# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 216718Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

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| **Application Type** | NME |
| **Application Number(s)** | 216718 |
| **Priority or Standard** | Priority |
| **Submit Date(s)** | March 30, 2022 |
| **Received Date(s)** | March 30, 2022 |
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| **Division/Office** | DNI, ON |
| **Reviewer Name(s)** | Veneeta Tandon |
| **Review Completion Date** | February 27, 2023 |
| **Established/Proper Name** | Omaveloxolone |
| **(Proposed) Trade Name** | SKYCLARYS |
| **Applicant** | Reata Pharmaceuticals |
| **Dosage Form(s)** | Capsules, 50 mg |
| **Applicant Proposed Dosing Regimen(s)** | 150 mg Once daily |
| **Applicant Proposed Indication(s)/Population(s)** | For the treatment of Friedreich's ataxia |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | For the treatment of Friedreich's ataxia |

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|---|---|
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |

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|---|---|
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Omaveloxolone (SKYCLARYS™, also known as RTA 408 or referred as Omav) is a semi-synthetic oleanane triterpenoid compound that is postulated by the Applicant to activate the transcription factor nuclear factor, erythroid 2 like 2 (Nrf2) which restores mitochondrial function.

SKYCLARYS™ is indicated for the treatment of Friedreich's ataxia (FA).

Omaveloxolone is formulated as a 50 mg capsule for oral use.

SKYCLARYS capsules are taken orally. Dosing recommendations include:

- Recommended dose is 150 mg once daily, administered as three (3) 50 mg capsules.
- Swallow SKYCLARYS capsules whole and intact.
- Take SKYCLARYS on an empty stomach at least 1 hour before eating

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness has been established for omaveloxolone in FA patients based on a single adequate and well-controlled study and confirmatory evidence. I recommend approval of this application. Please refer to section 7.2 for the Integrated Assessment of Effectiveness.

## 1.3. Benefit-Risk Assessment

## Benefit-Risk Integrated Assessment

Omaveloxolone (SKYCLARYS™) is a semi-synthetic oleanane triterpenoid compound that is proposed for the treatment of Friedreich's ataxia (FA). The recommended dose is 150 mg omaveloxolone, taken orally once daily on an empty stomach, one hour before eating. The Applicant has postulated that it activates the transcription factor nuclear factor, erythroid 2 like 2 (Nrf2), which regulates the response to cellular oxidative stress and restores mitochondrial function, restores redox balance, and reduces inflammation. The Applicant describes these processes to be implicated in the pathophysiology of FA as they translate to ataxia and neurodegeneration. Clinically, these effects may translate to improvements in neurological function, muscle function, mobility, and quality of life for patients with FA.

There are no approved treatments for FA.

The effectiveness of omaveloxolone in the treatment of FA was evaluated in a single, adequate, well-controlled Study 1402 (MOXIe) that consisted of 2 parts, followed by an open-label extension study with up to 3 years of omaveloxolone exposure. Study 1402 Part 1 was a 12-week dose ranging study in FA patients and Study 1402 Part 2 was a 48-week study in FA patients 16-40 years of age. Part 2 was the primary basis of assessing the effectiveness of 150 mg omaveloxolone in the treatment of FA. In Part 2, a total of 103 FA patients with or without pes cavus received placebo (n=52) or omaveloxolone (n=51) in the 'All Randomized' population. A total of 82 FA patients without pes cavus received placebo (n=42) or omaveloxolone (n=40), which was the Applicant's pre-specified primary 'Full Analysis' population. There was a statistically significant improvement in modified Friedreich's Ataxia Rating Scale (mFARS) at Week 48 of -2.41 points 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 experienced a mean worsening from baseline of mFARS of 0.85 points at Week 48. The 'All Randomized' patients also showed an improvement of -1.94 points in the omaveloxolone arm compared to placebo (nominal p=0.0331). The key secondary endpoints, PGIC and CGIC, did not reach statistical significance in the 'Full Analysis' population (p=0.1300 and 0.5259), however, PGIC was nominally significant in the complete 'All Randomized' population (p=0.0282). Additionally, the Activities of Daily Living scale was nominally significant in the pre-specified Full Analysis population (p=0.04).

Additionally, a post hoc propensity-matched analysis of 3 year open-label extension data from Study 1402 OLE compared to the mFARS data from a natural history Study "Clinical Outcome Measures in Friedreich's Ataxia" (FA-COMS; NCT0309078) showed a statistically significant difference in mFARs change from baseline between Study 1402 Extension and FA-COMS. The mFARs change from baseline comparison was made between the FA-COMs patients and those patients in the OLE in three separate populations of pooled patients: those who had been on

omaveloxolone or placebo in Study 1402 Part 2 (pooled analysis), patients who had been on placebo in Part 2 (placebo to omaveloxolone), and patients who had been on omaveloxolone in Part 2 (omaveloxolone to omaveloxolone). In the total pooled population, there was a mean difference in mFARs change from baseline of -3.354 points in favor of omaveloxolone treated patient (p=0.0002), with similarly significant changes of -4.096 points in favor of omaveloxolone treated patients (p=0.0001) in the placebo to omaveloxolone group and -4.240 points in favor of omaveloxolone treated patients (p=0.0190) in the omaveloxolone to omaveoloxolone group.

Omaveloxolone was generally well tolerated. Increases in liver enzymes (AST, ALT and GGT), *B-natriuretic peptide (*BNP) and N-Terminal Prohormone of B-Type Natriuretic Peptide (NT-Pro BNP), and lipids were observed in patients taking omaveloxolone, which can be monitored in patients in the postmarketing setting.

Overall, given the unmet need in FA, with no currently available therapies, the observed evidence of effectiveness from a single adequate and well-controlled study, Study 1402, in the pre specified FA population without pes cavus, the observed effect in all randomized population consisting of patients with or without pes cavus, with confirmatory evidence from the natural history comparison, in addition to the pharmacodynamic data supporting the biologic plausibility of the treatment effect, adequate to provide substantial evidence of effectiveness of omaveloxolone in the treatment of FA. There are no safety issues that would preclude approval. The benefit-risk profile appears acceptable for omaveloxolone for the treatment of FA.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Friedreich's ataxia (FA) is a rare, genetic, rapidly, and cumulatively progressive, neurodegenerative disorder. Friedreich's ataxia is caused by a defect in a gene called Frataxin (FXN), which is located on chromosome 9, leading to low levels of frataxin protein. This protein is essential for proper functioning of mitochondria. Changes in frataxin gene causes an increase in part of DNA called trinucleotide repeat (GAA). | • Friedreich's ataxia (FA) is a rare, genetic, rapidly, and cumulatively progressive, neurodegenerative disorder.<br>• Neurological symptoms such as poor balance, impaired coordination, loss of motor skills, dysarthria, and weakness are major disease burdens. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • The typical onset of serious symptoms occurs between 5 and 15 years of age, although the age of onset can range from 2 years to >70 years.<br>• Symptoms include neurological features, such as poor balance, impaired coordination, dysarthria, weakness, ocular fixation instability, deep sensory loss, and visual and hearing impairment, and also diverse non-neurological features such as hypertrophic cardiomyopathy, kyphoscoliosis, and foot deformities (i.e., pes cavus).<br>• For patients with FA, balance issues, loss of motor skills, and speech impairment are major disease burdens that lead to the loss of ambulation and becoming wheelchair-dependent by their mid-20s, contributing to a loss of independence.<br>• Ultimately, FA leads to a shortened life expectancy, with the average age of death being 37.5 years of age.<br>• Cardiac dysfunction, as a consequence of dilated cardiomyopathy and arrhythmias, is widely accepted as the most common cause of mortality in patients with FA. | • Cardiac dysfunction, as a consequence of dilated cardiomyopathy and related arrhythmias, is widely accepted as the most common cause of mortality in patients with FA. |
| Current Treatment Options | • There are no approved treatments for FA. | With no approved treatments, there remains an unmet need. |
| Benefit | • The effectiveness of omaveloxolone in the treatment of FA was evaluated in a single, adequate well-controlled Study 1402 (MOXIe) that consisted of 2 parts followed by an open-label extension with up to 3 years of omaveloxolone exposure.<br>• Part 2 of Study 1402 randomized FA patients ages 16-40 years with or | • There was a statistically significant improvement in modified Friedreich's Ataxia Rating Scale (mFARS) at Week 48 of -2.41 points in the omaveloxolone arm compared to placebo (p=0.0138). |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | without pes cavus to omaveloxolone 150 mg (N=51) and placebo (N=52) for 48 weeks.<br>• A total of 82 FA patients without pes cavus constituted the primary efficacy Full Analysis population.<br>• Change from baseline in the modified Friedreich's Ataxia Rating Scale (mFARS) scores at Week 48 was the primary efficacy endpoint.<br>• There was a statistically significant improvement in mFARS at Week 48 of -2.41 points 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 experienced a worsening from baseline of mFARS of 0.85 points at Week 48.<br>• The 'All Randomized' patients also showed an improvement of -1.94 points in the omaveloxolone arm compared to placebo (nominal p=0.0331).<br>• The key secondary endpoints PGIC and CGIC did not reach statistical significance in the 'Full Analysis' population (p=0.1300 and 0.5259), however, PGIC was nominally significant in the 'All Randomized' population (p=0.0282). Additionally, Activities of Daily Living was nominally significant in the pre-specified Full Analysis population (p=0.04).<br>• A post hoc propensity matched analysis of 3 year open label extension of Study 1402 compared to the mFARS data from a natural history Study "Clinical Outcome Measures in Friedreich's Ataxia" (FA-COMS; NCT0309078) showed a statistically significant difference in mFARs change from baseline between Study 1402 Extension and FA-COMS of -3.354 points in favor of omaveloxolone treated for the pooled (placebo to omaveloxolone and omaveloxolone to omaveloxolone) analysis (p=0.0002), | • Secondary endpoint Activities of Daily Living was nominally significant in the pre-specified Full Analysis population (p=0.04). PGIC was also nominally significant in the 'All Randomized' population (p=0.0282).<br>• As confirmatory evidence, a propensity matched natural history comparison of the 3 years open label extension phase showed a statistically significant deviation from the decline in mFARS scores after 3 years of treatment with omaveloxolone (p=-0.0002). |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | -4.096 points in favor of Study 1402 extension for the primary placebo to omaveloxolone switch population (p=0.0001) and -4.240 points in favor of Study 1402 extension for the primary Omaveloxolone to omaveloxolone population (p=0.0190).<br>• Based on a mechanistic biological plausibility of ferritin increase with the Nrf2 activation, omaveloxolone treatment has shown dose dependent increase in ferritin observed in Part 1 of the study (doses 5 mg to 300 mg) that provides additional confirmatory evidence of effectiveness of omaveloxolone in the treatment of FA. | |
| Risk and Risk Management | • A total of 103 FA patients provided safety of 150 mg omaveloxolone compared to placebo. This included a total of 24 adolescent patients (≥ 16 to <18 years).<br>• A total of 137 patients provided long term safety of 150 mg omaveloxolone for ≥48 Weeks of exposure. Of the 24 adolescent patients, 14 (63.6%) had ≥48 weeks of exposure, and 11 (50.0%) had >96 weeks of exposure to omaveloxolone.<br>• There were no deaths in the FA studies.<br>• Common TEAES that occurred in ≥15% of omaveloxolone-treated patients include elevated liver enzymes, headache, nausea, abdominal pain, skin abrasion, fatigue, diarrhea, musculoskeletal pain, oropharyngeal pain, and vomiting.<br>• Increases in alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase were observed without an associated increase in total bilirubin or alkaline phosphate. A total of 31%, 16% and 4% patients in the omaveloxolone group exceeded the threshold criterion of ALT or AST >3× | • Increases in ALT, AST, and GGT were observed in the safety database without concurrent elevations of total bilirubin or alkaline phosphatase. Clinical data indicates that there were no cases of jaundice, Hy's law or cholestatic liver injury with omaveloxolone; however, the clinical database is small to detect a significant drug-induced liver injury with omaveloxolone. Increases in liver enzymes will be described as a Warning in Section 5 of the prescribing information. Enhanced pharmacovigilance will be required.<br>• Mean increases in BNP and NT-Pro BNP were observed in the omaveloxolone treated patients compared to placebo |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | the ULN, >5X ULN or >10x the ULN respectively compared to none in placebo group. Increases in liver enzymes generally peaked within 2 to 4 weeks after initiation of omaveloxolone treatment and were higher in the first 12 weeks of treatment, declining to baseline values within 4 weeks following drug withdrawal.<br>• Mean increases 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 arm.<br>• Mean increases in BNP and NT-Pro BNP were observed in the omaveloxolone treated patients compared to placebo patients. BNP values were >100 pg/L in 10 (20%) of the omaveloxolone treated patients compared to 3 (6%) of the placebo treated patients at one or more time points. Two patients in the omaveloxolone arm had BNP levels >200 pg/ml. NT-Pro-BNP values were >125 pg/L in 24 (47%) of the omaveloxolone treated patients.<br>• The effect of omaveloxolone on the QTc interval has not been adequately characterized.<br>• Patients 16 and older have a similar safety profile to adults. | patients. A greater baseline history of CV events and cardiomyopathy in the omaveloxolone group compared to placebo and a high background rate of cardiomyopathy and arrhythmias in FA further complicate interpretation of cardiac safety of omaveloxolone in FA patients. Increases in BNP will be described as a Warning in Section 5 of the prescribing information. Enhanced pharmacovigilance will be required.<br>• Increases in cholesterol were observed in patients treated with omaveloxolone and will be described in Section 5 of the prescribing information.<br>• Pediatric patients 16 and older had similar safety profile to adults. |

### 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

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| □ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | × | Clinical outcome assessment (COA) data, such as | | Sec 6.1 Study endpoints |
| | | × | Patient reported outcome (PRO) | |
| | | □ | Observer reported outcome (ObsRO) | |
| | | × | Clinician reported outcome (ClinRO) | |
| | | □ | Performance outcome (PerfO) | |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | [e.g., Sec 2.1 Analysis of Condition] |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | × | Natural history studies | | Sec 6.1 Study Resuls |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | □ | Other: (Please specify) | | |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | □ | Input informed from participation in meetings with patient stakeholders | |
| | | □ | Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| | | □ | Observational survey studies designed to capture patient experience data | |
| | | □ | Other: (Please specify) | |
| □ | Patient experience data was not submitted as part of this application. | | | |

## 2. Therapeutic Context

### 2.1. Analysis of Condition

Friedreich's ataxia (FA) is a rare, genetic, rapidly, and cumulatively progressive, neurodegenerative disorder.

**Clinical Features:** Present at birth, the typical onset of serious symptoms, manifestations and accumulations of damage from FA occur between 5 and 15 years of age, although the age of onset can range from 2 years to >70 years.

FA is a multisystem disease encompassing both characteristic neurological features, such as poor balance, impaired coordination, dysarthria, weakness, ocular fixation instability, deep sensory loss, and visual and hearing impairment, and also diverse non-neurological features such as hypertrophic cardiomyopathy, kyphoscoliosis, and foot deformities.
Motor weakness involving the feet and legs occurs in up to 88 percent of patients, followed later in the course by weakness involving the hands and arms. For patients with FA, balance issues, and loss of motor skills and speech, are major disease burdens that lead to the loss of ambulation and becoming wheelchair-dependent by their mid-20s, contributing to the loss of independence. Ultimately, FA leads to a shortened life expectancy, with the average age of death being 37.5 years of age. Cardiac dysfunction, as a consequence of dilated cardiomyopathy and arrhythmias is widely accepted as the most common cause of mortality in patients with FA.

**Etiology:** Friedreich's ataxia is caused by a deficiency in frataxin, and in most patients, this is a consequence of an expansion of the guanine-adenine-adenine (GAA) triplet repeat within the first intron of the frataxin gene, which impairs its transcription. Frataxin is a mitochondrial protein that facilitates the formation of iron-sulfur clusters (ISCs), which are important protein cofactors necessary for the activity of many cytosolic and mitochondrial enzymes, including those in the respiratory chain complexes that control adenosine triphosphate (ATP) production. Thus, frataxin deficiency leads to mitochondrial dysfunction, decreased ATP production, oxidative stress, and neuroinflammation, which ultimately leads to neurodegeneration and the associated clinical symptoms, including ataxia.

The Applicant postulates that impairment of Nrf2 signaling associated with frataxin deficiency and mitochondrial dysfunction is involved in the pathogenesis and progression of FA.

**Prevalence:** FA affects approximately 5,000 patients in the US and 22,000 patients globally.

## 2.2. Analysis of Current Treatment Options

Currently, there are no approved therapies for the treatment of FA.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Omaveloxolone is not marketed in any country.

## 3.2. Summary of Pre-submission/Submission Regulatory Activity

| Date | Summary |
|---|---|
| June 10, 2014 | Pre-IND<br>• Applicant: proposed [redacted] (b) (4) as the primary endpoint<br>• Division: [redacted] (b) (4) does not directly measure clinical benefit<br>• Applicant proposed peak workload as primary endpoint and 25-foot walk as key secondary<br>• Division: Parameters of peak workload are not a direct measure of clinical benefit. This approach might be more appropriate for accelerated approval pathway if positive and other clinical functional endpoints are supportive. |
| July 29, 2014 | IND<br>• Opened with Phase 2 study to evaluate S/T and PD (Study 408-C-1402-MOXIe) that included 2 Parts: Part 1 included a double-blind dose escalation phase with plans for Part 2 as a randomized, double-blind, placebo-controlled phase @ 2 doses<br>• Primary endpoint for Part 1 was **peak workload during exercise testing**; Secondary endpoint was **modified FARS (mFARS)** |
| April 19, 2017 | MOXIe Study Protocol 7th amendment:<br>• Proposed 1 dose for Part 2 of the study @150 mg based on completed Part 1 of the study<br>• **Proposed mFARs** as the primary endpoint for Part 2, secondary endpoints included 25-Foot Walk Distance, the 9-hole PEG, the SF-36, and FARS-ADL. |
| April 29, 2017 | Division Advice Letter to Applicant based on April 19, 2017 submission:<br>• **Recommended** using "Activities of Daily Living" component of the FARS (**FARS-ADL**) as primary instead of mFARS |
| July 6, 2017 | MOXIe Study Protocol 8th amendment:<br>• Proposed PGIC and CGIC as key secondary endpoints to support mFARs |

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| August 2, 2017 | Division Advice Letter to Applicant after Meeting request dated May 26, 2017, key points:<br>• Division acknowledged the difficulty of using ADL component of FARS as primary based on recent published studies<br>• **Agreed that the modified FARS (mFARS) was an acceptable primary endpoint for the planned trial.**<br>• Unable to comment on approval pathway (accelerated or standard), as this would depend on the overall results of the study endpoints<br>• Recommended inclusion of patient-reported outcome (PRO) and/or a performance-based outcome (PerfO)<br>• **Recommended longer study (1-2 years) than the proposed 24 weeks** |
| August 22, 2017 | MOXIe Study Protocol 9th amendment:<br>• Increased study duration to 48 weeks |
| December 19, 2017 | Breakthrough Designation Request based on results of Part 1 of MOXIe study |
| February 15, 2018 | Breakthrough Designation Request was denied:<br>(b) (4) [redacted] |
| June 10, 2019 | SAP for MOXIe Part 2 (comments conveyed August 5, 2019)<br>• Proposed primary analysis in a subgroup of patients without pes cavus based on efficacy findings from Study 1402 Part 1 because the Applicant believed that the presence of this deformity may represent a different subtype of FA with a different pathophysiology and clinical phenotype. This was acceptable to the Division.<br>• Sensitivity analyses were recommended. |
| December 18, 2019 | Type C EOP2/3 meeting<br>• Division **did not agree** that MOXIe study (Part 1 and 2) are adequate to support an NDA as a **single adequate and well-controlled study** (based on effect size, statistical significance, and lack of support from secondary endpoints) |

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| | • mFARS at week 48 in patients without pes cavus (p=0.014); key secondary endpoints PGIC and CGIC negative, ADL nominally positive (p-0.042) and last in the hierarchy of multiple secondary endpoints; no dose response in Part 1<br>• **Division recommended a second study**<br>• Division was willing to consider an argument of **mFARS as an intermediate clinical endpoint; however, the standard for substantial evidence of effectiveness would still need to be met, which would likely require** the results of a second study with a magnitude similar to MOXIe study. Time dependency of mFARs was discussed. With this approach, a confirmatory trial would be required<br>• Applicant proposed additional analyses of Part 2 and OLE compared to external controls<br>• Division expressed concerns on such analyses unless treatment effect was large. Division expressed **willingness to review additional analyses**<br>• Division agreed on providing omaveloxolone through an expanded access program |
| December 23, 2019 | Applicant provided written responses/comments post EOP2/3 meeting<br>• Requested to discuss the possibility of using the open-label extension study to provide confirmatory evidence of effectiveness<br>• Asserted mFARS is a direct measure of clinical benefit and the magnitude of change in mFARS (2 points on a scale of 99) is clinically meaningful |
| August 6, 2020 | Type C meeting<br>• Applicant presented additional sensitivity and post hoc analyses on primary and secondary endpoints of the MOXIe trial to enhance the persuasiveness of the study<br>• Division **did not agree that the post hoc analyses on mFARS and FA-ADL, PGIC, CGIC increased the persuasiveness to support approval based on single study**<br>• Division reiterated the December 2019 recommendations<br>• Applicant proposed a 3 year long confirmatory study in 450 patients, with primary endpoint as FA-ADL<br>• Division also **recommended to consider an adequate and well-controlled study of longer duration with mFARS as primary and FA-ADL as secondary with an interim analysis based on mFARS to support accelerated approval and the complete study as confirmatory study**. Division advised that the approval pathway |

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| | would depend on the magnitude of effect on mFARS and overall efficacy results and cannot be decided prospectively without the second study<br>• Applicant requested ability of an analysis of placebo arm crossed over to omaveloxolone treatment in the extension study to provide evidence of effectiveness<br>• Division recommended the sponsor provide a 1-page summary of this plan and agreed to provide informal feedback on the plan. |
| September 8, 2020 | SAP for analyzing the extension study where placebo patients are rolled over to treatment (referred to as cross-over analysis) |
| September 11, 2020 | Applicant submitted a one-page synopsis of their plan on the cross-over analysis or Baseline-Controlled Analysis (based on Division's request) |
| September 22, 2020 | Email indicating that the analysis from the SAP dated September 8, 2020 has been completed (Note: Division's review comments on the SAP were not sent) |
| October 8, 2020 | Applicant sent Email with results of the cross-over analysis and requested T-con |
| November 24, 2020 | Advice letter to Applicant<br>• Analyses were not what the Division expected and were completed before comments were given on the SAP<br>• The baseline-controlled analyses that were conducted lack an independent comparison group.<br>• Division gave recommendations on the analysis, however cautioned the sponsor that these exploratory analysis in small number of patients in the OLE appear questionable to strengthen the study results |
| March 8, 2021 | Applicant provided a 5-page summary of the analysis of the Open label Extension study referred to as "Delayed Start analysis" at the Division request prior to granting another meeting (meeting request February 26, 2021) |
| May 18, 2021 | An email communication acknowledging the submission of a briefing package dated April 2, 2021 for a Type C meeting to discuss the results of additional analyses from data of Study 1402 Part 2 and based on the review of this, advised the Applicant to withdraw the briefing package and instead submit of a pre-NDA meeting package for further discussion. |
| Sep 28, 2021 | Pre-NDA Meeting<br>• The Division noted the adequacy of the efficacy data will be a matter of review of the application. Applicant confirmed it intends to provide sufficient data to support standard full approval with |

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| | positive results of the Study 1402 Part 2, and data from the Delayed-start analysis and open-label extension study results.<br>• The Division confirmed the proposed safety database appears adequate for NDA submission. |

### 3.3. Foreign Regulatory Actions and Marketing History

Omaveloxolone is not marketed in any country at the time of the filing of this Application.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

There are no issues.

