ≥ 25 in omaveloxolone treatment group), caution should be taken with interpretation and there were no apparent differences in safety in patients in the two weight groups.

Hepatic impairment and renal impairment

Patients with clinically significant hepatic impairment were excluded from the study and no patients with renal impairment were enrolled.

Use in Pregnancy and Lactation

The effect of omaveloxolone have not been investigated in pregnant or breastfeeding woman. Pregnancy and breastfeeding were criteria for permanent discontinuation in all omaveloxolone studies and women and men with reproductive potential were required to use a reliable method of birth control during the clinical studies. No women who were exposed to omaveloxolone became pregnant during any omaveloxolone study. Additionally, there were no pregnancies in partners of male patients exposed to omaveloxolone during their participation in a study.

Studies in animals have shown reproductive toxicity, such as increased number of stillbirths, delayed sexual maturation in offspring males and reduced reproductive function in offspring females at dose levels that were not related to maternal toxicity.

Because there is no confirmed identified risk in humans during pregnancy and lactation, adding pregnancy as a contraindication or as a warning and precaution is not warranted. However due to the non-clinical findings, it has been added as important potential risk. The applicant has updated the SmPC section 4.6 as requested.

Overdose

No cases of overdose have been observed in the omaveloxolone development programme. From Study 1402 Part 1 in doses up to 300 mg (up to 12 weeks) have been used. No specific safety concerns were observed related to the higher dose.

Drug abuse

Based on its mechanism of action, omaveloxolone is not considered a drug for potential abuse and a drug abuse study was not conducted. This is acknowledged.

Withdrawal and Rebound

There is no clinical data indicating withdrawal or rebound effect of omaveloxolone.

Effects on the Ability to Drive or Operate Machinery or Impairment of Mental Ability

Somnolence were reported in 2 (3.9%) patients in the omaveloxolone treatment group and 0 in the placebo group in Analysis Set A. The applicant presented details on the two cases of somnolence. Since the two events were both mild in severity and one of the patients had a relevant medical history of anxiety, depression and fatigue and concomitant medication of fluoxetine 60 mg, it is agreed not to change the SmPC section 4.7 due to these observations.

However, fatigue is an adverse drug reaction with the frequency very common in the SmPC section 4.8. Therefore, the wording in the SmPC section 4.7 has been changes to: "Omaveloxolone may have a minor influence on the ability to drive and use machines. Fatigue may occur following administration of omaveloxolone (see section 4.8)."

Safety related to drug-drug interactions

See pharmacology.

Discontinuation due to adverse events

There was a high discontinuation rate in the omaveloxolone treated patients compared to placebo treated patients. 7 patients (13.7%) discontinued treatment and 6 patients (11.8%) discontinued the study in active arm while these numbers were 2 (3.8%) and 1 (1.9%) for placebo group over 48 weeks. 3 other patients withdrew consent in the omaveloxolone treatment arm. Of the 7 patients who discontinued treatment, 4 patients discontinued treatment due to the occurrence of an AE and 3 patients discontinued treatment due to voluntary withdrawal.

4 patients (7.8%) had a TEAE that led to study drug discontinuation in the active arm (ventricular tachycardia, rosacea, ALT increased, AST increased and muscle spasm) compared to 2 patients (3.8%) in the placebo arm (atrial fibrillation and erythrosis) in Analysis Set A. In analysis C, 9.1% of patients reported a TEAE resulting in study drug discontinuation. 5 (3.0%) were related to AST and ALT increase.

In Analysis Set A, 9 (17.6%) patients in the omaveloxolone group and 1 (1.9%) patient in the placebo group interrupted study drug temporarily due to TEAEs. The most common TEAEs leading to study drug interruption were in the Investigations SOC and included ALT increased (11.8%), AST increased (5.9%) and GGT increased (3.9%).

Results for all omaveloxolone-treated patients in Analysis Set C (N=165) showed 39 (23.6%) patients reporting a TEAE resulting in study drug interruption. 12.7% were related to infections (corona virus infection 10.3%) and 7.9% were related to investigations, predominantly ALT (7.3%), AST (3.6%) and GGT (1.8%) increased.

