CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Memorandum

Date	February 28, 2023
From	Emily R. Freilich, MD Cross-Disciplinary Team Lead Deputy Director (Acting) Division of Neurology 1 (DN1) Teresa Buracchio, MD Director, DN1 Director (Acting), Office of Neuroscience
Subject	Summary Memorandum
NDA/BLA # and Supplement#	216718
Applicant	Reata Pharmaceuticals, Inc.
Date of Submission	March 30, 2022
PDUFA Goal Date	February 28, 2023
Proprietary Name	Skyclarys
Established or Proper Name	Omaveloxolone
Dosage Form(s)	Capsules, 50 mg
Applicant Proposed Indication(s)/Population(s)	For the treatment of Friedreich's Ataxia
Applicant Proposed Dosing Regimen(s)	150 mg once daily
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Friedreich's Ataxia (FA) in patients 16 years and older
Recommended Dosing Regimen(s) (if applicable)	150 mg once daily

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Friedreich's Ataxia (FA) is a rare, genetic, cumulatively progressive neurodegenerative disorder caused by a defect in the Frataxin (FXN) gene, typically an expansion of the guanine-adenine-adenine (GAA) triplet repeat within the FXN gene, which impairs transcription, leading to deficiency of the frataxin protein. Frataxin is essential for proper functioning of the mitochondria, and deficiency leads to mitochondrial dysfunction, oxidative stress, and neuroinflammation. Patients develop ataxia, balance issues, loss of motor skills, and speech impairment, among other neurological impairments including weakness, visual impairment, and sensory loss. Patients with FA also have diverse non-neurological features such as cardiomyopathy, kyphoscoliosis, and foot deformities, such as pes cavus. Patients typically have loss of ambulation and wheelchair dependence by their mid-20s, leading to significant disability, and a shortened life expectancy, with an average age of death around 37.5 years of age. There are currently no approved drugs for the treatment of FA.

Omaveloxolone is proposed for the treatment of FA. The Applicant postulates that omaveloxolone activates the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which regulates the cellular response to oxidative stress and restores mitochondrial function, thus restoring redox balance and reducing inflammation. The proposed dose is 150 mg by mouth daily on an empty stomach, one hour before eating.

The Applicant has provided data from a single, randomized, double-blind, placebo-controlled study (Study 1402 Part 2) and an open-label extension study (Study 1402 OLE). In Study 1402 Part 2, a total of 103 patients with FA with or without pes cavus received placebo (N = 52) or omaveloxolone (N = 51) daily for 48 weeks (All Randomized population). A total of 82 FA patients without pes cavus (Full Analysis Population) were included in the Applicant's prespecified primary analysis population. There was a statistically significant improvement in the modified Friedreich's Ataxia Rating Scale (mFARS) at Week 48 in the omaveloxolone arm compared to the placebo arm (-2.41 points, p = 0.0138) in the Full Analysis population. Patients randomized to omaveloxolone (N = 42) had a mean improvement from baseline in mFARS with a change from baseline of -1.56 points, and patients randomized to placebo (N = 40) had a mean worsening from baseline of 0.85 points at Week 48. In the prespecified Full Analysis Population, the key secondary endpoints did not reach statistical significance; however, the secondary endpoint of Activities of Daily Living (ADL) scale was nominally significant (p = 0.04). In the All Randomized population, there was also a nominally significant improvement in mFARS of -1.94 compared to placebo (p = 0.0331) and the Patient Global Impression of Change (PGIC) showed nominally significant improvement compared to placebo (p = 0.0282).

Overall, Study 1402 Part 2 demonstrated a statistically significant treatment benefit of omaveloxolone compared to placebo on an acceptable primary endpoint, the change from baseline in mFARS, in both the primary Full Analysis Population and the All-Randomized Population (ITT). There were trends favoring omaveloxolone on the secondary endpoints, and nominally significant positive result on a scale of Activities of Daily Living in the full analysis population and on the PGIC in the all randomized population, supporting a treatment benefit of omaveloxolone compared to placebo.

A post hoc exploratory analysis compared patients who enrolled in Study 1402 OLE for up to 3 years to a propensity-matched cohort of patients from the natural history study, Clinical Outcome Measures in Friedreich's Ataxia (FA-COMS). This analysis showed a statistically significant difference in mFARS change from baseline in patients treated with omaveloxolone in Study 1402 OLE compared to matched FA-COMS patients. In the total pooled population of patients in Study 1402 OLE, there was a mean difference in mFARS change from baseline of -3.354 points compared to placebo ($p = 0.0002$).

Additionally, ferritin is proposed to be pharmacodynamic marker of Nrf2 activation. Omaveloxolone has shown dose-dependent increase in ferritin observed in Part 1 of Study 1402 (dose range finding study 5 mg to 300 mg) and increases in ferritin in patients receiving omaveloxolone compared to placebo in Study 1402 Part 2.

Omaveloxolone was generally well tolerated. In Study 1402 Part 2, there were no deaths or differences in serious adverse events between omaveloxolone and placebo. Many of the serious adverse events were related to progression of the underlying disease. The most common treatment-emergent adverse events (TEAEs) occurring in more than 20% of patients treated with omaveloxolone and greater than placebo include elevated liver enzymes, headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain. Increases in liver enzymes (AST, ALT, and GGT), B-natriuretic peptide (BNP) and lipids were observed in patients taking omaveloxolone, which can be monitored in the postmarketing setting. The Applicant postulates that the laboratory abnormalities are related to Nrf2 activation; however, mild drug-induced liver injury and increased risk for cardiac failure cannot be ruled out given the small sample size.

Given the serious and life-threatening nature of FA and the substantial unmet need with no approved treatments, some level of uncertainty is acceptable in this instance and consideration of these results in the context of regulatory flexibility is appropriate. The single adequate and well-controlled study with positive results on a clinically meaningful primary outcome, accompanied by confirmatory evidence from the natural history comparison, in addition to the pharmacodynamic data supporting the biologic plausibility of the treatment effect, are adequate to provide substantial evidence of effectiveness. There are no safety issues that would preclude approval. Additional pharmacovigilance and adequate monitoring for risks of liver injury and cardiac events are warranted in the postmarketing setting.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Friedreich's Ataxia (FA) is a rare, genetic, rapidly progressive neurodegenerative disorder. • FA is caused by a deficiency in frataxin, as a consequence of an expansion of the guanine-adenine-adenine (GAA) triplet repeat within the first intron of the frataxin gene, impairing transcription. Frataxin is a mitochondrial protein that facilitates production of cofactors necessary for many mitochondrial enzymes; frataxin deficiency leads to mitochondrial dysfunction, decreased ATP production, oxidative stress and neuroinflammation. • Symptom onset is typically between 5 and 15 years of age, although age of onset can range from 2 years to > 70 years. • Symptoms include poor balance, impaired coordination, dysarthria, weakness, ocular fixation instability, sensory loss, visual and hearing impairment, as well as non-neurological symptoms such as hypertrophic cardiomyopathy, kyphoscoliosis, and foot deformities (i.e., pes cavus). • Patients typically have progressive balance issues, loss of motor skills, and speech impairment, with loss of ambulation by the mid-20s, and loss of independence in daily activities. • Typically, patients with FA have a shortened life expectancy, with average age of death around 37.5 years of age. • Cardiac dysfunction related to dilated cardiomyopathy and related arrhythmias is widely accepted as the most common cause of mortality in patients with FA.	FA is a rare, serious, and life-threatening disease which results in mitochondrial dysfunction leading to progressive neurologic symptoms and non-neurologic manifestations, loss of ambulation and independence, and a shortened life expectancy. Primary neurologic manifestations include poor balance, loss of motor skills, dysarthria, and weakness. Cardiac dysfunction secondary to dilated cardiomyopathy and arrhythmias is widely accepted as the most common cause of death in patients with FA.
Current Treatment Options	• There are no approved treatments for FA.	There is a significant unmet need for therapies that treat FA.
Benefit	• The effectiveness of omaveloxolone in the treatment of FA was evaluated in a single, adequate, and well-controlled study (Study 1402 Part 2). • Study 1402 Part 2 randomized FA patients aged 16 to 40 years with or without pes cavus to omaveloxolone (N = 51) or placebo (N = 52) for 48 weeks	Study 1402 Part 2 demonstrated a statistically significant treatment benefit of omaveloxolone compared to placebo on the prespecified primary endpoint, the change from baseline in the mFARS score. Exploratory post hoc analyses of long-term

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The primary efficacy endpoint was change from baseline in the modified Friedreich's Ataxia Rating Scale (mFARS) score at Week 48 in patients without pes cavus (Full Analysis population; N =82). • There was a statistically significant improvement in mFARS at Week 48 of 2.41 points in the omaveloxolone treatment arm compared to placebo (p = 0.0138), with a mean improvement from baseline in mFARS of -1.56 points in patients receiving omaveloxolone, while patients randomized to placebo had a mean worsening of 0.85 points at Week 48. • The All Randomized population (patients with and without pes cavus) showed an improvement of -1.94 points in the omaveloxolone treated patients compared to placebo patients (nominal p = 0.0331). • The key secondary endpoints PGIC and Clinician Global Impression of Change (CGIC) did not reach statistical significance in the Full Analysis Population; however, PGIC was nominally significant in the All-Randomized patient (p = 0.0282). Another secondary endpoint, the Activities of Daily Living scale (ADL) was nominally significant in the prespecified Full Analysis population (p = 0.04). • A post hoc, propensity matched analysis of patients in Study 1402 OLE for 3 years compared to natural history data demonstrated a significant difference in mFARS change from baseline of -3.354 points in favor of omaveloxolone compared to placebo (p = 0.0002). • Ferritin is proposed to be pharmacodynamic marker of Nrf2 activation. Omaveloxolone has shown dose dependent increases in ferritin observed in Part 1 of study 1402 (dose range finding study 5 mg to 300 mg) and increased ferritin in patients treated with omaveloxolone compared to placebo in Study 1402 part 2.	treatment with omaveloxolone in the Study 1402 Open-Label Extension pooled population compared to a natural history cohort in a propensity matched analysis demonstrated a nominally statistically significant improvement in mFARS after 3 years of treatment with omaveloxolone (p =0.0002). Additional confirmatory evidence of the effectiveness of omaveloxolone in the treatment of FA comes from demonstrated increases in ferritin, based on a mechanistic biologic plausibility of ferritin increase secondary to Nrf2 activation. Overall, the single positive study accompanied by confirmatory evidence of pharmacodynamic evidence of Nrf2 activation and long-term treatment benefit compared to a propensity matched natural history population provide substantial evidence of effectiveness.
Risk and Risk Management	• A total of 103 patients provided safety data of 150 mg omaveloxolone compared to placebo. This included 24 adolescent patients age ≥ 16 years to < 18 years of age. • A total of 137 patients provided long-term safety data of 150 mg omaveloxolone for ≥ 48 weeks of exposure. • There were no deaths in the FA studies. • Common TEAEs that occurred in > 20% of the omaveloxolone-treated patients and greater than placebo included elevated liver enzymes, headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal	There were no differences in deaths or serious adverse events between the treatment arms. Omaveloxolone was generally well tolerated. Pediatric patients 16 years and older had similar safety profile to adults. Elevations in liver enzymes, BNP, and cholesterol were noted in patients receiving omaveloxolone compared to placebo. There were no clinical cases of Hy's law, jaundice, or cholestatic liver injury