### 4.2. Product Quality

Refer to CMC Review.

### 4.3. Clinical Microbiology

Not Applicable.

### 4.4. Nonclinical Pharmacology/Toxicology

Refer to Nonclinical Review.

### 4.5. Clinical Pharmacology

Refer to Clinical Pharmacology.

### 4.6. Devices and Companion Diagnostic Issues

Not Applicable.

### 4.7. Consumer Study Reviews

Not Applicable.

## 5. Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

**Table 1 Listing of Clinical Efficacy and Safety Trials**

| Study Identifier NCT# | Study Design (Duration)<br>Status<br>Database Lock | Location (s) | Treatment | Number of Patients Enrolled Adolescents (<18 years old) |
|---|---|---|---|---|
| **Study 1402 Part 2**<br>NCT02255435 | Pivotal study<br>Randomized, double-blind, parallel-group<br>Placebo-controlled<br>**(52 weeks: 48 weeks on treatment plus 4 weeks off treatment)**<br>**Ages 16-40 years**<br>Completed<br>12 Nov 2019 (final) | United States, Austria, Italy, United Kingdom, and Australia | Omav: 150 mg, oral, QD<br><br>Placebo, oral, QD | 103: 51 Omav/ 52 placebo<br><br>24: 9 Omav/ 15 placebo |
| **Study 1402 Extension**<br>NCT02255435 | Open-label, long-term extended access<br>(extended access<br>**Omav treatment duration is 2.8 years [Study 1402 Extension only] and 3.7 years**<br>[combined exposure with Study Part 2 duration])<br>Ongoing<br>17 Aug 2021 (interim) | United States, Austria, Italy, United Kingdom, and Australia | Omav: 150 mg, oral, QD | 149 Omav<br><br>(Placebo- Omav = 106;<br><br>Omav-Omav = 43)<br><br>11 Omav |
| **Study 1402 Part 1**<br>NCT02255435 | Randomized, double-blind, dose-ranging<br>Placebo-controlled<br>**(16 weeks: 12 weeks on treatment plus 4 weeks off treatment)**<br>Completed<br>27 Jun 2017 (final) | United States, Austria, and Australia | Omav: 2.5 mg for 2 weeks followed by dose escalation to 5 mg / 10 mg / 20 mg / 40 mg / 80 mg / 160 mg / 300 mg, oral, QD | 69: 52 Omav/ 17 placebo<br><br>9: 6 Omav/ 3 placebo |

Omaveloxolone capsules were also evaluated in 7 studies in indications other than FA, including 1 placebo-controlled study in patients with mitochondrial myopathies, 2 open-label oncology studies, and 4 clinical pharmacology studies in healthy subjects or patients with hepatic impairment.

### 5.2. Review Strategy

The evidence of effectiveness of omaveloxolone in the treatment of Friedreich's ataxia was based on a single Study 408-C-1402 Part 2 (MoXIe) and its open label extension. The statistical parameters were validated by the statisticians (Drs. Jinnan Liu, Kun Jin). Data Analyst Dr. Rui Li assisted with the safety analyses for the Application. Consult review was requested to the Division of Cardiology (Drs, Selena DeConti, Mary Ross Southworth, Norman Stockbridge) for assessing the cardiac risks associated with omaveloxolone and Drug Induced Liver Injury (DILI) group (Drs. Ling Lan, Edwige Chiogo Vouffo, Paul Hayashi, Frank A. Anania, Mark Avigan) in the Division of Hepatology and Nutrition and Office of Pharmacoepidemiology to evaluate the DILI risk with omaveloxolone.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. Study 408-C-1402 PT 1 and PT2

#### 6.1.1. Study Design

**Overview and Objectives**

Study 408-C1402 was a 2-part study (Part 1 or PT1 and Part 2 or PT2) evaluating the efficacy, safety, PK, and PD of omaveloxolone in the treatment of patients with FA. The Applicant has submitted separate Clinical Study Reports for both parts of the study. PT1 was a placebo-controlled dose-escalating phase evaluating doses 2.5-300 mg omaveloxolone in FA patients. PT2 was a randomized, double-blind placebo-controlled phase that further evaluated 150 mg omaveloxolone for 48 weeks. I will summarize the trial design for all parts of the study but first discuss the results of Study 408-C1402 PT2 as this is the main study in the application in support of effectiveness of omaveloxolone in FA patients, followed by results of Part 1 and the extension phase.

The primary objectives of Part 2 of the study were:

- To evaluate the change in the modified FA rating scale (mFARS) score at Week 48
- To evaluate the safety and tolerability of omaveloxolone

**Trial Design**

**Part 1** of this study was a randomized, placebo-controlled, double-blind, dose-ranging study to evaluate the safety, efficacy, and pharmacokinetics (PK) and pharmacodynamic (PD) activity of omaveloxolone at 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, and 300 mg in patients with FA. A cohort consisted of the next 8 eligible patients randomized 3:1 to omaveloxolone at the cohort-specific dose (n = 6) or placebo (n = 2). Intra-patient dose-escalation was utilized in the first cohort 1 to evaluate omaveloxolone at the first two dose levels (2.5 mg and 5 mg). Patients were escalated to 5 mg dose after 2 weeks unless a dose limiting toxicity was reported. Subsequent to that, patients stayed at that dose up to Week 12. Patients in Cohort 2-9 were treated at their dose levels for 12 weeks.

**Part 2** of this study was a randomized, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of omaveloxolone 150 mg in patients with FA for 48 weeks. The omaveloxolone dose of 150 mg for Part 2 was selected based on the data from Part 1, including safety, efficacy, PK, and PD data. Patients enrolled in Part 2 were randomized 1:1 to receive omaveloxolone 150 mg or placebo. **Randomization was stratified by pes cavus status (pes cavus vs no pes cavus).**

Pes cavus is a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing. Presence of this deformity can affect patients' ability to use their legs, walk, and perform neurologic and exercise testing independent of their ataxia. The protocol for Study 1402 Part 2 limited patients with pes cavus to 20% of the study population based on efficacy findings from Study 1402 Part 1 because the Applicant believed that the presence of this deformity may represent a different subtype of FA with a different pathophysiology and clinical phenotype (Lynch, 2018[1]). For Study 1402 Part 2, the clinical diagnosis of pes cavus was defined as having a loss of lateral support and was determined by having the patient stand barefoot and bearing weight; if light from a flashlight could be seen under the patient's arch, the patient was defined as having pes cavus.

Following randomization on Day 1, patients were to self-administer treatment once daily for 48 weeks. A follow-up visit for safety would occur at Week 52 (4 weeks after the last dose).

Patients were to take 3 capsules (50 mg each) once daily, self-administered in the morning on an empty stomach (approximately 1 hour before or 2 hours after eating). On Day 1, Day 14 (Week 2), Day 84 (Week 12), Day 168 (Week 24), and Day 336 (Week 48), the study staff administered study drug at the clinic following all assessments on Day 1, and after the predose blood sample for PK on Days 14, 84, 168, and 336.

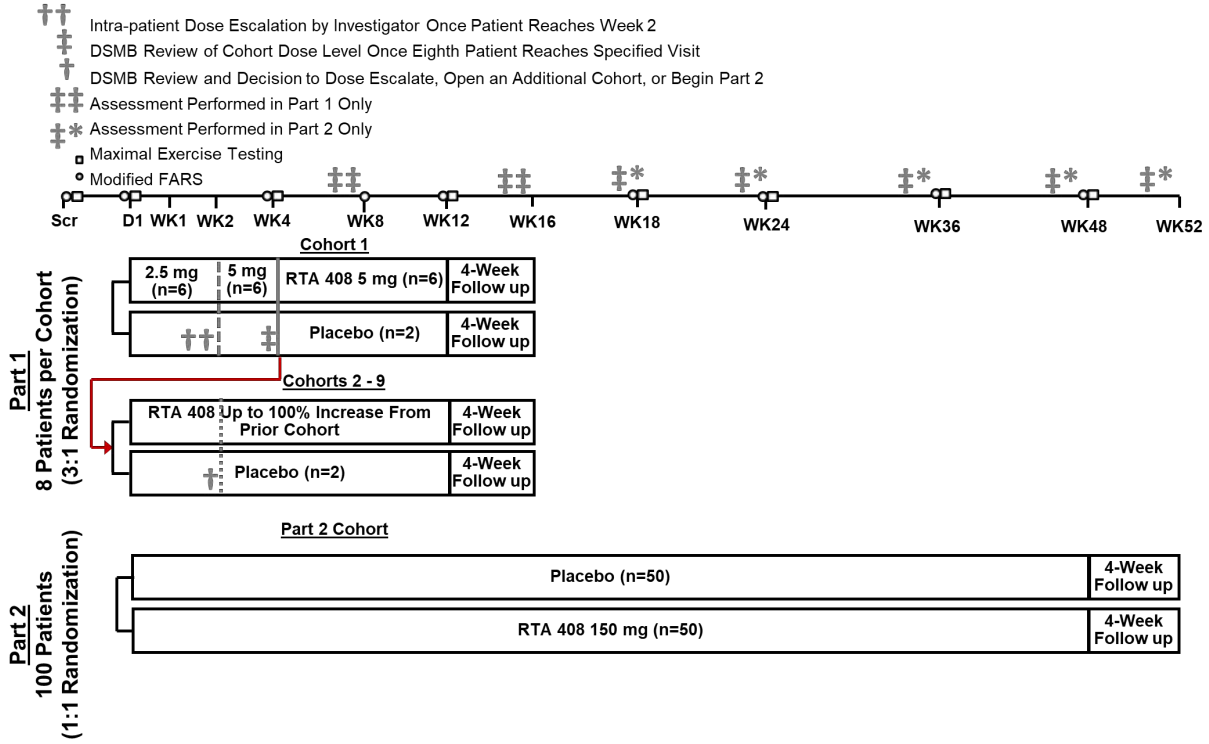
[1] Lynch DR, Farmer J, Hauser L, et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. Ann Clin Transl Neurol. 2018 Nov 10;6(1);15-26. doi: 10.1002/acn3.660. PMID: 30656180.

A vomited dose was not to be replaced. Missed doses were to be taken in the afternoon or evening of the same day approximately 1 hour before or 2 hours after a meal. A double dose (e.g., missed dose from previous day and dose for current day) was not to be taken. Patients were provided a dosing diary to track all doses administered, including the date and time of each dose.

***Reviewer's Comment:***
*The Applicant selected the dose of 150 mg for the Part 2 based results from Part 1 that they believed had the optimal safety, tolerability, and PK/PD parameters in Part 1 with the 160 mg dose. The Applicant had initially planned to include 2 doses in Part 2, but the protocol was amended after the results for Part 1 were available. Results from Part 1 showed larger decrease in mFARS in subset of patients without pes cavus in a post hoc analysis in a very small number of patients (4 on Omaveloxolone and 7 on placebo). In addition, the Applicant believed that the change from baseline in pharmacodynamic biomarkers (ferritin, ALT, AST) in Part 1 were maximal at the 160 mg dose. Please refer to Clinical Pharmacology review for discussion on these biomarkers. Results of Part 1 are also briefly discussed after Part 2 results in this review.*

The schematic of the Study design is shown in Figure 1.

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




Source: Applicant's Clinical Study Report page 22

**Extension Phase:** All subjects from Part 1 and Part 2 had the option to enroll in an open-label extension (OLE) phase. The extension study is ongoing at the time of this application and will assess long-term safety and tolerability of omaveloxolone in patients with FA following completion of Part 1 or Part 2 of the study. **Patients were not unblinded to study treatment in Part 1 or Part** 2 upon entering the extension study.

Patients had in-person assessments during treatment in the OLE at Day 1, Week 4, Week 24, and every 24 weeks thereafter. Patients were also to be assessed by telephone contact on Day 14. Since Part 2 patients were followed continuously within the study, eligibility for the extension was assessed at the Week 52 visit and a separate screening visit was not required. Part 1 patients were not followed continuously within this study, and therefore, had to complete a screening visit to confirm eligibility.

**Inclusion criteria (Part 1 and Part 2):**

- Have genetically confirmed Friedreich's ataxia
- Have a modified FARS score ≥ 20 and ≤ 80. The average of the two mFARS values collected at Screening and Day 1 visits must fall within the allowable range, and they must be within 4.5 points of each other.
- Be male or female and ≥ 16 years of age and ≤ 40 years of age
- Have no changes to their exercise regimen within 30 days prior to Study Day 1 and be willing to remain on the same exercise regimen during the study period
- Have the ability to complete maximal exercise testing
- Have adequate kidney function defined as an estimated glomerular filtration rate (eGFR ≥ 60 mL/min/1.73 m2 using the Modification of Diet in Renal Disease (MDRD) 4-variable formula
- Have a left ventricular ejection fraction ≥ 40% (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
- Be able to swallow capsules
- Be willing to practice medically acceptable methods of birth control

**Exclusion criteria (Part 1 and Part 2):**

- Have uncontrolled diabetes (HbA1c > 11.0%)
- Have B-type natriuretic peptide level > 200 pg/mL
- Have a history of clinically significant left-sided heart disease and/or clinically significant
- cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia, including but not limited to any of the following:
    - Clinically significant congenital or acquired valvular disease
    - Pericardial constriction (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)

  - Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
  - Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina)
  - History of hospitalization for heart failure in the last five years
  - Cardiac insufficiency, defined as New York Heart Association Class > 2
  - History of atrial fibrillation
  - History of unstable arrhythmias
- Have known active fungal, bacterial, and/or viral infection, including human immunodeficiency virus or hepatitis virus (B or C)
- Have known or suspected active drug or alcohol abuse, as per investigator judgment
- Have clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations greater than 1.5 times the upper limit of normal of aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Levels above this threshold are allowable if attributable to muscle injury.
- Have any abnormal laboratory test value or clinically significant pre-existing medical condition
- Have taken any of the following drugs within 7 days prior to Study Day 1 or plan to take any of these drugs during the time of study participation:
  - Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
  - Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)
  - Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)
- Have a history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), or has, at screening, clinically relevant deviations in laboratory tests including any one of the following:
  - alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 1.5-fold ULN
  - bilirubin > 1.2-fold ULN
  - alkaline phosphatase (ALP) > 2-fold ULN
  - albumin < lower limit of normal (LLN)
- Have participated in any other interventional clinical study within 30 days prior to Study Day 1
- Have a cognitive impairment that may preclude ability to comply with study procedures
- Be unable to comply with the requirements of the study protocol
- Have used antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and vitamin E above the recommended daily allowance, within 14 days prior to Study Day 1, or plan to take any of these supplements during the time of study participation
- Have previously documented mitochondrial respiratory chain disease

- Have a history of thromboembolic events within the past 5 years
- Have taken anticoagulant therapy within 30 days prior to Study Day 1
- Have scheduled surgical treatment for scoliosis or foot deformity during the study
- Have had significant suicidal ideation within 1 month prior to Screening Visit as per investigator judgment or any history of suicide attempts
- Be pregnant or breastfeeding
- Prior participation in a trial with RTA 408

**Extension Phase:**

The inclusion/exclusion criteria for the extension study were the same as Part 2 of the study. Patients from Study 1402 Part 1 or Study 1402 Part 2 had to have completed assessments through the follow-up visit with no major protocol deviations.

**Patient Discontinuation Criteria**
Patients were to be permanently discontinued from the study drug if any of the following occurred:
• ALT or AST >8 × ULN
• ALT or AST >5 × ULN for more than 2 weeks
• ALT or AST >3 × ULN and total bilirubin >2 × ULN
• ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Patients permanently discontinued from study drug during the extension study were to complete the end of study assessments and be terminated from the study.

**Study Endpoints**

**Part 2:**
Most efficacy endpoints were assessed at Weeks 12, 24, 36 and 48. 9-Hole peg test and 25-Foot Timed Walt Test, SF-36 Heath Survey Update was analyzed on Weeks 24 and 48 only.

Primary Endpoint:

- The change in the modified Friedreich's Ataxia Rating Scale (mFARS) scores from Baseline to Week 48

Key Secondary Endpoint:

- The proportion of patients who are a treatment success at Week 48, based on the Patient Global Impression of Change (PGIC). A treatment success is defined as "Much Improved" or "Very Much Improved" on the Patient Global Impression of Change.
- The proportion of patients who are a treatment success at Week 48, based on the

Clinical Global Impression of Change (CGIC). A treatment success is defined as "Much Improved" or "Very Much Improved" on the Clinical Global Impression of Change.

Other secondary endpoints:

- The change in performance on a 9-hole peg test (9-HPT) at Week 48
- The change in performance on the 25-foot timed walk test (T25-FWT) at Week 48
- The frequency of falls over 48 weeks
- The changes in peak work and oxygen utilization during maximal exercise testing at Week 48
- The change in activities of daily living (ADL) at Week 48

Exploratory endpoints

- The change in raters' assessments of videos of normal walking at Week 48
- The change in SF-36 patient-reported outcome scores at Week 48
- The proportion of patients at Week 48 with an mFARS change from baseline at or lower than specified cutoff values

**Part 1**

Primary Endpoint:

- The mean change from baseline in peak work (watts/kg) at Week 12 (regardless of pes cavus status).
- Evaluation of safety and tolerability

Secondary endpoints

- The change from baseline on mFARS at Week 12

Exploratory Endpoints:

- The change in peak oxygen utilization during maximal exercise testing
- The change in performance on a 25-foot timed walk test
- The change in performance on a low-contrast letter visual acuity test
- The change in performance on a 9-hole peg test (9-HPT)
- The change in Fatigue Severity Scale score
- The change in SF-36® Health Survey Update (SF-36) score
- The change in the full FARS score

Pharmacodynamic endpoints (part 1 only):

- Biochemical changes in the frataxin levels and the activities of mitochondrial enzymes succinate dehydrogenase, aconitase, citrate synthase, and iron-sulfur enzymes in muscle biopsies (analysis not done)
- Mitochondrial function and biochemical changes in metabolites of interest in platelet

samples
- Biochemical changes in the frataxin levels from cheek swab samples (not done)
- Cardiac MRI (not analyzed, done in 5 patients, not all parameters were available)

**FARS** is a neurological-exam-based rating scale (maximum score 125) with five sections: Bulbar (section A, score 0 to 11), Upper Limb Coordination (section B, score 0 to 36), Lower Limb Coordination (section C, score 0 to 16), Peripheral Nervous System (section D, score 0-26), and Upright Stability (section E, score 0-36).

**mFARS** removed section D of the FARS, which contains items that are less clinically meaningful, and consists of components A, B, C and E, with **maximum score of 99.**

A higher score on the FARS or mFARS examination signifies more severe physical impairment, and **a reduction in FARS or mFARS score signifies improvement in functioning**.

**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 an intervention. The PGIC is assessed by completing the following statement "since I began trial treatment, my overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7).

**CGIC** is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention. The CGIC is assessed by completing the following statement "Compared to the patient's condition at the start of the trial, this patient's overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7).

For **9-Hole Peg Test,** both the dominant and non-dominant hands are tested twice at each assessment. The times recorded for the two trials for each hand are averaged, and the average value for each hand is used in analyses. The number of pegs per second (pegs/second) for each hand was calculated based on nine pegs placed compared to the time needed to complete the test: 9 / (average time). The reciprocal of the average time was calculated as 1 / (average time).

**T25-FWT** is the number of feet per second (feet/second) for walk based on the 25 feet distance and the total time needed to complete the test: 25 / (average time). The reciprocal of the walk time is calculated as 1 / (average time)

The **ADL (part of FARS-ADL)** examines the ability of patients to complete everyday tasks (e.g., holding a fork, dressing). The Activities of Daily Living is a 9-question assessment, which assesses 9 concepts: (1) speech, (2) swallowing, (3) cutting food and handling utensils, (4)

dressing, (5) personal hygiene, (6) falling, (7) walking, (8) quality of sitting position, and (9) bladder function.

**SF-36 Update** includes 36 questions that assesses 8 health concepts: (1) limitations in physical activities because of health problems, (2) limitations in social activities because of physical or emotional problems, (3) limitations in usual role activities because of physical health problems, (4) bodily pain, (5) general mental health (psychological distress and well-being), (6) limitations in usual role activities because of emotional problems, (7) vitality (energy and fatigue), and (8) general health perceptions.

