COVER PAGE

Official Title:	An Observational, Multinational, Post-Marketing Registry of Omaveloxolone-Treated Patients With Friedreich's Ataxia
Protocol ID:	296FA401
Study Condition:	Friedreich's Ataxia
Document Date:	16-Dec-2024

STUDY PROTOCOL 296FA401 (408-C-2301)

Title	An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia
Protocol version identifier	6.0
Date of protocol	16 December 2024
EU PAS register number	EUPAS1000000196
Active substance	Omaveloxolone (RTA 408)
Medicinal product	SKYCLARYS®, as 50 mg capsules for oral use
Marketing authorization holder (MAH)	US MAH: Biogen U.S. Corporation, 225 Binney Street, Cambridge, MA 02142 United States EU MAH: Biogen Netherlands B.V. Prins Mauritslaan 13, 1171 LP Badhoevedorp, The Netherlands
Joint PASS	No
Research question and objectives	The goal of this study is to further characterize the long-term safety profile of omaveloxolone under real-world conditions and to characterize Friedreich's ataxia (FA) clinical management and outcomes in omaveloxolone-treated patients. This post-marketing study will collect data from patients with FA enrolled in the Friedreich's Ataxia Global Clinical Consortium (FA-GCC) UNIFIED Natural History Study (UNIFAI) who are omaveloxolone naive and are prescribed omaveloxolone and treated per its approved label (omaveloxolone-naive cohort) or who initiated omaveloxolone treatment per its approved label following their enrollment in UNIFAI but less than 12 months prior to enrollment in this study (non-naive cohort). The primary objectives of this study are to: • Assess the long-term safety of omaveloxolone as prescribed to patients with FA in the real-world setting. • Document and characterize all drug-induced liver injury (DILI) or congestive heart failure (CHF) adverse events (AEs) The secondary objective of this study is to: • Capture reasons and timing of treatment interruptions, treatment discontinuations, and drug overdose [redacted]

Countries of study	The countries in this study are determined by the FA-GCC and according to market uptake after omaveloxolone launch. The list of countries can change depending on changes in this consortium, and currently includes European countries and non-European countries (including the US).

Marketing authorization holder(s)

MAH contact person	EU Qualified Person for Pharmacovigilance (QPPV): Dr. [redacted]

Confidentiality notice

This document contains confidential and proprietary information belonging to the marketing authorization holder (MAH).

The information contained in this document should only be used for the purposes required to conduct this study and should not be copied or disclosed to any third party (except where required by applicable law) without the prior written consent of the MAH.

SIGNATURE PAGE

Protocol 296FA401 (408-C-2301) was approved by:

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Date (*DD MMM YYYY*)

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_____ _____

[redacted], MD Date (*DD MMM YYYY*)

[redacted]

Biogen

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2 List of Abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDI-2	Beck Depression Inventory-2
BMI	Body mass index
BNP	B-type natriuretic peptide
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic kidney disease
CRO	Contract Research Organization
DILI	Drug-induced liver injury
EC	Ethics committee
eCRF	Electronic case report form
EDC	Electronic data capture
EFACTS	European Friedreich's ataxia Consortium for Translational Studies
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FA	Friedreich's ataxia
FA-COMS	FA-Clinical Outcome Measures
FA-GCC	Friedreich's Ataxia Global Clinical Consortium
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FXN	Frataxin
GDPR	General Data Protection Regulation
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
HDL	High-density lipoprotein
HLGT	High Level Group Term
HLT	High Level Term
HMA	Heads of Medicines Agencies
[redacted]	[redacted]
ICF	Informed consent form
ICH	International Conference of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEA	International Epidemiological Association
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
ISPOR	Professional Society for Health Economics and Outcomes Research
L95	Lower 95%
LDL	Low-density lipoprotein
LPI	Last patient in
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mFARS	Modified Friedreich's Ataxia Rating Scale
[redacted]	[redacted]
MRI	Magnetic resonance imaging
N/A	Not applicable
Nrf2	Nuclear factor erythroid 2-related factor 2
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OTC	Over the counter
PASS	Post-authorization safety study
[redacted]	[redacted]
PT	Preferred Term
PY	Patient-year
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk management plan
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Definition
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard operating procedure
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
UNIFAI/UNIFAI study	UNIFIED Natural History Study
US	United States
USPI	United States Package Insert

3 Responsible parties

Global Safety Officer:	[redacted], MD
Qualified Person for Pharmacovigilance	[redacted], MD
Main Author	[redacted], ScD

4 Abstract

Protocol version: V 6.0

Protocol version date:
16 December 2024

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

Rationale and background:
Friedreich's ataxia (FA) is a rare, autosomal-recessive neurodegenerative disease that affects multiple systems in the body, including the central and peripheral nervous systems, the musculoskeletal system, the myocardium, and the endocrine pancreas [Cook and Giunti 2017]. The onset of symptoms typically starts around the time of puberty, and the average life expectancy is 39 years [Indelicato 2024; Tsou 2011; Williams and De Jesus 2023]. The primary cause of death in FA is cardiac dysfunction, specifically congestive heart failure (CHF) and arrhythmia [Tsou 2011]. FA is typically caused by a homozygous GAA trinucleotide repeat expansion in the frataxin (FXN) gene, which manifests a phenotype of mitochondrial iron overload and oxidative stress [Cook and Giunti 2017; Dürr 2002]. Once the patient starts to display symptoms, a genetic test is typically performed to confirm the diagnosis [Lynch 2021b].

Until recently, there was no approved treatment available for patients with FA, and disease management focused on treating the patients' symptoms, prolonging independence, and maintaining quality of life [Cook and Giunti 2017; Rufini 2022]. In early 2023, the US Food and Drug Administration (FDA) approved SKYCLARYS® (omaveloxolone) for the treatment of patients with FA aged ≥ 16 years [Reata Pharmaceuticals 2023]. In 2019, the pivotal trial was completed, and results showed a significant improvement of neurological function after 48 weeks in patients with FA who were treated with omaveloxolone in comparison to placebo. In addition, the treatment was considered generally safe and well tolerated [Lynch 2021a].

Relative to placebo, omaveloxolone was associated with transient increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and slight increases in B-type natriuretic peptide (BNP). As per the risk management plan (RMP), drug-induced liver injury (DILI) and CHF are important potential risks (RMP for SKYCLARYS 150 mg capsules [omaveloxolone], data on file). This study will assess the safety profile of omaveloxolone in patients with FA and document FA clinical management and outcomes in omaveloxolone-treated patients in a real-world setting.

Research question and objectives:
This post-marketing study will collect data from patients with FA who are prescribed omaveloxolone per its approved label in order to further characterize the long-term safety profile of omaveloxolone under real-world conditions and to characterize FA clinical management and outcomes in omaveloxolone-treated patients.

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Primary objectives:

- To assess the long-term safety of omaveloxolone in patients with FA in the real-world setting
- To document and characterize all DILI and CHF adverse events (AEs)

Secondary objective:

- To capture reasons and timing of omaveloxolone treatment interruptions, discontinuations, and drug overdose

[redacted]

Study design:

These objectives will be addressed in an observational, multi-country registry-based cohort study of patients with FA who are treated with omaveloxolone per its approved label.

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

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

Population:

Patients who are initiating treatment with omaveloxolone per its approved label (omaveloxolone-naive cohort) or who have initiated omaveloxolone treatment per its approved label less than 12 months prior to enrollment in this study (non-naive cohort) will be included in the study. Due to the rarity of FA and the already established infrastructure of the UNIFAI study, patients for this study will be identified and enrolled via the sites of the UNIFAI study platform. Patient selection will be based on the inclusion and exclusion criteria listed below.

Inclusion criteria:

- Patients aged 16 years and older at initiation of omaveloxolone treatment
- Documented diagnosis of FA, including confirmation via genetic testing
- For the omaveloxolone-naive cohort
  - omaveloxolone naive
  - initiating omaveloxolone treatment as per an approved label concurrent with enrolling in this study
- For the non-naive cohort
  - initiated omaveloxolone treatment as per an approved label less than 12 months prior to enrollment in this study
  - prior to enrollment, maintained omaveloxolone treatment with no discontinuation of more than 60 days

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  - actively on treatment at the time of enrollment in this study
  - treating physician is the study site principal investigator or sub-investigator
  - study site confirms ability to provide required baseline data through medical record review, UNIFAI database, or other site-collected data
- Enrolled in the UNIFAI study prior to initiation of omaveloxolone treatment
- Willing and able to comply with visits as per the relevant approved label, and other study procedures
- Evidence of a personally signed and dated informed consent document (and assent form, if necessary) indicating that the patient (or a legally authorized representative) has been informed of all pertinent aspects of participation in the study prior to data collection for this study

Exclusion criteria:

- Received off-label prescription of omaveloxolone at any time
- Previously enrolled in a clinical trial of omaveloxolone
- Participating in a blinded interventional trial at the time of enrollment in the study; patients may participate in other clinical trials after baseline data are collected.
- Patient is, in the opinion of the prescriber and/or study investigator, unable to comply with the requirements of the study or is unsuitable for any reason

Variables:

Variables collected at the earlier of baseline visit or omaveloxolone treatment initiation

<u>Demographics</u>

- Age
- Sex
- Reproductive status (females only)

<u>Medical history and comorbidities</u>

- Clinically significant disease and comorbidities of interest, including but not limited to:
  - Cardiomyopathy
  - Other cardiac conditions
  - Ambulation status
  - Diabetes
  - Scoliosis
- Hepatic impairment (if available prior to omaveloxolone initiation)
  - Child-Pugh class A
  - Child-Pugh class B
  - Child-Pugh class C
- History of depression (Beck Depression Inventory-2) [if available prior to omaveloxolone initiation]
- History of substance use

<u>Clinical characteristics of FA</u>

- Genetic diagnosis
- Family history
- Age at symptom onset
- Age at diagnosis
- Stage of disease
- Modified Friedreich's Ataxia Rating Scale (mFARS) and Scale for Assessment and Rating of Ataxia

<u>Treatment history</u>

- Previous enrollment in a clinical trial for the treatment of FA

Reproductive status (females only)

- Pregnancies
  - Number of prior pregnancies and fetuses
  - Outcome of each pregnancy
- Lactations
  - Number of prior lactation events
  - Start and end dates

Anthropometric measurements

- Height (m)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Clinical parameters

- Liver panel
  - Serum aminotransferases
    - ALT
    - AST
  - Total bilirubin (TBL)
- Lipid panel
  - Low-density lipoprotein (LDL)
  - High-density lipoprotein (HDL)
  - Triglycerides
- Echocardiogram
- Electrocardiogram
- Cardiac magnetic resonance imaging (MRI), if available
- CHF panel
  - B-type natriuretic peptide (BNP) and/or
  - N-terminal prohormone B-type natriuretic peptide (NT-proBNP)

Omaveloxolone treatment

- Start date and, if applicable, end date
- Daily dose in mg
- Frequency of administration

Recent and concomitant medications (within 30 days prior to the earlier of baseline visit or omaveloxololone treatment initiation date)

- Prescription drugs
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Indication
  - Reason for treatment discontinuation/withdrawal
- Over-the-counter (OTC) drugs
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Indication
  - Reason for treatment discontinuation/withdrawal

- Herbal or homeopathic remedies
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Reason for treatment discontinuation/withdrawal
- Nutritional supplements
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Reason for treatment discontinuation/withdrawal

[redacted]

Variables collected at routine follow-up visits (up to 60 months)

All serious adverse events (SAEs), as defined in Section 9.3.1.1

- SAE term and its description
- Start and end dates of the SAE
- Outcome of the SAE
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)
- Severity of the SAE
- Hospitalization dates, if applicable

DILI and CHF AEs, as defined in Section 9.3.1.1

- Start and end dates of the AE
- Outcome of the AE
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)
- Severity of the AE
- Seriousness of the AE
- Date of AE treatment initiation by the treating physician
- Lipid panel
  - LDL
  - HDL
  - Triglycerides
- Signals for DILI at time of DILI diagnosis, as applicable
  - Liver panel
    - Serum aminotransferases
      - ALT
      - AST
    - TBL
- Signals for CHF at time of CHF diagnosis, as applicable
  - Date of AE treatment initiation by the treating physician
  - Electrocardiogram
  - Echocardiogram
  - Cardiac MRI, if available
  - CHF panel
    - BNP and/or
    - NT-proBNP

Reproductive status (females only)

- Pregnancies
  - Number of pregnancies and fetuses
  - Start and end dates
  - Outcome of each pregnancy
  - Adverse effects on the developing fetus and neonate
- Lactations
  - Number of lactation events
  - Start and end dates
  - Adverse effects on the infant
  - Infant outcomes for at least the first year of life