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pain. • Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) were observed without an associated increase in total bilirubin or alkaline phosphatase. There were no cases of Hy's Law. A total of 31%, 16% and 4% of patients in the omaveloxolone group exceeded the threshold of ALT or AST > 3x upper limit normal (ULN), > 5x ULN, or > 10x ULN respectively, compared to no patients in the placebo group. Increases in LFTs generally peaked within two to four weeks after initiation and were higher in the first 12 weeks of treatment. Levels declined to baseline within 4 weeks following drug withdrawal. • Mean increases in B-natriuretic peptide (BNP) were observed in omaveloxolone treated patients compared to placebo patients. BNP values were > 100 pg/mL in 20% of omaveloxolone treated patients compared to 6% of patients receiving placebo at one or more time points. Two patients in the omaveloxolone arm had BNP levels > 200 pg/mL. • There were no differences in the rates of cardiac events between the treatment arms. There was a higher level of cardiomyopathy at baseline in the omaveloxolone treated arm. • The effect of omaveloxolone on QTc has not been adequately characterized. • Mean increase in cholesterol and low-density lipoprotein cholesterol (LDL-C) and decreases in high-density lipoprotein cholesterol (HDL-C) were observed within 2 weeks in the omaveloxolone arm compared to placebo. • Pediatric patients 16 years and older have a similar safety profile to adults.	with omaveloxolone; however, the clinical database is too small to detect a significant drug-induced liver injury. Increases in liver enzymes will be described as a warning in Section 5 of the prescribing information and there will be enhanced pharmacovigilance for liver toxicity. Similarly, a greater baseline history of cardiac events and cardiomyopathy in the omaveloxolone treatment arm as well as high background rates of cardiac disease in patients with FA complicate the ability to interpret the cardiac safety of omaveloxolone in FA patients. The implications of the elevations in BNP are unclear and warrant further monitoring in the postmarketing setting. Increases in BNP will be described as a Warning in Section 5 of the prescribing information and there will be enhanced pharmacovigilance for cardiac events. Increases in cholesterol will be described in Section 5 of the prescribing information. As there is inadequate data to characterize the risk of QT prolongation with omaveloxolone, a thorough QT study will be required as a post-marketing requirement.

2. Background

This application under review is for omaveloxolone for the treatment of Friedreich's Ataxia (FA).

FA is a rare, genetic, progressive, neurodegenerative disorder caused by a deficiency in frataxin. In most patients, there is an expansion of the guanine-adenine-adenine (GAA) triplet repeat within the first intron of the frataxin gene, which impairs its transcription and leads to frataxin deficiency. Frataxin is a mitochondrial protein that facilitates the formation of iron-sulfur clusters, important cofactors for the activity of many enzymes, including those in the respiratory chain complexes that control adenosine triphosphate (ATP) production. Therefore, frataxin deficiency leads to mitochondrial dysfunction, decreased ATP production, oxidative stress, and neuroinflammation, which leads to neurodegeneration and its associated symptoms.

Patients typically present with symptoms between ages 5 and 15 years, although the age of onset can range from 2 years to > 70 years. FA is a multisystem disorder that encompasses both neurological features and non-neurological features such as cardiomyopathy, kyphoscoliosis, and foot deformities (i.e., pes cavus). The neurologic features include ataxia, poor balance, impaired coordination, dysarthria, motor weakness, deep sensory loss, and visual and hearing impairment, among others. Motor weakness occurs in up to 88% of patients with FA, and typically begins in the feet and legs and is followed by weakness in the hands and arms later in the disease. The major disease burdens for patients include balance issues, loss of motor function, and loss of speech, leading to loss of ambulation and wheelchair dependence within 10 to 20 years of symptom onset. Patients with FA typically have a shortened life expectancy, with the average age of death around 37.5 years of age. Cardiac dysfunction related to dilated cardiomyopathy and arrhythmias is the most common cause of death.

Omaveloxolone is proposed for the treatment of FA. The Applicant postulates that omaveloxolone activates the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which regulates the cellular response to oxidative stress and restores mitochondrial function, thus restoring redox balance and reducing inflammation. The proposed dose is 150 mg by mouth daily on an empty stomach, one hour before eating.

There are no approved therapies for FA.

This application provides efficacy and safety data from a single clinical study, Study 1402 Part 2, and the long-term, open-label extension study (Study 1402 OLE). Study 1402 Part 2 is a randomized, double-blind, placebo-controlled study for 48 weeks intended to serve as the basis for the effectiveness of omaveloxolone in the treatment of FA. Confirmatory evidence is proposed by the Applicant to come from biomarkers that provide mechanistic support of Nrf2 activation in the pathophysiology of the disease, as well as post hoc analysis of clinical endpoints and benefit from Study 1402 OLE compared to a propensity matched natural history cohort.

The regulatory history for omaveloxolone is detailed in Dr. Veneeta Tandon's clinical review.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) Review team assessed this application with respect to Chemistry, Manufacturing, and Controls (CMC). The technical lead for this application was Dr. Martha Heimann (see OPQ review for a list of the entire team that was involved with the review of this application).

The OPQ team found that the application met all applicable standards to support the identity, strength, quality, and purity that it purports to possess. Deficiencies related to drug substance and drug product controls, manufacturing process, and biopharmaceutics were identified through the review process and were adequately addressed by the Applicant. The drug substance manufacturing process, characterization, release specification, container closure system, and stability were all deemed satisfactory. There were no potentially genotoxic impurities detected in the drug substance and a (b) (4) risk assessment demonstrated that the risk of (b) (4) presence in omaveloxolone drug substance is very low. The submitted stability data are considered adequate for the currently proposed retest period of (b) (4) months for the drug substance when stored at (b) (4) degrees Celsius and protected from light.

The Applicant has provided release results for three registration batches of drug product, all of which met the proposed specifications. Based on the drug product control strategies, release data, and stability results the proposed drug product is adequate. There are no drug product-specific impurities/degradants. OPQ recommends approval of this NDA from a quality perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. David Lee, with Dr. Lois Freed performing the secondary review. Please see Dr. Lee's Pharmacology/Toxicology Review and Dr. Freed's supervisory memo for a full review of the nonclinical considerations for this application. The key findings are summarized below.

The Applicant conducted the full battery of GLP-compliant nonclinical studies agreed to by the Division, including toxicity studies of up to 6 and 9 months in rat and monkey, respectively, reproductive and developmental toxicology studies, and genetic toxicology studies.

In vitro assays in rodent and human cell lines and in vivo studies in animals to characterize the pharmacological activity of omaveloxolone demonstrated activation of the NrF2 pathway.

In vivo metabolism studies in humans indicated the presence of two major circulating metabolites, M22 (1,2-dihydro-30-COOH omaveloxolone) and M17 (1,2-dihydro-29-OH omaveloxolone). Neither of these metabolites were quantitated in GLP-compliant nonclinical studies. The Applicant conducted analyses on pooled plasma samples in Tg.ratH2 mouse, rat, and monkey, which indicated that plasma levels of M22 in monkey and rat were only 25.6 %

and 5%, respectively, of that in FA patients at steady state, indicating that the safety of M22 was not adequately tested in the completed nonclinical studies. Plasma levels of M17 in mouse, rat, and monkey were similar or higher than in patients in all three species.

In the oral toxicity studies in rats and monkeys, liver and kidney were target organs in both species; rat was the more sensitive species.

A standard battery of reproductive and developmental toxicology studies was conducted for omaveloxolone. The no-effect dose for adverse effects on fertility was associated with exposures approximately 2 times that in humans at the recommended human dose of 150 mg/day.

In the GLP-compliant embryofetal development study in rabbit, oral administration of omaveloxolone resulted in increased embryofetal mortality and skeletal variations and reduced fetal weight at the highest dose tested. At the no-effect dose for adverse effects on embryofetal development, plasma exposure was less than that in humans at the recommended human dose.

Potential effects on pre- and postnatal development were tested in the rat; a no-effect dose for adverse effects was not identified. Plasma exposure at the lowest dose tested was less than that in humans at the recommended human dose.

Omaveloxolone was negative in a bacterial reverse mutation (Ames) assay, and positive in a chromosomal aberration assay in human peripheral blood lymphocytes but negative in in vivo assays. Carcinogenicity studies are ongoing and may be submitted post-approval, as previously agreed to, and will be a postmarketing requirement.

Dr. Lee concludes that the nonclinical data support approval of omaveloxolone. Plasma exposures to metabolite M22 were substantially lower than in humans at the recommended human dose. It is expected that M22 will be adequately tested in the ongoing 26-week carcinogenicity study in the Tg.rasH2 mouse. However, the chronic toxicity and reproductive/developmental effects of M22 have not been assessed in animals. A postmarketing requirement for the chronic toxicity study and an embryofetal development study of M22, each in one species, is recommended. Additional postmarketing requirements are outlined below in Section 13.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Xioahan Ciao (primary reviewer) and Dr. Bilal Abuasal (clinical pharmacology team leader). Overall, OCP did not find any clinical pharmacology issues that preclude approval.

The following table is adapted from the OCP review and describes the key findings from the pharmacology studies:

General Information	
Dose Proportionality	AUC of Omav was dose proportional from 50-150 mg single dose for AUC, and less than dose proportional for C_{max}.
Accumulation	The exposures in FA patients after multiple (QD) dosing of 150 mg shows accumulation ratio (RAC) for C_{max} and AUC to be between 1.7 to 2.3.
Variability	In FA patients, the coefficient of variation (CV%) was approximately 46% for $C_{max,0-24h}$ and 35% for AUC_{0-24h}. The coefficient of variation (CV%) was approximately 34% for $C_{max,ss}$ and 35% for AUC_{ss}.
Absorption	
Bioavailability	The absolute oral bioavailability of Omav was not determined
Tmax	The median T_{max} for Omav is 7 to 14 h under fasting condition
Food effect (high-fat meal) GMR relative to fasted state	A high-fat meal increased C_{max} by ~350% and AUC by ~15%
Distribution	
Volume of Distribution	Based on population PK analysis (Study REAT-PMXOMAV-2081), the typical apparent volume (Vc/F) is 410 L. The typical apparent peripheral volume (Vp/F) is 6951 L.
Plasma Protein Binding	97%
Substrate transporter systems	The following information was concluded from in vitro studies: • Omav is a weak substrate of P-gp. • Omav inhibited OAT1,OCT1, P-gp, and OATP1B3, however IC_{50} values were much greater than clinically relevant concentrations.
Elimination	
Mean Terminal Elimination half-life	Approximately 57 h in healthy subjects (from different Phase 1 studies)
Metabolism	
Primary metabolic pathway(s)	Omav was metabolized majorly by CYP3A4 followed by minor contribution by CYP2C8 and CYP2J2
Inhibitor/Inducer (in vitro)	• Omav has inhibition potential on CYP3A4 and CYP2C8 • Omav is a weak inducer of CYP3A4
Excretion	
Primary excretion pathways	Human mass balance study showed that Omav is primarily excreted in feces. Approximately 92% was recovered in feces (~40% excreted as unchanged Omav and ~90% of radioactivity was recovered in first 96h post-dose). Less than 0.1% radioactivity was recovered in urine (Study 408-C-1805).