***Reviewer's comment:***

*In an Advice Letter to the Applicant dated August 2, 2017, the Division agreed that mFARS was an acceptable primary endpoint. However, the regulatory history behind the acceptance of this endpoint as the primary endpoint is long which is provided in the regulatory history section 3.2 of this review. I again summarize the key steps to this regulatory decision:*

- *The Applicant had initially proposed* (b) (4) *as the primary endpoint. The Division was concerned that* (b) (4) *and did not directly measure clinical benefit and therefore recommended Activities of Daily Living component of FARS (FARS-ADL) as the primary endpoint. However, as published, and internal data became available, the Division acknowledged the challenges of adequately powering a trial with FARS-ADL as the primary endpoint due to high variability in the assessment and hence, agreed to Applicant's proposal of a modified version of the FARS, mFARS, as the primary endpoint. Published data had shown that the coefficient of variation for FARS-ADL was 7.44 (n=429) compared to 3.32 for mFARS (n=475); therefore, a study would require a large number of subjects to power the trial on FARS-ADL. However, it was also unclear to the Division if mFARS could support full approval or could be considered an intermediate clinical endpoint supporting accelerated approval, as the mFARS still contained items that were of uncertain clinical meaningfulness. The Division encouraged the Applicant to include straight forward patient reported outcome (PRO) or performance-based outcome (PerfO) for this purpose. The Applicant Proposed PGIC and CGIC as key secondary endpoints, which was considered acceptable to provide clinical meaningfulness of the results on mFARS.*

**Statistical Analysis Plan**

**The statistical analysis plan (SAP) dated May 16, 2019 is based on: Protocol No. 408-C-1402, Version 9, dated August 17, 2017**
**SAP Version 1.1: 4 June 2019**
**SAP Version 2.0: 18 September 2019 (Site added as covariate)**
**SAP Addendum Oct 9, 2019**

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

**Full Analysis Set (FAS):** The primary analysis of efficacy was based on patients **without pes cavus**. The FAS included all patients enrolled without pes cavus who had at least 1 post-baseline measurement, categorized by their randomized treatment group (whether or not they received study drug).
**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). Only descriptive analyses of efficacy are presented using the PCP.
**Safety Population:** Safety analyses were based on all enrolled patients. The Safety Population included all patients who received at least 1 dose of randomized study drug and was used for evaluation of safety variables. Patients who received at least 1 dose of omaveloxolone were classified in the omaveloxolone group. Patients who received at least 1 dose of placebo and no dose of omaveloxolone were classified in the placebo group.
**Per-Protocol (PP) Population:** A sensitivity analysis exploring the robustness of the primary FAS findings were based on the patients in the PP Population. The PP Population was defined as patients without pes cavus who received study drug through Week 48 and had no major protocol deviation that could potentially affect the efficacy assessments.
Primary analysis of the efficacy data was based on the FAS (i.e., patients without pes cavus).

**Baseline Definition (SAP May 16, 2019)**
Baseline values are defined as the last non-missing assessment prior to the first study drug administration, unless otherwise specified below. If the first study drug administration occurs after the date of randomization, the last measurement prior to the first study drug administration was considered the Day 1 measurement for the calculation of baseline.
The protocol specified that the Screening and Day 1 mFARS must be within 4.5 points to meet inclusion criteria for enrollment. If mFARS scores for Screening and Day 1 exceed the protocol allowed difference of 4.5 points for enrollment by at least two-fold (i.e., at least 9 points different), then the Screening mFARS assessment was considered invalid, and the mFARS collected closest to randomization (i.e., Day 1) was used as the baseline. Otherwise, the mean of Screening and Day 1 assessments was used as the baseline mFARS.

The average of Screening and Day 1 assessments was to be used as baseline for FARS, modified FARS, maximal exercise test parameters, 25FWT, and 9HPT. For all other parameters, study baseline was defined as the last non-missing observation obtained prior to administration of the first dose on Study Day 1. Baseline was defined as analysis visit 0.

**Missing Efficacy Endpoint Data**
Missing efficacy data were not imputed for the primary analysis of efficacy. The primary analysis of the primary endpoint was based on an assumption of missing at random (MAR) and used only available data (whether on- or off-treatment), a set of sensitivity analyses was included to assess the robustness of conclusions to the MAR assumption.

**Efficacy Analyses (SAP Version 2.0, 18 September 2019)**

Primary: The primary endpoint of this study was the change in mFARS score at Week 48. Primary efficacy analysis was performed in the **Full Analysis Set including only patients without pes cavus**. The primary endpoint was analyzed at the 0.05 level.

The mFARS scores for patients treated with omaveloxolone were compared with placebo at Week 48 using mixed models repeated measures (MMRM) analysis, with site (SITE) and baseline mFARS (BASE_MFARS) as covariates and the following fixed factors: treatment group (TRT), time (VISITNUM), the interaction between treatment and time (TRT*VISITNUM), the interaction between baseline and time (BASE_MFARS*VISITNUM). The analysis used visits 4, 12, 18, 24, 36, and 48. An unstructured covariance matrix is assumed.

For the primary efficacy objective, the null hypothesis states that the difference between the Week 48 mean (μOMAV) change from baseline in mFARS and the Week 48 mean (μplacebo) change from baseline in mFARS = 0. The alternative hypothesis states that the difference ≠ 0. Because mFARS scores increase with disease progression, a decrease in mFARS score is considered evidence of benefit.

In the event data by site was too sparse for a given analysis to execute, the following covariates was to be used in the order listed in place of site:
1. Region (USA/Non-USA) was to be used instead of site.
2. If analyses did not execute with region (USA/Non-USA) then no covariates were to be used to replace site.

Secondary: This study has a single primary efficacy outcome: change in mFARS score at Week 48. If the study shows statistically significant evidence of benefit for this endpoint (change in mFARS score at Week 48), then the key secondary and secondary endpoints were to be analyzed using a hierarchical approach to maintain the family-wise overall Type I error rate of 0.05.

Each endpoint was tested at the 0.05 significance 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

The SAP states "**Formal testing in the hierarchy may proceed so long as statistically significant evidence of benefit continues to be shown. At such point in the hierarchy that one endpoint does not show statistically significant evidence of benefit, formal statistical testing of subsequent endpoints will not occur".**

***Reviewer's Comment:***
*The initial protocol intended to include all enrolled patients in the primary analysis; however, the results of Part 1 of the study suggested improvements in patients without pes cavus, therefore the SAP included only the subset of patients without pes cavus as the Full Analysis Population. The protocol was amended accordingly prior to finalization of the SAP. Other than the fact that a pos hoc analysis of Part 1 showed a greater effect on mFARS in a small subset of patients without pes cavus at 150 mg dose, the rationale of selecting only patients without pes cavus for the primary efficacy analysis is unclear. Only performance of 'Upright Stability' component of mFARS would likely be impacted in patients with or without pes cavus. Presence of pes cavus is unlikely to impact assessment of other components of mFARS.*

*The initial sample size for the study was proposed based on 'All Randomized Patients'; however, the protocol was amended to include only patients without pes cavus in the primary analysis. This may have impacted the power calculations for primary analysis as only 82 of the planned 103 were included in the primary analysis.*

*Study Site was added as a covariate in the SAP Version 2.0 when study was completed. This SAP mentions under sample size considerations that there are at least 76 patients with post baseline measurements and are included in the primary analysis (section 4.3.1 page 21 of SAP V2.0). The impact of this is addressed in the Statistical Review of the application, where the statistician analyzed the data with and without addition of site as a covariate*

**Efficacy Analyses from the open-label extension phase:**

**Handling of Dropouts or Missing Data**

Missing data were not imputed for efficacy endpoints, except for mFARS. If the mFARS assessment was not completed, there was no imputation; imputation rules only applied to partially missing data. For Bulbar (section A), Upper Limb Coordination (section B), Lower Limb Coordination (section C), and Peripheral Nervous System (section D), if a question was left blank but the mFARS assessment was completed, the question responses from the last visit were used. For Upright Stability (section E), if the mFARS assessment was completed but questions 1 to 5 were left blank, the average of existing responses was used. If there were no existing responses at the current visit for questions 1 to 5, the question responses from the last visit were used. For questions 6 and 7, the responses from the last visit were used.

For ADL, if an ADL question was unanswered, then the total ADL score was considered missing.

Missing data due to COVID-19 were not imputed.

**Protocol Amendments**

| **Protocol Revision Chronology:** | | |
|---|---|---|
| Protocol version 1 | 23-July-2014 | Original |
| Amendment 1<br>(Protocol version 2) | 11-Sept-2014 | • The primary endpoint to evaluate peak workload (watts) was changed to evaluate peak work (watts/kg)<br>• Part 1 study design was modified based on FDA feedback. The design was changed to a randomized, placebo-controlled, double-blind, dose-escalation study to evaluate the safety of omaveloxolone at 2.5 mg, 5 mg, and 10 mg |
| Amendment 2<br>(Protocol version 3) | 13-Oct-2014 | • Per FDA recommendation, PK characterization was added as an objective of the study |
| Amendment 3<br>(Protocol version 4) | 12-May-2015 | • Part 1 of the study was modified to allow for up to 2 additional cohorts of 8 patients each |
| Amendment 4<br>(Protocol version 5) | 29-Sept-2015 | • Part 1 of the study was modified to include 8 cohorts for dose ranging analysis<br>• A statement was added to indicate 2 dose levels would be used in Part 2 of the study |

| | | |
|---|---|---|
| Amendment 5<br>(Protocol version 6) | 23-May-2016 | • Part 1 of the study included 9 cohorts and enrollment was increased to 108 patients.<br>• The maximum permitted dose of omaveloxolone was raised to 300 mg |
| Amendment 6<br>(Protocol version 7) | 13-Apr-2017 | • Part 2 enrollment was increased to 100 patients<br>• Part 2 study design was modified based on FDA feedback<br>• Part 2 of the study was revised to a single dose of 150 mg omaveloxolone versus placebo, extended to 24 weeks of treatment, and patients were stratified by pes cavus status.<br>• Increased total study enrollment from 108 to 172 patients (72 in part 1 and 100 in part 2)<br>• Statements were added to clarify that Part 2 of the study had over 80% power to test differences between the 2 treatment groups and the assumptions for this analysis were added. |
| Amendment 7<br>(Protocol version 8) | 29-July-2017 | • Patient Global Impression of Change and Clinical Global Impression of Change were added as secondary endpoints |
| Amendment 8<br>(Protocol version 9) | 17-Aug-2017 | • Part 2 study treatment duration was extended to 48 weeks |

***Reviewer's Comment:***
*Biases associated with the protocol amendments are unlikely. However, the power of the study may be impacted as the final analysis was done only in patients without pes cavus as patients with pes cavus were limited to 20% of the total study population, thereby leading to a reduction of 20% in the power of the study.*

### 6.1.2. Study Results

**Compliance with Good Clinical Practices**

principles in the Declaration of Helsinki and the GCP principles defined in the International Council for Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and in compliance with the applicable regulatory requirements in the US Code of Federal Regulations.

**Financial Disclosure**

Dr. Paola Giunti had provided FDA Form 3455 that she has received grant for participating. None of the other investigators have received any financial agreement from the Applicant.

**Patient Disposition**

Part 2:

A total of 103 patients were randomized into the study.

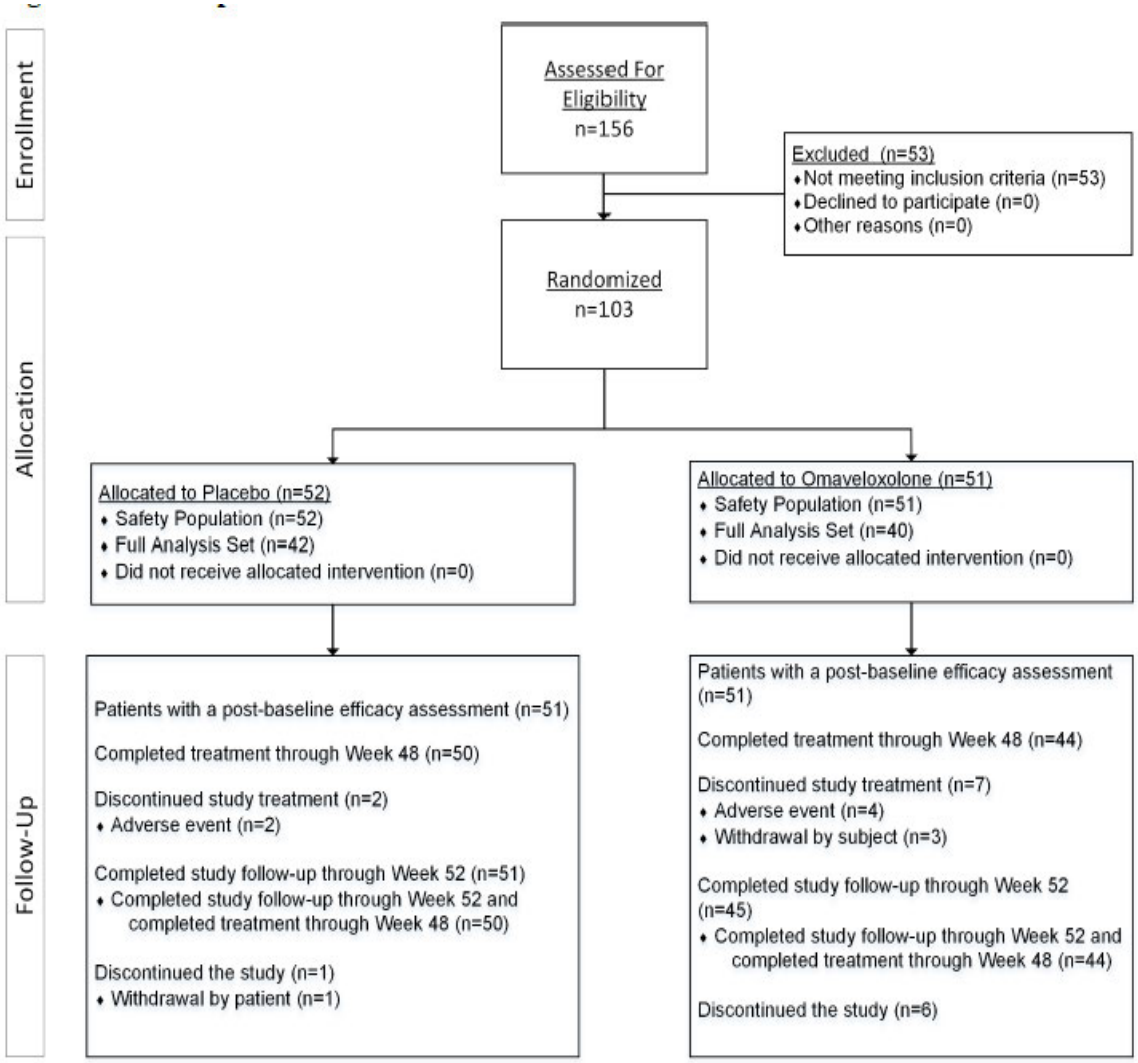
- Patients randomized to omaveloxolone (150 mg) group: N=51
- Patients randomized to placebo group: N=52

A total of 94 (91%) patients completed treatment through Week 48 of the study, including:

- 44/51 (86.3%) patients randomized to the omaveloxolone group and
- 50/52 (96.2%) patients randomized to the placebo group.

A total of 4/51 (7.8%) patients in the omaveloxolone group and 2/52 (3.8%) patients in the placebo group discontinued treatment prior to Week 48 due to the occurrence of an AE. An additional 3/51 (5.9%) patients in the omaveloxolone group withdrew consent before Week 48 (Figure 2).

**Figure 2 Disposition of Patients in Part 2**




Source: Clinical Study Report, Page 56

Patients were stratified based on pes cavus status. Disposition of all patients (safety population) and without pes cavus (Full Analysis Population) is shown in Table 2.

**Table 2 Disposition of Patients in Part 2**

| Number of: | All Subjects (N = 103) | | Without Pes Cavus (N = 83) | |
|---|---|---|---|---|
| | Omaveloxolone 150 mg (N = 51) n, (%) | Placebo (N = 52) n, (%) | Omaveloxolone 150 mg (N = 41) n, (%) | Placebo (N = 42) n, (%) |
| Safety Population | 51 (100) | 52 (100) | 41 (100) | 42 (100) |
| Full Analysis Set* | 40 (78.4) | 42 (80.8) | 40 (97.6) | 42 (100) |
| All Randomized Population | 51 (100) | 52 (100) | 40 (100) | 42 (100) |
| Per-Protocol Population | 29 (56.9) | 32 (61.5) | 29 (70.7) | 32 (76.2) |
| Pes Cavus Population | 10 (19.6) | 10 (19.2) | 0 | 0 |
| Completed treatment through Week 48 | 44 (86.3) | 50 (96.2) | 35 (85.4) | 40 (95.2) |
| Discontinued study treatment | 7 (13.7) | 2 (3.8) | 6 (14.6) | 2 (4.8) |
| Adverse events | 4 (7.8) | 2 (3.8) | 3 (7.3) | 2 (4.8) |
| Withdrawal by subject | 3 (5.9) | 0 | 3 (7.3) | 0 |
| Completed study follow-up through Week 52** | 45 (88.2) | 51 (98.1) | 36 (87.8) | 41 (97.6) |
| Completed study follow-up visits through Week 52 and completed treatment through Week 48 | 44 (86.3) | 50 (96.2) | 35 (85.4) | 40 (95.2) |
| Completed study follow-up visits through Week 52 but did not complete treatment through Week 48 | 1 (2.0) | 1 (1.9) | 1 (2.4) | 1 (2.4) |
| Discontinued study | 6 (11.8) | 1 (1.9) | 5 (12.2) | 1 (2.4) |
| Administrative reasons | 2 (3.9) | 0 | 2* (4.9) | 0 |
| Withdrawal by subject | 4 (7.8) | 1 (1.9) | 3 (7.3) | 1 (2.4) |

Data source: ADSL.xpt

*Patient [redacted] (b) (6) did not have post-baseline mFARS though received omaveloxolone for 6.9 weeks before withdrawing, and therefore was not included in the FAS population and discontinued for administrative reasons. Additionally, patient [redacted] (b) (6) discontinued for administrative reasons from the FAS Population

** Applicant counts 41 for mFARS assessment in the placebo arm, although subject discontinued from the study. See Reviewer's comment for additional details.

Nine patients (7 in the omaveloxolone group and 2 in the placebo group) discontinued study treatment on or before Week 48 in the Safety Population. Seven patients (5 in the

omaveloxolone group and 2 in the placebo group) discontinued study treatment on or before Week 48 in the FAS Population.

Note that there were 20 patients (10 in each group) with pes cavus enrolled in this study.

***Reviewer's Comment:***

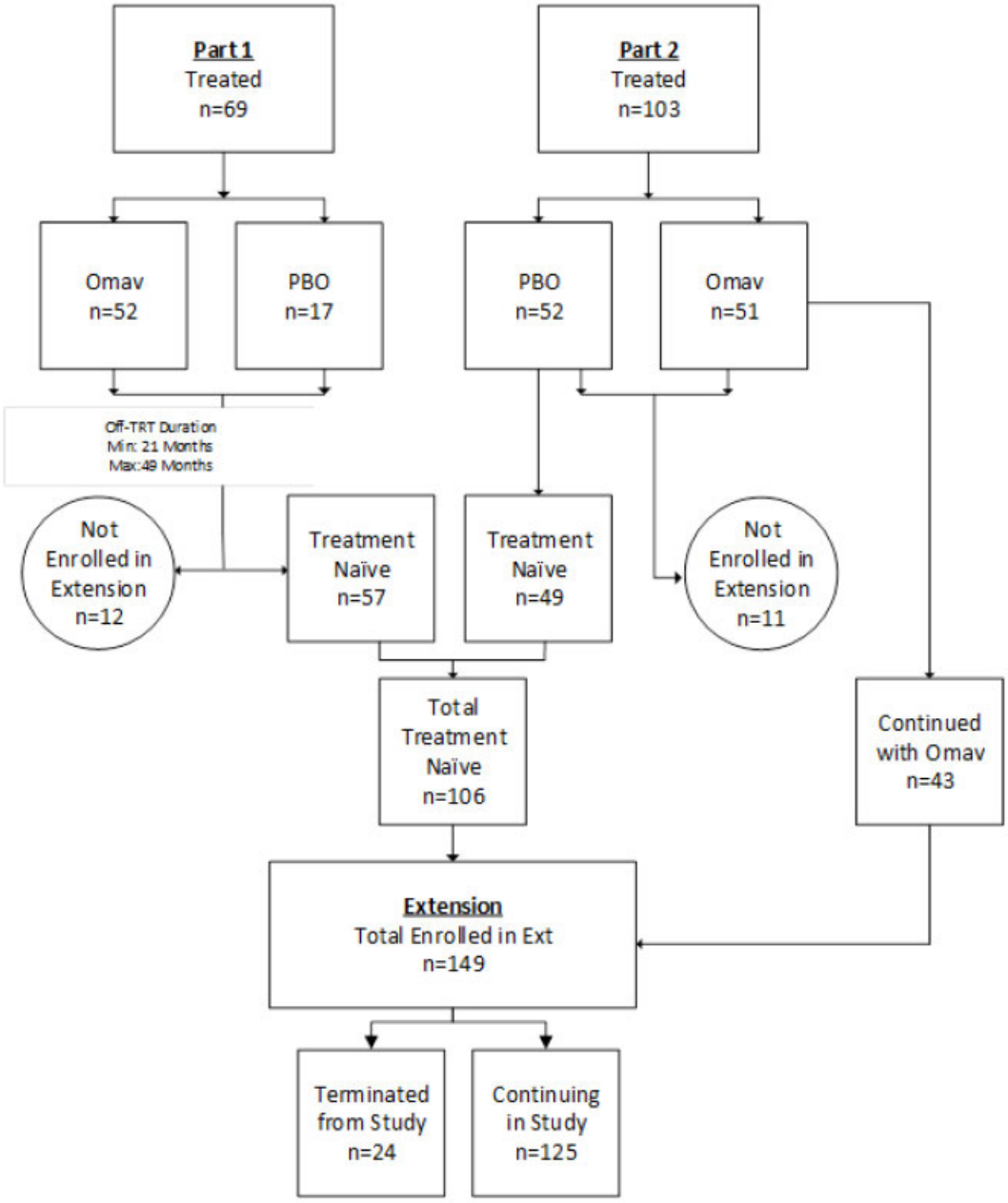
- *As seen in* Table 2*, there were 83 patients without pes cavus that were enrolled in the study, however only 82 patients were included in the FAS Population. Patient* (b) (6) *was not marked as FAS population and discontinued from the study for administrative reasons although had received 6.9 weeks of omaveloxolone 150 mg. A query to the Applicant indicated that this patient did not have any post-baseline mFARS at Week 4 as the patient left due to flight delay/missed flight.*
- *It is not clear why patient* (b) (6) *had all assessments performed except mFARS, therefore showing 34 mFARS completers at Weak 48. Without clear reasons, this could bias the study outcome. A query to the Applicant indicated that this patient was rushing to catch the flight. It appears unclear why the primary endpoint was not assessed prior to other tests including exploratory endpoints. A major protocol deviation was noted.*
- *Patient* (b) (6) *shows treatment was discontinued on Day 131, but study status shows completed through Week 52. A query to the Applicant clarified that there was no specification in the protocol or SAP to exclude patients from the analysis after early treatment discontinuation. The following Study 1402 protocol and SAP sections prespecify data handling for scheduled efficacy assessments: "Protocol Section 8.5.1 (Patient Discontinuation Criteria): Patients who discontinued from study drug in Part 1 or Part 2 should still complete all study visits and undergo all scheduled study assessments, if possible. SAP Section 6.5.4 (Visit Windows): Data analysis and summaries are based on the collection date that is closest to the protocol scheduled target study day and did not specify exclusion after treatment discontinuation." This appears to follow the protocol.*
- *It was also unclear that a patient who discontinued from the study on Day 146 had efficacy measures taken and was also included in the primary analysis (patient* (b) (6) *on placebo). This patient discontinued for the adverse event of erythroses but stayed in the study and completed all scheduled visits and assessments. As mentioned in the previous bullet, patients could undergo study assessments even after discontinuing the study per protocol.*

**Extension Phase:**

A total of 149/172 (86.6%) patients from either Part 1 (N=69) and Part 2 (N=103) enrolled in the extension study.