Anthropometric measurements

- Height (m)
- Weight (kg)
- BMI (kg/m^2)

Omaveloxolone treatment

- Changes in regimen
  - Date of change(s)
  - Type of change (dose, frequency)
  - Reason(s) for change
    - Physician decision
    - Patient/parent decision

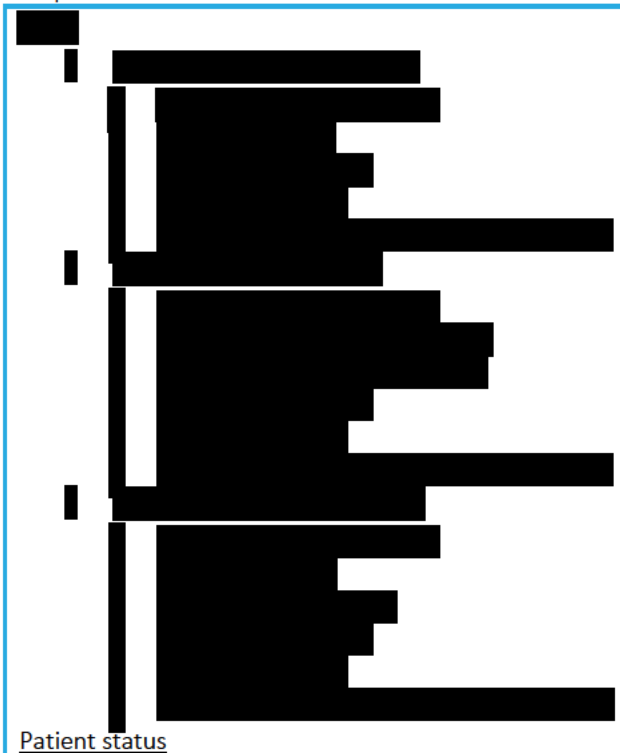
        - Any SAE or any DILI or CHF AE
        - New-onset comorbidities
- Drug overdose
    - Date(s) of the drug overdose
    - Daily dose(s) during the overdose
    - Reason for overdose
    - Outcome/consequence
- Treatment interruption and discontinuation, as defined in Section 9.3.2.1
    - Date of last omaveloxolone administration
    - Time to interruption/discontinuation (derived variable)
    - Reason(s) for each interruption/discontinuation
        - Physician decision
        - Patient/parent decision
        - AE/SAE
        - New-onset comorbidities
    - Date(s) of each stop of omaveloxolone administration
    - Date(s) of each restart of omaveloxolone administration, if applicable
    - Daily dose at restart(s), if applicable
    - Reason for restart(s), if applicable

Concomitant medications

- Prescription drugs
    - Drug name(s)
    - Start and end dates
    - Daily dose
    - Route of administration
    - Indication
    - Reason for treatment discontinuation/withdrawal
- OTC drugs
    - Drug name(s)
    - Start and end dates
    - Daily dose
    - Route of administration
    - Indication
    - Reason for treatment discontinuation/withdrawal
- Herbal or homeopathic remedies
    - Drug name(s)
    - Start and end dates
    - Daily dose
    - Route of administration
    - Reason for treatment discontinuation/withdrawal
- Nutritional supplements
    - Drug name(s)
    - Start and end dates
    - Daily dose
    - Route of administration
    - Reason for treatment discontinuation/withdrawal

[redacted]

[redacted]



Patient status

- Death, lost to follow-up, withdrew consent
- If applicable: date of death, primary cause of death, date of loss to follow-up, date of consent withdrawal and reason for consent withdrawal

Variables collected at 60-day safety follow-up (for patients who discontinue study or omaveloxolone treatment)

All SAEs, as defined in Section 9.3.1.1

- SAE term and its description
- Start and end dates
- Outcome
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)
- Severity
- Hospitalization dates, if applicable

DILI and CHF AEs, as defined in Section 9.3.1.1

- Start and end dates
- Outcome
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)
- Severity
- Seriousness
- Date of treatment initiation for the AE

Information collected as part of this observational study may lead to the need for additional follow-up, management, and treatment of patients, based on the judgment of the investigator. If the investigator is not the treating physician, communication of such judgment by the investigator to the treating physician is recommended.

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Data sources:

When not collected by the UNIFAI study, clinical information recorded in patients' medical records and/or diagnostic reports will be abstracted.

Each electronic case report form (eCRF) will have a unique number within the study (Patient Identification). Each site will maintain a Patient Identification list linking the patient to the Patient Identification within the study. Only the investigator and/or authorized personnel will be able to identify the patient based on the Patient Identification list, which will be held only at the site.

As all sites and patients are participating in the UNIFAI study, overlapping data will be extracted from the UNIFAI study where possible to avoid any additional burden to the investigators.

Study size:

The design of the study is descriptive. The study will aim to enroll approximately 300 patients. Precision tables were created to estimate the precision of different sample sizes based on the occurrence of any SAE, and the occurrence of DILI and CHF AEs.

Data analysis:

The analyses will be descriptive and presented separately for the omaveloxolone-naive cohort and non-naive cohort. Continuous variables will be described with summary statistics such as n, mean, standard deviation, median, first quartile, third quartile, and minimum and maximum values. For each categorical variable, the frequency and percentage will be reported.

Incidence rates will be calculated by dividing the number of new cases of SAEs (all) and all DILI and CHF AEs by the number of patient-years (PYs) at risk, which will be calculated over the follow-up period. In addition, 2-sided 95% confidence intervals (CIs) of incidence rates will be calculated.

There will be no imputation of missing data except for incomplete start dates for the purpose of time-to-event analyses.

A full annual report will be provided for EMA, and interim analyses on AEs of DILI and CHF are to be performed for the FDA biannually.

Milestones:

- Start of data collection: First Patient In ("X", study start December 2024)
- First biannual FDA report on DILI and CHF: X + 9 months (Q3 2025)
- First annual EMA report and second biannual FDA report on DILI and CHF: X + 15 months (Q1 2026)
- Third biannual FDA report on DILI and CHF: X + 21 months (Q3 2026)
- Second annual EMA report and fourth biannual FDA report on DILI and CHF: X + 27 months (Q1 2027)
- Fifth biannual FDA report on DILI and CHF: X + 33 months (Q3 2027)
- Third annual EMA report and sixth biannual FDA report on DILI and CHF: X + 39 months (Q1 2028)
- Seventh biannual FDA report on DILI and CHF: X + 45 months (Q3 2028)
- Fourth annual EMA report and eighth biannual FDA report on DILI and CHF: X + 51 months (Q1 2029)
- Ninth biannual FDA report on DILI and CHF: X + 57 months (Q3 2029)
- Fifth annual EMA report and tenth biannual FDA report on DILI and CHF: X + 63 months (Q1 2030)
- Eleventh biannual FDA report on DILI and CHF: X + 69 months (Q3 2030)

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- Planned end of data collection, with the assumption that enrollment is estimated to be completed within 1 year and that the last patient in will be followed for 5 years (60 months in total): X + 72 months (Q1 2031)
- Sixth annual EMA report and twelfth biannual FDA report on DILI and CHF: X + 75 months (Q2 2031)
- Final report: X + 78 months (Q3 2031)

Assumptions:

- Enrollment is estimated to be completed within 1 year.
- Each biannual report will include an additional 6 months of patient data, with the 1st biannual report forecast after 6 months of data collection and 3 months of report preparation.
- Data collection to end within 5 years after enrollment of Last Patient In.
- Final report forecast 6 months after final data collection.

5 Amendments and updates

Substantial amendments and updates to the study protocol are summarized in the table below.

Protocol Amendment Version Number	Version Date	Protocol Section	Summary of Relevant Updates	Reason
Original (version 1.0)	02 June 2023	Not applicable	Not applicable	Not applicable
Amendment 1 (version 2.0)	06 November 2023	Throughout	Edits for clarity or to make minor corrections	Not applicable
		4. Abstract (updates in abstract are also reflected in any corresponding protocol sections)	Changed collection of all DILI and CHF AEs to be one of the primary objectives instead of a secondary objective	Changes made based on regulatory feedback
			Extended safety follow-up from 30 to 60 days	
			Clarified eligible patients as omaveloxolone naive before SKYCLARYS approval, including both those who are current vs new users	Changes made based on investigator feedback
			Clarified that schedule of assessments is based on recommended clinical practice/monitoring per a SKYCLARYS approved label and per the UNIFAI study	

Protocol Amendment Version Number	Version Date	Protocol Section	Summary of Relevant Updates	Reason
			Removed collection of pes cavus and disease stage in medical history	
			Collection of direct and indirect bilirubin	
			Clarified roles of investigator vs treating physician and their communication	
			Amended sample size calculations to reflect frequency of SAEs rather than any AE	
			Updated milestones and timelines; clarified assumptions	
		5. Amendments and Updates	Added changes made to version 2.0	Changes based on timing of omaveloxolone launch and feedback from investigators
		6. Milestones	Updated planned start of data collection timing; update of subsequent milestones	Omaveloxolone launched ahead of study operations
		7. Rationale and background	Amended rationale to evaluate all SAEs, and any DILI and CHF AEs	Based on investigator feedback
		8.2 Objectives	Moved collection of DILI and CHF AEs from secondary objectives to be one of the primary objectives	Change made based on regulatory feedback
		9. Research Methods	Changes to reflect changes in the abstract (including eligibility criteria, description of outcomes and their analyses, and removal of collection of vital signs)	See rationale described for changes in abstract
			Extended safety follow-up from 30 to 60 days	Change made based on regulatory feedback
			Clarified current vs new users and associated analyses	Based on timing of launch of omaveloxolone

Protocol Amendment Version Number	Version Date	Protocol Section	Summary of Relevant Updates	Reason
			Removed the restriction on current users to only include patients who had started omaveloxolone within the 6 months prior to enrollment	
		11. Management and reporting of adverse events	Updated to describe general standards	Removal of previously planned safety vendor
			Extended safety follow-up from 30 to 60 days	Change made based on regulatory feedback
		12. Protocol deviations	Added section on protocol deviations	As requested by investigators
		13. Plans for results	Clarified data ownership	Not applicable
Amendment 2 (version 3.0)	04 March 2024	Throughout	Current omaveloxolone users will no longer be allowed to enroll, which affected language throughout the protocol (eg, no longer any need for sensitivity analyses).	Adverse events that occur commonly in the first 12 weeks of treatment would not be captured if current users are allowed to enroll (ie, the first 12 weeks will have already passed).
		Throughout	Only patients who discontinue the study or treatment are required to attend the 60-day safety follow-up visit.	Clarification to ensure that patients who complete the study are not required to return after 60 months.
		Throughout	Removed alkaline phosphatase, gamma-glutamyl transferase, direct bilirubin, and indirect bilirubin from liver panel.	These laboratory tests are not required as part of the liver panel, per labeling recommendations.
		Throughout	Added lipid panel: LDL, HDL, and triglycerides	These laboratory tests are required per labeling recommendations.
		9.2 Setting	Removed Table 9-1.	Information was redundant to the schedule of assessments.
			Separated the schedule of assessments into Tables 9-1, 9-2, and 9-3.	Per request from key medical experts (KMEs), assessments were separated to indicate which assessments are required per protocol/label, which are

Protocol Amendment Version Number	Version Date	Protocol Section	Summary of Relevant Updates	Reason
				optional, and which are already covered in UNIFAI.
		9.3.5.4 Collected at 60-day safety follow-up (for patients who discontinue study or treatment)	Section added to clarify the assessments collected at the 60-day safety follow-up visit.	Clarity and consistency with the synopsis.
		9.7.10 Statistical software	Updated information about SAS software that will be used for this study.	Correction to SAS software information.
		11.2 Assessment, recording, and reporting of AEs and SAEs	Revisions were made to clarify the reporting requirements for DILI, CHF, and SAEs.	Clarifications to reduce redundancy and ensure thorough instructions.
		11.2.3.1	Justification was added to explain why the only non-serious AEs collected are for CHF and DILI.	Regulatory requirement.
		11.2.3.4 Reporting of overdose	Section added.	For compliance with standard Biogen PASS template content.
		13.4 Ethics Committee notification of study completion or termination	Section added.	For compliance with standard Biogen PASS template content.
		13.5 Registration of study and disclosure of study results	Section added.	For compliance with standard Biogen PASS template content.
Amendment 3 (version 4.0)	17 July 2024	4. Abstract and 6. Milestones	Updated estimated study start date.	Changes made based on regulatory feedback.
		9.2 Setting	Updated timepoints for data collection and analysis.	Typographical and inconsistency error correction.
		10.2 Data Protection and 14. Key roles	Clarity provided on key roles and responsibilities.	Changes made based on regulatory feedback.