Dosage

OCP recommends a dosage of omaveloxolone of 150 mg taken orally daily, on an empty stomach, at least one hour before eating. This dosing regimen is the same as used in Study 1402 Part 2.

QT assessment

Refer to the Interdisciplinary Review Team for Cardiac Studies (IRT) for further discussion of cardiac safety. The effect of omaveloxolone on the QTc had not been adequately characterized to date. The submitted clinical ECG data are not sufficient to exclude a 10-msec mean increase in the QTc interval. A thorough QT study will be required as a postmarketing requirement; the study protocol has already been submitted for feedback and the study is ongoing.

Biomarker support for efficacy

Omaveloxolone is proposed to activate Nrf2, a transcription factor known to be decreased in FA patients. Nrf2 is a transcription factor that regulates the expression of over 300 target genes with roles in antioxidant and anti-inflammatory actions, electrophile detoxification, cell metabolism, proliferation differentiation, and general cyto-protection. Based on the known biology of Nrf2 activation, measurement of target gene expression in PBMCs (e.g., NQO1, GCLM, FTH1, FTL), and plasma glutathione, can provide a direct link for Nrf2 activation and can serve as pharmacodynamic biomarkers to provide direct link to support Nrf2 activation; however, these were not collected in Study 1402.

The Applicant submitted clinical data for five biomarkers measured in the plasma of patients treated with omaveloxolone in study 408-C-1402 to provide mechanistic support for Nrf2 activation. These biomarkers were the liver enzymes (ALT, AST, GGT), ferritin, and creatinine kinase (CK). These biomarkers showed elevation following omaveloxolone administration in Study 1402. OCP evaluated whether these biomarkers can serve as pharmacodynamic biomarkers to confirm Nrf2 activation in patients. OCP performed an extensive literature search to investigate the Applicant's hypothesis on whether the observed increase in these five biomarkers is a downstream effect of Nrf2 activation. OCP also consulted the Division of Applied Regulatory Sciences (DARS) within OCP to get their input. Overall, the review team was concerned about the lack of specificity of these markers to support Nrf2 activation.

The review team focused on ferritin, as it appeared to have the strongest support for a role in Nrf2 activation. However, ferritin can be a non-specific marker of other pathological conditions, including infection, inflammation, iron overload, or metabolic syndromes. OCP sent an information request to the sponsor to ask for additional information to support the use of increases in ferritin levels in plasma as a specific pharmacodynamic biomarker for Nrf2 activation in humans. In their response dated January 12, 2023, the Applicant cited a published study in which a dose-dependent increase in ferritin-H mRNA was observed in human peripheral blood mononuclear cells 8 hours after initiation of treatment with omaveloxolone in an oncology clinical trial. The Applicant also cited nonclinical studies showing an increase in ferritin mRNA in mouse and monkey liver tissues after

omaveloxolone administration. The Applicant also noted in previous submissions that both GGT and ferritin were transcriptionally regulated by Nrf2 in rodent cells based on Zhang et al.[1] The Applicant also noted that there were no imbalances in adverse events (AEs) or serious adverse events (SAEs) that that would suggest pathological conditions could account for the elevated serum ferritin levels in Study 1402.

Overall, OCP considered that increases in ferritin in the plasma may suggest Nrf2 activation; however, increase in ferritin due to cell damage cannot be ruled out.

OCP review conclusions
OCP recommends approval of omaveloxolone for the treatment of FA. They recommend that post-marketing requirements be issued for a clinical drug interaction study to determine the effect of concomitant administration of a moderate CYP3A4 inducer on pharmacokinetics of omaveloxolone in healthy volunteers, and a clinical trial to assess the risk of QT prolongation with omaveloxolone to exclude mean QTc effects greater than 10ms.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Veneeta Tandon was the clinical reviewer for this application. Dr. Jinnan Liu was the biometrics reviewer, and Dr. John Lawrence was the biometrics team leader for this application. Please refer to both the clinical and statistical reviews for additional details on the efficacy analyses outlined below. The limitations of the effectiveness data described in the clinical and statistical reviews by Drs. Tandon and Liu are acknowledged and have been carefully considered. As further detailed below, we conclude that the Applicant has submitted sufficient data to support the approval of omaveloxolone for the treatment of Friedreich's Ataxia based on the results of a single adequate and well-controlled investigation accompanied by confirmatory evidence.

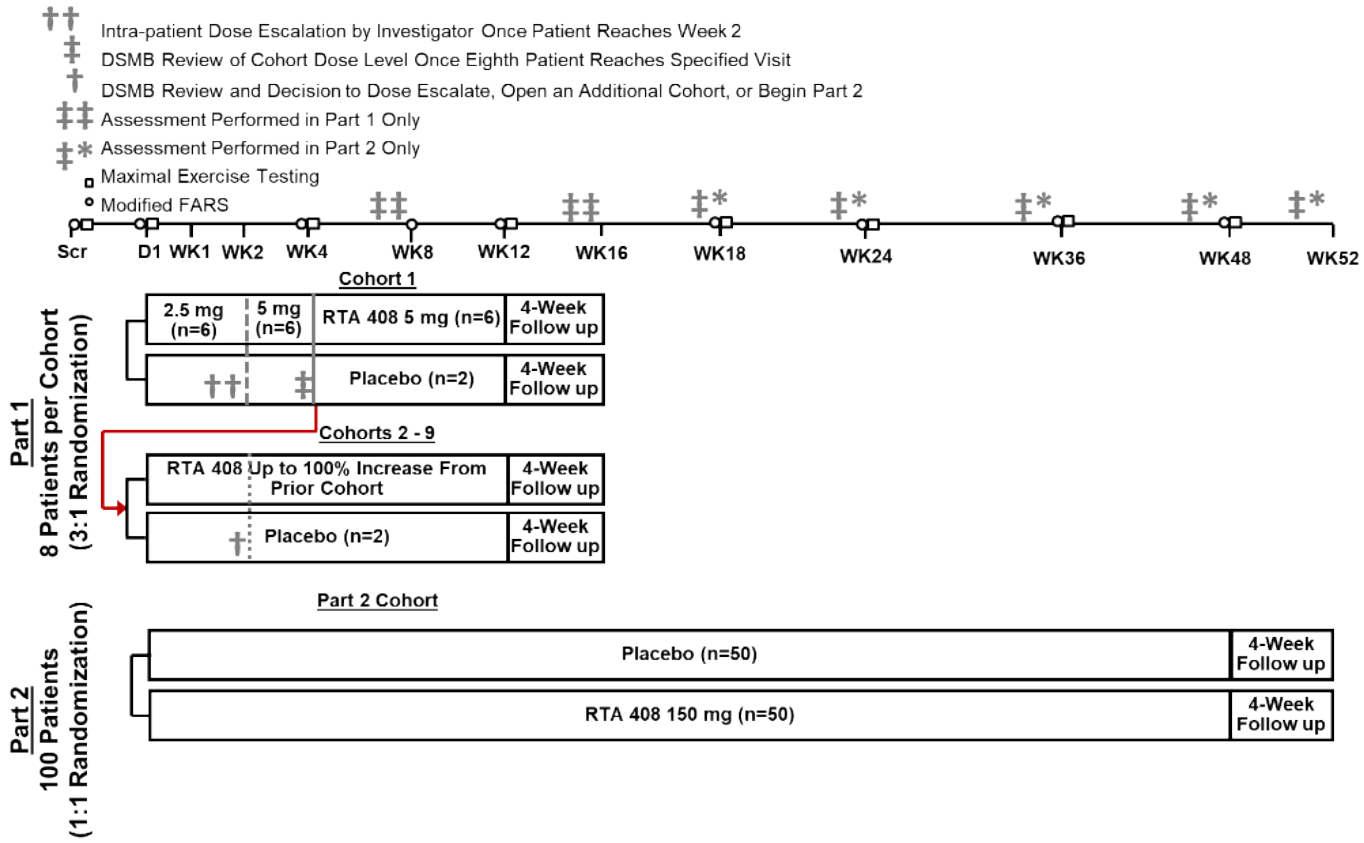
The Applicant conducted a single, two-part clinical trial, Study 408-C-1402, Part 2 of which serves as the primary basis for assessing effectiveness of the drug, with additional supportive analyses coming from Part 1 of the study, the long-term, open-label, extension study, and a comparison of the open-label extension study to a propensity-matched natural history cohort.

Study 408-C-1402 (MOXIe) Part 2
Part 2 of Study 1402 was a randomized, double-blind, parallel-group study to evaluate the safety and efficacy of omaveloxolone 150 mg in patients with FA for 48 weeks compared to

[1] Zhang H et. al; γ-Glutamyl transpeptidase is induced by 4-hydroxynonenal via EpRE/Nrf2 signaling in rat epithelial type II cells. Free Radical Biol Med. 2006; 40(8):1281-1292.

placebo (see Figure 1). Patients were randomized 1:1 to receive omaveloxolone or placebo, and randomization was stratified by pes cavus status (with pes cavus vs. without pes cavus).

Figure 1 Schematic for Part 1 and Part 2 of Study 408-C-1402



Source: Applicant's Clinical Study Report page 22

Efficacy Endpoints

The primary efficacy endpoint for Part 2 was the change in the modified Friedreich's Ataxia Rating Scale (mFARS) score from baseline to Week 48.

The Friedreich's Ataxia Rating Scale (FARS) is a neurological-exam-based rating scale with five sections: bulbar (score 0 to 11), upper limb coordination (score 0 to 36), lower limb coordination (score 0 to 16), peripheral nervous system (score 0 to 25), and upright stability (score 0 to 36). The maximum score is 125. The modified FARS (mFARS) removes section D on the peripheral nervous system, with a maximum total score of 99. A higher score signifies more severe physical impairment, and a reduction in mFARS score signifies improvement in function. In an Advice Letter to the Applicant dated August 2, 2017, the Division agreed that the mFARS was an acceptable primary endpoint.