Of the 6 patients who discontinued the study, 2 patients discontinued the study due to administrative reasons (lost to follow up) and 4 patients discontinued the study due to withdrawal of consent by the patient. Two patients discontinued treatment due to the occurrence of an AE and 2 patients discontinued treatment due to voluntary withdrawal (no additional information available). The 2 patients experienced 3 AEs (Constipation, Abdominal pain, Frequent bowel movements). The investigator considered the NSAEs of Constipation, Abdominal pain, Frequent bowel movements as moderate in severity and probably related to study drug. Overall, increase in ALT and AST were the most common reason for study drug discontinuations and coronavirus infection, increase in ALT and AST were the most common reason for study drug interruption.

2.6.10. Conclusions on the clinical safety

Overall, the safety database is considered small. The restricted population with limited experience with cardiac disease and diabetes mellitus is a drawback in such a chronic indication. The exceeded risk of heart failure and long-term safety is therefore included in the RMP.

Overall, available safety data from the clinical development programme show that omaveloxolone was generally well tolerated. Increase in AST and ALT are also important risks that need to be followed in a PASS.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 69: 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

2.7.2. Pharmacovigilance plan

Table 70: Summary of ongoing and planned additional pharmacovigilance activities

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

2.7.3. Risk minimisation measures

Table 71: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important potential risk: Drug-induced liver injury	Routine risk minimisation measures: SmPC section 4.4. PIL sections 2 and 4. SmPC section 4.4: ALT, AST, and bilirubin should be monitored prior to initiation of omaveloxolone monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated. If ALT or AST increases to > 5 × the ULN, omaveloxolone should be immediately discontinued and liver function tests should be repeated as soon as possible. (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 minimisation 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 minimisation measures: SmPC section 4.4. PIL sections 2 and 4 SmPC section 4.4: Patients should be advised of the signs and symptoms of congestive heart failure associated with fluid overload, such as sudden weight gain (≥1.4 kg in one day or ≥2.3 kg in one week), peripheral oedema, and shortness of breath. If signs and symptoms of fluid overload develop, BNP (or NT proBNP) should be monitored and managed according to standard clinical guidance. Treatment with 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 hospitalisation 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 minimisation 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

Missing information: Use in pregnancy	Routine risk minimisation 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 minimisation measures: None	Routine Pharmacovigilance Activities

Missing information: Long-term safety	Routine risk minimisation measures: NA	Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: None.
	Additional risk minimisation measures: None	Additional Pharmacovigilance Activities: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28 February 2023.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Skyclarys (omaveloxolone) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

FA is a genetic, life-shortening, debilitating, and degenerative neuromuscular disorder caused by a trinucleotide repeat expansion in the first intron of the frataxin gene, which encodes the mitochondrial protein frataxin. For the majority of patients, onset of symptoms occurs between 5 and 15 years of age, with a mean duration until loss of independent gait of 8 years and until wheelchair use of 11 to 14 years after disease onset (range 3 to 44 years), and a median survival of 34 to 37 years after disease onset.

The clinical phenotype of FA represents a multisystem disease encompassing not only characteristic neurological features, but also diverse non-neurological features such as hypertrophic cardiomyopathy, kyphoscoliosis, foot deformities (pes cavus) and diabetes mellitus. Age and GAA1 repeat length are known as prognostic factors. One fifth of patients are younger than 5 years at onset. Disease onset before the age of 20 and cardiac involvement are associated with faster progression of neurological symptoms. Cardiac dysfunction as a consequence of dilated cardiomyopathy and arrhythmias is widely accepted as the most common cause of mortality in patients with FA. Severe pes cavus is present in up to 25% of the typical onset FA population (Reetz, 2018).

Genetic diagnosis is necessary as only 75% of patients could be diagnosed correctly based on the original Harding criteria. LOFA or VLOFA have a slower progression with less frequent non-neurological symptoms.

Omaveloxolone is an investigational, oral, once-daily, activator of Nrf2. Omaveloxolone is hypothesised to work by inducing molecular pathways that promote the resolution of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signaling.

3.1.2. Available therapies and unmet medical need

Currently, there are no approved therapies for FA. The standard of care for FA is similar globally and includes palliative and symptomatic treatments. Thus, FA is a devastating, rapidly progressive, life-limiting disease with a significant unmet need.

While a cure for the disease is needed, a slowing or stopping of disease progression or prolongation of independence would be most valuable for the treatment of FA.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase II multicentre, randomised, double-blind, 48 weeks study comparing omaveloxolone 150 mg/day with placebo in a 16-40 year old FA population stratified according to pes cavus presence.