Out of these, 24 (16%) discontinued from the OLE study and 125 (72.6%) patients continued in the extension study. A summary of the disposition of patients (safety population) in Study 1402 Extension is shown in Figure 3 and Table 3.

**Figure 3 Disposition of Patients in Extension Study (All Randomized Population)**




Source: Extension Interim CSR, page 44

The last patient enrolled in Study 1402 Part 1 completed their last visit on 13 Jun 2017. The extension study was not open until 30 Oct 2018. Thus, all patients from the Study 1402 Part 1 had been off treatment for 21 to 49 months prior to enrolling in the Study 1402 Extension. Since Study 1402 Part 1 patients only received study drug for a short duration (12 weeks) and were off study drug for at least 21 months prior to enrolling in Study 1402 Extension, these patients are treated as treatment naïve upon enrollment in the Study 1402 Extension and for the Study 1402 Extension analysis. These patients were analyzed as Placebo–Omav group. Part 2 patients were enrolled directly after Week 52. Patients were off-treatment for 4 weeks prior to enrolling in the extension phase. Patients randomized to omaveloxolone in Study 1402 Part 2 are analyzed as Omav–Omav group. Patients randomized to placebo in Study 1402 Part 2 are analyzed as placebo–Omav group.

**Table 3 Disposition Summary of Patients in the Extension Phase (All Randomized Population)**

| | Placebo – Omav (N=106) n (%) | Omav – Omav (N=43) n (%) | Overall Omav (N=149) n (%) |
|---|---|---|---|
| All Randomized population in Study 1402 Extension | | | |
| From Study 1402 Part 1 | 57 (53.8) | 0 | 57 (38.3) |
| From Study 1402 Part 2 | 49 (46.2) | 43 (100) | 92 (61.7) |
| Continuing treatment | 85 (80.2) | 40 (93.0) | 125 (83.9) |
| Terminated early from treatment | 21 (19.8) | 3 (7.0) | 24 (16.1) |
| Reason for terminating treatment/Study | | | |
| Withdrawal by subject | 12 (11.3) | 2 (4.7) | 14 (9.4) |
| Adverse event | 8 (7.5) | 1 (2.3) | 9 (6.0) |
| Other (Administrative) | 1 (0.9) | 0 | 1 (0.7) |

Note: 12/69 Patients from Part 1 and 11/103 from Part 2 did not enroll in the extension phase.

The number of patients by study duration in the extension phase is summarized in Table 4.

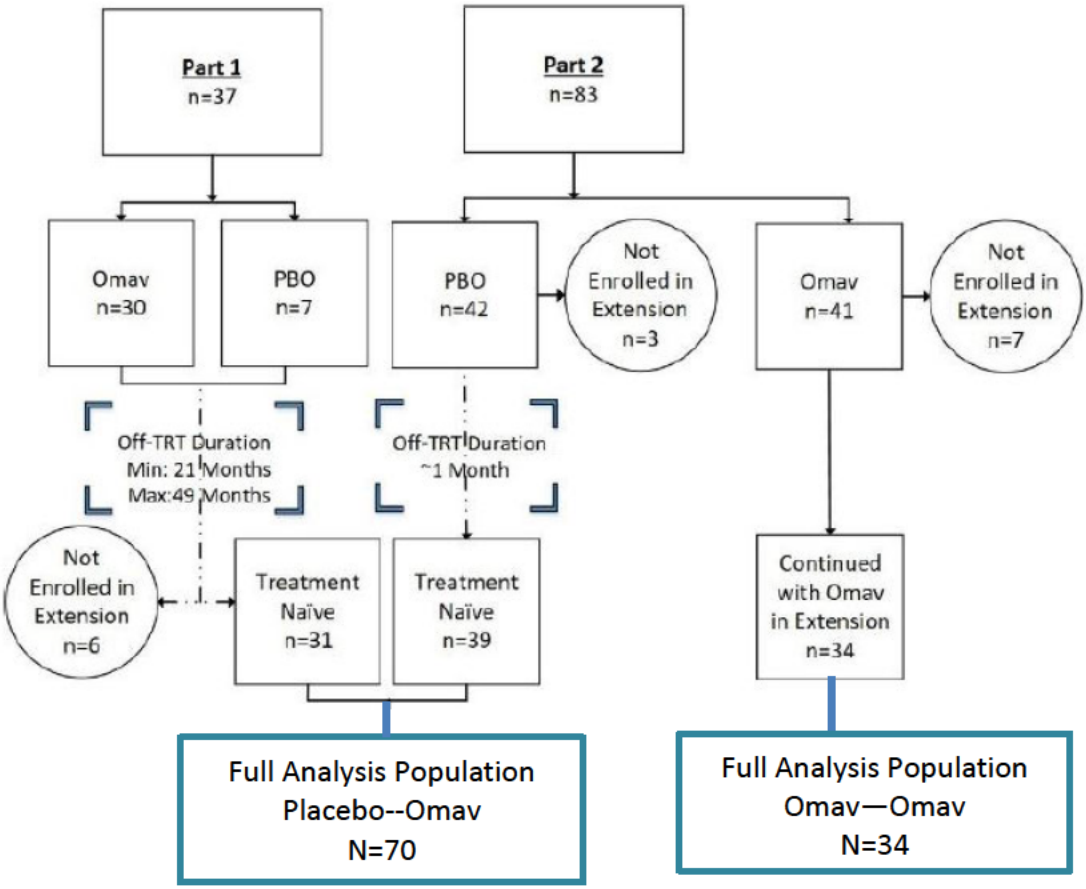
**Table 4 Duration of Exposure During Extension Study**

| Study Week | **Placebo – Omav (N=106) n (%)** | **Omav – Omav (N=43) n (%)** | **Overall Omav (N=149) n (%)** |
|---|---|---|---|
| ≤ 24 weeks | 106 (100%) | 43 (100 %) | 149 (100%) |
| >24 weeks | 95 (89.6%) | 41 (95.3%) | 136 (91.3%) |
| >48 weeks | 92 (86.8%) | 40 (93.0%) | 132 (88.6%) |
| >72 weeks | 85 (65.2%) | 40 (93.0%) | 125 (83.9%) |
| >96 weeks | 68 (64.2%) | 30 (69.8%) | 98 (65.8%) |

Note: All Part 1 patients are grouped in the placebo-Omav group, as were considered treatment naïve due to gap in the treatment period.
Source: Extension CSR Table 14.1.6.3 page 374

Figure 4 shows the disposition of patients in the OLE study in the Full Analysis Population.

**Figure 4 Disposition of Patients in the Extension Study (Full Analysis Population)**




Overall, study medication was interrupted during the OLE in a small proportion of patients (5.4%; 8 patients) because of the COVID-19 pandemic. Five patients (4.7%) in the Placebo–Omav group and 3 patients (7%) in the Omav-Omav group were reported to have a COVID-19–related interruption in omaveloxolone. The COVID-19–related interruption reasons included: insufficient IP supply (reported by 3 patients), medical monitor/sponsor recommendation (reported by 2 patients), other (reported by 2 patients), and patient choice (reported by 1 patient).

The affected visits due to COVID-19 were at Week 24, affecting 13 patients (8.7%), Week 48, affecting 39 patients (26.2%), Week 72, affecting 67 patients (45.0%), Week 96, affecting 52 patients (34.9%), and Week 120 affecting 19 patients (12.8%). At all visits, the most commonly

reported effect was "1 or more procedures not performed." The most common change in the data collection method was use of telephone visit instead of in-clinic visit.

**Protocol Violations/Deviations**

A total of 37 patients had major protocol deviation. Types of major protocol deviations are presented in Table 5. These were related to study procedures (mostly timing of study procedure), inclusion/exclusion criteria, and ICF (signing of the updated version of the ICF).

**Table 5 Major Protocol Deviations-Part 2 (Safety Population)**

| | Omaveloxolone 150 mg (N = 51) | Placebo (N = 52) |
|---|---|---|
| Number of patients with at least 1 major protocol deviation | 20 | 17 |
| **Types of Major Protocol Deviations** | | |
| Study procedures | 12 | 5 |
| Informed consent form | 6 | 8 |
| Inclusion/exclusion criteria | 3 | 7 |
| Excluded concomitant medications | 3 | 2 |
| Drug dispensing | 1 | 0 |

Source: Clinical Study Report Table 6, page 58 and Listing 16.2.2.1

***Reviewer's Comment:***

*These deviations were reviewed. In one case all endpoints were measured except the primary endpoint as the patient was in a rush to catch a flight, leading to missing data. The impact of this missing data on a single patient in the primary analysis remains unclear.*

**Table of Demographic Characteristics**

The baseline demographics are shown in the Table 6. Overall, the proportion of male patients was higher in the placebo group (67%) and the proportion of female patients was higher in the omaveloxolone group (60%). There was a higher proportion of patients <18 year of age in the placebo group (31%), compared to omaveloxolone group (17.5%), and proportionally a higher percentage of patients were ≥18 years of age in the omaveloxolone group (82.5%) compared to placebo group (68%). The remaining demographic characteristics were generally similar for the FAS Population.

**Table 6 Baseline Demographics (FAS and Safety Population)**

| Parameter (units) | Statistics | FAS Population | | Safety Population | |
|---|---|---|---|---|---|
| | | Placebo (N = 42) n (%) | Omaveloxolone 150 mg (N = 40) n (%) | Placebo (N = 52) n (%) | Omaveloxolone 150 mg (N = 51) n (%) |
| Age at Screening (Years) | n | 42 | 40 | 52 | 51 |
| | Mean (SD) | 23.6 (7.79) | 24.2 (6.48) | 24.1 (7.85) | 23.4 (6.08) |
| | Median | 21.0 | 23.0 | 21.0 | 22.0 |
| | Min, Max | 16, 40 | 16, 39 | 16, 40 | 16, 39 |
| Age Group at Screening (Years) | <18 | 13 (31.0) | 7 (17.5) | 15 (28.8) | 9 (17.6) |
| | ≥18 | 29 (69.0) | 33 (82.5) | 37 (71.2) | 42 (82.4) |
| Sex | Female | 14 (33.3) | 24 (60.0) | 17 (32.7) | 31 (60.8) |
| | Male | 28 (66.7) | 16 (40.0) | 35 (67.3) | 20 (39.2) |
| Ethnicity | Hispanic or Latino | 3 (7.1) | 1 (2.5) | 3 (5.8) | 2 (3.9) |
| | Not Hispanic or Latino | 39 (92.9) | 39 (97.5) | 49 (94.2) | 49 (96.1) |
| Race | White | 40 (95.2) | 40 (100.0) | 50 (96.2) | 50 (98.0) |
| | Other | 2 (4.8) | 0 | 2 (3.8) | 1 (2.0) |

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Other baseline disease characteristics are summarized in Table 7.

**Table 7 Baseline Disease Characteristics**

| Parameter (Units) | Statistics | FAS Population | | Pes Cavus Population | |
|---|---|---|---|---|---|
| | | Placebo (N = 42) | Omaveloxolone 150 mg (N = 40) | Placebo (N = 10) | Omaveloxolone 150 mg (N = 10) |
| Weight (kg) | n | 42 | 40 | 10 | 10 |
| | Mean (SD) | 66.3 (17.9) | 68.9 (18.4) | 66.97 (12.3) | 55.92 (7.8) |
| | Median | 64.7 | 65.8 | 65.0 | 57.2 |
| | Min, Max | 40.8, 127.0 | 42.2, 112.3 | 53.4, 90.5 | 41.2, 66.0 |
| BMI ($kg/m^2$) | n | 42 | 40 | 10 | 10 |
| | Mean (SD) | 22.9 (5.1) | 23.6 (5.4) | 22.6 (3.1) | 20.8 (3.1) |
| | Median | 21.9 | 23.3 | 21.4 | 20.7 |
| | Min, Max | 15.6, 40.5 | 17.4, 43.0 | 18.3, 28.6 | 16.1, 24.7 |
| Peak work (watt/kg) | n | 42 | 40 | 10 | 10 |
| | Mean (SD) | 1.18 (0.61) | 1.08 (0.54) | 1.42 (0.66) | 1.09 (0.75) |
| | Median | 1.06 | 1.02 | 1.36 | 0.76 |
| | Min, Max | 0.23, 2.65 | 0.16, 2.05 | 0.74, 2.66 | 0.34, 2.55 |
| mFARS | n | 42 | 40 | 10 | 10 |
| | Mean (SD) | 38.78 (11.03) | 40.95 (10.39) | 34.43 (9.28) | 41.15 (9.93) |
| | Median | 35.70 | 39.15 | 35.60 | 41.45 |
| | Min, Max | 19.8, 63.0 | 24.3, 59.3 | 19.8 (45.4) | 21.5, 52.5 |
| ADL | n | 42 | 40 | 10 | 10 |
| | Mean (SD) | 9.87 (4.83) | 10.74 (4.77) | 9.75 (4.42) | 12.20 (3.39) |
| | Median | 10.00 | 11.50 | 10.00 | 12.25 |
| | Min, Max | 1.0, 20.5 | 2.0, 21.0 | 4.0, 18.0 | 7.0, 18.0 |
| Age at FA onset (Years) | n | 42 | 40 | 10 | 10 |
| | Mean (SD) | 15.1 (5.34) | 15.9 (5.74) | 16.4 (5.34) | 10.9 (3.60) |
| | Median | 15.0 | 15.0 | 16.5 | 11.0 |
| | Min, Max | 5, 30 | 7, 36 | 6, 25 | 5, 16 |
| Years since FA | n | 42 | 40 | 10 | 10 |

| | | | | | |
|---|---|---|---|---|---|
| onset (Years) | Mean (SD) | 4.7 (4.70) | 4.8 (3.98) | 3.0 (2.71) | 4.6 (3.17) |
| | Median | 3.0 | 4.0 | 2.0 | 5.0 |
| | Min, Max | 0, 17 | 0, 16 | 0, 7 | 0, 9 |
| GAA1 repeat length | n | 36 | 31 | 7 | 9 |
| | Mean (SD) | 693.8 (227.19) | 739.2 (214.88) | 585.6 | 736.6 (200.08) |
| | Median | 684.5 | 700.0 | 650.0 | 833.0 |
| | Min, Max | 170, 1270 | 230, 1160 | 280, 850 | 375, 923 |
| GAA1 repeat ≥675, n (%) | No | 18 (42.9) | 10 (25.0) | 4 (40.0) | 4 (40.0) |
| | Yes | 18 (42.9) | 21 (52.5) | 3 (30.0) | 5 (50.0) |
| Ambulatory status, n (%) | Ambulatory | 39 (92.9) | 37 (92.5) | 10 (100) | 8 (80.0) |
| | Non-ambulatory | 3 (7.1) | 3 (7.5) | 0 | 2 (20.0) |
| History of cardiomyopathy, n (%) | No | 30 (71.4) | 21 (52.5) | 7 (70.0) | 4 (40.0) |
| | Yes | 12 (28.6) | 19 (47.5) | 3 (30.0) | 6 (60.0) |
| History of areflexia, n (%) | No | 1 (2.4) | 4 (10.0) | 0 | 0 |
| | Yes | 41 (97.6) | 36 (90.0) | 10 (100) | 10 (100) |
| History of scoliosis, n (%) | No | 10 (23.8) | 11 (27.5) | 5 (50.0) | 0 |
| | Yes | 32 (76.2) | 29 (72.5) | 5 (50.0) | 10 (100) |
| History of scoliosis surgery, n (%) | No | 35 (83.3) | 28 (70.0) | 7 (70.0) | 6 (60.0) |
| | Yes | 7 (16.7) | 12 (30.0) | 3 (30.0) | 4 (40.0) |

***Reviewer's comment:***

*Baseline disease characteristics were generally similar between treatment groups. Although some differences were observed suggesting greater disease severity in the omaveloxolone arm, there were no obvious trends of correlation of these differences to the clinical endpoints suggestive of any bias, except for the age of onset of FA. Definitive conclusions on such biases are difficult to ascertain and are therefore considered potential in nature.*

*The characteristics that suggested higher disease severity in the omaveloxolone arm were the mean baseline mFARs, activities of daily living score (ADL) and number of GAA1 repeat lengths.*

*<u>Impact of baseline mFARS:</u> Mean baseline mFARs was higher in the omaveloxolone arm which could potentially introduce bias into the results. However, outliers were observed in the placebo arm suggesting higher severity in placebo arm in a few patients. (i.e., 3 Patients with baseline mFARS greater than 60 were observed in placebo arm: #* (b) (6) *and no*

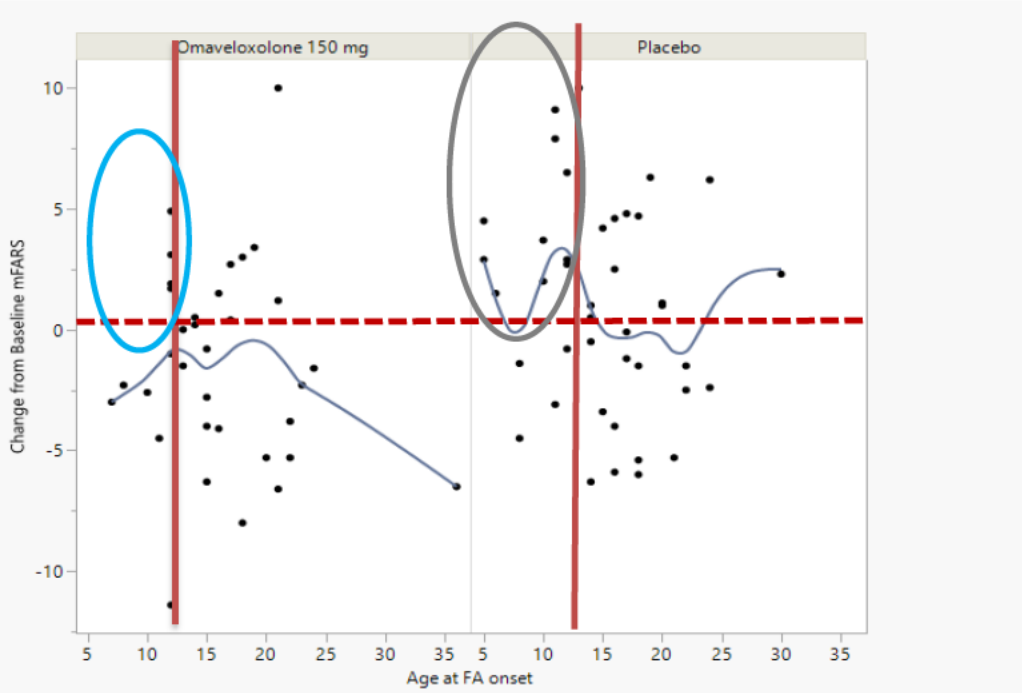
*patients in Omaveloxolone arm had baseline mFARS greater than 60). I explored the relationship between these higher values and change in mFARS at Week 48. No direct correlation was found.*

*Impact of baseline GAA1 Repeat Length: In patients with FA, the overt heterogeneity in age at onset and disease severity is explained partly by GAA1 repeat length. There was also no apparent correlation when looking at the continuum of GAA1 repeat length and observed changes in mFARS or ADL over 48 weeks in either treatment arm. There were 43% of patients in the placebo arm versus 25% in the omaveloxolone arm with GAA1 repeat length <700. Patients with lower GAA1 repeat length have milder disease, suggesting greater disease severity in the omaveloxolone group. However, it is important to note that there were* ***15 missing GAA1 assessments*** *at baseline (9 on omaveloxolone and 6 on placebo); therefore, baseline values in each arm may not be actual differences between arms, and the impact of these baseline differences on the overall efficacy results remain unclear. Rodden et al.[2] have shown that patients with GAA1 >700 represent a subgroup in which the severity of clinical manifestations based on GAA1 repeat length reaches maximum level, and therefore, display limited clinical variability or less heterogeneity in disease progression. Therefore, the outlier placebo patients with higher GAA1 repeats appear less of a concern. However, the same authors have further shown that GAA1 repeat length is predictive of age of onset and frataxin levels in patients with GAA1 length <700, where the disease is more heterogenous. Therefore, patients with missing GAA1 repeat length remains a concern to assess the true balance within treatment groups.*

*Impact of baseline mean age of onset: Although the mean age of onset was not appreciably different between treatment groups, there were some differences in the distribution of age of onset across age range. Younger age of onset of FA generally presents with more severe disease and poorer prognosis. There were 3 patients with age of onset below 7 years in the placebo arm and none in the omaveloxolone arm. In addition, there were 24% of patients with disease age of onset ≤12 years of age in the placebo arm compared to 18% in the omaveloxolone arm. Exploring the relationship of these differences in age of disease onset to the extent of change from baseline in mFARS, a worsening of mFARS was observed in these patients at Week 48 (*Figure 5*). In a small study such as this study, some of these outliers could have the potential to bias the efficacy results; however, these age cutoffs in a small number of patients could be arbitrary.*

[2] Rodden et al, 2022. Clinical Evidence for Variegated Silencing in Patients With Friedreich Ataxia. Neurol Genet. 2022 May 17;8(3): e683.