The key secondary endpoints were the proportion of patients who were a treatment success at Week 48, based on the Patient Global Impression of Change (PGIC), defined as "much

improved" or "very much improved", and the proportion of patients who were a treatment success at Week 48, based on the Clinical Global Impression of Change (CGIC), defined as "much improved" or "very much improved".

The PGIC is a 7-point scale that requires the patient to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The PGIC is assessed by completing the following statement, "since I began my trial treatment, my overall status is: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, or (7) very much worse. The CGIC is a similar 7-point scale that requests the clinician to assess how much the patient's illness has improved or worsened compared to baseline. The same scoring responses are used to complete the statement, "compared to the patient's condition at the start of the trial, this patient's overall status is."

Other secondary endpoints included change in performance at Week 48 on a 9-hole peg test (9-HPT), change in performance at Week 48 on the 25-foot timed walk test (T25-FWT), frequency of falls over 48 weeks, change in peak work and oxygen utilization during maximal exercise testing at Week 48, and the change in activities of daily living (ADL) at Week 48 based on the FARS-ADL scale.

There were additional exploratory endpoints that include the change in raters' assessment of videos of normal walking at Week 48, change in SF-36 patient reported outcome scores at Week 48, and the proportion of patients at Week 48 with an mFARS change from baseline at or lower than a specified cutoff value.

Statistical Analysis

The primary efficacy endpoint is the change from baseline in the mFARS score at week 48 of the 48-week double-blind treatment period. The primary endpoint was analyzed using a mixed effect repeated measures (MMRM) model that included treatment group, mFARS score at baseline, site, visit, baseline-by-visit, and the treatment-by-visit interactions, using analysis visits 4, 12, 18, 24, 36, and 48 and assuming an unstructured covariance matrix. The SAP was changed three times close to the end of the study and site was added to be a covariate in the latest version of the SAP. However, the model produced very similar results whether including site as a covariate or not, so it did not significantly change the outcome of the study.

The following analysis sets were defined for Part 2 of the study:

Full Analyses Set (FAS): All randomized patients without pes cavus who were treated and had at least 1 post-baseline efficacy assessment. Pes cavus was defined as having a loss of lateral support, and was determined to be present if light from a flashlight could be seen under the patient's foot arch when barefoot and weight-bearing.

All Randomized Population (ARP): The ARP included all patients randomized, categorized by their randomized treatment group (whether or not they received study drug). Only descriptive analyses of efficacy are presented using the ARP.

Pes Cavus Population (PCP): The PCP included all patients in the pes cavus stratum categorized by their randomized treatment group (whether or not they received study drug).

The primary analysis of efficacy was based on the full analysis population (FAS).

Type 1 error was controlled by hierarchical testing. The primary endpoint was analyzed at the 0.05 level. If the primary endpoint was significant, the 2 key secondary and 5 secondary endpoints were to be analyzed at the 0.05 level in the following pre-specified order:

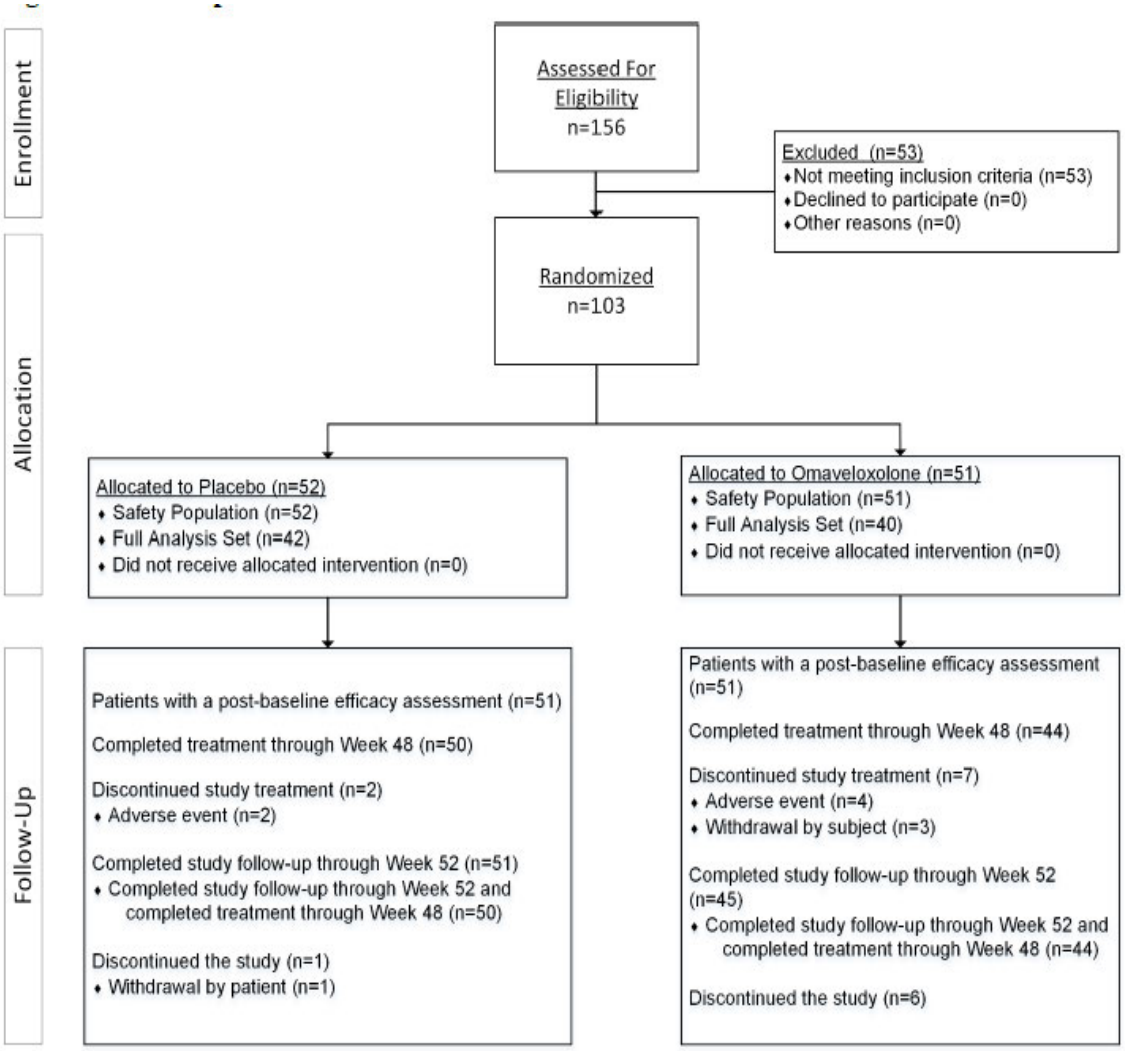
1. PGIC at Week 48 (key secondary)
2. CGIC at Week 48 (key secondary)
3. Change in 9-HPT (reciprocal time measure of the non-dominant hand) at Week 48
4. Change in T25-FWT (reciprocal time measure) at Week 48
5. Frequency of falls over 48 weeks
6. Change in peak work during maximal exercise testing at Week 48
7. Change in ADL score at Week 48

Results

A total of 103 patients were randomized into the study, with 51 patients randomized to omaveloxolone and 52 patients randomized to placebo. A total of 94 patients completed treatment through Week 48, including 44/51 (86%) of patients receiving omaveloxolone and 50/52 (96%) of patients receiving placebo. Patients were stratified based on the presence or absence of pes cavus. The Full Analysis population included patients without pes cavus (n = 82).

Figure 2 details the disposition of the patients in the study:

Figure 2 Study 1402 Part 2 Patient Disposition



Source: Study 1402 Part 2, Clinical Study Report, Pg 56

Demographics

The baseline demographics were generally similar between treatment groups. There was a higher proportion of male patients in the placebo group (67%) and a higher proportion of female patients in the omaveloxolone group (60%). There were also a higher proportion of patients < 18 years of age in the placebo group (31%) compared to omaveloxolone group (17%). The remaining demographic characteristics were similar in the Full Analysis population. Baseline disease characteristics were also similar between the arms, although the omaveloxolone group has a slightly higher baseline mFARS score (40.95) compared to placebo (38.78). There were also baseline differences in the mean GAA1 repeat length between the arms; however, there were also 15 patients with missing GAA1 assessments at baseline, and the clinical significance of this slight difference is unclear. There was a baseline

difference of cardiomyopathy in 48% of patients in the omaveloxolone arm and 29% of patients in the placebo arm. In general, these baseline differences may be suggestive of higher disease severity in the omaveloxolone treatment arm.

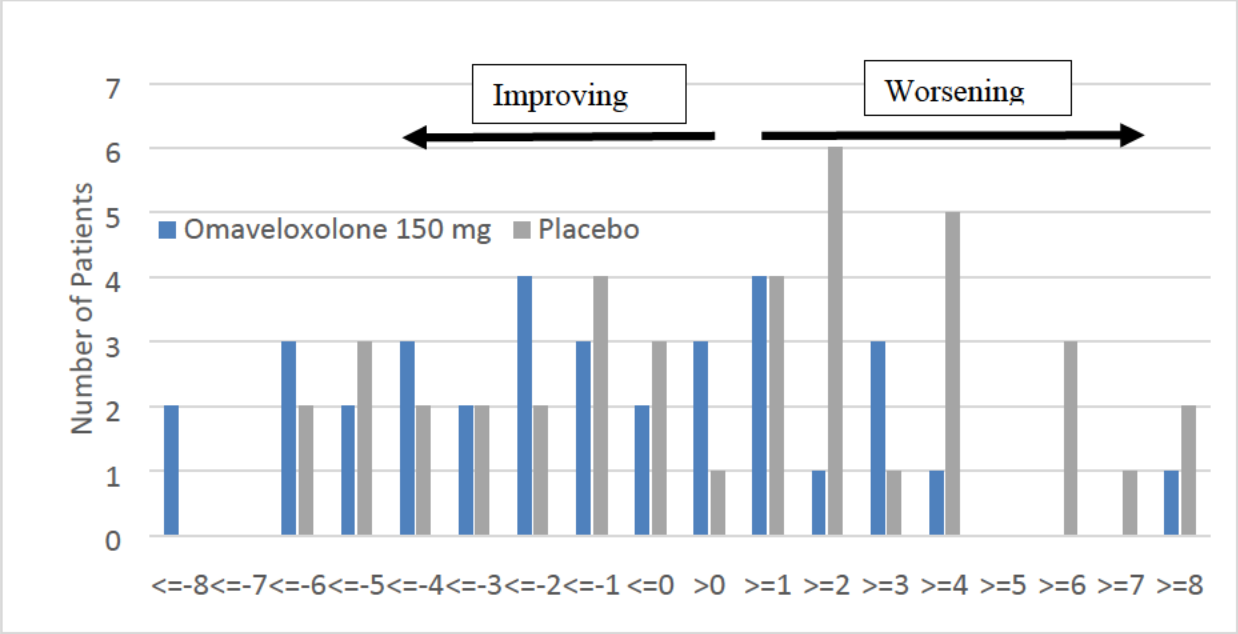
Primary Endpoint

The study met its prespecified primary endpoint in the Full Analysis population, demonstrating a statistically significant improvement in mFARS at Week 48 of -2.41 points (out of 99) in the omaveloxolone arm compared to placebo (p = 0.0138). Patients randomized to omaveloxolone had a mean improvement from baseline in mFARS of -1.56 points, while patients randomized to placebo had a mean change from baseline of 0.85 points (worsening) at Week 48.