Protocol Amendment Version Number	Version Date	Protocol Section	Summary of Relevant Updates	Reason
		and responsibilities		
Amendment 4 (version 5.0)	09 December 2024	Refer to the amendment summary document version 5.0.		
Amendment 5 (version 6.0)	16 December 2024	4. Abstract (updates in abstract are also reflected in any corresponding protocol sections)	Updated data collection timing	Changes based on timing of First Patient In
		5. Amendments and Updates	Added changes made to version 6.0	Changes based on timing of First Patient In
		6. Milestones	Updated planned start of data collection timing and subsequent milestones	First Patient In milestone achieved
		9.1.2 Study duration and follow-up	Updated study start date	First Patient In milestone achieved

6 Milestones

Milestone and Assumptions	Planned estimate date(s)
Start of data collection	First Patient In (X, study start December 2024)
First biannual report (to fulfill commitment to FDA) on DILI and CHF, assuming 6 months of initial data collection and 3 months of report preparation	X + 9 months
First EMA annual report and second FDA biannual report on DILI and CHF	X + 15 months
Third FDA biannual report on DILI and CHF	X + 21 months
Second EMA annual report and fourth FDA biannual report on DILI and CHF	X + 27 months
Fifth FDA biannual report on DILI and CHF	X + 33 months
Third EMA annual report and sixth FDA biannual report on DILI and CHF	X + 39 months
Seventh FDA biannual report on DILI and CHF	X + 45 months
Fourth EMA annual report and eighth FDA biannual report on DILI and CHF	X + 51 months
Ninth FDA biannual report on DILI and CHF	X + 57 months
Fifth EMA annual report and tenth FDA biannual report on DILI and CHF	X + 63 months
Eleventh FDA biannual report on DILI and CHF	X + 69 months
Planned end of data collection, with the assumption that enrollment is estimated to be completed within 1 year and that the last patient in will be followed for 5 years (60 months total)	X + 72 months
Sixth EMA annual report and twelfth FDA biannual report on DILI and CHF	X + 75 months
Final report of study results, 6 months after end of data collection	X + 78 months

7 Rationale and background

7.1 Friedreich's ataxia

7.1.1 Signs and symptoms

Friedreich's ataxia (FA) is an autosomal-recessive neurodegenerative disease that affects multiple systems in the body, including the central and peripheral nervous systems, the musculoskeletal system, the myocardium, and the endocrine pancreas [Cook and Giunti 2017]. Patients can experience many neurological symptoms, such as gait and limb ataxia, impaired speech (dysarthria), lower limb areflexia, loss of sensation and proprioception, and muscle weakness [Cook and Giunti 2017; Schulz 2009; Williams and De Jesus 2023]. Due to the multisystem nature of the disease, patients also experience non-neurological symptoms, including cardiomyopathy, diabetes mellitus, and scoliosis [Schulz 2009; Williams and De Jesus 2023].

With the classical phenotype of FA, symptom onset occurs during puberty, between the age of 10 to 16 years [Delatycki 1999; Dürr 1996; Harding 1981]. If the onset of symptoms starts on or after the age of 25 years, the patient is considered to have late-onset FA [Indelicato 2020]. Patients with a delayed onset have a milder phenotype and a slower progression of the disease [Martinez 2017]. The life expectancy of patients with FA is heavily impacted by the disease, with an average age at death of 39 years [Indelicato 2024]. The primary cause of death in FA has been documented as cardiac dysfunction, specifically congestive heart failure (CHF) and arrhythmia [Tsou 2011].

7.1.2 Epidemiology

FA is considered the most common form of hereditary ataxia [Schulz 2009]. It is estimated that the prevalence of FA in the United States (US) is 1 in every 50,000 people [National Institute of Neurological Disorders and Stroke 2023]. In Europe, there are large regional differences in the prevalence of FA, with a prevalence of 1 in 20,000 in southwest Europe, compared to 1 in 250,000 in north and east Europe [Vankan 2013].

7.1.3 Etiology

In almost all patients with FA, the disease is caused by a homozygous GAA trinucleotide repeat expansion in the frataxin (FXN) gene[Cook and Giunti 2017], which encodes frataxin, a small mitochondrial protein [Koeppen 2011]. Frataxin is involved in iron homeostasis and may protect mitochondria from oxidative damage. FXN gene mutation suppresses the levels of the frataxin protein and manifests a phenotype of mitochondrial iron overload and oxidative stress. Patients with FA suffer from a deficiency of frataxin, which causes a severe disruption of iron–sulfur cluster biosynthesis, a mitochondrial iron overload coupled to cellular iron dysregulation, and an increased sensitivity to oxidative stress [Cook and Giunti 2017; Dürr 2002].

Large natural history studies have reported that age at onset is inversely correlated with the number of GAA repeats in the FXN gene and that earlier age at onset is associated with a more rapid disease progression [Reetz 2015; Rummey 2022].

7.1.4 Diagnosis

Once the patient starts to display symptoms, a genetic test for the expanded GAA repeats in the FXN gene is typically performed. If the genetic test is positive for biallelic expansions in an appropriate clinical context (ataxia, cardiomyopathy, scoliosis), an FA diagnosis is confirmed [Lynch 2021b]. This genetic test will be diagnostic in 96% of patients with FA; however, 4% of patients will require FXN sequencing, which identifies one expanded allele and one normal allele by GAA repeat sizing, but with a mutation in FXN [Lynch 2021b].

7.1.5 Disease management and current treatment options

Due to the complexity of the disease, a multidisciplinary approach is required for FA management. Until recently, there was no approved treatment available for patients with FA, and its management was focused on treating patients' symptoms, prolonging independence, and maintaining quality of life [Cook and Giunti 2017; Rufini 2022]. Pharmacological treatments are available for clinical symptoms, such as spasticity and neuropathic pain, but, until recently, there were no treatments for weakness and ataxia [Lynch 2021b]. Patients could be treated with antioxidants or iron chelators, but unfortunately these do not significantly impact the neurological dysfunctions associated with FA. The most straightforward therapeutic approaches were aimed at increasing frataxin protein levels [Rufini 2022]. Thus, there was a need for effective treatments that can modify the disease and stop its progression [Cook and Giunti 2017].

7.2 Omaveloxolone

On 28 February 2023, the US Food and Drug Administration (FDA) approved SKYCLARYS® (omaveloxolone) as the first therapy specifically indicated for the treatment of FA in adults and adolescents aged 16 years and older [Reata Pharmaceuticals 2023]. On 09 February 2024, approval was also received from the European Medicines Agency (EMA). On 24 September 2024, approval was also received from Swissmedic. Omaveloxolone previously received an orphan drug designation from the FDA, the European Commission, and Swissmedic for the treatment of patients with FA [Reata Pharmaceuticals 2022]. Omaveloxolone is an orally bioavailable triterpenoid analog that works by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) [Lynch 2021a]. In vitro research with omaveloxolone demonstrated improved mitochondrial function in human primary fibroblasts from patients with FA. In addition, restoration of the mitochondrial function was shown in cerebellar granule neurons in FA mouse models. The authors of the in vitro research indicated that omaveloxolone is a very good candidate for the treatment of FA [Abeti 2018].

Following the in vitro research, the safety, efficacy, and pharmacodynamics of omaveloxolone have been studied in a phase II clinical trial (Study 408-C-1402; MOXIe; hereafter referred to as Study 1402) consisting of 2 placebo-controlled parts and an open-label extension [ClinicalTrials.gov 2022; Lynch 2023; Lynch 2021a; Lynch 2019]. The results of the pivotal, placebo-controlled part of the trial published in 2021 focus on neurological function. Neurological function assessments (modified Friedreich's Ataxia Rating Scale [mFARS]) were conducted throughout the 48-week treatment phase. Patients randomized to omaveloxolone (n = 40) experienced a mean decrease (indicating less impairment) from baseline in mFARS of −1.55±0.69, while patients randomized to placebo (n = 42) had a mean increase of 0.85±0.64. Thus, treatment with omaveloxolone resulted in statistically significant lower mFARS scores (less

impairment) relative to placebo, with a treatment difference of -2.41 (p = 0.0138). In addition, the treatment was generally safe and well tolerated [Lynch 2021a].

7.2.1 Safety profile

In Study 1402 Part 2 (pivotal trial), at least 1 treatment-emergent adverse event (TEAE) occurred in all (100%) omaveloxolone-treated patients and in all (100%) placebo-treated patients. The majority of TEAEs reported during the study were mild or moderate in intensity in both the treatment groups. The most common (≥ 20% incidence in either treatment group) TEAEs with ≥ 5% difference in incidence in the omaveloxolone group compared with placebo were increased ALT (37.3% in the omaveloxolone group vs 1.9% in the placebo group), headache (37.3% vs 25.0%), nausea (33.3% vs 13.5%), fatigue (21.6% vs 13.5%), abdominal pain (21.6% vs 5.8%), and increased AST (21.6% vs 1.9%). Apart from increases in ALT and abdominal pain, a higher incidence (≥ 5% difference) of these AEs in omaveloxolone patients compared with placebo patients was generally limited to the first 12 weeks of treatment as patients adjusted to omaveloxolone treatment and developed improved tolerability to the drug. These AEs were less frequently reported after Week 12.

Although drug-induced liver injury (DILI) and CHF are both listed as important potential risks in the proposed European Medicines Agency (EMA) risk management plan (RMP) for omaveloxolone (RMP for SKYCLARYS 150 mg capsules [omaveloxolone], data on file), as yet, there has been no report of DILI or CHF in association with the use of omaveloxolone in patients with FA.

Treatment with omaveloxolone has been associated with an increased incidence of ALT and aspartate aminotransferase (AST) elevations relative to treatment with placebo. Although no serious adverse events (SAEs) related to AST/ALT elevations were reported in clinical studies, it is important to follow any such AEs in the post-marketing setting and to monitor for potential occurrence of DILI.

CHF is also listed as an important potential risk in the RMP due to the results of a clinical trial in patients with type 2 diabetes with advanced chronic kidney disease (CKD) treated with bardoxolone methyl, a structural analog of omaveloxolone. A total of 8.8% of all patients in this trial who were treated with bardoxolone methyl reported adjudicated heart failure events. Most of these events occurred during the first four weeks after initiation of bardoxolone methyl treatment. A review of this study identified 2 risk factors for heart failure: baseline B-type natriuretic peptide (BNP) levels greater than 200 pg/mL and a prior hospitalization for fluid overload in patients who had Stage 4 CKD. CHF has not been reported in patients with FA who were treated with omaveloxolone, but omaveloxolone trials such as Study 1402 excluded patients with a BNP level of > 200 pg/mL or with a history of clinically significant cardiac disease [ClinicalTrials.gov 2022]. Therefore, it is important to evaluate the potential risk of CHF in a larger group of patients with FA who receive this treatment (RMP for SKYCLARYS 150 mg capsules [omaveloxolone], data on file).

7.3 Study rationale

Based on the research that has been performed on omaveloxolone, there is a need to investigate its safety profile in a real-world setting. Omaveloxolone will be administered as a chronic long-term treatment, hence the need to assess the safety profile and any potential risks. All SAEs will be recorded, and all DILI and CHF AEs will also be recorded.

In addition to the assessment of the safety profile of omaveloxolone, this observational study will assess the long-term clinical management, and outcomes of patients with FA who are treated with omaveloxolone in the real-world setting.

8 Research question and objectives

8.1 Research question

This post-marketing registry-based study will collect data from omaveloxolone-naive patients with FA who are initiating omaveloxolone per an approved label (omaveloxolone-naive cohort) and patients with FA who have, following enrollment in the Friedreich's Ataxia Global Clinical Consortium (FA-GCC) UNIFIED Natural History Study (UNIFAI study), initiated omaveloxolone treatment per its approved label less than 12 months prior to enrollment in this study (non-naive cohort). This study is being conducted to further characterize the long-term safety profile of omaveloxolone under real-world conditions and to characterize FA clinical management and outcomes in omaveloxolone-treated patients.

8.2 Objectives

8.2.1 Primary objectives

The primary objectives of this study are:

- To assess the long-term safety of omaveloxolone as prescribed to patients with FA in the real-world setting
- To document and characterize all DILI and CHF AEs

The definitions of DILI and CHF events are provided in Section 9.3.1.1.