3.2. Favourable effects

The study met its primary efficacy endpoint: omaveloxolone significantly improved mFARS relative to placebo (mean difference of -2.40, p = 0.014) after 48 weeks of treatment in patients without pes cavus (n = 82, FAS). Each component of the mFARS favoured omaveloxolone. All sensitivity analyses were supportive of the primary analysis. A sensitivity analysis showed that the distribution of changes from baseline in mFARS were significantly different between omaveloxolone and placebo (p = 0.028) at Week 48. The tipping point for the trial, where the treatment effect loses significance, is a shift of +2 points (worsening) in the imputed data for missing omaveloxolone mFARS values at Week 48. The shift required to change the conclusion of the trial is more than twice the magnitude of worsening in the placebo group (+0.85 points). The pivotal results regarding changes in mFARS seems robust to the sensitivity analyses.

Maintenance of efficacy is supported by the ongoing extension study and its comparison to an external natural history cohort at 1 year and 3 years.

The subgroup of adolescent patients in the FAS seemed to have benefited significantly. Placebo-treated adolescent patients worsened by +2.17 points at Week 48, while omaveloxolone-treated adolescent patients improved by -3.42 points at Week 48 resulting in a placebo-corrected improvement of -4.16 points (n = 20; p= 0.0565). This is not surprising as the youngest age group shows the highest mean yearly changes in mFARS score, which decreases with age.

As a secondary endpoint, the improvements with omaveloxolone in FA-ADL, relative to baseline, achieved nominal significance relative to placebo (mean ± SE difference of -1.30 ± 0.629; p= 0.0420) which is considered highly important and clinically relevant. This is supportive of the primary analysis with functional improvement of all items of the FA-ADL scale.

3.3. Uncertainties and limitations about favourable effects

Overall, the pivotal study is a single pivotal trial in a treatment area with no approved therapies and many prior failures. It has a small sample size that is further limited during the analyses to FAS which only includes patients without pes cavus.

Representativeness of the patient population expected to be treated with the product (external validity) is limited due to small numbers and exclusion of severe population, FA patients with common concomitant diseases e.g., advanced cardiac disease, diabetes mellitus, and the paediatric population under the age of 16.

Positive findings on primary efficacy endpoint(s) are only supported by favourable trends in pre-specified key secondary efficacy measures. The key secondary endpoints, PGIC and CGIC scores, were only directionally supportive for omaveloxolone compared with placebo in the FAS. PGIC and CGIC scores were numerically improved in omaveloxolone-treated patients (mean difference of -0.43, p = 0.1251; and -0.13, p = 0.5199; respectively).

Treatment with omaveloxolone also improved mFARS relative to placebo (mean difference of -1.93, p = 0.0342) in all randomised FA patients (ARP; n = 103) as an exploratory predefined analysis and was supported by propensity matched analysis in longer term (1 and 3 years).

In the subset of patients with severe pes cavus (PCP; n = 20), the improvement with omaveloxolone in mFARS relative to placebo was not statistically significant (-1.19 points; p = 0.5379). A variety of pes cavus severities have been included in the pivotal study. Pes cavus population is variably classified or detected in the literature. No distinct phenotypical or clinical profile could be established from the literature for the

severe pes cavus population. Baseline characteristics or safety data did not show any major differences according to pes cavus severity. Consequently, no reason for a different pharmacodynamic effect could be thought of in the severe pes cavus population. Insignificant differences in effect size in severe pes cavus subgroup is considered due to small sample size, although an impact of foot structure on performance cannot be excluded.

The variability of the findings in important subgroups (e.g. age, gender, region, disease characteristics) were considered mainly as linked to small sample size and all subgroups were directionally favouring omaveloxolone treatment over placebo.

3.4. Unfavourable effects

In study 1402 Part 2, at least 1 TEAE occurred in all omaveloxolone-treated patients and all placebo-treated patients. TEAEs related to study drug were higher in the omaveloxolone treatment group (72.5%) compared to placebo (36.5%). The proportion of patients who interrupted study drug administration because of a TEAE was greater in the omaveloxolone group (17.6%) than the placebo group (1.9%). Discontinuations due to TEAEs were reported in 7.8% in the omaveloxolone treatment group and 3.8% in the placebo group. TEAEs were mostly mild or moderate in severity in both treatment groups (90.2% omaveloxolone; 100% placebo) and most TEAEs resolved within 2 months of the event start date. The overall patterns of TEAEs in the adolescent population were similar to the adult population. Serious TEAEs were reported in 5 (9.8%) omaveloxolone-treated patients, and 3 (5.8%) placebo-treated patients. Within the SOC Cardiac disorders 3 (5.9%) omaveloxolone treated patients and 1 (1.9%) placebo treated patients experienced serious TEAEs. No deaths were reported in the FA studies.