**Figure 5 Relationship Between Age of Disease Onset versus Change from Baseline in mFARS**




*There were also more patients with a history of cardiomyopathy in omaveloxolone arm (47.5%) compared to placebo arm (28.6%). There were more patients with a history of scoliosis in omaveloxolone arm (30%%) compared to placebo arm (16.7%). The impact of these differences with the potential to bias the outcome was not apparent.*

*Overall, some imbalances favor the omaveloxolone arm and some the placebo arm. Hence, while any imbalances between treatment arms have the potential to bias the outcome in a small study, the direction of the bias in each arm and its overall effect on the primary results are unclear.*

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Compliance was measured by counting pills to determine the number of missed doses from one visit to the next. Patients were also provided a dosing diary to document that the pills were taken as instructed and to document the date and time of dosing. To be considered compliant with study drug, patients could miss no more than 25% of the total planned doses (i.e., 84 doses during Part 2) during the study. In the double-blind phase, the mean compliance was 89.7% for the placebo group and 86.2% for the omaveloxolone group.

In the extension phase, the Mean (SD) compliance was 87% (±16) for the Placebo-Omav group, 89 (±11) for the Omav-Omav group, and 87% (±15) for the Overall Omav group.

The most common concomitant medications in the omaveloxolone group and placebo group, respectively during the study were ibuprofen (27 [52.9%] and 21 [40.4%]) and paracetamol (18 [35.3%] and 15 [28.8%]). There were no meaningful differences in the use of other concomitant medications.

No rescue medication was given.

**Efficacy Results – Primary Endpoint**

**Change in mFARS Score at Week 48**

**Applicant's Primary Analysis:** In the prespecified primary analysis in the FAS population, the Applicant reports a statistically significant improvement in mFARS at Week 48 of -2.41 points (on a scale 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 experienced a worsening from baseline of mFARS of 0.85 points at Week 48 (Table 8).

Table 8 also includes analyses on All randomized patients in the right two columns for completeness, which also shows a nominally significant improvement of -1.94 points in the omaveloxolone arm compared to placebo (nominal p=0.0331).

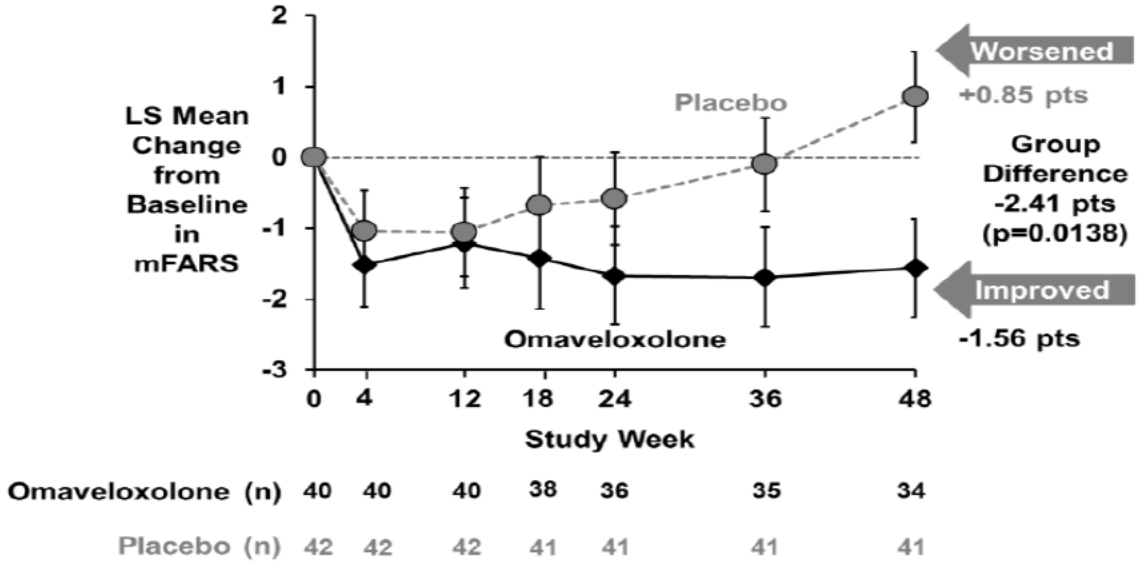
**Table 8 Applicant's Primary Analysis: mFARS Least Squares Mean Change from Baseline at Week 48 (FAS) (All randomized patients shown in the right 2 columns)**

| | | Full Analysis Population Without Pes Cavus (Primary Analysis) | | All Randomized Patients | |
|---|---|---|---|---|---|
| Visit | Statistic | Placebo (N = 42) | Omaveloxolone 150 mg (N = 40) | Placebo (N = 52) | Omaveloxolone 150 mg (N = 51) |
| Baseline | n | 42 | 40 | 52 | 51 |
| | Mean (SD) | 38.77 (11.026) | 40.95 (10.394) | 37.94 (10.76) | 40.85 (10.148) |
| | Median | 35.65 | 39.15 | 35.65 | 39.5 |
| | Min, Max | 19.8, 63.0 | 24.3, 59.3 | 19.8, 63.0 | 21.5, 59.3 |
| Week 48 | n | 41 | 34 | 50 | 42 |
| | Mean (SD) | 39.54 (11.568) | 39.17 (10.019) | 38.76 (11.508) | 39.44 (11.102) |
| | Median | 38.70 | 38.10 | 37.45 | 39.60 |
| | Min, Max | 18.3, 64.5 | 26.0, 56.7 | 17.7, 64.5 | 9.5, 60 |
| Week 48 | LS Mean[a] difference | -- | -2.41 (0.955) | | -1.94 (0.894) |
| | 95% CI | -- | -4.31, -0.51 | | -3.71, -0.16 |
| | p-value | -- | 0.0138 | | 0.0331 |

Source: Amended CSR pages 8, 240, 246; CSR pages 66, 440, 452 (Confirmed by FDA Statistics Reviewer)

The Applicant reports a time dependent change in mFARS, where significant improvements from baseline were observed in mFARS only by Week 24 as shown in Figure 6.

**Figure 6 mFARS Change from Baseline by Visit (FAS Population)**




Source: Applicant's Amended CSR page 10

***Reviewer's Analyses/Comment:***

*The mFARS mean (SD) scores at each visit are shown in Table 9.*

**Table 9 mFARS Mean scores by Visit**

| | Omaveloxolone 150 mg | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| Analysis Visit | N | Mean | Std Dev | Median | N | Mean | Std Dev | Median |
| Baseline | 40 | 40.95 | 10.39 | 39.15 | 42 | 38.78 | 11.03 | 35.65 |
| Week 4 | 40 | 39.31 | 11.02 | 39.10 | 42 | 37.75 | 10.24 | 36.00 |
| Week 12 | 40 | 39.72 | 11.8 | 39.60 | 42 | 37.66 | 11.22 | 37.35 |
| Week 18 | 38 | 39.53 | 11.47 | 38.35 | 41 | 37.94 | 12.33 | 35.30 |
| Week 24 | 36 | 39.13 | 10.98 | 38.25 | 41 | 38.04 | 11.68 | 36.00 |
| Week 36 | 35 | 39.17 | 11.04 | 38.00 | 41 | 38.57 | 10.97 | 37.50 |
| Week 48 | 34 | 39.17 | 10.02 | 38.10 | 41 | 39.54 | 11.57 | 38.70 |

*As seen, there is a 1-point drop in mFARS in both treatment arms at Week 4 which stays maintained through Week 48 in the omaveloxolone arm but stays maintained in the placebo arm till week 24 and slowly rises up to 1-point in the placebo arm at Week 48. It is puzzling that the effect starts at Week 4 and also strange that the response wears-off in the placebo group after 36 weeks, although could potentially be explained by a placebo response which wears off*

*as the disease progresses. At 36 weeks the mean mFARS score in the placebo arm is back at baseline value. The reason for this time dependent effect is unclear. A confounding factor could be the higher percentage of missing data in the omaveloxolone arm (15%) compared to placebo arm (2.3%).*

*The mean change from baseline raw statistics (mean-SD) is shown in Table 10 and* ***Error! Reference source not found.****. Patients randomized to omaveloxolone had a mean improvement from baseline in mFARS of -1.46 points, while patients randomized to placebo experienced a worsening from baseline of mFARS of 0.90 points at Week 48, with a treatment difference of -* ***2.34 points****.*

**Table 10 Observed Mean Change from Baseline- raw statistics**

| Analysis Visit | Omaveloxolone 150 mg Mean (SD) | Placebo Mean (SD) |
|---|---|---|
| Baseline | 0 | 0 |
| Week 4 | -1.64 (3.80) | -1.03 (3.94) |
| Week 12 | -1.24 (4.31) | -1.12 (4.18) |
| Week 18 | -1.25 (3.99) | -0.71 (4.97) |
| Week 24 | -1.64 (4.41) | -0.60 (4.25) |
| Week 36 | -1.61 (4.65) | -0.07 (4.04) |
| **Week 48** | **-1.46 (4.21)** | **0.90 (4.30)** |

**Applicant's Pre-specified Sensitivity Analyses:**

**Distribution of Change from Baseline in mFARS:**
The Applicant's pre-specified analysis showed that the distribution of changes from baseline in mFARS was significantly different between omaveloxolone and placebo (p = 0.028) at Week 48, with greater proportion of omaveloxolone patients who had improvements in mFARS (mFARS ≤0) compared to placebo.

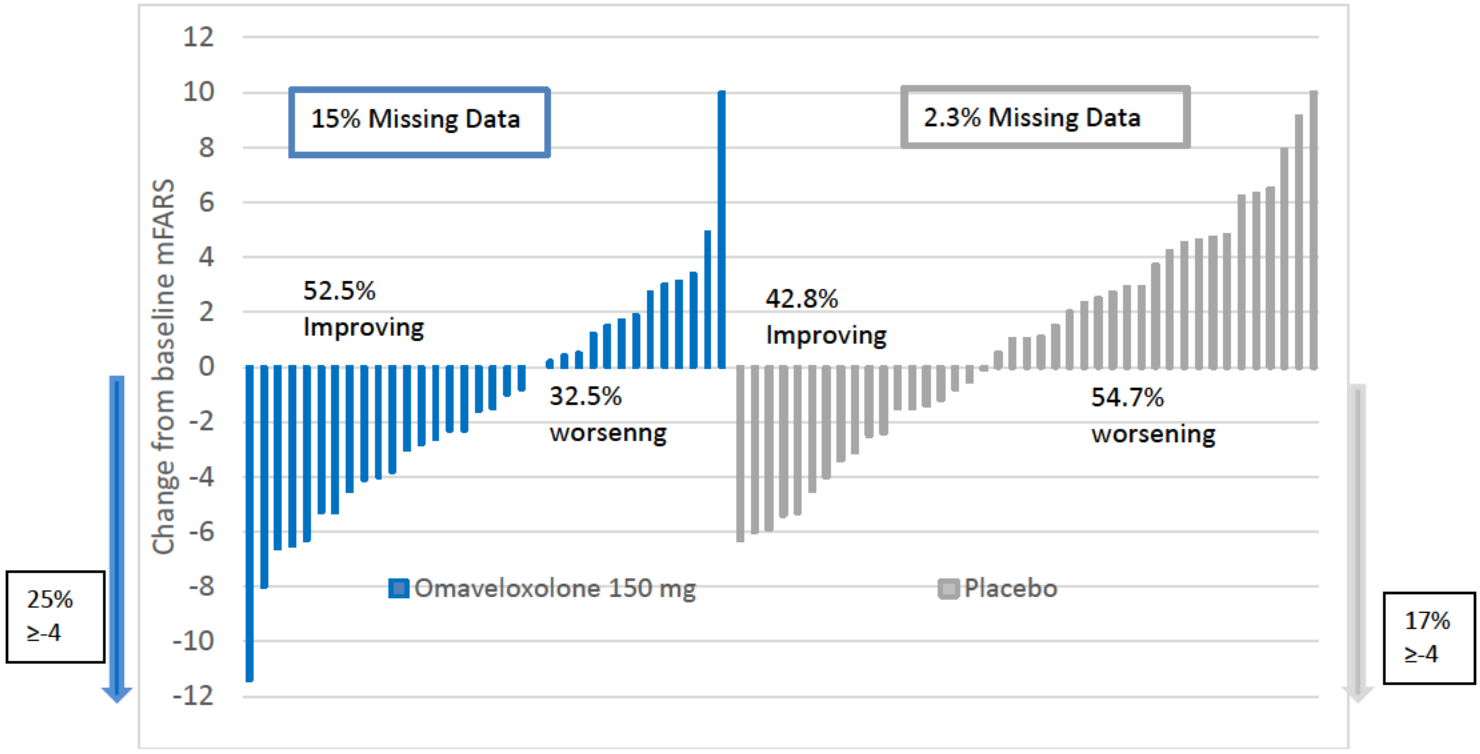
**Change from baseline in mFARS in other populations:**
The Applicant also showed change from baseline in mFARS in other populations:

- In All Randomized patients (ARP) omaveloxolone treatment significantly improved mFARS by -1.94 points relative to that for placebo (n = 103; p = 0.0331).
- In patients *with* pes cavus, omaveloxolone numerically improved mFARS relative to placebo by -1.25 points; the change was not statistically significant (n = 20; p = 0.5128)
- In patients <18 years of age, omaveloxolone improved mFARS by -1.69 points at Week 48, resulting in a placebo-corrected improvement of -4.21 points (n = 20; p = 0.0532)

***Reviewer's Comment:***

*The distribution of change from baseline in shown in* Figure 7.

**Figure 7 Distribution of Change from Baseline (FAS Population)**




Reviewer Analysis

*While a greater proportion of patients in the omaveloxolone arm (52.50%) did show improvement compared to placebo arm (42.8%), the 15% missing data in the omaveloxolone arm and 2.3% in the placebo arm decreases the persuasiveness of these data. However, a modest treatment effect favoring omaveloxolone can be speculated as only one placebo patient had missing Week 48 data, who had shown improvement up to Week 12. The 15% missing in the omaveloxolone group could fall into either improving or worsening groups; however, with only a few patients missing data in the placebo group suggests that the number of patients worsening on placebo is larger than the number of patients on improving on placebo. A lesser percentage (32.5%) of patients in the omaveloxolone arm showed worsening (mFARS >0) compared to placebo arm (54.7%). More patients have worsening of greater than 4-points in the placebo arm, and there is one subject with a maximum worsening of 10-points in the omaveloxolone arm as well which may decrease the overall treatment benefit seen. A total of*

*25% of the patients on omaveloxolone had improvement of ≥4 points, compared to 17% of patients on placebo.*

- *Dr. Jinnan Liu (Statistics Reviewer) and the Applicant have performed sensitivity analysis to address missing data that show a modest treatment effect in favor of omaveloxolone. The results of the sensitivity analyses were consistent with those of the primary analyses for the following analyses. Control-based multiple imputation, LS mean difference -2.15 (p = 0.0386)*
- *Treatment-based multiple imputation LS mean difference -2.38(p = 0.014)*

*Dr. Jinnan Liu's own sensitivity analysis using patients with complete (all 6 data points) data only also provided results consistent to the primary analyses, LS mean difference -1.46 (p=0.0178). Please refer to statistic review for further details on these analyses.*

*The change from baseline during the study visits for patients that have missing data are shown in Table 11 with the reasons for missing the assessment. Four out of the 6 on omaveloxolone trended towards worsening and 1 placebo trended towards improving. The mFARS value fluctuates between visits such that the direction of change at Week 48 is difficult to gauge. However, the worst case controlled base multiple imputation suggest a modest treatment benefit on omaveloxolone (p=0.04) and a treatment base multiple imputation had a p=0.022.*

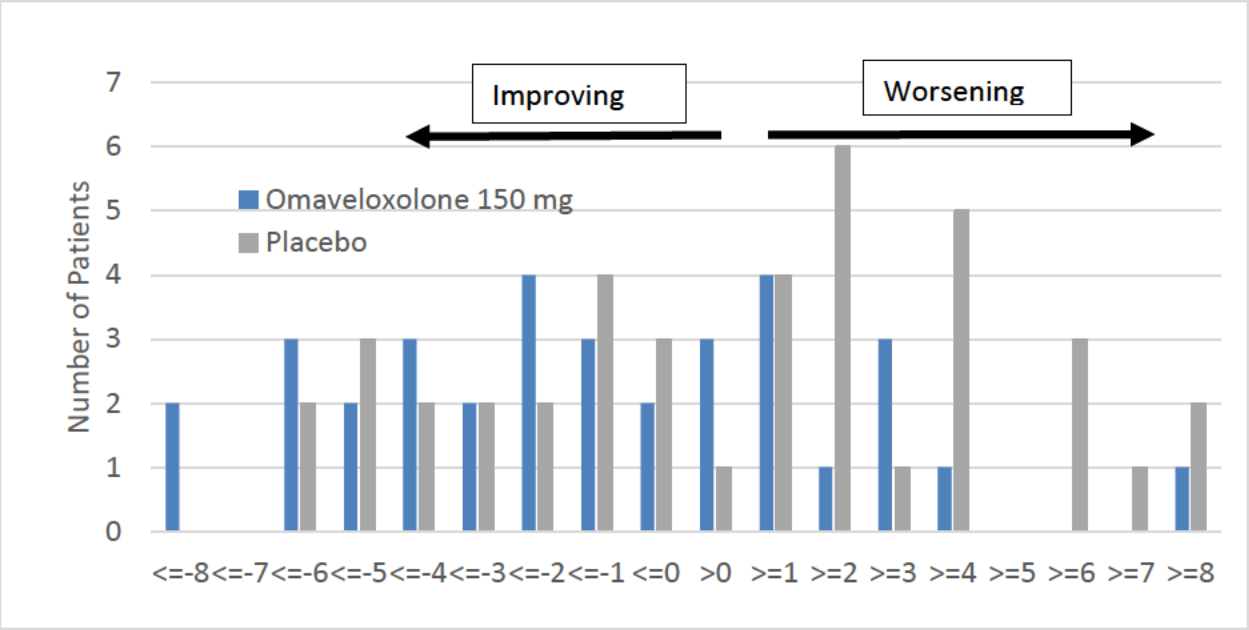
**Table 11 Patients who have Missing mFARS due to Discontinuation.**

| Trt | Patient | Reason | Exposure (Weeks) | Baseline | Change from Baseline[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Wk 4 | Wk 12 | Wk 18 | Wk 24 | Wk 36 | Wk 48 |
| Pbo | (b) (6) | Atrial Fibrillation Withdrew consent | 8.1 | 44.5 | -4.5 | -4.8* | - | - | - | - |
| Omav | | Withdrew consent | 9.1 | 58 | -13 | -2.3* | - | - | - | - |
| | | Administrative | 12.1 | 30.4 | -5.4 | -4.7 | - | - | - | - |
| | | Ventricular tachycardia Withdrew consent | 2.4 | 27.3 | -1.1 | -5* | -1.6* | - | - | - |
| | | Withdrew consent | 20.1 | 54.7 | 3.3 | 7.3 | 2.3 | - | - | - |
| | | Patient too fatigued to perform test | 18.7 | 40.3 | -2.8 | -3.5 | -5 | -6.1* | - | - |
| | | Patient rushed to catch a flight | 47.9 | 46.1 | -3.8 | 2.9 | 0.2 | -8.1 | 0.9 | - |

*Note: * = post-treatment mFARS assessed after drug washout (more than 14 days after date of last dose)*

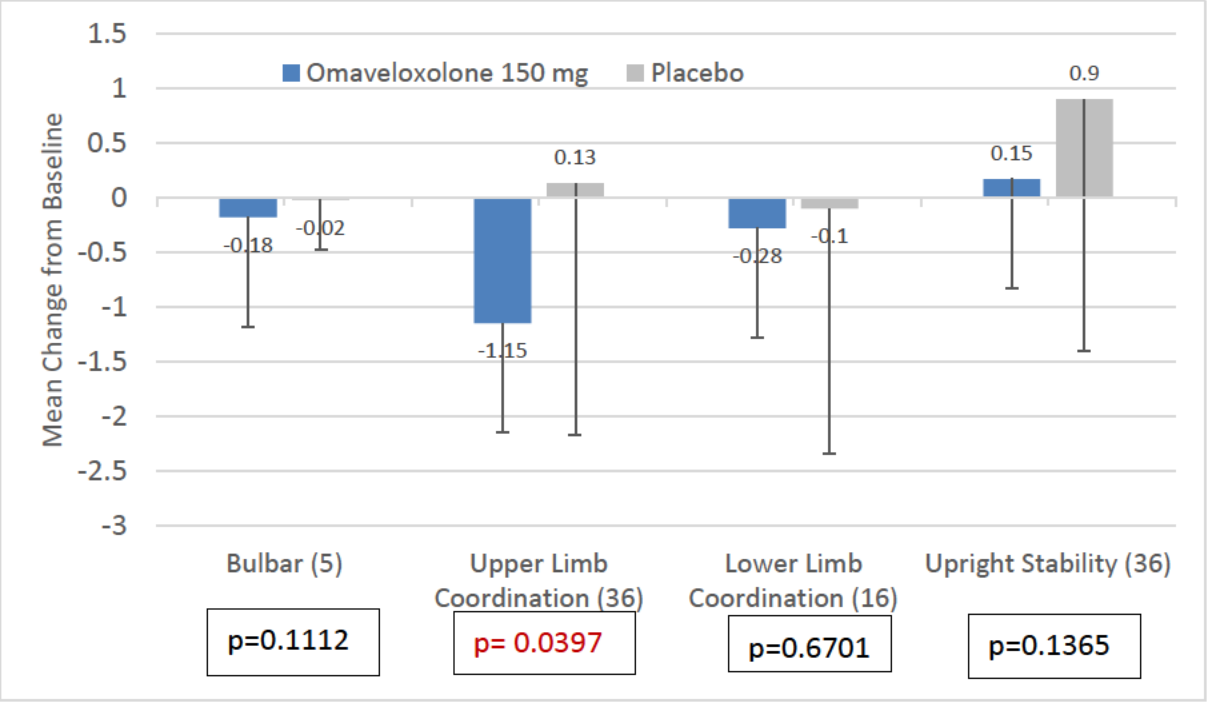
*I have also explored the distribution of change in mFARS at Week 48 based on change categories by 1-point difference (Figure 8). However, the missing data is the confounder in all interpretations of the results decreasing the persuasiveness of the results in a small study. The majority of the patients worsening belong to two sites [1875 (n=7) and site 1914 (N=4)].*