8.2.2 Secondary objective

The secondary objective of this study is:

- To capture reasons and timing of omaveloxolone treatment interruptions, discontinuations, and drug overdose

[redacted]

9 Research methods

9.1 Study design

9.1.1 Study overview

The objectives will be addressed via an observational, multi-country, registry-based cohort study of patients with FA treated with omaveloxolone per an approved label.

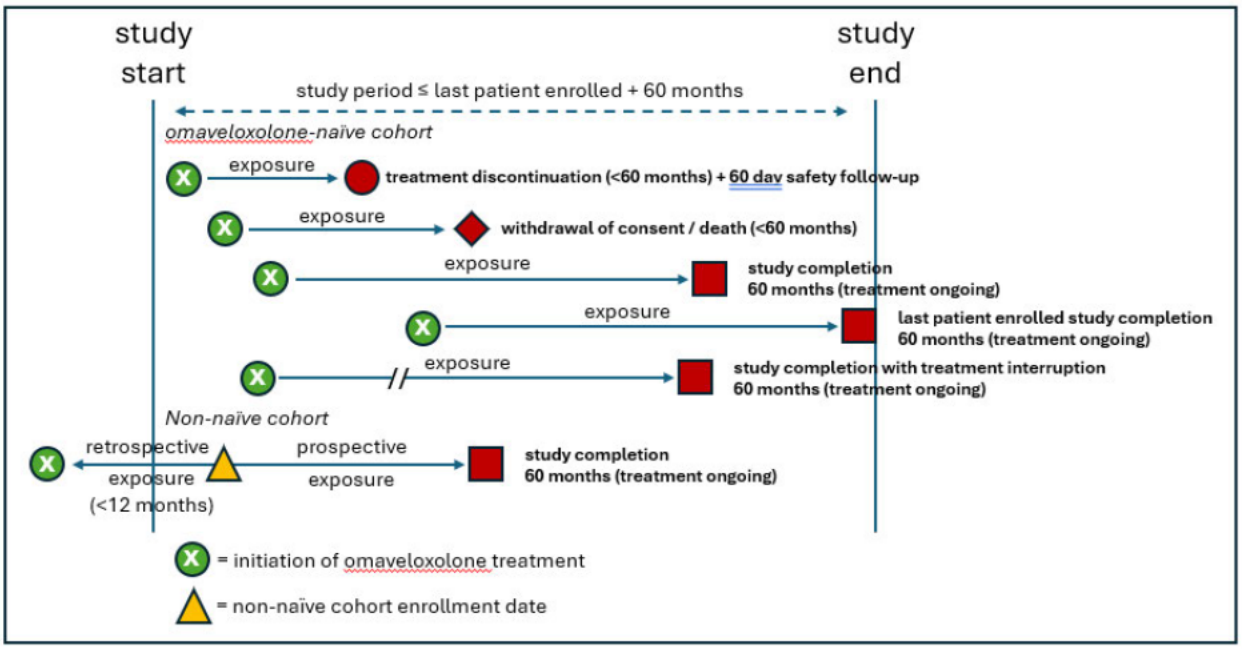
The list of countries participating in the study will be defined by the FA-GCC and according to market uptake after omaveloxolone launch.

9.1.2 Study duration and follow-up

This study begins after product availability in a country that has approval for omaveloxolone, and when the first participating site begins enrollment, following approval of the protocol by the relevant ethics committee (EC) or institutional review board (IRB). The study start date is December 2024. Each patient's participation will last no longer than 60 months after omaveloxolone initiation, although treatment is expected to continue past this timepoint.

Participation of each patient will begin at the date of informed consent/assent. The index date will be the date at which prospective data collection begins. For the omaveloxolone-naive cohort, this will be the date of initiation of omaveloxolone treatment. For the non-naive cohort, this will be the date of enrollment. After signing informed consent/assent, the patient will be followed for 60 months following date of initiation of omaveloxolone treatment or for 60 days after discontinuation of omaveloxolone treatment or discontinuation from the study. Discontinuation is defined as an interruption in omaveloxolone treatment in which the patient does not reinitiate omaveloxolone treatment within 60 days of the date of the last administration. The date of treatment discontinuation will be defined as the date of the last administration of omaveloxolone. Patients will have completed the study when they complete 60 months of treatment, discontinue treatment and complete the 60-day safety follow-up, withdraw consent, or death. More details on the study time periods are provided in Section 9.2. A study design schematic is presented in Figure 1.

Figure 1. Study design schematic



Each patient will be asked to provide informed consent/assent for participation in this study and for marketing authorization holder (MAH) access to relevant medical history data. Once informed consent/assent is signed, the patient will receive their study identification (ID) and move to baseline data collection, following which they will be considered enrolled in the study. The initiation date of omaveloxolone treatment will set the study visit cadence, with each visit scheduled based on time passed from this date.

- For the omaveloxolone-naive cohort, baseline data collection will begin following informed consent/assent. If omaveloxolone treatment is not initiated at the time of enrollment and baseline data collection, certain laboratory assessments may be repeated if recommended by the treating physician and the results will be used as baseline for those variables. Patients will be allowed a maximum window of up to 6 months between enrollment and treatment initiation, beyond which they will be subject to re-evaluation for enrollment.
- For the non-naive cohort, baseline data will be collected retrospectively from patient medical records, the UNIFAI study database, and study site patient records looking back to the period prior to initiation of omaveloxolone treatment. Post-baseline data (including the reporting of any SAEs and DILI/CHF AEs) will only be collected prospectively from non-naive cohort patients beginning at their enrollment date. Any potential events that may have occurred between omaveloxolone initiation and enrollment will not be collected. Non-naive cohort patients will participate in the next scheduled assessment of the study visit cadence following their informed consent/assent.

Each patient's participation will last no longer than 60 months after omaveloxolone initiation although treatment is expected to continue past this timepoint. The follow-up period of 60 months after omaveloxolone initiation may end before 5 years in the following circumstances: if the patient dies, if the patient is lost to follow-up, or if the patient withdraws consent, or if the patient discontinues

omaveloxolone treatment. The end of follow-up in deceased patients will be defined as the date of death. The end of follow-up in patients lost to follow-up or who withdraw consent will be defined as the date of the last known assessment. If a patient permanently discontinues omaveloxolone treatment or discontinues from the study during the follow-up phase, the last follow-up visit will be 60 days after the last administration of omaveloxolone (unless discontinued due to death or withdrawal of consent).

9.2 Setting

This study is strictly observational; the assignment of patients to omaveloxolone or any drug will not be determined in advance by the protocol and will be clearly separated from the decision to include the patients in the study. The treating physician will determine the patient visits and assessments according to routine practice and as per the relevant approved product label (eg, USPI or European Union [EU] SmPC). The schedule of assessments proposed in this study is based on anticipated visits as per the prescribing label and as per the UNIFAI study. No additional in-person visits are expected solely for this omaveloxolone study. The plan is to collect as much information as possible without imposing any additional burden on patients and families.

Data from all routine clinical care assessments that occur during the follow-up period will be collected and analyzed by specified timepoints: at 1 month, 2 months, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months. A 60-day safety follow-up visit is required for patients who discontinue omaveloxolone treatment or discontinue from the study (unless discontinued due to death or withdrawal of consent). These timepoints approximately match the routine follow-up for patients initiating omaveloxolone treatment and/or the annual visits for the UNIFAI study. If any additional assessments occur between these timepoints, these data will be collected via additional forms.

Table 9-1 presents the schedule of assessments to be collected solely for this study. Table 9-2 presents the schedule of optional assessments, which are not specified per prescribing label but may be requested by the prescribing/treating physician. The schedule of assessments collected per the UNIFAI study is presented in Table 9-3.

Table 9-1. Schedule of assessments for this PASS

	Baseline[a]	1[b]	2[b]	3[b]	6[b]	12	24	36	48	60[c] (EOS)	60-Day Discon Follow-up[c] (EOS)
History of depression (Beck Depression Inventory)	X[d]										
Adverse event data collection	X	X	X	X	X	X	X	X	X	X	X
Treatment data collection	X	X	X	X	X	X	X	X	X	X	
Liver panel[b,e]: ALT, AST, TBL	X	X	X	X	X	X	X	X	X	X	

	Baseline[a]	1[b]	2[b]	3[b]	6[b]	12	24	36	48	60[c] (EOS)	60-Day Discon Follow-up[c] (EOS)
Reproductive status (females only)	X			X	X	X	X	X	X	X	X
[redacted]											
Reasons/timing for treatment interruption		X	X	X	X	X	X	X	X	X	
Reasons/timing for treatment discontinuation		X	X	X	X	X	X	X	X	X	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; Discon=discontinuation; EOS=end of study; [redacted] PASS=post-authorization safety study; TBL=total bilirubin

[a] For the omaveloxolone-naive cohort, if omaveloxolone treatment is not available within 60 days after baseline data collection, certain laboratory assessments may be repeated if recommended by the treating physician and the results will be used as baseline for those variables. For the non-naive cohort, baseline data collection will be collected at enrollment and be retrospective back to the period just prior to omaveloxolone treatment initiation. The non-naive cohort patient will begin prospective data collection at their enrollment date.

[b] Assessments at 1 month, 2 months, 3 months, and 6 months will be conducted as a telephone contact. Samples for the liver panel can be collected at the patient's local laboratory.

[c] Each patient will be followed until the end of the study period (60 months following their individual omaveloxolone initiation) or for 60 days after discontinuation of treatment or discontinuation from the study, if applicable.

[d] If available prior to omaveloxolone initiation

[e] These data are to be collected periodically based on tests/examinations being performed as per an approved label (expected routine clinical practice).

Table 9-2. Schedule of assessments: Optional assessments

Assessments (Months)	Baseline[a]	1[b]	2[b]	3[b]	6[b]	12	24	36	48	60[c] (EOS)
Lipid panel[b,d]: LDL, HDL, triglycerides	X			X	X	X	X	X	X	X
CHF panel[b,d]: BNP and/or NT-proBNP	X			X	X	X	X	X	X	X
Electrocardiogram[d]	X			X	X	X	X	X	X	X
Echocardiogram or MRI[d]	X					X	X	X	X	X

Abbreviations: BNP=B-type natriuretic peptide; CHF=congestive heart failure; EOS=end of study; HDL=high-density lipoprotein; LDL=low-density lipoprotein; MRI=magnetic resonance imaging; NT-proBNP=N-terminal pro B-type natriuretic peptide

[a] For the omaveloxolone-naive cohort, if omaveloxolone treatment is not available within 60 days after baseline data collection, certain laboratory assessments may be repeated if recommended by the treating physician and the results will be used as baseline for those variables. For the non-naive cohort, baseline data collection will be collected at enrollment and be retrospective back to the period just prior to omaveloxolone treatment initiation. The non-naive cohort patient will begin prospective data collection at their enrollment date.

[b] Assessments at 1 month, 2 months, 3 months, and 6 months will be conducted as a telephone contact. Samples for the lipid panel and CHF panel can be collected at the patient's local laboratory.

[c] Each patient will be followed until the end of the study period (60 months following their individual omaveloxolone initiation) or for 60 days after discontinuation of treatment or discontinuation from the study, if applicable.

[d] These data are to be collected periodically based on tests/examinations being performed as per an approved label (expected routine clinical practice).

Table 9-3. Schedule of assessments as collected in UNIFAI

Assessments (Months)	Baseline[a]	1[b]	2[b]	3[b]	6[b]	12				24	36	48	60[c] (EOS)
Demographics	X												
Medical and treatment history	X												
Comorbidities	X								X	X	X	X	X
Clinical characteristics of FA	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI: weight, height	X								X	X	X	X	X
[redacted]													

Abbreviations: BMI=body mass index; EOS=end of study; FA=Friedreich's ataxia; [redacted] UNIFAI=UNIFIED Natural History Study

[a] For the non-naive cohort, baseline data collection will be collected at enrollment and be retrospective back to the period just prior to omaveloxolone treatment initiation. The non-naive cohort patient will begin prospective data collection at their enrollment date

[b] Assessments at 1 month, 2 months, 3 months, and 6 months will be conducted as a telephone contact.

[c] Each patient will be followed until the end of the study period (60 months following their individual omaveloxolone initiation) or for 60 days after discontinuation of treatment or discontinuation from the study, if applicable.

9.2.1 Study sites

This study will be conducted using the UNIFAI study, so the participant pool can be leveraged to identify and enroll patients. This approach is expected to optimize patient recruitment, leverage any existing data collection, and minimize the burden on reporting sites.