The most frequent TEAEs were reported in the SOC of gastrointestinal disorders (60.8% in the omaveloxolone treatment group and 36.5% in the placebo group). Nausea was the most frequent PT within the SOC (33.3% and 13.5%, respectively) followed by Diarrhoea (19.6% and 9.6%, respectively) and vomiting (15.7% and 11.5%, respectively).

Within the SOC of nervous system disorders (39.2% and 19.2%, respectively), headache was the most common PT and reported more frequently in the omaveloxolone treatment group (37.3% vs. 25.0%).

Increases in Alanine aminotransferase (37.3% vs. 1.9%), Aspartate aminotransferase (21.6% vs. 1.9%) and Gamma-glutamyltransferase (5.9% vs. 0%) were reported more frequent in the omaveloxolone treatment group compared to the placebo group. A peak of mean absolute ALT and AST levels were observed at week 2 in the omaveloxolone treatment group with a subsequent decrease in values through week 48 toward baseline. More omaveloxolone-treated patients with normal baseline values had increases in ALT above the ULN while taking study drug than placebo-treated patients. Adolescent patients had similar transient increases in ALT and AST, but the magnitude of increases was less than that observed in the adult population. None of the omaveloxolone-treated patients had maximum ALT, AST or total bilirubin values that met potential Hy’s law criteria.

Small mean increases in BNP were observed with omaveloxolone treatment relative to placebo and 2 (3.9%) patients had BNP values that exceeded 200 pg/mL. Small numerical increases from baseline in BNP were also seen in omaveloxolone-treated adolescent patients at Week 48.

Omaveloxolone-treated patients had a higher incidence of total cholesterol (33.3% vs. 6.8%) and LDL (19.0% vs. 9.1%) values above the ULN and a higher incidence of low HDL (6.0% vs 4.3) values under the ULN compared to placebo.

3 (7.0%) omaveloxolone treated patients had QTcF interval >450 to 480 ms vs. 0 in the placebo group. Further, 5 (11.6%) omaveloxolone treated vs. 3 (6.0%) placebo treated patients had QTcB interval >450 to 480 ms and 1 (2.3%) vs. 0 had QTcB interval >480 to 500 ms.

Number of patients reporting TEAEs in the Cardiac disorders SOC was similar for omaveloxolone-treated and placebo-treated patients and overall, the number of patients reporting TEAEs in the Cardiovascular SMQs were well balanced between omaveloxolone treated patients and placebo treated patients. However, evaluation of the Cardiac failure SMQ showed slightly more patients who reported TEAEs in the omaveloxolone group compared with the placebo group (3 (5.9%) patients vs. 1 (1.9%) patient, respectively).

Three omaveloxolone-treated patients reported SAEs within the Cardiac disorders SOC; 1 patient experienced 1 SAE of atrial fibrillation, 1 patient experienced SAEs of recurrent palpitations, worsening sinus tachycardia and noncardiac chest pain and 1 patient experienced the SAE of ventricular tachycardia. The patient experienced SAEs of recurrent palpitations, worsening sinus tachycardia and noncardiac chest pain were assessed as possibly related by the investigator.

Overall, 66.7% of the omaveloxolone treated patients reported TEAEs within the SOC infections and infestations compared to 57.7% of the placebo treated patients. None of the Infections and infestations TEAEs were considered severe. Influenza was the most frequently reported PT in the omaveloxolone treatment group that were reported more often in the omaveloxolone treatment group (13.7% vs. 3.8%) followed by urinary tract infection (7.8% vs. 0%) and Gastroenteritis viral (5.9% vs. 1.9%).

A mean decrease of 1.35 ± 3.585 kg in weight relative to baseline was observed with omaveloxolone treatment over 48 weeks, while it increased 1.17 ± 4.108 kg for placebo-treated patients. Mean decreases in weight in omaveloxolone-treated patients were more pronounced in patients with higher baseline BMI (≥25 kg/m2) compared to patients with baseline BMI <25 kg/m2. Adolescent patients treated with omaveloxolone had mean changes in weight that were comparable to adolescent patients treated with placebo and adolescent patients generally continued along their growth curves for weight during treatment with omaveloxolone.