**Figure 8 Change Category in mFARS at Week 48 (FAS Population)**




*I also explored mean changes within each domain of mFARS as shown in Figure 9. Bulbar (assessing Cough and Speech) and Lower Limb Coordination Domains (assessing Heel-Shin Slide and Heel-Shin Tap) had negligible difference between treatment arms, though the direction favored omaveloxolone arm. It is noteworthy that the baseline scoring for Bulbar was between normal and mild (score 0 and 1) for all patients, therefore it is likely insensitive to show any further improvement in 48 weeks of treatment. Only nominally significant difference was observed in the upper limb coordination domain within mFARS* ***based on Applicant's analyses****. There were no apparent baseline differences between treatment arms in the mFARS domains that could favor treatment arm.*

**Figure 9 Mean Changes in mFARS Domains (FAS Population)**




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

*I also explored the mFARS scores based on GAA1 repeat length subgroups (<675 or ≥675). Data suggests greater worsening in placebo patients with GAA1 ≥ 675 (Table 12). Given the high inter-individual variability and the small number of patients in each group, any conclusions of such exploratory analyses are not conclusive. Missing GAA1 length data on several patients is another confounder in such analyses.*

**Table 12 Mean Change from Baseline in mFARS scores by GAA1 Repeat Length Category**

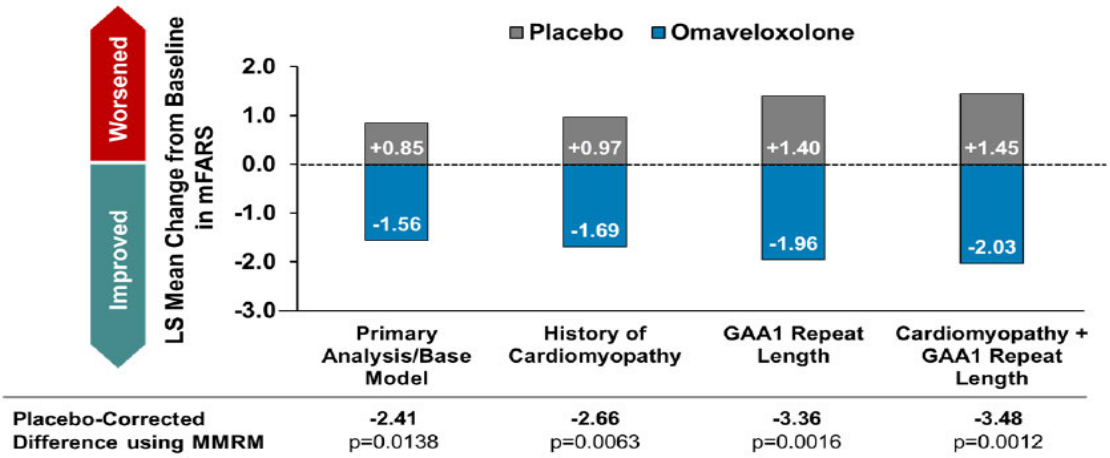
| | GAA1 <675 | | GAA1≥ 675 | | Missing GAA1 | |
|---|---|---|---|---|---|---|
| mFARS | Omav (N=9) | Placebo (N=18) | Omav (n=19) | Placebo (N=18) | Omav (n=6) | Placebo (N=7) |
| (Mean ± SD) | -0.64 ± 3.79 | 0.54 ± 4.03 | -2.28 ± 3.94 | 2.04 ± 4.57 | -0.02 ± 5.63 | -1.88 ± 3.37 |

**Applicant's Post Hoc Analyses in mFARS:**

Applicant performed several post-hoc analyses of change from baseline in mFARS using MMRM methodology with additional baseline covariates added that show nominally positive p-values as shown in

Figure 10.

**Figure 10 Applicant's post-hoc analyses of mFARS**




Source: Amended Clinical Study Report Page 19

**Data Quality and Integrity**

There did not appear to be any concerns with data quality and integrity. However, during the review cycle, in August 2022, the Applicant informed the Agency that a data entry error in Section E in subpart 2a, 2b, 3a and 3b of the mFARS scale was identified that occurred in a single site that participated in Part 1, Part 2, and the extension phase of Study 1402. These specific subparts of the mFARS Section E Upright Stability exam required the investigator to make 3 assessments of the time the patient could stand if the patient could not stand for at least one minute on the first try. According to the mFARS instructions, if trial 1 is at least one minute, no further trial (trial 2 and trial 3) was required. However, if trial 1 is less than one minute, both trial 2 and trial 3 were to be attempted. If trial 1 was greater than one minute, the score for the item would be a zero, and if trial 1 was less than one minute, the score for the item would be the average of all three trials. One clinical site (#1875) did not consistently perform the third timed trial when the patient could not stand for at least one minute on the first trial but could stand for at least one minute on the second trial. The investigator accurately noted when the third trial was not attempted, but the site sometimes incorrectly recorded the third trial value as "0" rather than missing. This caused a small error in the computation of the mFARS score because the average value for the item was computed using a 3 in the denominator rather than a 2.

This data entry error was made for both placebo (n=5) and omaveloxolone (n=4) patient data in

Part 2 (FAS population) and omaveloxolone-to-omaveloxolone (n=6) and placebo-to-omaveloxolone (n=10) patient data from the extension study.

The investigation determined that the error impacted 13 mFARS scores (14 mFARS data entries) out of a total of 792 mFARS assessments (1.6%) in the All Randomized Population, 8 mFARS scores (9 mFARS data entries) out of a total of 635 mFARS assessments (1.3%) in the Full Analysis Set in Study 1402 Part 2, and impacted 16 mFARS scores (16 mFARS data entries) out of 725 mFARS assessments (2.2%) in Study 1402 Extension. The Applicant further performed sensitivity analyses applying a "worst case" imputation of data for the missing 3rd trial value. The impact of this error appears small.
The originally calculated primary endpoint in Study 1402 Part 2 was a treatment difference in mFARS of -2.40 (p=0.0141), and the corrected results for the primary endpoint in Study 1402 Part 2 was a difference in mFARS of -2.41 (p=0.0138). Corrected data have been used in all Tables and Figures in this review.

**Efficacy Results – Secondary and other relevant endpoints**

**Patient Global Impression of Change and Clinical Global Impression of Change at Week 48:**

**Applicant's Secondary Analyses**

Mean PGIC and CGIC scores were not statistically different from placebo but PGIC and CGIC scores numerically favored omaveloxolone arm in the FAS population. LS Mean treatment difference for PGIC was -0.43 (p=0.1300) and that for CGIC was -0.13 (p=0.5259). Higher scores in PGIC and CGIC indicate worsening.

In the All-Randomized population, a nominally positive p-value was observed with PGIC (p=0.0282), however CGIC remained negative in this population.

**Table 13 Applicant's Key Secondary Analysis: Patient Global Impression of Change and Clinical Global Impression of Change Responses at Week 48**

| | Full Analysis Set | | All Randomized Population | |
|---|---|---|---|---|
| | Placebo (n = 42) | Omaveloxolone (n = 40) | Placebo (n = 52) | Omaveloxolone (n = 51) |
| **PGIC** | | | | |
| LS mean | 4.32 | 3.89 | 4.47 | 3.91 |
| LS mean difference between treatment | - | -0.43 (p = 0.1300) | - | -0.56 (p = 0.0282) |
| **CGIC** | | | | |
| LS mean | 4.06 | 3.92 | 4.18 | 3.90 |
| LS mean difference between treatment | - | -0.13 (p = 0.5259) | - | -0.28 (p = 0.1328) |

Source: Clinical Study Report Page 75

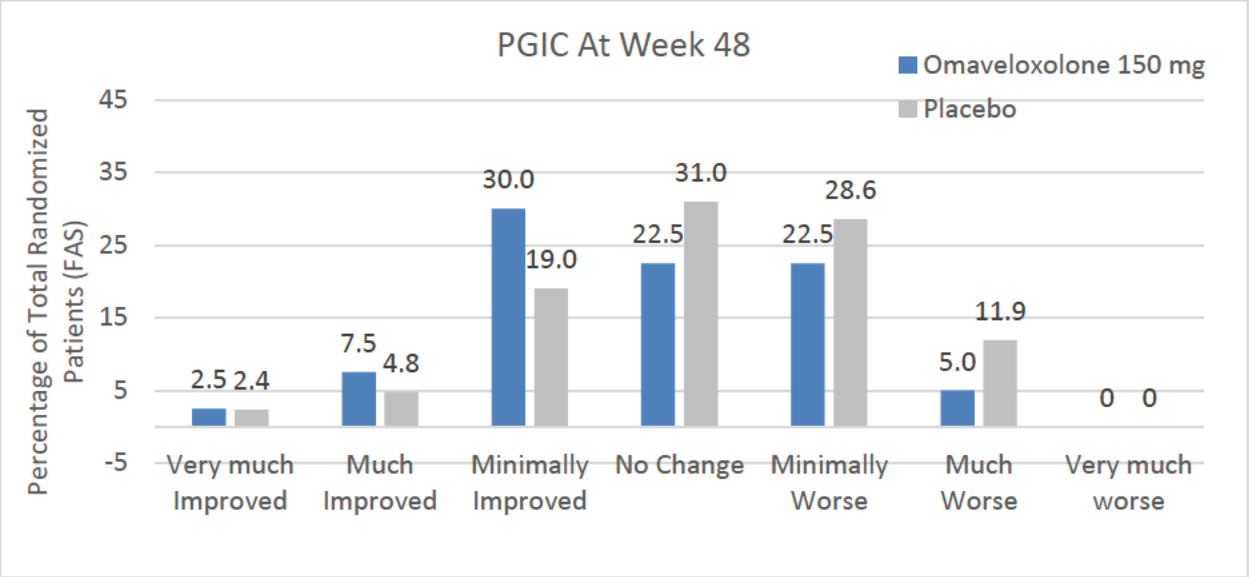
***Reviewer's Comment:***

*The number of patients at week 48 with PGIC and CGIC data were different from that available for mFARS. The number of patients on omaveloxolone with PGIC and CGIC data were 35 (34 for mFARS) and 41 for placebo (41 for mFARS).*

*The categorical responses of PGIC and CGIC are shown in Figure 11 and Figure 12. As seen in the Figures, more patients rated responses of 'Minimal Improvement' with omaveloxolone (30%) on PGIC and CGIC assessments compared to placebo arm (19% and 24% respectively). Also noteworthy is that the majority of the patients showed minimal improvement in both PGIC and CGIC, with few patients rating 'Much' or 'Very Much Improved'. A confounder here too is the higher missing data in the omaveloxolone arm.*

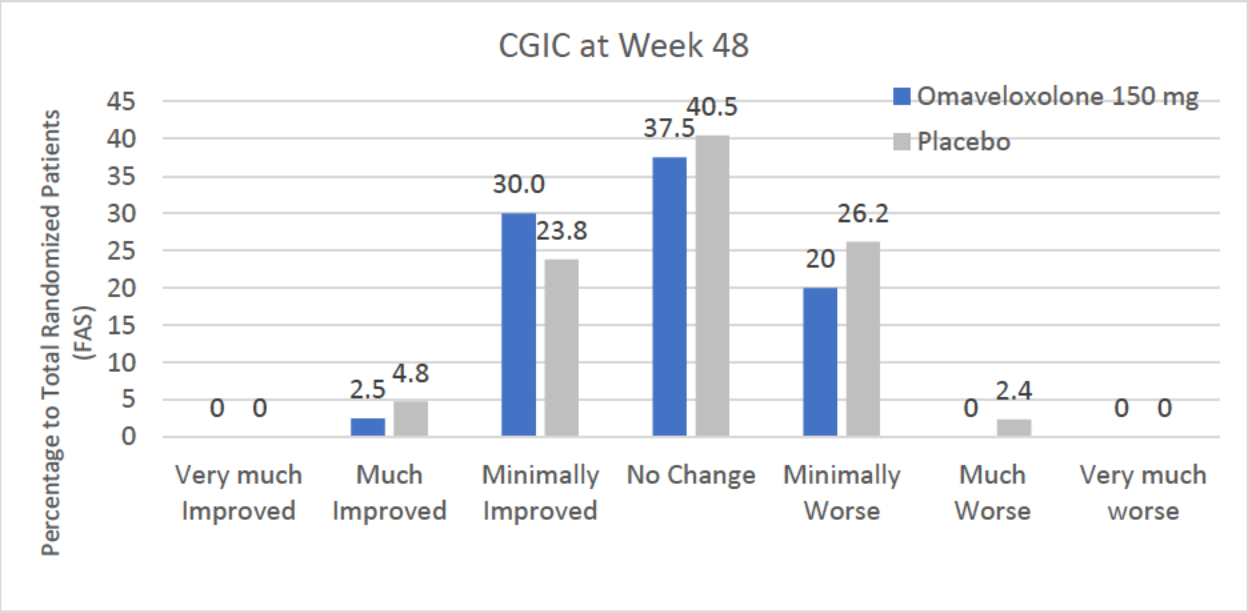
*The PGIC and CGIC ratings do suggest greater worsening in the placebo arm.*

**Figure 11 Categorical Responses of PGIC at Week 48 (FAS Population)**




*Reviewer Analysis*

**Figure 12 Categorical Responses of CGIC at Week 48 (FAS Population)**

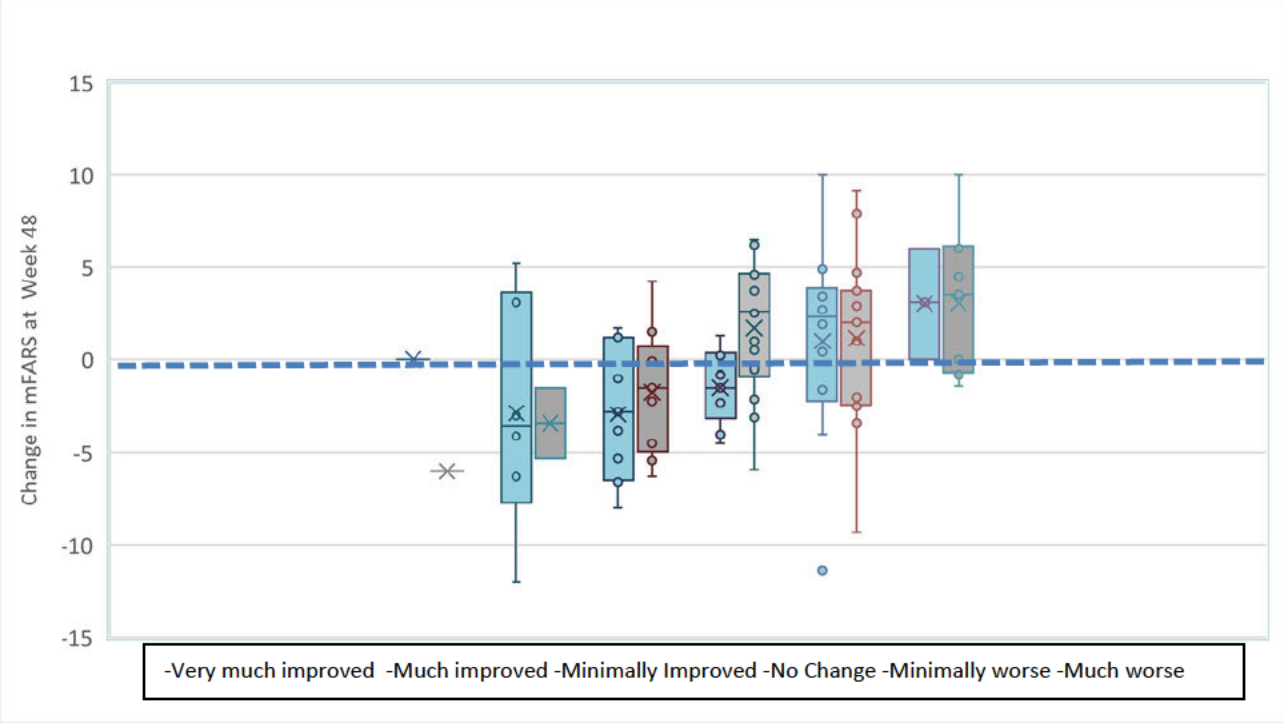



*Reviewer Analysis*

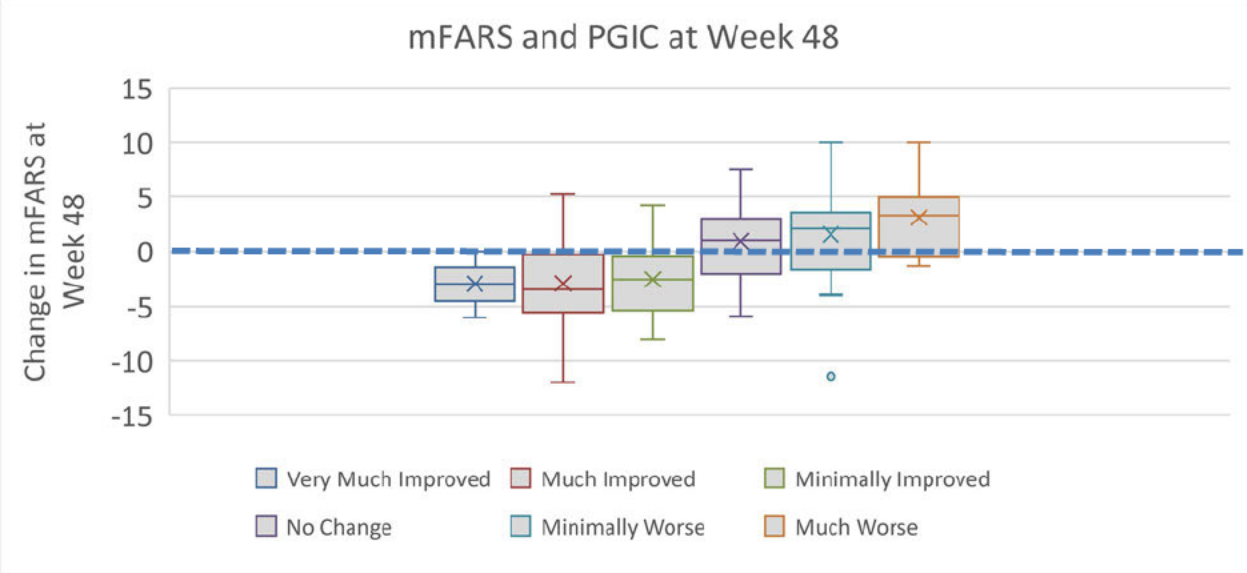
The following box plot of change in mFARS vs PGIC shows that changes (improvement or worsening) in mFARS scores generally corresponded to ratings of improvement or worsening in

PGIC when compared across treatment groups or overall without regards to treatment groups. (Figure 13 A, Figure 13 B).

**Figure 13 (A) Box Plot of Change in mFARS vs PGIC Ratings for Omaveloxolone and Placebo arms**




**(B) Box Plot of Change in mFARS vs PGIC Ratings Overall Without Regard to Treatment Arm**




*Reviewer Analysis*

**Other Secondary Endpoints:**

The other secondary endpoints in the study were analyzed using a fixed-sequence hierarchical approach to maintain the family-wise overall Type I error rate of 0.05 in the FAS population.

Omaveloxolone treatment did not statistically significantly improve the 9-HPT, 25-foot timed walk test, frequency of falls, or peak work relative to placebo. Numerically, frequency of falls favored omaveloxolone. During the 48-week treatment period, omaveloxolone patients reported a median of 3.0 falls (range, 1 to 89), while placebo patients reported a median of 8.5 falls (range, 0 to 131).

ADL scores at Week 48 were last in the hierarchy of statistical testing and showed improvement from baseline with omaveloxolone treatment that reached nominal statistical significance relative to placebo (p = 0.04).

The Applicant asserts that the secondary endpoints are not ideally powered. The Applicant's statistical analysis of secondary endpoints is shown in Table 14.

**Table 14 Applicant's Analysis of Other Secondary Efficacy Endpoints (Full Analysis Set)**

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

Source: Clinical Study Report, Page 79

In addition, the Applicant included an exploratory endpoint of Impression of change based on video of the 25-foot walk test, and reports no treatment-related trends were observed that could affect the quality of life for patients with FA (p=0.1988).

I further reviewed the Activities of Daily Living as the nominal p-value was 0.04 and is a clinically meaningful endpoint.

**Activities of Daily Living (ADL)**

ADL has nine components, each of which are scored between 0-4, with 0 being normal and 4 being worst. The Applicant's least square mean change from baseline from Mixed Model Repeated Measure analysis of individual components of Activities of Daily Living in the FAS population is shown in Table 15. Each component numerically favored omaveloxolone arm, although very small improvements were observed in speech, swallowing, cutting food, personal hygiene, dressing, quality of sitting position, and walking. Falling and Bladder function showed less worsening in the omaveloxolone arm compared to placebo arm. None of the components, except Quality of Sitting Position, showed nominally significant treatment difference between groups (p=0.005).

**Table 15 ADL Components at Week 48 (FAS Population)**

| ADL Component | LS Mean Change ± SE from Baseline | | LS Mean Difference ± SE Between Treatment Groups |
|---|---|---|---|
| | Placebo (n = 42) | Omaveloxolone (n = 40) | |
| Speech | 0.05 ± 0.102 | 0.03 ± 0.109 | -0.01 ± 0.152 (p = 0.962) |
| Swallowing | 0.11 ± 0.101 | -0.08 ± 0.108 | -0.18 ± 0.150 (p = 0.225) |
| Cutting Food and Handling Utensils | -0.02 ± 0.083 | -0.10 ± 0.088 | -0.07 ± 0.124 (p = 0.553) |
| Dressing | 0.09 ± 0.099 | -0.03 ± 0.106 | -0.11 ± 0.147 (p = 0.444) |
| Personal Hygiene | 0.13 ± 0.105 | -0.02 ± 0.112 | -0.15 ± 0.156 (p = 0.356) |
| Falling | 0.10 ± 0.126 | 0.04 ± 0.135 | -0.06 ± 0.189 (p = 0.756) |
| Walking | 0.18 ± 0.086 | 0.00 ± 0.092 | -0.19 ± 0.128 (p = 0.149) |
| Quality of Sitting Position | 0.22 ± 0.076 | -0.11 ± 0.081 | -0.32 ± 0.113 (p = 0.005) |
| Bladder Function | 0.26 ± 0.076 | 0.13 ± 0.100 | -0.13 ± 0.140 (p = 0.341) |

Source: Clinical Study Report, Table 14.2.33.1, Page 1592

In the ARP population, Quality of Sitting Position was also the only component that showed nominal significant difference between treatment groups (-0.26 ± 0.107, p=0.0175).