The UNIFAI study is the result of a combination of two well-established, long-standing natural history studies in FA: FA-Clinical Outcome Measures (FA-COMS; US, Canada, Australia, New Zealand, and India) and the European FA Consortium for Translational Studies (EFACTS; European countries). These studies have been conducted in parallel and have many similarities in protocol design and study conduct. FA-COMS has enrolled 1,370 participants at 14 sites, including nine in the US. EFACTS has enrolled 1,050 participants at 15 sites, including sites in Germany, France, and Italy.

9.2.2 Study population, eligibility, and selection criteria

9.2.2.1 Study population

Due to the rarity of FA and the already established infrastructure of the UNIFAI study, patients for this registry-based study will be identified and enrolled via the UNIFAI platform. Patient selection will be based on the inclusion and exclusion criteria listed in Section 9.2.2.2.

9.2.2.2 Eligibility

Patients who meet all inclusion criteria and none of the exclusion criteria will be eligible for inclusion in the study.

Inclusion criteria

- Patients aged 16 years and older at initiation of omaveloxolone treatment
- Documented diagnosis of FA, including confirmation via genetic testing
- For the omaveloxolone-naive cohort
  - omaveloxolone naive
  - initiating omaveloxolone treatment as per an approved label concurrent with enrolling in this study
- For the non-naive cohort
  - initiated omaveloxolone treatment as per an approved label less than 12 months prior to enrollment in this study
  - prior to enrollment, maintained omaveloxolone treatment with no discontinuation of more than 60 days
  - actively on treatment at the time of enrollment in this study
  - treating physician is the study site principal investigator or sub-investigator
  - study site confirms ability to provide required baseline data through medical record review, UNIFAI database, or other site-collected data
- Enrolled in the UNIFAI study prior to initiation of omaveloxolone treatment
- Willing and able to comply with visits as per the relevant approved label, and other study procedures
- Evidence of a personally signed and dated informed consent document (and assent form, if necessary) indicating that the patient (or a legally authorized representative) has been informed of all pertinent aspects of participation in the study prior to data collection for this study

Exclusion criteria

- Received off-label prescription of omaveloxolone at any time
- Previously enrolled in a clinical trial of omaveloxolone
- Participating in a blinded interventional trial at the time of enrollment in the study; patients may participate in other clinical trials after baseline data are collected

- Patient is, in the opinion of the prescriber and/or study investigator, unable to comply with the requirements of the study or is unsuitable for any reason

Sampling strategy

There is no sampling strategy, and patients will be enrolled consecutively. The investigators and sites will be made aware of this study, and patients who seek care for FA and meet the eligibility criteria will be invited to participate.

9.2.3 Withdrawal criteria

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and without giving a reason. Any withdrawal will be fully documented in the electronic case report form (eCRF) and source documents. Discontinuation from the study for any other reasons (eg, lost to follow-up, death) will also be recorded in the eCRF.

A patient must be withdrawn from the study if:

- The patient and/or their legal representative (if applicable) withdraw(s) their consent (defined as a patient and/or their legal representative [if applicable] who explicitly take(s) back their consent).
- The investigator considers it in the patient's best interests that they be withdrawn.

If the patient withdraws consent for disclosing future information, no additional data should be collected. All use of any data collected before the date of withdrawal of consent will be in accordance with the General Data Protection Regulation (GDPR).

9.3 Variables

Most variables of interest for this study are being collected as part of the UNIFAI study and will be extracted from the UNIFAI data platform. Information collected as part of this observational study may lead to the need for additional follow-up, management, and treatment of patients, based on the judgment of the investigator. If the investigator is not the treating physician, communication of such judgment by the investigator to the treating physician is generally recommended.

9.3.1 Primary outcomes

9.3.1.1 Primary outcome definitions

The primary outcomes are the description and incidence of all DILI and CHF AEs and the description and incidence of all SAEs over time.

Long-term safety

The study will collect all SAEs regardless of causality assessment, and these will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Incidence will be presented for all SAEs that occurred from the initiation date of omaveloxolone treatment for the omaveloxolone-naive cohort (with onset date on or after the first treatment of omaveloxolone) or from enrollment date for the non-naive cohort until study completion. In both cohorts, these are referred to as treatment-emergent SAEs

(TESEAs). The primary outcomes will be assessed via the safety event data collection that takes place during the omaveloxolone treatment period and up to 60 days following omaveloxolone discontinuation; this includes TESAEs that started or worsened after the first treatment.

DILI and CHF AEs

Any clinically significant abnormality in liver function that would be evaluated as a potential DILI event as part of normal clinical practice based on the judgment of the investigator may be considered (as described in Section 11.2). As a guide, AEs that will be considered a DILI AE by the investigator are generally events that fall within the MedDRA System Organ Class (SOC) Hepatobiliary disorders, but classification of events is at the discretion of the investigator. As per the omaveloxolone prescribing label, if transaminases increase to levels > 5X ULN, or > 3X ULN with evidence of liver dysfunction (eg, elevated bilirubin), the treating physician must immediately discontinue the drug and repeat liver function tests as soon as possible. If transaminase levels stabilize or resolve, omaveloxolone may be reinitiated with an appropriate increased frequency of monitoring of liver function.

Any clinically significant abnormalities in cardiac function that would be evaluated as a potential CHF event as part of normal clinical practice based on the judgment of the investigator may be considered (as described in Section 11.2). For example, a CHF event may be defined as a New York Heart Association (NYHA) class III or IV or death related to CHF utilizing the Standardized MedDRA Query (SMQ) cardiac failure. As a guide, AEs that will be considered a CHF AE generally include events that fall within the MedDRA High Level Group Term (HLGT) of Heart failures, including the High Level Terms (HLTs) of Heart failure signs and symptoms, Heart failures Not Elsewhere Classified, Left ventricular failures, and Right ventricular failures, but classification of events is at the discretion of the investigator. As per the omaveloxolone prescribing label, monitoring patients for the signs and symptoms of fluid overload, such as sudden weight gain (3 pounds or more of weight gain in one day, or 5 pounds or more of weight gain in a week), peripheral edema, palpitations, and shortness of breath is recommended. If signs and symptoms of fluid overload develop, worsen, or require hospitalization, evaluation of BNP (or NT-proBNP) and cardiac function and management by the treating physician in accordance with medical practice is recommended. Management of fluid overload and heart failure may require discontinuation of the drug.

Descriptions of and incidence data for DILI and CHF events will be collected via the AE/SAE data collection forms. Incidence will be presented for all events of DILI and CHF that occurred from the initiation date of omaveloxolone treatment for the omaveloxolone-naive cohort (with onset date on or after the first treatment of omaveloxolone) or from enrollment date for the non-naive cohort until study completion.

9.3.1.2 Primary outcome variables

Primary outcome variables for all SAEs include:

- SAE term and its description
- Start and end dates of the SAE
- Outcome of the SAE
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)

- Severity of the SAE
- Hospitalization dates, if applicable

Outcome variables related to DILI and CHF include:

- Start and end dates of the AE
- Outcome of the AE
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)
- Severity of the AE
- Seriousness of the AE
- Date of AE treatment initiation by the treating physician
- Lipid panel
  - Low-density lipoprotein (LDL)
  - High-density lipoprotein (HDL)
  - Triglycerides
- Signals for DILI at time of DILI diagnosis, as applicable
  - Liver panel
    - Serum aminotransferases
      - ALT
      - AST
    - TBL
- Signals for CHF at time of CHF diagnosis, as applicable
  - Date of AE treatment initiation by the treating physician
  - Electrocardiogram
  - Echocardiogram
  - Cardiac magnetic resonance imaging (MRI), if available
  - CHF panel
    - B-type natriuretic peptide (BNP) and/or
    - N-terminal prohormone B-type natriuretic peptide (NT-proBNP)

Information on all DILI and CHF AEs and all SAEs will be collected, and patients will be encouraged to contact their treating physician in between visits as per routine clinical practice to report any potential events.

9.3.2 Secondary outcomes

9.3.2.1 Secondary outcome definitions

Treatment interruptions and discontinuations

Omaveloxolone treatment interruption will be assessed using treatment discontinuation data. If patients start omaveloxolone again within 60 days of treatment discontinuation, this will be classified as a treatment interruption.

Information on omaveloxolone treatment discontinuation will be collected during routine follow-up visits, where applicable. If the patient does not reinitiate omaveloxolone treatment within 60 days of the date of the last administration, this will be defined as a treatment discontinuation. The date of treatment discontinuation will be defined as the date of the last administration of omaveloxolone.

Omaveloxolone drug overdose

Omaveloxolone drug overdose data will be collected during the follow-up period. If a patient takes more than the daily recommended dose of 150 mg of omaveloxolone, this will be considered a drug overdose. This information will be captured in the treatment regimen details.

9.3.2.2 Secondary outcome variables

Treatment interruptions and discontinuations

Omaveloxolone treatment interruptions and discontinuations will be collected for all patients. The variables to be collected will include, but not be limited to:

- Date of last omaveloxolone administration
- Time to interruption/discontinuation (derived variable)
- Reason(s) for interruption/discontinuation
  - Physician decision
  - Patient/parent decision
  - AE/SAE
  - New-onset comorbidities
- Date(s) of each stop of omaveloxolone administration
- Date(s) of restarting omaveloxolone administration, if applicable
- Daily dose at restart(s), if applicable
- Reason for restart(s), if applicable

Omaveloxolone drug overdose

Omaveloxolone drug overdose data will be collected for all patients with the following variables:

- Date(s) of the drug overdose
- Daily dose(s) during the overdose

- Reason for overdose
- Outcome/consequence
  - AE/SAE
    - Overdose-related medical outcomes, in which overdose is defined as any dose higher than the daily recommended dose of 150 mg of omaveloxolone

[redacted]

[redacted]

9.3.4 Exposure

For the omaveloxolone-naive cohort, treatment characteristics of omaveloxolone will be collected starting at omaveloxolone initiation until the earlier of their end of participation in the study or omaveloxolone discontinuation. For the non-naive cohort, treatment characteristics at baseline will be collected retrospectively at enrollment and then prospectively from enrollment until the earlier of their end of participation in the study or omaveloxolone discontinuation.

The omaveloxolone treatment characteristics will include the following variables:

- Start dates and, as applicable, end dates
- Treatment duration (derived variable)
- Daily dose in mg
- Frequency of administration

- Any omaveloxolone treatment change (excluding retrospective changes prior to enrollment in patients in the non-naive cohort) in terms of daily dose or frequency of administration, including omaveloxolone treatment discontinuation
    - Date of change(s)
    - Type of change (dose, frequency)
    - Reason(s) for change
        - Physician decision
        - Patient/parent decision
        - Any SAE or any DILI or CHF AE
        - New-onset comorbidities

9.3.5 Other assessments

9.3.5.1 Collected at the earlier of baseline visit or omaveloxolone treatment initiation

Demographics

- Age
- Sex
- Reproductive status (females only)

Medical history and comorbidities

- Clinically significant disease and comorbidities of interest, including but not limited to:
    - Cardiomyopathy
    - Other Cardiac conditions
    - Ambulation status
    - Diabetes
    - Scoliosis
- Hepatic impairment (if available prior to omaveloxolone initiation)
    - Child-Pugh class A
    - Child-Pugh class B
    - Child-Pugh class C
- History of depression (Beck Depression Inventory-2 [BDI-2]) (if available prior to omaveloxolone initiation)

  The BDI-2 is a 21-item self-report instrument for measuring the severity of depression in adults and adolescents aged 13 years and older [Beck 1996]. This instrument was developed for the assessment of symptoms corresponding to criteria for diagnosing depressive disorders listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV).

- History of substance use

Anthropometric measurements

- Weight (kg)
- Height (cm)
- BMI (kg/m^2), derived from weight and height

Clinical characteristics of FA

- Genetic diagnosis
- Family history
- Age at symptom onset
- Age at diagnosis
- Stage of disease
- mFARS and Scale for Assessment and Rating of Ataxia

Treatment history

- Previous enrollment in a clinical trial for the treatment of FA

Reproductive status (females only)

- Pregnancies
  - Number of prior pregnancies and fetuses
  - Outcome of each pregnancy
- Lactations
  - Number of prior lactation events
  - Start and end dates

Recent and concomitant medications (given within 30 days prior to the earlier of baseline visit or omaveloxolone treatment initiation date)

- Prescription drugs
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Indication
  - Reason for treatment discontinuation/withdrawal
- Over-the-counter (OTC) drugs
  - Drug name(s)
  - Start and end dates

- Daily dose
- Route of administration
- Indication
- Reason for treatment discontinuation/withdrawal

- Herbal or homeopathic remedies
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Reason for treatment discontinuation/withdrawal
- Nutritional supplements
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Reason for treatment discontinuation/withdrawal

9.3.5.2 Collected during routine follow-up visits (up to 60 months)

Anthropometric measurements

- Weight (kg)
- Height (cm)
- BMI (kg/m^2), derived from weight and height

Reproductive status (females only)

- Pregnancies
  - Number of pregnancies and fetuses
  - Start and end dates
  - Outcome of each pregnancy
  - Adverse effects on the developing fetus and neonate
- Lactations
  - Number of lactation events
  - Start and end dates
  - Adverse effects on the infant
  - Infant outcomes for at least the first year of life

Patient status

- Death, lost to follow-up, withdrew consent

  If applicable: date of death, primary cause of death, date of loss to follow-up, date of consent withdrawal, or reason for consent withdrawal.