Studies in animals have shown reproductive toxicity, such as increased number of stillbirths, delayed sexual maturation in offspring males and reduced reproductive function in offspring females at dose levels that were not related to maternal toxicity.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety database consisting of a total of 167 FA patients treated with omaveloxolone 150/160 mg is considered small and hardly fulfils the requirements of ICH E1 Population exposure. The restricted population with very limited experience with cardiac disease and diabetes mellitus is a drawback in such a chronic indication.

Due to the observations of congestive heart failure in a study with another NrF2 activator (bardoxolone methyl) and the cardiovascular risk in FA patients, a major concern was raised. The mechanism of action for cardiotoxicity suggested for bardoxolone by Chin et al. (2014) was fluid overload through modulation of endothelin in the kidneys in subjects with an underlying risk of heart failure. The risk factors for heart failure in that study were identified and used as population selection criteria to mitigate cardiovascular risk in patients in subsequent studies with NrF2 activators. Elevated baseline BNP and prior hospitalisation for heart failure were among the major risk factors identified for the events in the study with bardoxolone.

Omaveloxolone and bardoxolone methyl are both Nrf2 activators in the same chemical series of semi-synthetic triterpenoid compounds and share a common pharmacophore. Although they exhibit differences in their structural and chemical properties, available nonclinical data suggest that the pharmacology and safety profiles of omaveloxolone and other Nrf2 activators are similar. However, the patient population in the BEACON study of bardoxolone methyl was different from the FA population. In the BEACON study all the patients suffered with type 2 diabetes mellitus together with Stage 4 chronic kidney disease. These patients were in increased risk of heart failure based on fluid overload and increased heart pressure. Compared to that, the cause of cardiac dysfunction in the FA patient population is myocardial fibrosis. That means that morphology of end stage heart failure in those two populations is different. The FA patient population has a low likelihood of advanced CKD (Stage 4 and 5) and cardiac diastolic dysfunction. Further, there has been no safety signal for heart failure presenting with fluid overload and increased BP in clinical trials of omaveloxolone in FA, including in patients with mild to moderate cardiomyopathy. Therefore, it is accepted not to include a contraindication in the SmPC. However, approximately 2% of the FA population had T2DM and either Stage 4 or 5 CKD and therefore, it is agreed to updated section 4.4 of the SmPC regarding increases in BNP with warnings regarding fluid overload and congestive heart failure in patients with Stage 4 CKD. Congestive heart failure is included in the RMP as an important potential risk. To further investigate the potential risk, the applicant plans to conduct an observational, multinational, post-marketing registry of omaveloxolone-treated patients with FA, which will continue to monitor and characterise any congestive heart failure events.

Patients with liver enzyme, bilirubin, albumin abnormalities or with history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis) were not treated in the pivotal study. Currently it is unknown if the background liver abnormalities are a risk factor for drug-induced liver injury. Drug induced liver injury is included in the safety specification in the RMP as an important potential risk.

Due to non-clinical findings of hyperplasia in rodent and non-rodent species, specifically without correlating findings in control groups for larynx and esophagus, there are concerns regarding the carcinogenetic potential of omaveloxolone. A carcinogenicity study in mice (26-weeks in transgenic rasH2 mice) was performed where no findings of hyperplasia or carcinogenic potential were observed. However, since the outcome of the 2-year carcinogenicity study in rats is not available at the present time, a final conclusion cannot be drawn. Given that it is not considered feasible to obtain solid data from a PASS due to the rarity of the disease and the expected low number of patients who will be possible to include in a PASS, malignancy is not included as an important potential risk in the RMP. The risk will be addressed by inclusion of malignancy to the summary of safety concerns in the PSUR and have the 2-year rat carcinogenicity study as a PAM (**REC**).

The applicant plans to conduct a thorough QTc study in healthy subjects in which the exposure will be 5-fold higher (study in fed state) than the observed steady state exposure in FA patients receiving 150 mg once daily. An ongoing through QTc study is ongoing in health volunteers. If the study turns out positive, the applicant proposes to insert further precautions/instructions in the product information. This is acceptable. The results of study 408-C-2201 should be submitted (**REC**).

3.6. Effects Table

Effects Table for Omaveloxolone.