I also explored the percentage of patients worsening, improving, and staying stable in the two treatment groups by assessing a shift of 1-point in ADL score in either direction as shown in Table 16. These categories directionally favor omaveloxolone arm.

**Table 16 Change Categories in Change from Baseline ADL (Shift of 1 point in Total ADL score)**

| Total ADL | Omaveloxolone (N=36/40) | Placebo (N=41/42) |
|---|---|---|
| Missing | 4 (10%) | 1 (2.4%) |
| Worsened (CFB ≥ 1) | 16 (40%) | 26 (62%) |
| Stable (CFB = 0) | 7 (17.5%) | 9 (21%) |
| Improve (CFB ≤ 1) | 13 (32.5%) | 6 (14%) |

Percentages calculated from total randomized

I also explored the ADL scores based on GAA1 repeat length subgroups (<675 or ≥675). Given the high inter-individual variability and the small number of patients in each group, any conclusions of such exploratory analyses may not be conclusive. Missing GAA1 length data is another confounder in such analyses. This analysis suggests greatest worsening in the placebo group in patients with GAA1≥ 675 and missing GAA1 repeat information (Table 17).

**Table 17 Mean Change from Baseline in Total ADL scores by GAA1 Repeat Length Category**

| | GAA1 <675 | | GAA1≥ 675 | | Missing GAA1 | |
|---|---|---|---|---|---|---|
| Total ADL | Omav (N=10) | Placebo (N=18) | Omav (n=19) | Placebo (N=18) | Omav (n=7) | Placebo (N=7) |
| (Mean ± SD) | -0.3 ± 3.5 | 0.56 ± 2.41 | -0.03 ± 3.02 | 1.58 ± 2.22 | -0.643 ± 2.7 | 2 ± 3.93 |

**Study 1402 Part 1**

Part 1 was a dose ranging study that was not powered (N=6 at each lower dose, N=12 at 160 mg and N=10 at 300 mg) to provide reliable results of efficacy.

The primary endpoint peak workload during maximal exercise testing was not statistically significantly different across any doses in the ITT population without regard to pes cavus status.

The secondary endpoint in Part 1 was change from baseline in mFARS at Week 12, which was also negative across all doses, however the greatest reduction was observed at 160 mg dose. The sample size is too small to draw reliable conclusions on effectiveness from this study. In a post hoc analysis, the Applicant showed the maximum reduction in mFARS at the 160 mg dose in patients without pes cavus. However, this was based on 4 subjects on omaveloxolone and 7 on placebo; these observations are therefore not reliable. This appeared to be the Applicant's rationale to conduct the primary analysis in patients without pes cavus in Part 2 of the study and to select the 150 mg dose for Part 2. The reason for worsening at the 300 mg dose compared to other doses is also unclear. Additionally, the 5 mg dose provided the second

highest reduction in mFARS. The lack of clear dose response relation on the efficacy endpoints is likely due to the very small number of patients at each dose and should be interpreted cautiously.

The applicant also includes a discussion of pharmacodynamic biomarkers from Part 1 of the Study that are discussed in the subsequent section of this review to provide supportive mechanistic evidence of benefit from omaveloxolone.

**Pharmacodynamic Markers:**

The Applicant believes that there is strong mechanistic data from pharmacodynamic markers that support omaveloxolone treatment effects observed in Study 1402. The Applicant considered ferritin light chain (FTL), ferritin heavy chain (FTH1), and γ-glutamyl transferase (GGT1) as Nrf2 target genes that are affected by nuclear factor erythroid 2-related factor 2 (Nrf2). The Applicant cites that protein levels of ferritin light chain (FTL) and ferritin heavy chain (FTH1), two direct Nrf2 target genes that encode the components of ferritin, have been shown to be suppressed in heart tissue from frataxin-knockout mice [Huang 2009[3]]. The Applicant further asserts that induction of GGT1 was positively associated with suppression of inflammation in a rodent model of rheumatoid arthritis, supporting the use of GGT1 as a pharmacodynamic marker of Nrf2 activity. Although, the Applicant had initially included ALT and AST as additional pharmacodynamic markers of Nrf2 activation, were later disregarded. I agree that these appear further downstream targets and less interpretable.

Mechanistically ferritin appears to be a direct Nrf2 target genes as compared to GGT based on our literature search on these Nrf2 target genes, therefore, I only discuss ferritin as a supportive pharmacodynamic marker of Nrf2 activity. Division of Applied Regulatory Science, Office of Clinical Pharmacology (DARS/OCP) was consulted to review the mechanistic rationale for the Applicant's pharmacodynamic markers. Based on their review, I summarize the following published literature that appears to support the rationale for considering the observations from the select pharmacodynamic markers as supportive of the treatment effect of omaveloxolone.

As noted in the cited references, FA is caused by genetic mutations that result in insufficient amounts of frataxin. As a result of the frataxin deficiency, there are alterations in iron sulfur cluster biogenesis, mitochondrial iron homeostasis, and sensitivity to oxidative stress [Cook &

[3] Huang ML, Becker EM, Whitnall M, Suryo Rahmanto Y, Ponka P, Richardson DR. Elucidation of the mechanism of mitochondrial iron loading in Friedreich's ataxia by analysis of a mouse mutant. Proc Natl Acad Sci U S A. 2009;106(38):16381-16386.

Giunti, 2017[4]; La Rosa et al. 2020[5]]. This is aggravated by a faulty regulation of the expression and signaling pathway modulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) [La Rosa et al. 2020; Ghanekar et al. 2019[6]]. Nrf2 influences many attributes of intermediary metabolism and mitochondrial function, either through direct regulation of key metabolic genes or indirectly by crosstalk with other transcription factors changing gene expression [Hayes & Dinkova-Kostova 2014[7]]. These include those involved in heme and iron metabolism (e.g., ferritin) [Kerins & Ooi 2018[8]; Zhang et al. 2006[9]].

The Applicant also explains that iron is a critical cofactor for many redox enzymes, as well as those involved in the tricarboxylic acid (TCA) cycle, mitochondrial electron transport chain (ETC), oxygen transport, and heme synthesis. However, excess free iron can readily generate reactive oxygen species, impair mitochondrial function, and initiate ferroptosis. Therefore, the pool of free iron within the cell must be tightly regulated. Nrf2 regulates iron metabolism pathway in response to oxidative and electrophilic stress by directly increasing the expression of several genes involved in iron handling, including genes involved in iron buffering and sequestration [e.g., ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL), which combine to form ferritin] (Wasserman and Fahl[10], 1997; Tsuji, 2000[11]).

As a result, Nrf2 indirectly promotes iron storage and reduces the intracellular levels of redox-active free iron atoms. Therefore, the Nrf2 activation has been shown to induce ferritin protein expression.

The Office of Clinical Pharmacology review also concludes that the increase in ferritin in the plasma may be related to Nrf2 activation, however, further point out that the increase in ferritin due to Omaveloxolone mediated cell damage can't be ruled out. The review notes that ferritin may also be a marker of other pathological conditions, including liver disease, metabolic syndromes, and abnormal heart conditions or cell damage. In addition, increased synthesis

[4] Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. Br Med Bull. 2017; 124(1):19-30.
[5] La Rosa P, Bertini ES, Piemonte F. The NRF2 signaling network defines clinical biomarkers and therapeutic opportunity in Friedreich's Ataxia. Int J Mol Sci. 2020; 21(3):916.
[6] Ghanekar SD et. al. Orphan drugs in development for the treatment of Friedreich's Ataxia: Focus on omaveloxolone. Degener Neurol Neuromuscul Dis. 2019; 9:103-107.
[7] Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trend Biochem Sci. 2014; 39(4):199-218.
[8] Kerins MJ, Ooi A. The roles of NRF2 in modulating cellular iron homeostasis. Antioxid Redox Signal. 2018; 29(17):1756-1773.
[9] 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.
[10] Wasserman et. al 1997. Functional antioxidant responsive elements. Proc Natl Acad Sci USA. 1997; 94:5361-5366.
[11] Tsuji Y et. al; Coordinate transcriptional and translational regulation of ferritin in response to oxidative stress. Mol Cell Biol. 2000; 20:5818- 5827.

and/or secretion of ferritin may result from iron overload, infection, inflammation, and metabolic syndrome. However, as noted by the Applicant, there were no imbalances in adverse events (AEs) or serious adverse events (SAEs) that are reflective of pathological conditions generally associated with elevated serum ferritin levels in Study 1402.

The Applicant notes in the submission that dose dependent increases in ferritin were observed in Part 1 of the study (Table 18), as well as in Part 2 (Figure 14 and Figure 15). Based on this mechanistic biological plausibility of ferritin increase with the Nrf2 activation, the Applicant proposes that ferritin can be considered a pharmacodynamic effect of omaveloxolone that is suggestive of Nrf2 activation.

**Table 18 Mean (SD) Change from Baseline in Ferritin, a Mechanistic Marker of Nrf2 Activation**

| Parameter | Visit | Omaveloxolone | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5 mg (N=6) | 10 mg (N=6) | 20 mg (N=6) | 40 mg (N=6) | 80 mg (N=6) | 160 mg (N=12) | 300 mg (N=10) | Placebo (N=17) |
| Ferritin (µg/L) | Week 4 | -6.35 (11.243) | -17.87 (21.355) | 4.22 (13.570) | 15.38 (15.233) | 21.33 (16.870) | 34.23 (41.524) | 43.49 (62.560) | -4.86 (10.776) |

The Applicant also asserts that the magnitude of the changes in ferritin were positively associated with changes in neurologic function in Part 2 of the study, as assessed by mFARS scores. Omaveloxolone treated patients were categorized in tertiles based on mFARS score changes from baseline to Week 48 and the changes in ferritin and GGT from baseline to Week 48 were assessed for each tertile.

- Patients in the first tertile with mFARS score changes between 0.4 to 10, had ferritin changes of 7.6 ± 18.1 µg/L.
- Patients in the second tertile with mFARS score changes between -3 to < 0.4 had ferritin changes of 9.4 ± 23.2 µg/L.
- Patients in the third tertile with mFARS score changes between -3 and -11, indicating the largest improvements in neurologic function, had ferritin changes of 36.8 ± 66.4 µg/L.

However, when I looked at mFARS as a continuous variable rather than tertiles, such differences appeared to be driven by a ferritin measure from a single patient that was very high and also had the maximum reduction in mFARS at Week 48. Otherwise, no apparent correlation was found with magnitude of ferritin increase and change in mFARS at Week 48 (Figure 14). This plausibly could be because increase in ferritin in the omaveloxolone group still remained within the normal limits for all except the single patient or effect at Week 48. When change from baseline mFARS is plotted against Change from Baseline Ferritin at any Week during the

study (**Error! Reference source not found.**), a clearer separation in treatment arms is observed, suggesting the time course of change in ferritin may be different from the change in mFARS. A greater number of omaveloxolone-treated patients showed increase in ferritin at different time points during the study that also had improvement in mFARS, although some placebo patients also showed similar magnitudes of change from baseline in mFARS with no corresponding change in ferritin.

**Figure 14 Relation Between Change from Baseline in Ferritin versus Change from Baseline in mFARS scores at Week 48**

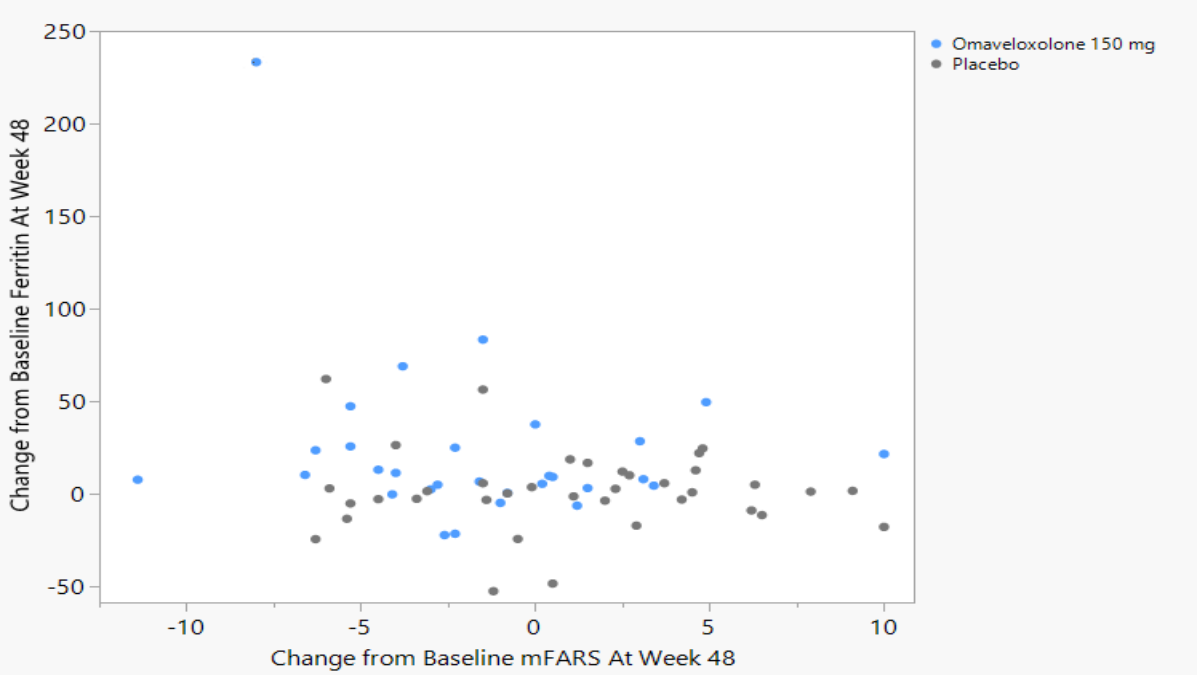
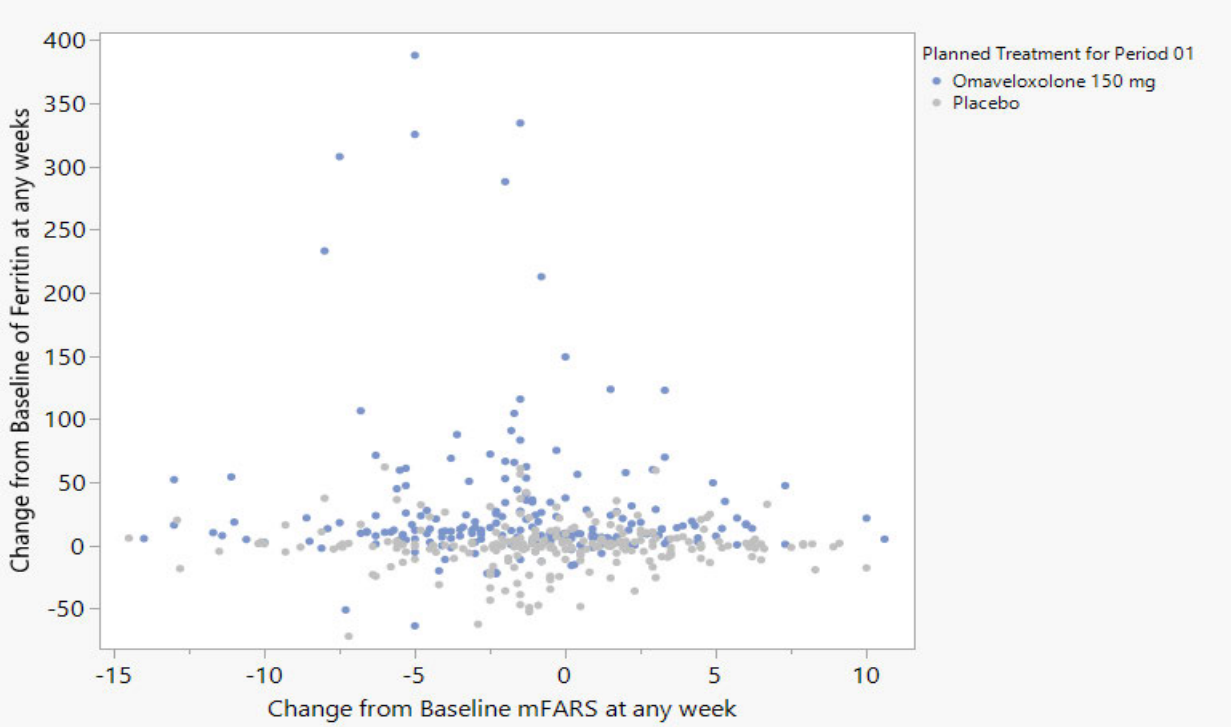


**Figure 15 Relation Between Change from Baseline in Ferritin versus Change from Baseline in mFARS scores at Any Week During the Study**




***Reviewer's Comment:***
*Increase in ferritin appears to be suggestive of a pharmacodynamic mechanistic effect and may be considered to provide confirmatory evidence for the benefit with omaveloxolone observed in Study 1402 Part 2.*

**Dose/Dose Response**

Only one dose was evaluated in the study in Part 2. In the Dose-Ranging Part 1 of the study, doses between 5-300 mg were evaluated in a small number of patients at each dose; therefore, no conclusions on effectiveness of any specific dose can be derived from Part 1 of the study.

**Additional Analyses Conducted on Study 1402**

**Post-hoc analyses on the extension phase of the study:**

The Applicant conducted post-hoc analyses on the extension phase of the study including a (1) Propensity Matching Natural History analysis and (2) Delayed Start Analysis.

Both Part 1 and Part 2 patients were enrolled in the extension study.

The treatment analysis groups for the Study 1402 Extension consist of:

1. Patients initially randomized to placebo in Study 1402 Part 2 or patients participating in Study 1402 Part 1 of the study (placebo – omaveloxolone **[Placebo-Omav]),** and
2. Patients initially randomized to omaveloxolone in Study 1402 Part 2 (omaveloxolone – omaveloxolone **[Omav-Omav]).**

The last patient enrolled in Study 1402 Part 1 completed their last visit on 13 Jun 2017. The extension study was not open until 30 Oct 2018. Thus, all patients from the Study 1402 Part 1 had been off treatment for **21 to 49 months** prior to enrolling in the Study 1402 Extension. Since Study 1402 Part 1 patients only received study drug for a short duration (12 weeks) and were off study drug for at least 21 months prior to enrolling in Study 1402 Extension, these patients are treated as treatment naïve upon enrollment in the Study 1402 Extension and for the Study 1402 Extension analysis. These patients were analyzed as Placebo–Omav group.

Part 2 patients were enrolled directly after Week 52. Patients were off-treatment for 4 weeks prior to enrolling in the extension phase. Patients randomized to omaveloxolone in Study 1402 Part 2 are analyzed as Omav–Omav group. Patients randomized to placebo in Study 1402 Part 2 are analyzed as placebo–Omav group.

**(1) Applicant's Post hoc Propensity Matched natural history analyses of Study 408-C-1402 Extension**

During the review cycle of this application, on August 3, 2022, the Applicant submitted a Post Hoc Propensity Matched Analysis of ongoing long-term, open-label extension Study 408-C-1402 data up to 3 years compared to the natural history data from Clinical Outcome Measures in Friedreich's Ataxia (FA-COMS; NCT0309078), a natural history study, to provide an external control as a comparator as additional confirmatory evidence of effectiveness for this application. On August 5, 2022, an updated data error report (error identified in July 2022 in the database) included updated Tables of the propensity matched analyses. This analysis uses data from the 24 March 2022 interim database lock for the ongoing Study 1402 Extension.

**In this analysis only extension data were included, not data from Part 1 or Part 2 of the study**. Study 1402 Extension Day 1 is defined as the first day that treatment was dispensed to the patient in the extension phase.

The FA-COMS study has enrolled more than 1000 patients where FARS and mFARS were assessed annually for up to 19 years in some patients. In Study 408-C-1402 Extension, outcomes were assessed every 24 weeks.

The Applicant asserts that the following strengths of these analyses:

- the centers participating in the FA-COMS study overlap with the centers in the ongoing Study 1402 Extension (which implies a more likely consistent standard of care and consistency in clinical assessments). A total of 8 sites, accounting for 84% of patients enrolled in Study 1402 Extension, are active sites for the FA-COMS study
- FA-COMS study systematically collected baseline characteristics that included variables considered prognostic for FA progression
- FA-COMS study has a large number of patients
- FA-COMS has a long duration of follow-up
- FA-COMS study used standardized assessment of the metric used in the Study 1402 clinical trial (mFARS) by trained experts at regular intervals
- There is a lack of confounding with off-label treatments as there are no effective agents for FA
- FA-COMS used standardized case report forms

Propensity score matching of the Open-label extension data and the FA-COMS data as controls was based on:

- Sex,
- baseline age,
- age of FA onset,
- baseline mFARS score, and
- baseline gait score.

For inclusion in either of the study groups, patients must have had:

- baseline mFARS
- at least one post-baseline mFARS within 3 years after baseline, and
- values for all propensity score model covariates

Baseline values were defined as the last non-missing assessment prior to the first study drug administration in Study 1402 Extension. The matching was carried out as optimal 1:1 matching without replacement.

For FA-COMS patients, baseline was defined as having a record marked VISIT = Day 1. As an example, if a patient had no recorded FARS assessment at the baseline visit, but they did have a FARS assessment at Year 2, the Year 2 assessment was not considered as baseline and the patient was not included in the analysis as they did not have a baseline assessment.
The goal of a propensity score analysis was to mimic randomization by creating groups that were balanced on important covariates that may affect the outcome of any efficacy analysis. The propensity score was estimated using logistic regression with covariates. Other covariates that were considered but not included were GAA1 repeat length and pes cavus. According to

the Applicant, GAA1 repeat length was not available for all patients (FA-COMS: 92% and Study 1402: 87.9%) and presence of pes cavus was not systematically collected in the natural history study (FA-COMS: 53.3% and Study 1402: 100%). The other covariates were available in at least 97.4% of the FA-COMS patients.