Concomitant medications (since previous visit)

- Prescription drugs
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Indication
  - Reason for treatment discontinuation/withdrawal
- OTC drugs
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Indication
  - Reason for treatment discontinuation/withdrawal
- Herbal or homeopathic remedies
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Reason for treatment discontinuation/withdrawal
- Nutritional supplements
  - Drug name(s)
  - Start and end dates
  - Daily dose
  - Route of administration
  - Reason for treatment discontinuation/withdrawal

9.3.5.3 Collected at 60-day safety follow-up (for patients who discontinue study or omaveloxolone treatment)

All SAEs (as defined in Section 9.3.1.1)

- SAE term and its description
- Start and end dates of the SAE
- Outcome of the SAE
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)
- Severity of the SAE
- Hospitalization dates, if applicable

DILI and CHF AEs (as defined in Section 9.3.1.1)

- Start and end dates of the AE
- Outcome of the AE
- Action(s) taken with omaveloxolone treatment by the treating physician
- Causal relationship to omaveloxolone treatment (per investigator)
- Severity of the AE
- Seriousness of the AE
- Date of treatment initiation for the AE

9.4 Data sources

Medical information will be recorded in patients' medical records during every routine clinic visit and each time a laboratory test is performed (according to omaveloxolone labeling: monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated; or per the UNIFAI study schedule of assessments). Additional timepoints can be defined if sufficient data are available. Patients' medical record information, research records, and any relevant diagnostic reports are the source documents for study data collection.

As all sites and patients are participating in the UNIFAI study, overlapping data will be extracted from the UNIFAI study where possible to avoid any additional burden to the investigators. When not collected by the UNIFAI study, clinical information recorded in patients' medical records and/or diagnostic reports will be abstracted and entered into the eCRF in the electronic data capture (EDC). [redacted]

Each patient will have a unique number within the study (Patient Identification). Each site will maintain a Patient Identification list linking the patient to the Patient Identification within the study. Only the investigator and/or authorized personnel will be able to identify the patient based on the Patient Identification list, which will be held only at the site.

The MAH will be the "controller" of the personal data collected for the study. The MAH will take appropriate steps to ensure that personal data are protected.

All SAEs, regardless of causality, as well as pregnancy or lactation-related infant SAE data, will be reported to the MAH's safety vendor within 24 hours of the investigator's knowledge of onset or notification of the

event. More details on the SAE reporting can be found in Section 11. DILI and CHF AEs and lactation non-SAEs should be reported to the MAH's safety vendor within 7 days (Section 11.2.3.1).

Remote monitoring visits will be conducted by the assigned clinical research associate, as described in the monitoring plan. The monitoring plan will be developed and available before monitoring begins. The eCRFs and patients' corresponding original medical records (source documents) will be fully available for review by the MAH's representatives, as needed, per the monitoring plan. All records at the site are subject to inspection by the local health authority and review by an independent ethics committee (IEC)/institutional review board (IRB).

9.5 Study size

The design of the study is descriptive; therefore, no formal sample size or power calculation is necessary. The sample size is based on both practical and statistical considerations. The safety context of the study requires that the sample size be sufficient to detect a signal, if any.

The study will aim to enroll approximately 300 patients. Tables are shown which assess the precision of different sample sizes based on the occurrence of any SAE and the occurrence of all DILI and CHF AEs.

Table 9-4 presents scenarios in which a certain proportion of patients will experience SAEs after 1, 3, and 5 years of exposure duration. This is based on the results of Study 1402 Part 2, in which 5 patients reported SAEs in 51 omaveloxolone-treated patients studied for 1 year and the Poisson SAE rate estimate per patient year was 0.098 [Lynch 2021a]. In Table 9-4, confidence interval widths and precision were calculated based on Poisson distribution. With sample sizes between 100 and 300 of 1, 3, and 5 years of exposure duration, the precision is reasonably tight.

Table 9-4. Sample size precision table for any SAE

	N	Years	Patient-Years	Expected Number of Events	Lower 95	Upper 95	CI Width	Precision (CI Width/2)
Primary (any SAE)	100	1	100	9.804	0.047	0.181	0.135	0.067
	100	3	300	29.412	0.066	0.140	0.075	0.037
	100	5	500	49.020	0.073	0.130	0.057	0.029
	200	1	200	19.608	0.060	0.152	0.093	0.046
	200	3	600	58.824	0.075	0.127	0.052	0.026
	200	5	1000	98.039	0.080	0.119	0.040	0.020
	300	**1**	**300**	**29.412**	**0.066**	**0.140**	**0.075**	**0.037**
	300	**3**	**900**	**88.235**	**0.079**	**0.121**	**0.042**	**0.021**
	300	**5**	**1500**	**147.059**	**0.083**	**0.115**	**0.032**	**0.016**

Abbreviations: CI=confidence interval; SAE=serious adverse event

In Table 9-5, confidence interval (CI) widths and precision were calculated using the exact confidence interval of Poisson distribution. With a sample size of 300, the precision is tight for all outcomes: smaller than 4% for the primary outcome and smaller than 3% for the secondary outcome (and with a sample size of 100, smaller than 7% and 5% respectively). Table 9-5 is designed for the objective of documenting the occurrence of all DILI and CHF AEs. There were no safety events of DILI or CHF reported in Study 1402,

but omaveloxolone has been associated with a higher incidence of ALT and AST increase, and with increases in BNP. For that reason, three different hypothetical rates of DILI or CHF AEs of 1%, 2%, and 5% are presented in Table 9-5.

Table 9-5. Sample size precision table for DILI or CHF AEs

	N	Year	Patient-Years	Rate	Expected Number of Events	Lower 95	Upper 95	CI Width		Precision (CI Width/2)
DILI or CHF events	100	1	100	0.01	1	0.000	0.056	0.055		0.028
	100	3	300	0.01	3	0.002	0.029	0.027		0.014
	100	5	500	0.01	5	0.003	0.023	0.020		0.010
	200	1	200	0.01	2	0.001	0.036	0.035		0.017
	200	3	600	0.01	6	0.004	0.022	0.018		0.009
	200	5	1000	0.01	10	0.005	0.018	0.014		0.007
	300	**1**	**300**	**0.01**	**3**	**0.002**	**0.029**	**0.027**		**0.014**
	300	**3**	**900**	**0.01**	**9**	**0.005**	**0.019**	**0.014**		**0.007**
	300	**5**	**1500**	**0.01**	**15**	**0.006**	**0.016**	**0.011**		**0.005**
	100	1	100	0.02	2	0.002	0.072	0.070		0.035
	100	3	300	0.02	6	0.007	0.044	0.036		0.018
	100	5	500	0.02	10	0.010	0.037	0.027		0.014
	200	1	200	0.02	4	0.005	0.051	0.046		0.023
	200	3	600	0.02	12	0.010	0.035	0.025		0.012
	200	5	1000	0.02	20	0.012	0.031	0.019		0.009
	300	**1**	**300**	**0.02**	**6**	**0.007**	**0.044**	**0.036**		**0.018**
	300	**3**	**900**	**0.02**	**18**	**0.012**	**0.032**	**0.020**		**0.010**
	300	**5**	**1500**	**0.02**	**30**	**0.013**	**0.029**	**0.015**		**0.008**
	100	1	100	0.05	5	0.016	0.117	0.100		0.050
	100	3	300	0.05	15	0.028	0.082	0.054		0.027
	100	5	500	0.05	25	0.032	0.074	0.041		0.021
	200	1	200	0.05	10	0.024	0.092	0.068		0.034
	200	3	600	0.05	30	0.034	0.071	0.038		0.019
	200	5	1000	0.05	50	0.037	0.066	0.029		0.014
	300	**1**	**300**	**0.05**	**15**	**0.028**	**0.082**	**0.054**		**0.027**
	300	**3**	**900**	**0.05**	**45**	**0.036**	**0.067**	**0.030**		**0.015**
	300	**5**	**1500**	**0.05**	**75**	**0.039**	**0.063**	**0.023**		**0.012**

Abbreviations: AE=adverse event; CHF=congestive heart failure; CI=confidence interval; DILI=drug-induced liver injury

FA is a rare disease; therefore, the decision was made to utilize the existing UNIFAI study and its infrastructure. This strategy provides an efficient way of finding eligible patients. To capture the outcomes of interest, a total follow-up period of five years will be applied for each patient. Because some patients may not complete all five years of follow-up, some assumptions were made regarding attrition. Table 9-6 presents the expected attrition over the course of the study follow-up.

Table 9-6. Estimated attrition in patients during the follow-up

Exposure Duration (years)	Anticipated # of Patients Completing Follow-up	PYs
1	260	260
3	230	690
5	180	900

Abbreviation: PY=patient-year

9.6 Data management

9.6.1 Data collection

The data required by the protocol will be collected in an eCRF and entered into a validated data management system that is compliant with all regulatory requirements. The web-based EDC system (provided by a vendor; Section 14) will aim to serve as an integrated, transparent tool to collect and manage data, and track study progress at the center and patient levels. Data collected specifically for the study will be kept in a central location. Data collected for the UNIFAI study will be held separately in the UNIFAI system.

Each investigator will have the ultimate responsibility for the collection and reporting of all data to the MAH's safety vendor or the eCRFs and any other data collection forms (source documents), while also ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be electronically signed prior to database lock by the investigator to attest that the data contained in the eCRFs are correctly recorded. The MAH's designated representative will inform sites when it is time for eCRF sign-off to occur.

In the present case, the source documents are the patient medical charts and UNIFAI research records. Therefore, data collected in the eCRFs should match the data in the charts.

To ensure completeness and quality of the study-specific forms including safety data, reportable AE dates and results will be required fields in the EDC platforms, with manual queries utilized to obtain any missing components. Both the study-specific and separate UNIFAI EDC platforms have built-in edit checks, skip-logic, and manual queries for data coherence. The data management plan (Data Validation Manual) will include details documenting all aspects of queries, listings to identify data issues, resolutions for findings, and timings for queries and responses.

A data management plan (Data Validation Manual) will be prepared that details the data management and data handling procedures. This will include information on the data transfer procedures for analysis purposes.

9.6.2 Data monitoring

[redacted] was chosen as the EDC platform, in part, to avoid duplicative training as site staff are already trained in the use of [redacted] systems. Specific guidance on the data collection in this study are covered in the eCRF Completion Guidelines.

The CRO or designee (Section 14) will supervise and perform remote site management and monitoring, as described in the study-specific data management plan (Data Validation Manual) and the site monitoring plan. All participating sites will only have access to view and enter the data for their own patients. Only data required by the protocol for the purposes of the study should be collected.

All data entries in the study-specific EDC will be reviewed for clarity, uniqueness (non-duplication), completeness, and coherence in accordance with the data management plan (Data Validation Manual), edit checks, and manual queries. Missing, inconsistent, or unclear data will be queried as necessary throughout the study. Sites will be responsible for responding to queries in a reasonable timeline. The CRO or designee will also be responsible for the quality control of the study-specific database and confirming the overall integrity of the study-specific data. Quality-control mechanisms (eg, verification of data completeness, validations, skip-logic, and edit checks) are built into the EDC and employed at the time of data entry. Queries will be generated for resolution by site staff within the EDC system. The EDC system has built-in methods for data validation (eg, drop-down lists, value range controls, and standardized response formats) to minimize data entry errors; however, a data cleaning method will be employed to correct inconsistencies or errors that were not captured during data entry (eg, outliers or inconsistent data). Data queries will be identified on an ongoing basis during data collection. Sites will receive a regular e-mail notifying them of any new or outstanding queries. Formal source data verification is not expected in this study.