Effect	Short Description	Unit	Treatment (n=40)	Control (n=42)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint, mFARS	Change in modified Friedreich's ataxia rating scale (mFARS) score at Week 48 in FAS	LS Mean [SE]	-1.55 (0.689)	0.85 (0.640)	Primary analyses is performed in FAS which includes FA patients without pes cavus. Missing data were not imputed (MAR assumption). The sensitivity analyses confirmed the robustness of the observed effect in the primary efficacy when MNAR is considered instead of MAR. The tipping point for the trial, where the treatment effect loses significance, is a shift of +2 points (worsening) in the imputed data for missing omaveloxolone mFARS values at Week 48. The shift required to change the conclusion of the trial is more than twice the magnitude of worsening in the placebo group (+0.85 points). The effect is more pronounced in adolescents (probably due to faster progression rate).	1
		95% CI	-2.93, -0.18	-0.43, 2.13		
		LS Mean Difference (SE)	-2.40 (0.956)		P-value vs placebo (MMRM)= 0.0141 In all randomised FA patients (n=103, ARP), mean difference was -1.93 (p=0.0342) as an exploratory predefined analysis. In the subset of patients with pes cavus, mFARS improved -1.19 points (n=20; p=0.5379).	
		95% CI	-4.31, -0.50			
Key secondary endpoint, PGIC	Patient Global Impression of Change (PGIC) at Week 48 in FAS	LS Mean [SE]	3.90 (0.209)	4.33 (0.210)		1
		95% CI	3.49, 4.31	3.91, 4.74		
		LS Mean Difference (SE)	-0.43 (0.281)		P-value vs placebo (ANCOVA)= 0.1251	
		95% CI	-0.98, 0.12			
Key secondary endpoint, CGIC	Clinical Global Impression of Change (CGIC) at Week 48 in FAS	LS Mean [SE]	3.93 (0.149)	4.06 (0.149)		1
		95% CI	3.64, 4.22	3.76, 4.35		

Effect	Short Description	Unit	Treatment (n=40)	Control (n=42)	Uncertainties/ Strength of evidence	References
		LS Mean Difference (SE)	-0.13 (0.199)		P-value vs placebo (ANCOVA)= 0.5199	
		95% CI	-0.52, 0.26			
Secondary endpoint, FA-ADL	Change in Friedreich's ataxia – Activities of Daily Living (FA-ADL) score at Week 48 in FAS	LS Mean [SE]	-0.17 (0.450)	1.14 (0.421)	Prespecified but secondary endpoint not protected by alpha. Missing data were not imputed.	1
		95% CI	-1.07, 0.73	0.30, 1.98		
		LS Mean Difference (SE)	-1.30 (0.629)		Nominal P-value vs placebo (MMRM)= 0.0420	
		95% CI	-2.56, -0.05			
Unfavourable Effects						
TEAEs	Incidence	%	100	100		2
TEAEs	Incidence	%	98.2		Not placebo controlled	4
TEAEs related to study drug	Incidence	%	72.5	36.5		2
TEAEs related to study drug	Incidence	%	64.8		Not placebo controlled	4
Serious TEAEs	Incidence	%	9.8	5.8		2
Serious TEAEs	Incidence	%	10.9		Not placebo controlled	4
Severe TEAEs	Incidence	%	9.8	0		2
Severe TEAEs	Incidence	%	12.7		Not placebo controlled	4
Discontinuations due to TEAEs	Incidence	%	7.8	3.8		2
Discontinuations due to TEAEs	Incidence	%	9.1		Not placebo controlled	4
ALT increased	Incidence	%	37.7	1.9		2
AST increased	Incidence	%	21.6	1.9		2
Nausea	Incidence	%	33.3	13.5		2
Diarrhoea	Incidence	%	19.6	9.6		2
Vomiting	Incidence	%	15.7	11.5		2

Effect	Short Description	Unit	Treatment (n=40)	Control (n=42)	Uncertainties/ Strength of evidence	References
Headache	Incidence	%	37.3	25.0		2
Influenza	Incidence	%	13.7	3.8		2
UTI	Incidence	%	7.8	0		2
Cholesterol above the ULN	Incidence	%	33.3	6.8		2
HDL cholesterol under the ULN	Incidence	%	6.0	4.3		2
LDL cholesterol above the ULN	Incidence	%	19.0	9.1		2
VLDL cholesterol above the ULN	Incidence	%	37.2	30.4		2

Notes: 1: Study 1402 Part 2; 2: Study 1402 Extension; 3: Matched natural history FA-COMS group; 4: Analysis Set C.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Omaveloxolone is a novel treatment being developed for the treatment of FA, a rare genetic disease, a devastating diagnosis with significant adverse impact on life expectancy and quality of life. At this time, there is no approved therapy. Therefore, a significant unmet medical need remains.