In the All-Randomized population, there was also a nominally statistically significant improvement of -1.94 points in the omaveloxolone arm compared to placebo (p = 0.0331). In the Pes Cavus population (N = 20), omaveloxolone numerically improved mFARS relative to placebo by -1.25 points although this change was not statistically significant. Additionally, in patients < 18 years of age, omaveloxolone improved mFARS by -1.69 points at Week 48, which resulted in a difference from placebo of -4.21 points (N = 20; p = 0.0532).

As noted by Dr. Tandon, there is a degree of missing data in the omaveloxolone treatment arm that decreases the persuasiveness of the data. However, the magnitude of the change and percentage of patients that showed worsening compared to placebo (Figure 3) indicates that there is likely a treatment effect of omaveloxolone. Dr. Liu's review of sensitivity analyses to address the missing data also show a treatment effect in favor of omaveloxolone, with results of multiple sensitivity analyses consistent with those of the primary analysis.

Figure 3 Change Category in mFARS at Week 48 (FAS Population)



Source: Clinical Reviewer's Analysis

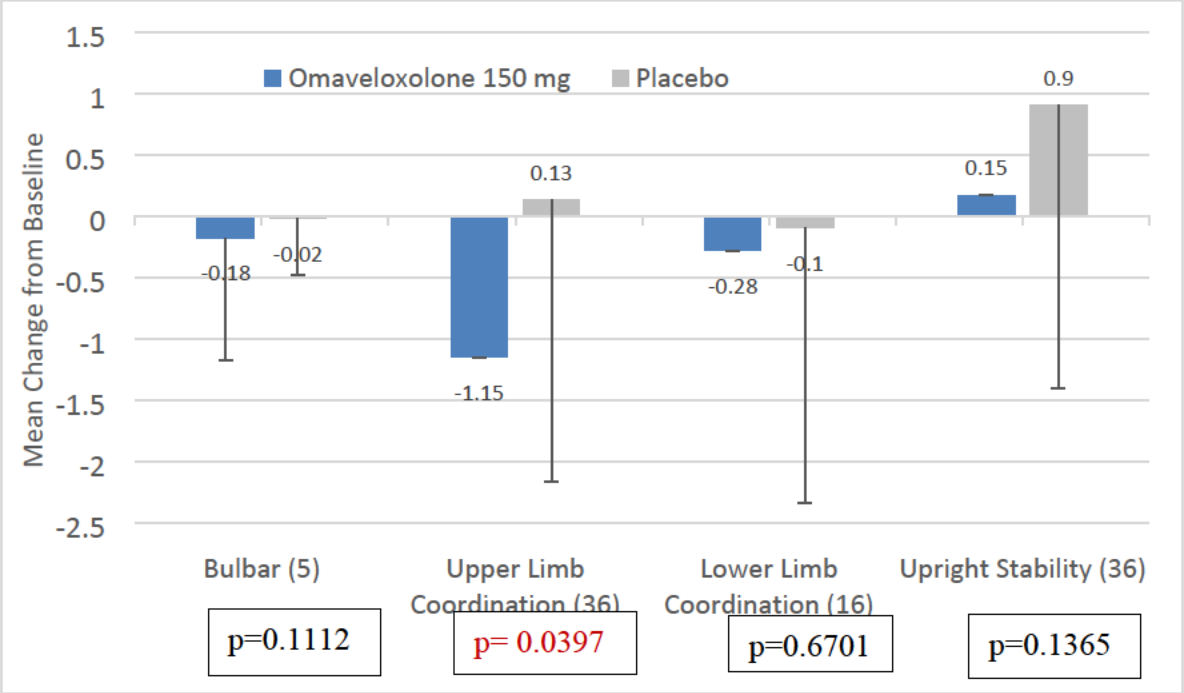
Secondary Endpoints
Mean PGIC and CGIC scores were not statistically different from placebo in the Full Analysis Population; however, the PGIC and CGIC scores did numerically favor omaveloxolone compared to placebo. The LS mean treatment difference for PGIC was -0.43 (p = 0.13) and for CGIC was -0.13 (p = 0.53). In the All-Randomized population, there was a nominally positive p-value for PGIC (-0.56, p = 0.03), but not for CGIC (-0.28, p = 0.13).

Other secondary endpoints were analyzed using a fixed-sequence hierarchical approach to maintain the family-wise overall Type 1 error rate of 0.05 in the full analysis population. Omaveloxolone did not demonstrate statistically significant improvement in the 9-HPT, 25-foot time walk test, frequency of falls, or peak work relative to placebo. The ADL scores, based on a 9-question FARS-ADL scale, did show a nominally statistically significant improvement relative to placebo (p = 0.04), although it was last in the hierarchy of statistical testing. As noted in Dr. Tandon's review, the ADL scale, although only nominally significant, is a clinically meaningful endpoint that looks at individual components such as speech, swallowing, cutting food, dressing, etc.

Exploratory Efficacy Analyses
Dr. Tandon considered additional exploratory analyses to better understand the clinical meaningfulness of the changes observed on the mFARS. The mFARS is based on the neurologic exam and is scored on a 99-point scale. Although the Division considers that mFARS to be an acceptable primary endpoint, it should be noted that there are items on the scale that are of uncertain clinical meaningfulness or may not be sensitive to change. A mean change of 2.4 points on a 99-point scale may appear to be small, but it is important to consider what items or domains are impacted by those changes and if the scale correlates with other clinically meaningful outcomes.

The Applicant performed an analysis of mean changes within each domain of mFARS (Figure 4). The analysis showed the largest difference in the upper limb coordination domain (e.g., finger taps, dysmetria) which was nominally statistically significant, and a smaller trend in the upright stability domain. There were only minimal differences in the bulbar and lower limb coordination domains. Dr. Tandon notes that baseline scores for the bulbar domain were largely in the normal or mild range, and were likely not sensitive to change in 48 weeks of treatment. The analyses suggest that observed benefit was greatest in the upper limb coordination domain, which would be expected to impact fine motor functional tasks with the hands or upper extremities.

Figure 4 Mean Changes in mFARS Domains (FAS Population)



Source: p values for least square mean difference from Clinical study Report Table 14.2.11 (confirmed by FDA statistician)

Dr. Tandon also examined categorical responses on the PGIC and CGIC. More patients rated responses of 'Minimal Improvement' with omaveloxolone (30%) on PGIC and CGIC assessments compared to placebo arm (19% and 24% respectively). She notes that very few individuals reported "much improved" or "very much improved" outcomes. The PGIC and CGIC ratings generally suggest greater worsening in the placebo arm. Dr. Tandon assessed box plot graphs of change in mFARS vs PGIC and notes that changes (improvement or worsening) in mFARS scores generally corresponded to ratings of improvement or worsening in PGIC when compared across treatment groups or overall without regards to treatment groups.

Overall, these explorations suggest that the change observed on the mFARS with omaveloxolone treatment represents a detectable and meaningful change for patients. However, future studies should consider the inclusion of other clinical endpoints or an optimized version of the mFARS that may be more sensitive to detecting clinically meaningful change in patients.

Open-Label Extension Study

After completion of the double-blind treatment period, patients were eligible to enroll in an open-label extension study. Patients from Study 1402 Part 1 were also enrolled in the open-label extension study; however, the last patient enrolled in Study 1402 Part 1 completed their

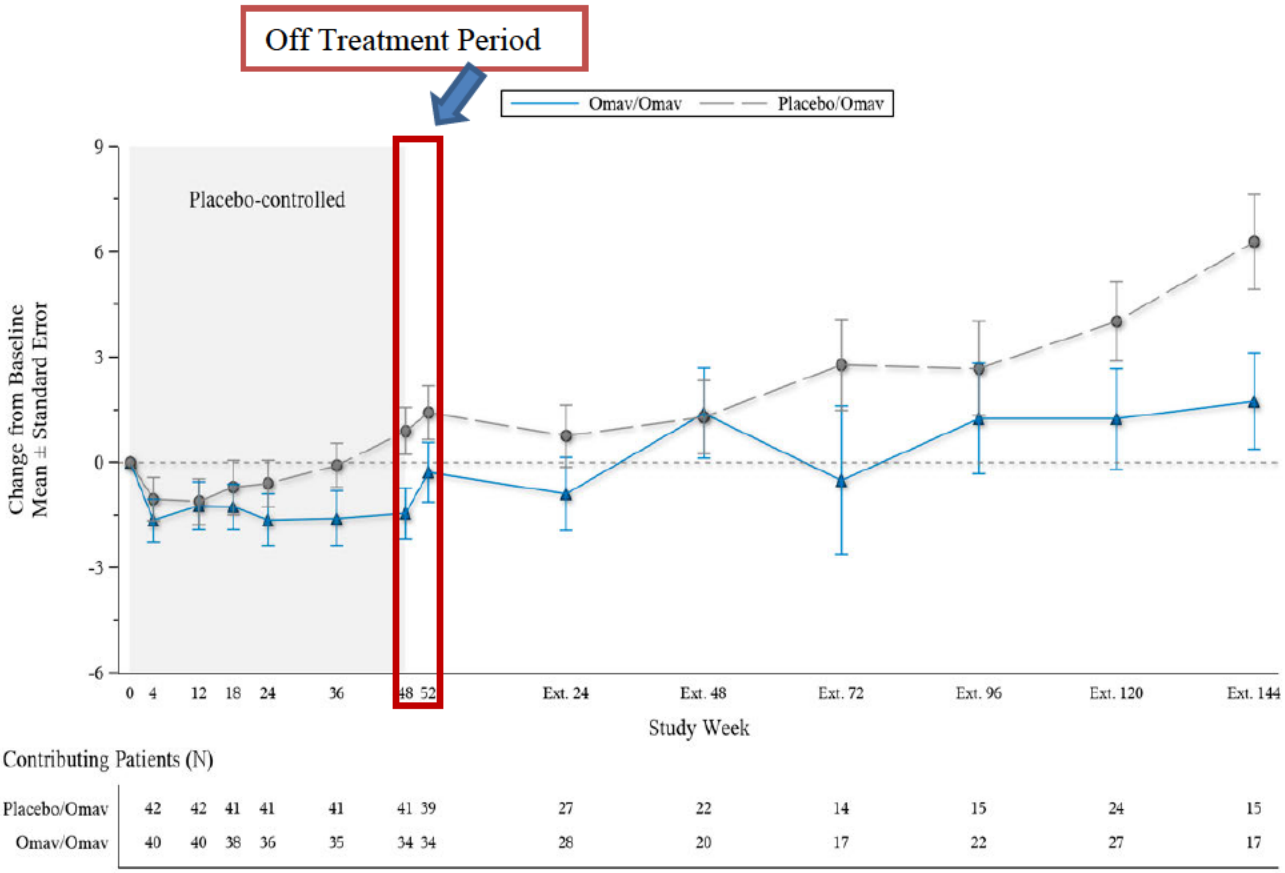
last visit in June 2017. The OLE was not open for enrollment until October 2018. Therefore, patients enrolling in the OLE from Study 1402 Part 1 had been off treatment for 21-49 months prior to enrolling in the OLE and were treated as treatment-naïve upon enrollment. These patients are analyzed along with the patients who received placebo in Study 1402 Part 2 and then enrolled in the OLE, compared to patients who received omaveloxolone in the Study 1402 Part 2. It is also noted that patients in Study 1402 Part 2 were also off treatment for 4 weeks prior to enrolling in the extension phase of the study.