9.6.3 Record keeping

Investigators must keep relevant study documents, including site agreements, the identity of all participating patients (sufficient information to link records, eg, eCRFs and medical charts), source documents, detailed records of patient disposition (eg, signed informed consent), and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports). This will enable evaluations and/or audits from regulatory authorities or the MAH in accordance with national requirements on archiving of medical records. The records should be retained by the investigator for the length of time specified in local regulations, or in the Site Contract Agreement (whichever time period is longer).

If the investigator becomes unable for any reason (eg, retirement or relocation) to continue to retain study records for the required period, the MAH should be prospectively notified. The study records must be transferred to a designee acceptable to the MAH, such as another investigator, another institution, or to an independent third party arranged by the MAH. The investigator must obtain the MAH's written permission before disposing of any records, even if retention requirements have been met.

9.7 Data analysis

Details of the planned analyses are summarized below and will be described in a separate statistical analysis plan (SAP).

As previously described, post-baseline study data (including the reporting of any SAEs and potential DILI/CHF events) will only be collected prospectively (i.e. from enrollment into the study). Any retrospective data, changes in treatment regimen, or events that may have occurred between

omaveloxolone initiation and enrollment in patients in the non-naive cohort will not be collected and will therefore not form part of any analysis.

Data analyses will be presented separately for patients in the omaveloxolone-naive cohort and the non-naive cohort.

9.7.1 Statistical analysis plan

The SAP will describe analyses that will be performed for annual reports, as well as details of changes in the planned analysis after protocol finalization, if applicable. It will also provide a detailed description of the analyses to be performed and describe methods to address missing data.

All analyses will be conducted in accordance with the study objectives, SAP, and applicable guidelines.

9.7.2 Analysis populations

The study population will consist of patients with FA who receive omaveloxolone, according to prescribing information, and who are enrolled in the UNIFAI study. Patients who meet all inclusion criteria and none of the exclusion criteria are eligible to participate in the study and will constitute the main analysis population (also referred to as the safety analysis set).

9.7.3 Descriptive statistics

Descriptive statistics will be used to summarize the study data in tables, listings, and figures as appropriate at baseline and post-index timepoints. These will cover descriptive analyses of patient demographics, clinical history, disease characteristics, clinical management, [redacted]. The BDI-2 will be scored as per the developer's guidelines. Continuous variables will be described with summary statistics such as n, mean, standard deviation, median, first quartile, third quartile, and minimum and maximum values. For each categorical variable, the frequency and percentage in each category will be reported. Percentages will be calculated using the specified denominator in the table. The frequency and percentage of patients with missing data for each data point will be presented. Two-sided CIs of 95% will be calculated when relevant. Exact 95% CIs will be calculated assuming a Poisson distribution. Percentages will be reported with one decimal place.

9.7.4 Primary analyses

All SAEs

An overall summary of TESAEs will be presented, consisting of the number and percentage of patients experiencing the total number of TESAEs. TESAEs will also be summarized by SOC and Preferred Term (PT) (see also Section 9.7.7). TESAEs will be presented overall and by severity and relationship to the omaveloxolone treatment.

Summary listings of TESAEs and SAEs by SOC and PT will be presented with all safety variables.

Where relevant, incidence rate variables will be described as event rates per patient-year (PY) while on treatment. Related two-sided 95% CIs will also be provided.

DILI and CHF AEs

Incidence rates of all DILI and CHF AEs will be estimated, with two-sided 95% CIs. The diagnostic variables (eg, liver panel, echocardiogram, and/or CHF panel) at the time of each DILI or CHF diagnosis will be summarized descriptively.

SAEs, DILI, and CHF outcomes may also be treated as time-to-event endpoints and analyzed using survival analysis approaches. More details are provided in the SAP.

9.7.5 Secondary analyses

Physical and clinical parameters

At each timepoint of interest, the continuous endpoints (eg, laboratory results and electrocardiogram results) and the change from baseline in the continuous endpoints will be summarized descriptively. The change from baseline will be derived for each patient by calculating the difference between the entry closest to each timepoint and the baseline information. Two-sided 95% CI will be calculated when relevant.

Treatment interruptions and discontinuations

Time to treatment interruption and time to discontinuation will be analyzed using the Kaplan-Meier method and competing risk-based survival analysis if needed. Reasons for treatment interruption and treatment discontinuation will be summarized descriptively.

Omaveloxolone drug overdose

Omaveloxolone drug overdose is defined as any dose higher than the daily recommended dose of 150 mg of omaveloxolone. Time to omaveloxolone drug overdose will be analyzed using the Kaplan-Meier method and competing risk-based survival analysis if needed. The daily dose and the reasons for the drug overdose will be summarized descriptively.

[redacted]

9.7.7 Analyses of adverse events and serious adverse events

All SAEs and serious adverse drug reactions (SADRs) will be reported to the MAH's safety vendor (Section 11) by the investigator or by the site staff and listed with information on the patients' baseline characteristics. Additionally, SAEs/SADRs with outcome death, and SAEs/SADRs leading to withdrawal

from the study will be presented in separate listings. An SADR is an SAE for which there is at least a reasonable suspicion of a causal relationship between the SAE and omaveloxolone.

MedDRA coding version 25.0 or later will be used to classify and tabulate the reportable AEs/ADRs. Frequencies (absolute and percentages) across SOCs for individual events within those classes and PT will be provided and calculated with 95% CIs. SAEs/SADRs will be summarized using counts and percentages for the entire study population and subgroups of interest (as applicable).

9.7.8 Subgroup analyses

There are no other defined subgroup analyses. However, subgroup analyses may be conducted if sample size allows.

9.7.9 Handling of missing data

There will be no imputation of missing data in this study except for incomplete start dates for the purpose of time-to-event analyses; analyses will be conducted for outcomes where data are available. All efforts will be made to collect data as completely as possible. However, the count and percentages of patients with missing values will be reported for both continuous and categorical variables. Further details on the handling of missing data, eg, partially missing dates, will be described in the SAP.

9.7.9.1 Statistical software

The analyses will be performed using the statistical software SAS version 9.4 or higher.

9.8 Quality control

The procedures to ensure data quality and integrity in the EDC, including the accuracy and legibility of the data collected and original documents, extent of source data verification and validation of endpoints, storage of records, and archiving of the statistical programming performed to generate the results, are summarized below and will be described in detail in the monitoring plan, Data Validation Manual, and the SAP. Each document will be a standalone document.

Systems with procedures will be implemented to ensure the quality of every aspect of the study.

The development of the protocol and SAP will follow relevant standard operating procedures (SOPs), which include detailed rounds of review. Quality control of the statistical programming will also follow the relevant SOPs.

The EDC system (Section 14) meets approved, established standards for the security of health information, is validated, and is compliant with 21 Code of Federal Regulations (CFR) Part 11. To ensure that patient data (as well as other confidential data) remain secure and intact, the providing vendor will follow SOPs and quality control processes that address patient data security. The EDC system has built-in edit checks and validations and supports electronically generated and manual queries.

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical study. All data shall be secured against unauthorized access. Sites will maintain patient privacy in accordance with local and national regulations and institutional requirements.

A unique pseudonym for each patient is created based on fixed data (site number and order of enrollment/consent). The key for the re-identification is held securely at the study site where the patient is registered with this study and can be used for re-identification if in the patient's interest / in case of emergency.

9.9 Limitations of the research methods

This study aims to investigate the long-term safety of omaveloxolone in patients treated for FA in a real-world setting. This study's limitations are inherent to non-interventional study design and rare disease studies. Potential limitations and proposed strategies to address them are outlined in the sections that follow.

9.9.1 Sample size

Because of the rarity of FA, the precision estimation for this study is limited. To achieve a large enough sample size and to provide clinically meaningful data, the target sample size was calculated using both practical and statistical considerations. Although several factors may affect patient recruitment, notably omaveloxolone market launch and uptake in different countries, continuous monitoring of patient recruitment at the site and country levels will allow the rapid deployment of mitigation strategies in response to any challenges. Such plans will be discussed by the MAH and the regulatory authorities. By using the UNIFAI study to contact investigators and enroll patients, we expect to optimize patient recruitment.

9.9.2 Observational study design limitations

Due to the observational nature of this study and the inherent characteristics of such a design, this study may be subject to bias, including selection bias, variability in local treatment practices, guidelines, and data quality across sites.

9.9.2.1 Study biases

Selection bias due to non-consent will be mitigated by providing clear information to patients and legal representatives regarding the importance of the study and the absence of burden for them. The extent of the selection bias will be monitored via maintenance of an enrollment log at the site, which will anonymously list all eligible patients, consenting status, and characteristics, and inform the implementation of mitigation strategies. Finally, eligible patients will be included in this study on a consecutively enrolled basis to ensure that they were not selected by the investigator in any way that might influence the nature of the study.

The data provided by the non-naive cohort may be impacted by immortal time bias because patients who initiate omaveloxolone treatment and discontinue due to an SAE or CHF/DILI AE will not have the opportunity to enroll and thus will fail to have their events recorded. Baseline data for this cohort will be collected retrospectively for the period just prior to the initiation date of omaveloxolone treatment and will be subject to recall bias to a greater extent than the omaveloxolone-naive cohort. Data will not be collected between the initiation date of omaveloxolone treatment and the date of enrollment for this cohort, so patients will be missing data varying from Month 1 to Month 6 but, per inclusion criteria, will begin providing prospective data no later than the Year 1 visit. However, even during the prospective data

collection, where data collection methods are identical between the 2 cohorts, the non-naive cohort may differ from the omaveloxolone-naive cohort in their experience of longer-term safety due to this bias. The mitigation strategy for this potential bias is to perform the analyses separately for the omaveloxolone-naive cohort and non-naive cohort. A sensitivity analysis using survival approaches may also be used to account for immortal time bias in non-naive users.

Most (but not all) FA patients receiving omaveloxolone treatment will also receive care at UNIFAI centers. This study will not be able to observe outcomes in patients who do not receive care at UNIFAI study centers. Some countries in the European Union are participating in the early access program. This may result in reduced recruitment of patients with severe cases of FA.

9.9.2.2 Adverse event classification

Misclassification of events by sites will be mitigated by standardized training and will utilize standardized documentation for reporting to the MAH's safety vendor (Section 14).

9.9.2.3 Recruitment

Recruitment of patients is dependent on several factors; the uptake of omaveloxolone is unpredictable and has the potential to affect the feasibility of meeting the recruitment targets. However, continuous monitoring of patient recruitment at the site and country levels will allow strategies to be employed in response to any such challenges and to reduce or eliminate the potential impact of these factors. These include enrollment extension in existing sites, potential initiation of additional sites within participating countries, and/or expanding the study into additional countries.

10 Protection of human participants

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the Professional Society for Health Economics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), and European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Good Pharmacovigilance Practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3).

Detailed patient characteristics of patient subgroups with five or fewer participants will not be reported in accordance with privacy regulations applied by an increasing number of data source custodians.

10.1 Patient information and consent

For the study , each patient or their legally acceptable representative will be provided with information related to the study, including specifics related to study participation. This will be documented in an informed consent form (ICF) that is compliant with local regulatory requirements and legal requirements.

The ICF used in this study will be approved by the same EC responsible for approval of the protocol at each site. In addition, pediatric assent will be obtained as appropriate according to the patient's age and institutional requirements. At the first study visit following the patient reaching legal age, those who provided assent will be asked to provide consent. The study information will also inform the patient or their legally acceptable representative that they have the right to withdraw from the study at any time. They will be informed that if they do withdraw, no further study data will be collected from the time of withdrawal and that their withdrawal will not affect the medical care that they receive. The MAH may retain and continue to use any data collected before such withdrawal of consent.

Prior to any data collection under this protocol, written informed consent (or assent as applicable) must be signed by the patient or the patient's legally acceptable representative, in accordance with local practice and regulations. A copy of the informed consent/assent form must be given to the patient or the patient's legally acceptable representative (as applicable).

No patient identifiable data will be used as all data will be de-identified, and where required, patient-level data will remain at the data source for analyses.

10.2 Data protection

Prior to any data collection under this protocol, participants must also provide all authorizations required by local law (eg, protected health information authorization in North America). All data collected in this study will be strictly confidential in accordance with applicable data privacy protection laws and regulations (eg, GDPR).

The eCRF in the EDC system will record participants only by means of a unique pseudonym to safeguard patient confidentiality. No information such as name, initials, or local medical record number that could subsequently be used to identify patients will be entered into the EDC system, study-related forms, study reports, and related publications; and these reports will be used for research purposes only. The MAH, its partners and designee(s), ethics committees, and government health agencies may inspect the records of this study. Every effort will be made to keep participant's personal medical data confidential. Only investigators, or delegated site personnel, will have the possibility of associating the de-identified assigned ID code to a specific participant. Site study staff will be instructed to maintain complete confidentiality of all collected data. The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. By signing the protocol, the institution and/or investigator commit to complying with all related applicable laws and regulations. Summary reports generated from the eCRF will not contain any patient identifying information.