Single pivotal trial of small size in a therapeutic area of many previous failures is counterbalanced with the rarity of the disease and clinically relevant effect on primary endpoint (mFARS) observed within a year for a treatment which claims to slow down the progression in FA patients. The primary endpoint could be criticised but is accepted, and it is supported by the maintained significance in all sensitivity analyses (including MAR or MNAR assumptions). The key secondary endpoints did not formally contribute to evidence for efficacy. Likewise, omaveloxolone did not significantly improve the other secondary endpoints compared to placebo, except for FA-ADL (specifically showing clinically relevant functional sparring). However, the totality of the evidence is considered clinically relevant. The slow progression of the disease should be taken into account, especially for the adult population. Supportive data comes from the extension study and a well-designed comparison to external natural history control (a well-known international cohort for FA). In a post hoc, propensity-matched analysis, lower mFARS scores were observed in patients treated with omaveloxolone after 3 years relative to a matched set of untreated patients from a natural history cohort (considered contemporaneous). These exploratory analyses allow for demonstrating maintenance of efficacy up to 3 years with better results obtained with earlier start of treatment. Caution should be exercised due to obvious limitations and potential bias linked to the extension study and the external comparison.

An important issue is that the indication sought (treatment of FA in adolescents ≥16 years and adults) is broader than the primary analysis (FA without pes cavus) and the population studied (adolescents ≥16 years and adults, without significant cardiac disease, without DM, without advanced disease, mostly ambulatory). Pes cavus is a characteristic of FA that is not really related with the severity of the disease. ”Severe” pes cavus population is not a distinct phenotype and pes cavus is not classified in a standard way in real life practice. The methods used for classifying as “severe” pes cavus population in the pivotal trial is not reflecting real diagnostic workup but a more practical solution (holding flashlight under the foot) to identify prominent cases. Furthermore, the pivotal trial did include patients with varying degrees of pes cavus in FAS population and “severe” pes cavus population was limited to 20% in the ARP. As expected by the nature of the physical condition and the scale used, those with pes cavus did worse than those without pes cavus. However, as pes cavus was pre-defined as randomisation factor, it is not expected that the analysis including all population is biased due to this. It should be noted that results in the overall population retained statistical significance and effect size (around 2 points). Additionally, in all randomised population which included all severities of the pes cavus population, the propensity matched analysis with the extended efficacy data up to 3 years supported the primary analysis in ARP.

Overall, the TEAEs were mild or moderate in severity and mostly they resolved within 2 months.

Important adverse events are the frequent increases in aminotransferases due to the potential risk of drug-induced liver injury. None of the omaveloxolone-treated patients had maximum ALT, AST or total bilirubin values that met potential Hy’s law criteria. However, due to the small sample size the potential risk cannot be ruled out. Further, congestive heart failure is included in the RMP as an important potential risk due to the observed increase in BNP and due to the observations of congestive heart failure in a study with another NrF2 activator (bardoxolone methyl). Liver enzymes, lipids and BNP are to be monitored before and during treatment.

The non-clinical findings of hyperplasia are of importance due to the early disease onset and life expectancy in the patient group. However, in the carcinogenicity study in mice, no findings of hyperplasia or carcinogenic potential were observed and therefore it is considered acceptable that the 2-year carcinogenicity study will be submitted as a PAM (**REC**).

Further, the reproductive toxicity found in animal studies is of importance, since the indicated population is 16-40 years old and pregnancy is desirable for some patients with FA.

3.7.2. Balance of benefits and risks

Study 1402 Part 2 demonstrates clinically relevant benefit of omaveloxolone treatment in patients ≥ 16 years of age when compared to placebo. When natural progression of the disease is considered, the treatment effect seems to have sustained over 3 years period.

Overall, treatment with omaveloxolone was well tolerated, with TEAEs that were mild or moderate in severity and mostly resolved within 2 months. Important potential risks are drug-induced liver injury, congestive heart failure, malignancy and reproductive toxicity.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Skyclarys is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Skyclarys is favourable in the following indication(s):

The treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that omaveloxolone is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.