Post hoc analyses were conducted by the Applicant on the extension phase of the study. There were two major analyses conducted, a delayed start analysis and a propensity matched analysis of the extension data to a natural history database

Delayed Start Analysis
A "delayed start analysis" compared patients who received omaveloxolone during the double-blind portion of Study 1402 Part 2 to patients who had received placebo (or enrolled in Part 1). The analysis compared the difference between the treatment groups in mFARS scores change from baseline at the end of the placebo-controlled period to the end of the OLE period. Patients remained blinded to treatment assignment in Study 1402 Part 2. There was substantial missing data due to the COVID-19 pandemic, which makes the analysis largely uninterpretable. The Applicant also performed a noninferiority test in this post hoc setting, which is not considered reliable by our statisticians.

It is worth noting that prior to enrolling in the OLE, all patients from Study 1402 Part 2 had a 4-week off-treatment period where treatment was discontinued. Figure 5 below demonstrates that mFARS scores appeared to increase (worsen) during this time period, and then decrease after Week 52 upon treatment reinitiation. These findings suggest a pharmacodynamic effect of omaveloxolone that showed worsening with treatment discontinuation and improvement with reinitiation; however, it is noted that patients were aware that no treatment was being received during this period despite remaining blinded to original treatment received.

Figure 5 Applicant's Change from Baseline in mFARS (Full Analysis Set) March 2022 Delayed Start Analysis



Source: DS Clinical Updated Study Report, page 24

Natural History Comparison

As part of the submission to the NDA on August 3, 2022, the Applicant also submitted a post hoc propensity matched analysis of the ongoing long-term OLE data after 3 years of omaveloxolone treatment to natural history data from the Clinical Outcome Measures in Friedreich's Ataxia (FA-COMS) study to serve as additional confirmatory evidence of effectiveness. The FA-COMS is a multicenter natural history study that has enrolled more than 1000 patients and has collected data on outcome measures in FA, including FARS and mFARS, that have been assessed annually for up to 19 years in some patients.

The analysis compares only data from the OLE (not Study 1402 Part 1 or Part 2 data). Day 1 of the Study 1402 OLE is defined as the first day of treatment in the open-label extension phase of the study. As part of the analysis, the Applicant notes that the centers participating in the FA-COMS natural history study overlap with many of the studies in the ongoing Study 1402 OLE, which suggests that there is more likely to be a consistent standard of care and consistency in the assessments between the two data sources. Propensity score matching was

based on sex, baseline age, age of onset of disease, baseline mFARS score, and baseline gait score.

The primary efficacy endpoint was the change from baseline in mFARS at Year 3 for Study 1402 OLE patients compared to the propensity score-matched FA-COMS patients, analyzed using a mixed model repeated measures (MMRM) analysis.

Three primary analysis populations were based on matches with the natural history population and the prior treatment status:
Match 1:All Pooled population
Match 2: Prior placebo or treatment-naïve to Omaveloxolone
Match 3:Omaveloxolone to Omaveloxolone (continued treatment)

The primary analysis for Match 1 assessed change from baseline on mFARS at Year 3 in the pooled OLE population compared to FA-COMS population. The change from baseline in the OLE population showed a progression of 2.983 points on mFARS, and the change from baseline in the natural history population showed a progression of 6.337 points, for a treatment difference of -3.354, p = 0.0002 (Table 1). Nominally significant differences favoring omaveloxolone were also observed at Years 1 and 2. The analysis also looked separately at those patients who had received placebo in the double-blind treatment period in Study 1402 Part 2 (Match 2), and those patients who had received omaveloxolone (Match 3). Both groups also demonstrated a nominally significant treatment effect compared to the matched FA-COMS population at Year 3.

Table 1 Propensity-Matched Natural History Analysis: mFARS Change from Baseline

Analysis Population	**mFARS Change from Baseline (LS Mean [±SE])**		
	Year 1	**Year 2**	**Year 3**
Match 1 Pooled Population Difference	-2.076 (0.7967) p=0.0095	-3.564 (0.8232) p< 0.0001	-3.354 (0.8923) p=0.0002
Match 2 Placebo-Omav Population Difference	-2.668 (0.9364) p=0.0047	-3.123 (0.9669) p=0.0014	-4.096 (1.0480) p=0.0001
Match 3 Omav-Omav Population Difference	-1.805 (1.5277) p=0.2397	-2.819 (1.6019) p=0.0807	-4.240 (1.7888) p=0.0190

Source: Adapated from Applicant's Amended Propensity Matched Report, p 16-19

Despite differences in the sample sizes for the different populations and sensitivity analyses, the change from baseline comparison was consistent across all the subgroups. It is also interesting to note that this may be a conservative approach of evaluating the extension data, because it excludes the exposure period in Study 1402 Part 2. Therefore, it may be considered to provide a confirmation of treatment benefit that is independent of the time period of the double-blind study in which benefit was already demonstrated.

There are limitations to this analysis, in that it is post hoc with knowledge of the data and without an agreed upon statistical analysis plan prior to analysis. However, as Dr. Tandon notes, the chosen matching factors appear to be clinically meaningful covariates that were appropriate for inclusion. See Dr. Tandon's review for additional strengths and limitations of this analysis. However, despite these limitations, the propensity matching analyses do suggest a deviation from natural history as measured by a decline in mFARS scores over the 3-year comparison. This may be considered to provide confirmatory evidence for the benefit of omaveloxolone observed in Study 1402 Part 2.

Evidence of Pharmacodynamic Mechanistic Effect
The rationale for the use of ferritin as a pharmacodynamic marker of Nrf2 activation is discussed in Section 5 of this review.

Omaveloxolone demonstrated dose-dependent increases in ferritin in Part 1 of Study 1402, and increases in ferritin in patients receiving omaveloxolone compared to placebo were noted in Part 2. Mechanistically, ferritin appears to be a direct target gene of Nrf2 and appears to be the most supportive pharmacodynamic marker of Nrf2 activation. Nrf2 indirectly promotes iron storage and reduces the intracellular levels of redox-active free iron atoms. Therefore, Nrf2 activation has been shown to induce ferritin protein expression. Based on this mechanistic biological plausibility of ferritin increase with Nrf2 activation, the Applicant proposes that increases in ferritin can be considered a pharmacodynamic effect of omaveloxolone, suggestive of Nrf2 activation. The observed increases in ferritin appear to be suggestive of such a mechanistic effect, and may be considered to provide additional confirmatory evidence of a treatment effect with omaveloxolone seen in Study 1402 Part 2.

Efficacy Conclusions
The Applicant has submitted data intended to support the approval of omaveloxolone for the treatment of FA based on a single, adequate, and well-controlled investigation and confirmatory evidence. The Applicant has conducted an adequate and well-controlled study (Study 1402 Part 2) of omaveloxolone in patients with FA that demonstrated a statistically significant benefit using a prespecified analysis on an acceptable efficacy endpoint of change from baseline in mFARS (-2.41 treatment difference, $p = 0.034$). In the All-Randomized population, which included patients with and without pes cavus, there was also a nominally statistically significant improvement of -1.94 points in the omaveloxolone arm compared to placebo ($p = 0.0331$). Although the secondary endpoints generally trended in a positive direction, no results reached statistical significance. There was a nominally significant benefit on the ADL scale, which is a clinically meaningful measure of patient function. There was also a nominally significant benefit on the PGI-C in the full randomized population (ITT), a key secondary endpoint which correlated well with the benefit seen on mFARS.

Although the results of the primary endpoint analysis are positive, the p-value is not highly persuasive and there is only limited support from secondary endpoints. Overall, Study 1402 Part 2 is not a highly persuasive study and does not appear to be capable of providing substantial evidence of effectiveness as a single study alone, without substantiation.

As confirmatory evidence, the Applicant also submitted analyses conducted in patients who continued in an open-label extension study following completion of Study 1402, Parts 1 and 2, comparing patients treated in the OLE for three years to a propensity-matched natural history cohort from the FA-COMS. The natural history comparison showed consistent treatment benefit that was sustained over the three years with a nominal p-value of 0.0002 in the All-Pooled population. Although this post hoc exploratory analysis has some limitations, the findings are supportive of the treatment benefit seen in Study 1402 Part 2 and can serve as confirmatory evidence of effectiveness. Additionally, there are noted increases in ferritin seen in omaveloxolone-treated patients compared to placebo, that suggest a pharmacodynamic effect of Nrf2 activation, which is the mechanism of action purported by the Applicant.

The 2019 FDA draft guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products further states, “In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need).” The guidance also outlines the general requirements for determination of substantial evidence of effectiveness, the situations in which a single adequate and well-controlled study could adequately support an effectiveness claim, and cites the ability of the Agency to consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence of effectiveness.

In this situation, there is a single adequate and well-controlled study that has won on an acceptable primary endpoint. The study won on the primary endpoint in a prespecified subgroup of patients with pes cavus and in the all randomized population. Although it is a positive study reaching statistical significance on the prespecified primary endpoint, Study 1402 Part 2 is not highly persuasive and does not appear to be capable of providing substantial evidence of effectiveness as a single study alone. In such a situation, the single study can be supported by confirmatory evidence to reach a conclusion that there is substantial evidence of effectiveness. The choice of outcome assessment (mFARS) used in the development program was acceptable and the observed change appears to be clinically meaningful. Because the long-term comparison to natural history excludes the treatment period in Study 1402 Part 2, in which a treatment benefit was observed, it may be considered to provide substantiation of a benefit that is independent of the primary study result, despite being in the largely same population that participated in the placebo-controlled portion of the study. Additional confirmatory evidence comes from the pharmacodynamic data that appear to be suggestive of a mechanistic effect on Nrf2 activation that the drug has its purported effect.