10.3 Ethics committee/institutional review board submission/notification

With assistance from the MAH, each investigator will be responsible for obtaining the necessary approval of the study protocol, protocol amendments, consent/assent (if needed), and other relevant documents, if applicable, from the central/local IRBs/IECs and for ensuring that the study complies with local legislation relating to data protection and privacy. When local approval is obtained, the documentation

indicating the IRB's/IEC's (if applicable) approval or favorable opinion and the names and qualifications of the committee members must be sent by the investigator to the MAH before the recruitment process begins.

10.4 Competent authority submission/notification

The approved protocol will be submitted to regulatory authorities in accordance with the regulations of the countries and participating sites' local clinical research regulatory requirements when applicable.

11 Management and reporting of adverse events

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the participant. If necessary, appropriate medical intervention should be provided.

Each participant or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of site staff for reporting AEs and medical emergencies (as defined in Section 11.2.3).

Before site activation and participant enrollment, the Clinical Monitor or designee is responsible for reviewing with site staff the definition of an AE and SAE (as defined in Section 11.1), as well as the instructions for monitoring, recording, and reporting SAEs (as defined in Section 11.2).

11.1 Definitions

11.1.1 Adverse events

According to the International Council for Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (eg, electrocardiogram, X-ray) that is associated with symptoms or leads to a change in treatment or concomitant medication or discontinuation from omaveloxolone

For this study, the medicinal product of interest is omaveloxolone.

11.1.2 Assessment of adverse events

Seriousness, relatedness, and severity need to be independently assessed for each AE.

11.1.3 Serious adverse events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the patient was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a patient who was exposed to the study drug)
- Other important medical events that may not be immediately life-threatening, or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the patient or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

11.1.4 Assessing relationship to study treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to study treatment:

Not related: An AE will be considered "not related" to the use of omaveloxolone if there is not a possibility that the event has been caused by it. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE (eg, the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.

Related: An AE will be considered "related" to the use of omaveloxolone if there is a possibility that the event may have been caused by it. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose

reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE. An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between the AE and omaveloxolone.

11.1.5 Classification of severity

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Mild: Symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s).

Moderate: Symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed.

Severe: Symptom(s) causes severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or participant hospitalized.

11.1.5.1 Expectedness of Events

Expectedness of all AEs will be determined by the MAH according to the approved local label.

11.2 Assessment, recording, and reporting of AEs and SAEs

11.2.1 Assessment of all DILI and CHF AEs and of all SAEs

It is the investigator's responsibility to assess CHF and DILI AEs and all SAEs. Data on AEs/SAEs will be obtained at regular visits and reported to the MAH.

The investigator should support each treating physician to make every effort to obtain all information necessary for appropriate reporting of events. For each DILI or CHF AE recorded, and for all SAEs, the investigator will assess seriousness and relatedness.

11.2.2 Recording of all DILI and CHF AEs and of all SAEs

Investigators should provide complete and accurate data on all events experienced for the duration of the recording period which are to be recorded on eCRFs on an ongoing basis for all DILI and CHF events and, for all SAEs, also via the additional reporting requirements described in Section 11.2.3.

Each report is to include a description of the event, whether it is considered serious (and if so, the criterion satisfied), its duration (onset and resolution dates), its relationship to omaveloxolone, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of omaveloxolone), and its outcome.

Investigators should use correct medical terminology/concepts when recording DILI and CHF AEs and all SAEs. Colloquialisms and abbreviations should be avoided. Only one AE term should be recorded per event.

All DILI and CHF AEs and all SAEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or the treating physician, will be recorded in the patient's medical record and in the AE section of the eCRF.

Once an omaveloxolone-naive cohort patient signs informed consent in the study, all DILI and CHF AEs and all SAEs will be collected from the first omaveloxolone dose through 60 days following discontinuation of omaveloxolone. Once a non-naive cohort patient signs informed consent in the study, all DILI and CHF AEs and all SAEs will be collected from the date of enrollment through 60 days following discontinuation of omaveloxolone.

11.2.2.1 Follow-up for ongoing DILI or CHF AEs and for all SAEs

In case of any ongoing DILI or CHF AEs and all ongoing SAEs at the end of study participation, the principal investigator should communicate the outcome of ongoing events to the MAH.

11.2.3 AE and SAE reporting procedures

11.2.3.1 Reporting of all non-serious DILI and CHF AEs

The primary objectives of this study are to assess the long-term safety of omaveloxolone as prescribed to patients with FA in the real-world setting and to document and characterize all AEs of CHF and DILI (both considered important potential risks of omaveloxolone).

The rationale for capturing all SAEs but only non-serious AEs for CHF and DILI is based mainly on the intention to keep the data collection as close as possible to standard study protocol procedures and to align with the general standard of care. This is expected to maximize participation and minimize participant burden. Furthermore, because FA is a progressive chronic multisystemic disease with early onset and is associated with significant comorbidities such as diabetes and cardiomyopathy, patients are expected to have a significant number of non-serious AEs as part of the normal course of their disease. By collecting all SAEs but focusing the collection of non-serious AEs on the areas of greatest concern, the MAH expects to optimize the collection of the most relevant safety information.

The investigator must record all DILI and CHF AEs, regardless of their relatedness to omaveloxolone, on the relevant eCRFs AND report on the AE/SAE form by e-mailing or faxing to the MAH no later than 7 calendar days from when the investigator becomes aware of the event.

It is very important that the AE/SAE report forms be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of relatedness.

Initial reports may be followed by detailed descriptions and, upon request, by copies of hospital case reports, autopsy reports, and other documents when applicable. Any follow-up information received on non-serious DILI and CHF events should be forwarded within 7 calendar days of its awareness. If the follow-up information changes the investigator's assessment of relatedness, this must also be noted on the follow-up AE/SAE form.

Follow-up of non-serious DILI and CHF AEs should be attempted up to resolution or, if resolution is unlikely, to stabilization.

The process for reporting all other non-serious AEs should be according to standard local postmarketing channels.

11.2.3.2 Reporting of all SAEs and serious DILI and CHF events

The investigator must record all SAEs (including serious DILI and CHF events), regardless of their relatedness to omaveloxolone, on both the relevant eCRFs and on the SAE Form and e-mail or fax to the MAH no later than 24 hours from when the investigator becomes aware of the event.

It is very important that the SAE report forms be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of relatedness.

Initial reports may be followed by detailed descriptions and, upon request, copies of hospital case reports, autopsy reports, and other documents when applicable. Any follow-up information received on SAEs should be forwarded within 24 hours of its awareness. If the follow-up information changes the investigator's assessment of relatedness, this must also be noted on the follow-up SAE form.

Follow-up of SAEs should be attempted up to resolution or, if resolution is unlikely, to stabilization.

11.2.3.3 Reporting of pregnancy

All pregnancies occurring from the first omaveloxolone dose (omaveloxolone-naive cohort) or signing of informed consent (non-naive cohort) until 60 days after the last omaveloxolone administration must be reported on the Pregnancy Report Form and faxed or e-mailed to the MAH within 24 hours of the investigator becoming aware of the pregnancy.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered SAEs and should be reported in the same timeframe and format as other SAEs.

Investigators must actively follow-up on and report the outcome of all pregnancies to the MAH within 24 hours after investigator's awareness.

11.2.3.4 Reporting of overdose

An overdose is any dose of omaveloxolone given to a participant or taken by a participant that exceeds the dose described in the local label. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed or e-mailed to the MAH within 24 hours. An overdose should be reported even if it does not result in an AE. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or e-mailed to the MAH.

11.2.3.5 Reporting to competent authorities

The MAH will notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

For AEs experienced by the participant and related to other products such as concomitant medication not manufactured by the MAH, the investigator should follow the standard procedures that are in place for spontaneous reporting, and account for and comply with the local applicable laws and regulations.

11.2.3.6 Evaluation

Reports received on new, important safety information will be processed and entered into the MAH's safety database and reviewed on a regular basis. If a potential safety signal is suspected, it will be investigated for further evaluation within the context of benefit-risk.

12 Protocol deviations

12.1 Overview

A protocol deviation is a failure to comply with the requirements specified within this study. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, ICH E6 Good Clinical Practices, and any conditions of approval imposed by their EC/IRB.

All reported deviations are to be reviewed and assessed for their impact on participant safety by the CRO or the MAH. The Investigator and designated study staff are responsible for knowing and adhering to their EC/IRB reporting requirements.

Due to the length of this observational study and as the protocol does not mandate any visits or assessments beyond those that are to occur in clinical practice, it is anticipated that missed visits or missed core assessments will occur and these will be documented directly on the eCRF along with an explanation for the missing data. Missing visits or core assessments will not be captured as a protocol deviation.

The protocol deviations for this protocol consist of, but not limited to the following:

- Failure to properly obtain and document participant's informed consent prior to any study-related activities.
- Participant did not meet the eligibility criteria.
- Failure to report SAE(s) and DILI/CHF AEs according to protocol requirements.

Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviations that affect the rights, safety or well-being of the participant or the scientific integrity of the clinical study may result in termination of the site's study participation.

12.2 Protocol deviation process

Investigators should report protocol deviations to the CRO or designee and the MAH within 5 working days of study site knowledge of the deviation. Any protocol deviations that affect the rights, safety or well-being of the participant or the scientific integrity of the clinical study, including those which occur under emergency circumstances must be reported within 24 hours to the MAH and EC/IRB, if required by the EC/IRB, or national regulations.

12.3 Corrective/preventive action

Deviations from protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions will be put into place.

13 Plans for results

13.1 Overview

The MAH or its designee will monitor data collection while the study is being conducted and will consider the implications for the benefit-risk balance of the medicinal product concerned.

Any new information that may affect the benefit-risk balance of the medicinal product will be communicated immediately to relevant competent authorities in accordance with GVP.

13.2 Study report

A full annual report will be provided for EMA, and interim analyses on AEs of DILI and CHF are to be performed for the FDA biannually. All interim and final reports will be submitted to the regulatory authorities by the MAH based on country/region reporting requirements and pursuant to required timeframes. A summary of the final report will also be published on the Heads of Medicines Agencies (HMA)-EMA Catalogues of real-world data sources and studies.

13.3 Data ownership

Each site will own the source data collected at the site. Hence, the source data will be jointly owned by the respective sites and the MAH. The overall data collected solely in this study will be the property of the MAH.

Copying or spreading information related to this study without the MAH's agreement is prohibited.

13.3.1 Publications

The MAH shall have the right to publish such data and information without approval from the sites. The MAH will establish a uniform procedure for analyzing, publishing, and disseminating findings from this study. Co-authors of publications may include participating investigators, the MAH's personnel, vendor, and/or other relevant thought leaders who contribute substantially to the publication (Section 14).

Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated December 2019.

All reporting will be consistent with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) Initiative checklist [von Elm 2007].

The MAH intends to prepare publications for peer review based on this study. The FDA and EMA will be informed in accordance with the guidelines. In order to allow competent authorities to review in advance the results and interpretations to be published, the MAH should communicate to the Agency and the competent authorities of the Member States in which the product is authorized the final manuscript of the article within two weeks after first acceptance for publication.

13.4 Ethics Committee notification of study completion or termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study and must be sent a copy of the study Synopsis in accordance with necessary timelines.

13.5 Registration of study and disclosure of study results

The MAH will register the study and post study results (CSR Synopsis), regardless of outcome, in the HMA-EMA Catalogues of real-world data sources and studies and on other publicly accessible websites in accordance with the applicable laws and regulations.

14 Key roles and responsibilities

14.1 Marketing authorization holder

Refer to page 1 for the listed MAH. The MAH will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

14.2 Vendors

The MAH reserves the right to change the selected CRO and vendors based on business needs.

14.2.1 Contract research organization

A CRO will be responsible for administrative aspects of the study, including but not limited to study initiation, management of SAE reports, monitoring, and data management. [redacted] has been selected as the CRO at study start.

14.2.2 Electronic or remote data capture

Participant information will be captured and managed by study sites on eCRFs by a Web-based EDC tool configured by the MAH or a CRO and hosted by the electronic/remote data capture vendor. [redacted] has been selected as the electronic/remote data capture vendor at study start.

14.2.3 Other

Other vendors selected at study start include [redacted], a non-profit research organization. [redacted] and will provide data to the MAH as detailed in Section 9.2.

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