Although there are limitations to the data that provide evidence of effectiveness for omaveloxolone in FA, the regulations allow for FDA to exercise regulatory flexibility in applying the statutory standards for establishing the safety and effectiveness of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists. For example, FDA’s regulation at 21 CFR 312.80 notes, “while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has

determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness."

FA is clearly such a severely debilitating and life-threatening disease with substantial unmet need, and the exercise of regulatory flexibility in applying our statutory standards is appropriate.

Therefore, we conclude that the single, positive study, along with confirmatory evidence from the long-term comparison to a natural history cohort and pharmacodynamic data that provide mechanistic support, together demonstrate substantial evidence of effectiveness to support approval of omaveloxolone for the treatment of FA.

8. Safety

Dr. Veneeta Tandon performed the safety review for this submission.

Dr. Tandon's safety review is primarily based on data from Study 408-C-1402 Part 2, the 48-week randomized, controlled study and the open-label extension Study 408-C-1402 OLE. The safety population included all randomized patients who received at least 1 dose of omaveloxolone. The controlled data from Study 1402 Part 2 was used for the calculation of the frequency of adverse events. Additional safety data was also reviewed for unique adverse events, serious adverse events, and deaths from the 12-week placebo-controlled dose-escalating study (Study 408-C-1402 Part 1) and studies in other indications. Overall, the quality and format of the safety data was adequate for review.

Overall Exposures
A total of 392 patients and healthy volunteers have been exposed to omaveloxolone across all indications and doses. There are 165 unique patients with Friedreich's Ataxia that have been exposed to omaveloxolone in Study 1402 Part 1, Study 1402 Part 2, and Study 1402 OLE. The duration of exposure in FA patients includes 137 patients treated for > 48 weeks, 112 patients treated for > 96 weeks, and 37 patients treated for > 144 weeks.

In general, the 137 patients treated for > 48 weeks is adequate for this patient population, given the very low prevalence of FA. The population is generalizable to the US population. There were 24 adolescents (>= 16 years of age to < 18 years of age) that were enrolled in Study 1402 Part 2, including 14 patients who received > 48 weeks of treatment.

Deaths and Serious Adverse Events
There were no deaths in Study 1402 Part 2 or the OLE. There were a total of 8 patients who experienced SAEs in Study 1402 Part 2. Of these, there were 5 SAEs in the omaveloxolone treatment arm (9.8%), and 3 SAEs in the placebo arm (5.8%). There were an additional 13 SAEs in the OLE.

No SAEs were reported by more than 1 patient during the 48-week controlled treatment period, except for atrial fibrillation, which was reported in 1 patient in each treatment arm. There were no SAEs in the pediatric subgroup.

Discontinuations due to Adverse Events

Overall, there were 4 patients in the omaveloxolone treatment group (7.8%) and 2 patients in the placebo group (3.8%) who discontinued from the study due to TEAEs. None of the TEAEs leading to discontinuation occurred in more than one patient in the treatment arm. There were no pediatric patients who discontinued or interrupted treatment due to a TEAE. The TEAEs that led to permanent discontinuation included atrial fibrillation in 2 placebo-treated patients, and AST/ALT increased, muscle spasms, ventricular tachycardia, and rosacea in 1 omaveloxolone-treated patient each.

Common Treatment Emergent Adverse Events (TEAEs)

Common TEAEs occurring ≥5% of the omaveloxolone-treated patients and 1% greater than placebo are shown in Table 2. TEAEs that occurred in ≥ 20% of the omaveloxolone-treated patients included elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain. Skin abrasions occurred in > 25% of the patients treated with omaveloxolone, but also occurred in 21% of patients receiving placebo and is unlikely to be a drug-related adverse event, so this will not be included in the adverse reaction table included in labeling.

Table 2 Common TEAEs Occurring in ≥5% of Omaveloxolone-treated Patients and ≥1% Difference from Placebo Patients

Preferred Terms	Omaveloxolone 150 mg (N = 51)	Placebo (N = 52)
Total Subjects with any Adverse Events	51 (100.0%)	52 (100.0%)
Elevated liver enzymes	19 (37.3%)	1 (1.9%)
Headache	19 (37.3%)	13 (25.0%)
Nausea	17 (33.3%)	7 (13.5%)
Abdominal pain	15 (29.4%)	3 (5.8%)
Skin abrasion	13 (25.5%)	11 (21.2%)
Fatigue	12 (23.5%)	7 (13.5%)
Diarrhea	10 (19.6%)	5 (9.6%)
Musculoskeletal pain	10 (19.6%)	8 (15.4%)
Oropharyngeal pain	9 (17.6%)	3 (5.8%)
Influenza	8 (15.7%)	3 (5.8%)

Preferred Terms	Omaveloxolone 150 mg (N = 51)	Placebo (N = 52)
Vomiting	8 (15.7%)	6 (11.5%)
Muscle spasms	7 (13.7%)	3 (5.8%)
Back Pain	7 (13.3%)	4 (7.7%)
Decreased appetite	6 (11.8%)	2 (3.8%)
Rash	5 (9.8%)	2 (3.8%)
Limb injury	4 (7.8%)	1 (1.9%)
Urinary tract infection	4 (7.8%)	0 (0.0%)
Blood creatine phosphokinase increased	3 (5.9%)	2 (3.8%)
Dysmenorrhea	3 (5.9%)	0 (0.0%)
Gastroenteritis	3 (5.9%)	2 (3.8%)
Hypercholesterolemia	3 (5.9%)	1 (1.9%)

*Note for regrouping of all PT terms refer to Dr. Tandon's primary review. For example:
PT terms pooled under Elevated Liver Enzymes include Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Gamma-glutamyl transferase increased, Liver function test increased, Hepatic steatosis.
PT Terms pooled under Abdominal pain included: Abdominal discomfort, Abdominal pain, Abdominal distension, Abdominal pain lower, Abdominal pain upper
PT Terms pooled under Fatigue included: Fatigue, Asthenia
PT Terms pooled under Diarrhea included Diarrhea, Fecal volume increased. Frequent bowel movements

Laboratory Findings and Vital Signs

There were significant laboratory findings including increase in liver enzymes, BNP, and cholesterol which are described below. There were no other notable findings for laboratory values or vital signs.

Liver enzymes

In total, there were 16 patients (31.4%) in the omaveloxolone group that exceeded the threshold for AST or ALT ≥ 3x the ULN, including 8 patients who exceeded the criterion for AST or ALT ≥ 5x the ULN. There was one patient (1.9%) in the placebo group who had an AST ≥ 3x the ULN. Mean increases in ALT, AST, and GGT induced by omaveloxolone were observed and were maximal at week 2 and gradually decreased. Increases in AST and ALT were not associated with concomitant increase in total bilirubin or alkaline phosphatase. There were a total of 2% of omaveloxolone treated patients in the controlled study who had to discontinue treatment due to protocol-driven stopping criteria for elevated AST and/or ALT. All of the TEAEs related to elevated liver enzymes resolved, and only one patient discontinued from the study drug due to the increases in ALT and AST. Most cases occurred early in the

study, with almost all TEAEs of elevated liver enzymes occurring within the first 12 weeks of treatment.

Aminotransferase increase is postulated by the Applicant to be a pharmacodynamic effect of omaveloxolone, related to restoration of mitochondrial function and activation of Nrf2, rather than drug-induced liver injury. Exposure of liver cells to increasing concentrations of omaveloxolone or its analog, bardoxolone methyl, also resulted in concentration-dependent induction of both ALT and AST messenger RNA levels. The Applicant concluded that the increases in GGT, AST, and ALT observed in the study are not associated with liver injury, but are consistent with Nrf-2-mediated increases in enzymes involved in glutathione synthesis and supports the hypothesis that aminotransferase elevations reflect an increased demand for glutamate to support increased glutathione production. Dr. Tandon notes that dimethyl fumarate, another Nrf2 activator approved for the treatment of relapsing forms of multiple sclerosis, also showed increases in transaminases without concomitant increases in bilirubin.

However, given the frequency of the elevation of transaminases in the omaveloxolone-treated population, the Drug-Induced Livery Injury (DILI) team was consulted, and Dr. Ling Lan and Dr. Paul Hayashi completed a review. The DILI team concluded that the nonclinical data do not suggest a high risk for DILI and suggest the possibility that there is a benign increase in AST and ALT gene expression. There were no cases of jaundice, Hy's law, or cholestatic liver injury. However, given the small size of the studies in patients with FA, the studies are underpowered to detect a significant DILI signal if there was one. The DILI team concluded that DILI with adaptation could explain the transient increase in aminotransferases; however, the rapid decline in AST and ALT after drug withdrawal is more consistent with benign increase in gene expression rather than liver injury. All patients recovered, and most had a decline in the enzymes without drug discontinuation, also suggesting a benign course. The DILI team recommended monitoring for liver enzymes on treatment, and an appropriate warning in labeling so that prescribers do not presume liver enzyme elevations are always benign.

B-Type Natriuretic Peptide (BNP)

BNP and N-terminal Prohormone of B-Type Natriuretic Peptide (Pro-BNP) are released in response to changes in pressure inside the heart, and can be a marker of cardiac failure. Mean increases in both BNP and Pro-BNP were noted in Study 1402 Part 2 in patients treated with omaveloxolone compared to placebo. Several patients had increases in BNP and Pro-BNP; however, BNP values remained within the ULN (< 100 pg/mL) for the majority of patients. There were 8 patients (16%) in the omaveloxolone group who had BNP values > 100 pg/mL at one or more time points, compared to 2 patients (4%) of placebo patients. At baseline, there were 4 patients in the omaveloxolone arm and 1 patient in the placebo arm that also had high BNP, and 4 omaveloxolone patients had a history of cardiomyopathy. Two patients receiving omaveloxolone had BNP levels > 200 pg/mL during the study.

The mean change from baseline was higher in those patients with a history of cardiomyopathy. No TEAEs of cardiac failure were observed during the study. However, patients with significant cardiac disease and BNP > 200 pg/mL at baseline were excluded from the study.

Although the Applicant did not report any cases of fluid overload in the study, Dr. Tandon did note that there were a few patients who reported peripheral edema of legs, fingers, and eyelid throughout the study. These patients with noted peripheral edema did not have a concomitant increase in BNP or NT-Pro BNP.

There was a larger number of patients who had a history of cardiomyopathy and/or increase in BNP at baseline in the omaveloxolone treatment arm at baseline compared to placebo. Therefore, the risk of omaveloxolone contributing to the higher BNP values during the study is unclear. At baseline, 49% of omaveloxolone-treated patients had cardiomyopathy compared to 29% placebo-treated patients. Patients with FA often die from cardiac failure; therefore, it is difficult to determine if the risk is increased with omaveloxolone given the small number of patients in the study.

The Division of Cardiology also reviewed the risk for cardiac failure and other cardiac events. See Dr. DeConti's review for additional details. The conclusion was that the safety database is too small to adequately characterize the cardiac safety of omaveloxolone. The high background rate of cardiomyopathy and arrhythmias in patients with FA, as well as the baseline imbalance in cardiomyopathy rates between the treatment arms complicate interpretation of the study results. However, elevations in BNP raise concern for an increased risk of cardiac effects and cardiac failure given the structural similarities to bardoxolone. It is also notable that the phase 3 study of bardoxolone in patients with chronic kidney disease was discontinued due to a safety signal for heart failure-related hospitalizations and deaths.

Cholesterol

Mean increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C) were seen in the omaveloxolone arm compared to placebo arm. A noted decrease in high-density lipoprotein cholesterol (HDL-C) was also noted. A total of 29% of patients on treatment had a shift from normal to high cholesterol (> ULN) at one or more time points, compared to 6% of placebo patients. A total of 16% of omaveloxolone treated patients had a shift in LDL-C from normal to high, compared to 8% of placebo, and a total of 6% of omaveloxolone-treated patients had a shift from normal to low HDL-C compared to 4% of placebo patients.
There were three patients in the treatment arm and 1 patient in the placebo arm that reported a TEAE of hypercholesterolemia. These changes were observed within 2 weeks of initiating omaveloxolone and remained within the reference range for the majority of patients. Values returned to baseline within 4 weeks of discontinuing treatment.

The Applicant postulates that the noted increases in serum lipid parameters may be a pharmacodynamic effect related to Nrf2 activation. The Applicant asserts a beneficial effect of omaveloxolone on lipid metabolism, glucose utilization, and mitochondrial function; this appears contradictory to the mechanism of increased cholesterol as a pharmacodynamic effect of Nrf2 activation. However, given the consistent increase in cholesterol compared to patients receiving placebo, lipid levels should be monitored throughout treatment and will be included as a warning in the labeling.

Cardiac Events/QT

Refer to Section 5 of the review for a discussion of the QT assessment. The ECG data are not adequate to exclude a 10 msec mean increase in the QTc; however, there are no clinical events concerning for a signal of QT prolongation. Therefore, a thorough QT study will be a postmarketing requirement.

Ferritin
Mean increases in ferritin were seen in the omaveloxolone group relative to baseline and compared to placebo. The majority of the increases remained within the normal reference range and were not clinically significant and do not raise a safety concern. One patient in Study 1402 Part 2 had a ferritin level above the reference range. Levels over 300 ng/mL may suggest inflammation, and ferritin is an acute phase reactant that may be a non-specific marker of inflammation.

As discussed in Sections 5 and 7, the Applicant postulates that ferritin is a pharmacodynamic marker for omaveloxolone, as Nrf2 activation induces the expression of the genes that encode the components of the ferritin complex, thus, increases in ferritin likely reflect the activation of Nrf2. A dose-dependent increase in ferritin was also observed in Part 1 of the Study, although the numbers were too small to draw significant conclusions from Part 1.

Adverse Events of Special Interest

Adverse Events related to Depression, Suicide, and Self-Injury
Depression is known to occur in patients with FA in 9 to 36% of patients, with increased risk of suicidality. Therefore, the Applicant included it as an adverse event of special interest. There were 5 patients treated with omaveloxolone who reported a TEAE related to suicide; one event in Study 1402 Part 2, and 4 events occurred in the OLE. All of the patients had a history of depression and the suicidal thoughts did not lead to discontinuation or withdrawal from the study in any of the patients.

Adverse Events related to Infections and Infestations
There is a hypothetical risk that Nrf2 activation may have anti-inflammatory effects that could potentially lead to a decreased immune response. Dr. Tandon explored TEAEs related to infections and infestations to see if there was any evidence of a decreased immune response in patients treated with omaveloxolone. The number of patients in total reporting infections were similar between treatment arms (67% omaveloxolone and 64% placebo). However, influenza (16%), urinary tract infection (8%), gastroenteritis (6%), and conjunctivitis (4%) occurred more frequently in the omaveloxolone treated patients compared to placebo (6%, 0%, 4%, and 0% respectively). There were additional infection-related TEAEs that occurred in a single patient in either arm. Respiratory tract infection, nasopharyngitis, and rhinitis occurred more in placebo than in the treatment arm.

In general, most infections were mild. Serious TEAEs included influenza, pilonidal cyst, laryngitis, coronavirus (SARS-CoV2) infection, and respiratory tract infection. Treatment was interrupted only for SARS-Cov2 infection. Time to onset of TEAEs of infection were similar between the treatment arms. There is no specific safety signal for infection or decreased immune response in patients receiving omaveloxolone.

Cardiac Adverse Events
Cardiac safety is a key event of interest given the underlying cardiac risk in patients with Friedreich's Ataxia, and due to the findings of increased cardiac failure observed with a related product, bardoxolone methyl, in a large study in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease. Patients enrolled in the bardoxolone study were already at higher risk for heart failure given their underlying conditions. Patients with FA also have a high risk of cardiac failure secondary to cardiomyopathy and arrythmias; however, there was no significant difference seen in total cardiac events that occurred with 14% placebo-treated patients and 10% in patients receiving omaveloxolone. See discussion of BNP elevation above for additional discussion of cardiac safety.

Pregnancy
No pregnancies occurred during the study.

Subgroup Analyses
Given the small sample size, subgroup analyses are challenging to interpret. However, there were 24 adolescent patients aged ≥ 16 years and < 18 years of age enrolled in Study 1402. The adverse events in patients < 18 years of age were similar to those > 18 years of age. The increase in ALT/AST and GGT were similar to adult patients, but the magnitude of the increase was smaller. Similarly lower magnitude increases in total cholesterol and LDL were seen in patients < 18 years of age. The decrease in HDL cholesterol was similar to that of adults. Similar increases in BNP and NT-Pro-BNP were seen in patients < 18 years of age. Adolescent patients continued along their growth curves for weight during the treatment period.

There were no gender-related differences in adverse events observed in the study. No subgroup analyses were conducted based on race, as 97% of the patients in the study were White.

Safety Conclusions
Overall, omaveloxolone was well tolerated with no major safety concerns. There were no deaths and few SAEs during the placebo-controlled study. The most common adverse events included elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, and fatigue. Omaveloxolone treatment caused elevations from baseline in liver enzymes (AST/ALT), BNP, Pro-N-BNP, and cholesterol. While the laboratory elevations may be downstream effects of omaveloxolone's Nrf2 pathway, the small sample size and comorbid cardiac myopathy in patients with FA make it challenging to rule out the possibility of a risk of drug-induced liver injury or increased risk of cardiac failure in some patients. Therefore, the laboratory abnormalities will be described in Section 5 Warnings and Precautions in labeling with recommendations for monitoring of these laboratory values during treatment with omaveloxolone.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the application did not raise significant safety or efficacy issues that were unexpected in the intended population.

10. Pediatrics

Omaveloxolone for the treatment of Friedreich's Ataxia was granted orphan drug designation on June 19, 2017, and is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

- Dr. Tandon concludes that the Applicant has adequately disclosed financial interests/arrangements with clinical investigators.

- The Office of Scientific Investigations (OSI) conducted investigations at 3 clinical sites. See the completed review by Dr. Cara Alfaro. Dr. Alfaro concluded that the study was conducted adequately and the data generated by these sites were acceptable in support of the respective indication.

12. Labeling

Labeling negotiations with the Applicant have been completed and the Applicant has accepted all recommended changes. Please refer to the final negotiated product labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The Division of Risk Management (DRISK) reviewer for this application is Dr. Carla Darling. Dr. Darling concludes that a risk evaluation and mitigation strategy (REMS) is not necessary for omaveloxolone**.**

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following PMRs will be imposed:

PMR 4410-1:
Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to omaveloxolone during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

PMR 4410-2:
Perform a lactation study (milk only) in lactating women who have received therapeutic doses of omaveloxolone using a validated assay to assess concentrations of omaveloxolone in breast milk and the effects on the breastfed infant as applicable.

PMR 4410-3:
Conduct a 26-week carcinogenicity study of omaveloxolone in Tg.rasH2 mouse.

PMR 4410-4:
Conduct a 2-year carcinogenicity study of omaveloxolone in rat.

PMR 4410-5:
Conduct an embryofetal development study of metabolite M22 in one species.

PMR 4410-6:
Conduct a 26-week toxicity study of metabolite M22 in rat.

PMR 4410-7:
Conduct a clinical trial to assess the risk of QT prolongation with omaveloxolone to exclude mean QTc effects greater than 10 ms.

PMR 4410-8:
Conduct a clinical drug interaction study to determine the effect of concomitant administration of a moderate CYP3A4 inducer on pharmacokinetics of omaveloxolone in healthy volunteers. Design and conduct the trial in accordance with the 2020 FDA Guidance for Industry entitled "Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" (https://www.fda.gov/media/134581/download).

14. Recommended Comments to the Applicant

The following requests for enhanced pharmacovigilance will be conveyed in the approval letter:

1. We request that you perform postmarketing pharmacovigilance to better characterize the risks of Skyclarys on cardiac function. Please provide biannual reports of events of worsening cardiac function and/or heart failure in patients taking Skyclarys. Provide narratives of individual cases as well as a synthesized summary and analysis, including incidence in clinical trial cases, postmarketing cases, and total cases. The narratives should include a description of baseline cardiac function and BNP levels, the signs and symptoms that prompted the cardiac evaluation, the management of the event, and patient outcome. Include information about whether Skyclarys was discontinued, either temporarily or permanently, and also provide information on concomitant

medications and other potentially confounding factors, time from the first dose of Skyclarys, time from the last dose of Skyclarys, as well as demographics.

2. We request that you perform postmarketing pharmacovigilance to characterize elevations in liver function tests (ALT, AST, and total bilirubin) and adverse effects on liver function in patients taking Skyclarys. Please provide biannual reports that include baseline and subsequent elevations of ALT or AST greater than 3 times the upper limit of normal (ULN) with evidence of liver dysfunction, and reports of levels greater than 5 times the ULN. Provide narratives of individual cases as well as a synthesized summary and analysis, including incidence in clinical trial cases, postmarketing cases, and total cases. Include information about whether Skyclarys was discontinued either temporarily or permanently, and patient outcome including resolution and time to resolution. Also provide information on concomitant medications and other potentially confounding factors, time from the first dose of Skyclarys, time from the last dose of Skyclarys, as well as demographics.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY R FREILICH
02/28/2023 01:41:21 PM

TERESA J BURACCHIO
02/28/2023 01:46:58 PM