Primary and Secondary endpoints included:

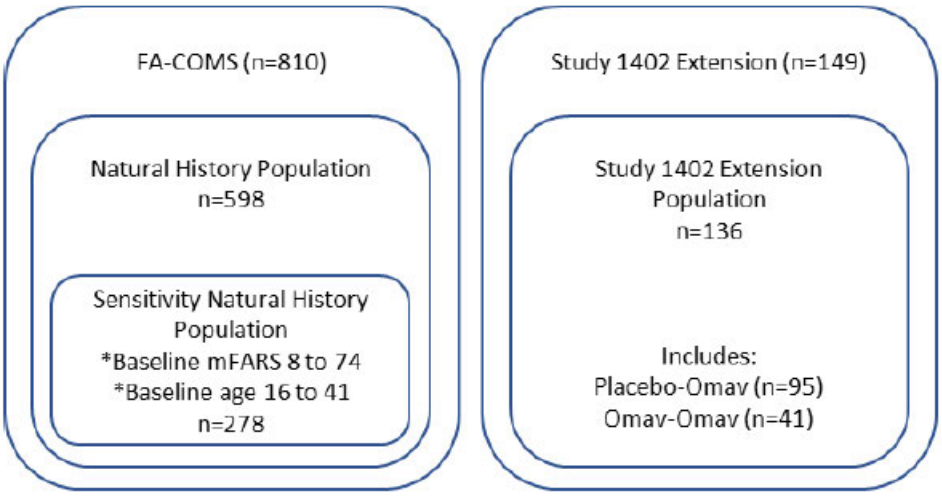
- The primary efficacy endpoint was the change from baseline in **mFARS at Year 3** for Study 1402 Extension patients compared to the propensity score-matched FA-COMS patients, analyzed using a mixed model repeated measures (MMRM) analysis.
- The secondary endpoints were the change from baseline in **mFARS at Years 1 and 2**.

The change from baseline in mFARS at Year 3 was analyzed using a mixed model repeated measures (MMRM) model which included treatment group, baseline mFARS, visit, and interaction terms for visit-by-baseline and treatment group-by-visit as covariates.

Comparison Populations:

- Study 1402 Extension population: derived from the full Study 1402 Extension dataset (n=149): included patients from both Part 1 and Part 2. A total of 136 patients had post baseline mFARS score. Extension population included both the Placebo-Omav group and Omav-Omav group.
- Matched FA-COMS natural history (NH) population: contains de-identified patient level data from 810 patients who consented to have their data shared outside of the core FA-COMS study, was current as of March 24, 2021, when it was shared with the Critical Path Institute (C-Path).
- Sensitivity NH population – the subset of patients from the NH population with the following additional requirements: (1) baseline mFARS score was within the range observed in Study 1402 Extension (mFARS 8 to 74) and (2) age at baseline was within the range observed in Study 1402 Extension (age 16 to 41 years).

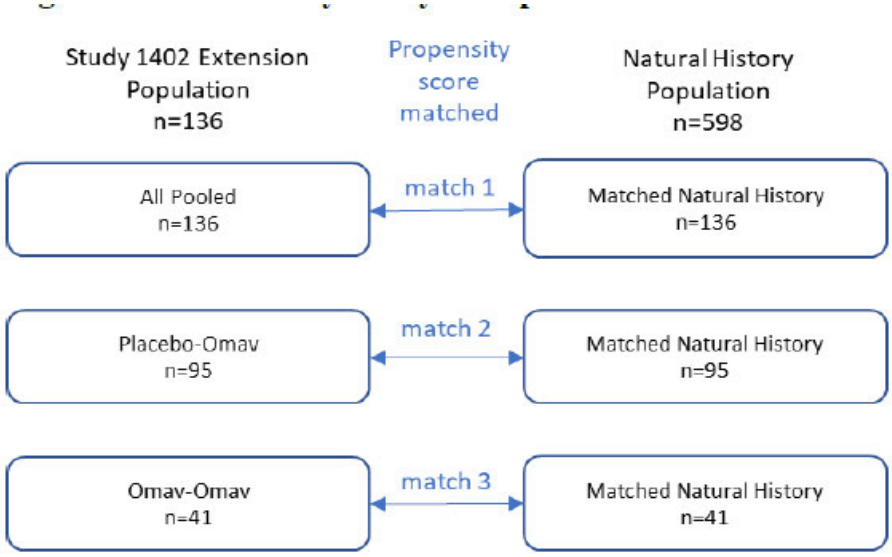
**Figure 16 Analysis Populations**




Source: Sponsor's 4108-v-1402-ext-pm-report body, page 15
Note: 13/149 discontinued with no post-baseline mFARS in Study 1402.

The primary analysis populations were based on matches with the NH population and the prior treatment status (i.e., treatment naïve, Placebo-Omav; continued treatment, Omav-Omav) (Figure 17). The sensitivity analysis populations were based on matches with the Sensitivity NH population.

**Figure 17 Primary Analysis Populations**




Source: Sponsor's 4108-v-1402-ext-pm-report body, page 16

**Primary Analysis Results:**

The Applicant reports that mean baseline age (26.2 vs. 26.6 years), baseline mFARS score (41 vs 42.2), age on onset (15.2 vs 15.5 years) and gait, as scored by the mFARS, (2.7 vs 2.8) were generally balanced between the two arms, FA-COMS vs Extension respectively.

The Applicant's analysis on mFARS change from baseline at Years 1, 2 and 3 for the Primary Pooled Population, Primary Placebo-Omav Population, and Primary Omav-Omav Population based on the Applicant's analyses is shown in the Table 19 (A-C) below for the Matches 1-3.

**Table 19 Applicant's Analysis: Change in mFARS Score at Years 1-3 (Matches 1-3 populations)**
**A)**

| | | | Pooled Population (Match 1) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | mFARS Change from Baseline | | | | | |
| | | | Year 1 (Secondary) | | Year 2 (Secondary) | | Year 3 (Primary) | |
| | N | Mean (SD) | N | LS Mean (±SE) | N | LS Mean (±SE) | N | LS Mean (±SE) |
| Study 1402 Extension | 136 | 42.234 (12.5978) | 133 | 0.011 (0.5471) | 102 | 1.154 (0.5839) | 77 (43% lost) | 2.983 (0.6433) |
| Matched FA-COMS | 136 | 41.505 (16.9092) | 108 | 2.087 (0.5789) | 104 | 4.718 (0.5801) | 87 (36% lost) | 6.337 (0.6183) |
| Difference | - | - | - | -2.076 (0.7967) p=0.0095 | - | -3.564 (0.8232) p< 0.0001 | - | -3.354 (0.8923) p=0.0002 |

**B)**

| | | | Primary Placebo-Omav Population (Match 2) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | mFARS Change from Baseline | | | | | |
| | | | Year 1 | | Year 2 | | Year 3 | |
| | N | Mean (SD) | N | LS Mean (±SE) | N | LS Mean (±SE) | N | LS Mean (±SE) |
| Study 1402 Extension | 95 | 42.816 (12.7918) | 95 | -0.417 (0.6310) | 69 | 1.180 (0.6869) | 56 | 3.238 (0.7604) |
| Matched FA-COMS | 95 | 44.281 (18.0639) | 72 | 2.251 (0.6908) | 71 | 4.304 (0.6800) | 64 | 7.334 (0.7212) |
| Difference | - | - | - | -2.668 (0.9364) p=0.0047 | - | -3.123 (0.9669) p=0.0014 | - | -4.096 (1.0480) p=0.0001 |

**C)**

| | | | Primary Omav-Omav Population (Match 3) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | mFARS Change from Baseline | | | | | |
| | | | Year 1 | | Year 2 | | Year 3 | |
| | N | Mean (SD) | N | LS Mean (±SE) | N | LS Mean (±SE) | N | LS Mean (±SE) |
| Study 1402 Extension | 41 | 40.886 (12.1831) | 38 | 0.962 (1.0649) | 33 | 0.959 (1.1120) | 21 | 2.208 (1.3122) |
| Matched FA-COMS | 41 | 41.781 (17.8419) | 35 | 2.767 (1.0960) | 30 | 3.778 (1.1456) | 26 | 6.448 (1.2136) |
| Difference | - | - | - | -1.805 (1.5277) p=0.2397 | - | -2.819 (1.6019) p=0.0807 | - | -4.240 (1.7888) p=0.0190 |

Source: Amended PM Report page 16-19

Applicant's **primary endpoint analysis at Year 3** shows a mFARs change from baseline difference between Study 1402 Extension and FA-COMS of -3.354 points in favor of Study 1402 extension for the primary pooled analysis Match 1 (p=0.0002) with the correction made to the data error identified in July 2022. **Matched FA-COMS patients had progressed 6.337 mFARS points whereas patients treated with omaveloxolone in Study 1402 Extension progressed only 2.983 points (difference = -3.354, nominal p=0.0002**).

A mFARs change from baseline difference between Study 1402 Extension and FA-COMS of -4.096 points in favor of Study 1402 extension for the primary placebo-omav population analysis Match 2 (p=0.0001) and -4.240 points in favor of Study 1402 extension for the primary Omav-omav population analysis Match 3 (p=0.0190).

Applicant's **secondary endpoint analysis at Year 1 and 2** shows nominally significant difference as well for Matches 1 and 2. However, Match 3, in the patients who were treated for omaveloxolone the longest were not nominally statistically significant at Year 1 and 2 as shown in Table 19. The Applicant hypothesizes that this is because these patients had already experienced a treatment benefit in Study 1402 Part 2 prior to entering the OLE, so some of the benefits of the treatment may have plateaued; however, the benefit at year 3 indicates that the initial benefits were sustained over time.

The Applicant also conducted sensitivity analyses. Sensitivity population included Match 4, 5, and 6 with more restrictions imposed on the natural population: (1) baseline mFARS score is within the range observed in Study 1402 Extension (mFARS 8 to 74) and (2) age at baseline is within the range observed in Study 1402 Extension (age 16 to 41 years). The sensitivity analyses for all groups also show nominal significance at each year except at Year 1 for the Omav-Omav group.

**Table 20 Sensitivity Analyses: mFARS Change from Baseline Treatment Differences Over Time (Sensitivity Populations)**

| Analysis Population | mFARS Change from Baseline (LS Mean [±SE]) | | |
|---|---|---|---|
| | Year 1 | Year 2 | Year 3 |
| Sensitivity Pooled (Match 4)<br>Difference | -1.679 (0.7055)<br>p=0.0178 | -1.615 (0.7376)<br>p=0.0291 | -2.388 (0.8237)<br>p=0.0039 |
| Sensitivity Placebo-Omav (Match 5)<br>Difference | -2.387 (0.8840)<br>p=0.0073 | -2.091 (0.9191)<br>p=0.0236 | -3.136 (1.0012)<br>p=0.0019 |
| Sensitivity Omav-Omav (Match 6)<br>Difference | -0.983 (1.3608)<br>p=0.4713 | -2.876 (1.3986)<br>p=0.0417 | -3.858 (1.6004)<br>p=0.0172 |

Source: Amended PM Report page 22

***Reviewer's Comments:***

- *One encouraging and reassuring point to note in these analyses is that the change from baseline mFARS data at Year 1, 2 and 3 in the FA-COMS database appears consistent across all the match subgroup 1-3 with **different sample sizes as shown in** Table 21: The natural history patients appeared to worsen with a 2.1-2.5 points increase in mFARs*

*by Year 1, 3.5-4.5 points increase by Year 2 and 6.1-7.3 points by Year 3 as shown below, suggesting an increase in mFARS score of an average 2 points every year.*

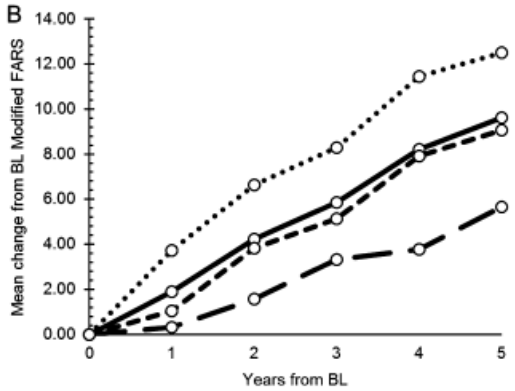
**Table 21 Change from Baseline in FA-COMS Patients in Different Population Subsets**

| Population | | | mFARS Change from Baseline | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Year 1 | | Year 2 | | Year 3 | |
| | N | Mean (SD) | N | LS Mean (±SE) | N | LS Mean (±SE) | N | LS Mean (±SE) |
| Matched FA-COMS | 136 | 41.505 (16.9092) | 108 | 2.087 (0.5789) | 103 | 4.718 (0.5801) | 87 | 6.337 (0.6183) |
| Matched FA-COMS | 95 | 44.281 (18.0639) | 72 | 2.251 (0.6908) | 71 | 4.304 (0.6800) | 64 | 7.334 (0.7212) |
| Matched FA-COMS | 41 | 41.781 (7.8419 | 35 | 2.767 (1.0960) | 30 | 3.778 (1.1456) | 26 | 6.448 (1.2146) |

*Similar increases are also reported by Patel et. al.[12] on the published natural history data in a much larger number of subjects (Figure 18). The small-dashed line in Figure 18 presents the change from baseline in patients ages 16-40 years in about 300 FA patients. Therefore, the fact that the magnitude of deterioration in the mFARS scores is the same in the natural history database regardless of the number of patients grouped, is reassuring of the consistent increase of about 2 points in mFARS each year in the natural history patients. Therefore, the change in mFARS obtained in Omav-treated groups appears to deviate from the natural progression of FA patients as measured by mFARS, and therefore may be considered a treatment benefit of omaveloxolone as discussed in the subsequent paragraphs.*

[12] Patel et. al 2016

**Figure 18 FA-COMS Natural History (Patel.et al)**




Source: Patel et. al. (Small dash line represent patients ages 16-40 years)

*Study 1402 extension overall (Match 1) shows improved scores at Year 1, however subsequently there appears to be a 1-point and 3-point increase in mFARS scores at Year 2 and 3 respectively.*

*The Placebo-Omav (Match 2) where placebo patients were switched to omaveloxolone showed improvement from baseline in mFARS scores at Year 1 with a difference from* FA-*COMS natural history of -2.668 mFARS points, nominal p=0.0047. (Table 19 B). These results are similar in magnitude to that observed in the double-blind phase of the study (a difference of -2.4 mFARS points compared to placebo over a 48-week treatment period.)*

- *The Omav-Omav group (Match 3) (Table 19C), on the other hand, in the extension phase has shown an increase in mFARS scores of 1-point (being the second year of treatment) that is maintained in the 3rd year of Omav treatment, suggesting persistent effect. These data do suggest a deviation from the natural history data as shown in Table 19A-C in the different propensity matched groups and likely changing the progression of the disease. It is noteworthy that no statistically significant difference was observed at Year 1 and 2 between the Omav-Omav and FA-COMS arms, the group that was on treatment the longest, but directionally favored omaveloxolone.*

  *However, these conclusions of the propensity-matched natural history analysis may be confounded by numerous known and unknown factors that can lead to bias that I discuss below:*

- *Another point of consideration is that this analysis may be a more conservative approach of evaluating extension data because it excludes the exposure period of Part 2 where*

*benefit was demonstrated and might therefore even be considered to provide somewhat independent confirmation of change in mFARS.*

- *For Match 3 in the patients who were treated for omaveloxolone the longest were not nominally statistically significant at Year 1 and 2 as shown in Table 19, but nominally significant at Year 3. The Applicant hypothesizes that this is because these patients had already experienced a treatment benefit in Study 1402 Part 2 prior to entering the OLE, so some of the benefits of the treatment may have plateaued. This could likely be plausible.*

- *These analyses were done post-hoc with complete knowledge of data for both Extension and FA-COMS patients. The propensity matching factors were picked with complete knowledge of the datasets, and therefore, patient and method selection biases remain unknown. The statistical analysis plan was not agreed upon with the Agency. However, I agree that the chosen matching factors included in the analysis are clinically meaningful covariates that should have been included. Additional factors such as GAA1 repeat length would also have been ideal to be included but missing GAA1 repeat length data precluded this to be included in the analysis and have been discussed below.*

- *For open label extension data to be used effectively in any analysis, it is typically recommended that the patient, investigator, site personnel, and site monitors should remain blinded to treatment group assignment from the randomized treatment period. Only sponsor staff involved in analysis of the blinded period results should have access to unblinded data and patient group assignments. In this case, only patients remained blinded in the extension phase. According to the protocol, there was no mention of blinding status of other study personnel.*

- *A critical confounding factor is the attrition of patients (30-50%) in both Study 1402 OLE and FA-COMS arms limiting the persuasiveness of these analyses. However, as noted above the natural history decline remains consistent without regard to the size of the subsets of patients evaluated from the natural history database.*

- *Additional concerns include the comparability of the two arms as discussed below:*
    - *The Applicant asserts that the two groups are comparable at baseline based on the propensity matching factors selected and standard of care as there was significant overlap in trial sites and investigators (some of whom helped develop FA standard of care guidelines), ensuring a similar approach to overall patient management for FA and comorbid conditions. However, the true comparability of the non-randomized groups cannot be determined.*

- *The comparability of clinical care of patients including physical therapy and training exercise, occupational therapy, routine orthopedic care, gait aid provisions etc., is not known.*

- *Study 1402 excluded patients with history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, uncontrolled diabetes (HbA1c >11.0%), mitochondrial respiratory chain disease, B-type natriuretic peptide value >200 pg/mL and cognitive impairment that may preclude ability to comply with study procedures. Hence, the comparability of severity of disease between the two populations also cannot be assured.*

- *The propensity matching model did not use important prognostic factors as GAA1 repeat length and pes cavus as covariates due to lack of availability of GAA1 in all patients and differences in the method of evaluation of pes cavus between studies. Rodden et al.[13] have shown that severity of clinical features of FA generally increases with increasing GAA1 length up to 700 triplets where a plateau occurs, creating a ceiling effect. The sub-cohort of patients with GAA1 of >700 triplets show limited clinical variability in disease progression due to GAA1 length and have been shown to have the greatest homogeneity in frataxin levels, hence likely less of a concern given the patient population enrolled in the study. There were 7 FA-COMS patients and 17 Extension Study patients that had missing GAA1 repeat length. The mean (SD) GAA1 repeat length was 597.3 (251.80) and 720.9 (269.58) for the FA-COMS and Extension studies, respectively. Reviewing the distribution of available GAA1 repeat length versus change in mFARS did not suggest the difference to favor omaveloxolone group. However, Rodden et. al. noted that the prevalence of cardiomyopathy and scoliosis was reported to be higher the patients with GAA1 of >700 triplets. This is not known in the comparison of the two populations and could have an impact on the mFARS assessments. Pes cavus is another factor that was not matched and could impact the performance of "Upright Stability" component of mFARS.*

- *Applicant asserts that FA is a condition for which there are no approved or effective therapies, which might otherwise confound the comparison of groups from 2 different studies. However, the comparability of the two groups in terms of other supplements used for in FA cannot be determined, such as antioxidants, including Quercetin, Idebenone, Coenzyme Q10, and vitamins and minerals, such as vitamin D and calcium and botulinum toxin [that can help with the impact of spasticity during mobility] that were allowed in the extension as well as the FA-*

[13] Rodden LN, Rummey C, Dong YN, Lynch DR. Clinical Evidence for Variegated Silencing in Patients With Friedreich Ataxia. Neurol Genet. 2022 May 17;8(3):e683.

*COMS Study. The use of these were not allowed during the double-blind phase of the Study 1402. It is unclear if these supplements are likely to change the progression of the disease.*

- *In addition, there are some methodology issues, the impact of which is not known. In the FA-COMS natural history study, mFARS was performed on an annual basis, whereas mFARS was scheduled to be performed every 24 weeks in Study 1402 Extension. The mFARS assessment collected closest to 1 (365 days), 2 (730 days), and 3 (1095 days) years after baseline was used for each of the annual assessments. The Applicant used a margin of window of ±182 days to select the clinical outcome measure timing for the comparison. Hence, the durations may not be completely comparable.*

*Overall, despite all the limitations cited above, the propensity matching analyses do suggest a deviation from the natural history as measured by the decline in mFARS scores over the 3-year comparison. This may be considered to provide confirmatory evidence for the benefit with omaveloxolone observed in Study 1402 Part 2.*

**(2) Applicant's Post hoc Delayed start analysis:**

Post-hoc analyses were conducted by the Applicant on the extension phase of the study to assess whether the effect observed in the Study 1402 Part 2 omaveloxolone group is a persistent effect on FA disease course, and to assess if the same effect cannot be recovered by patients who start omaveloxolone later in time. This was referred to as the post hoc Delayed-start analysis. The Applicant considers this also as supportive longer term efficacy data to support the New Drug Application based on a single study and supportive data based on this Delayed-start analysis.

The Applicant claims that Study 1402 Delayed-start analysis (n = 82) indicated a persistent omaveloxolone treatment effect on the course of FA. Patients who received omaveloxolone during the double-blind Study 1402 Part 2 had a benefit, measured by change from baseline in mFARS, that could not be recovered by patients initially randomized to placebo who began omaveloxolone 1 year later in Study 1402 Extension.

This post hoc analysis was to compare the difference between treatment groups in the mFARS scores change from baseline at the end of the placebo-controlled period (Study 1402 Part 2) and in the open-label period (Study 1402 Extension).

No patients were unblinded in Study 1402 Extension to their treatment assignment in Study 1402 Part 2.

The extension phase was impacted by COVID 19. Missing data due to COVID-19 were not imputed.

The primary efficacy endpoint of this Study 1402 Post Hoc Delayed-Start Analysis was the placebo-corrected difference in the "delayed-start period" (Δ2, Study 1402 Extension Week 72 change from baseline mFARS values) versus the placebo-corrected difference in the "placebo-controlled period" (Δ1, Study 1402 Part 2 Week 48 change from baseline mFARS values).

***Reviewer's Comment:***

*Only patients remained blinded in the extension phase. According to the protocol there was no mention of blinding status of other study personnel. It is typically recommended that the patient, investigator, site personnel, and site monitors should remain blinded to treatment group assignment from the randomized treatment period. Only sponsor staff involved in analysis of the blinded period results should have access to unblinded data and patient group assignments.*

**Only Part 2 patients were evaluated in the delayed start analyses.** The placebo-corrected difference in Study 1402 Extension was based on results from patients initially randomized to placebo in Study 1402 Part 2 who subsequently received omaveloxolone in Study 1402 Extension (the Placebo-Omav group). Patients in the Placebo-Omav group began treatment with omaveloxolone 52 weeks after patients in the Omav-Omav group. The initial analysis was submitted with a cutoff of August 2021 which was updated during the review cycle with a cutoff date of March 2022 to allow for an analysis with increased number of patients at each time point.

The number of patients receiving treatment at each time point and the number of patients with mFARS assessment at each time point in the Delayed-start analysis is shown in Table 22 using the August 2021 (initial application), and March 2022 cutoffs (second number) (submitted on June 21, 2022)

**Table 22 Number of Patients Receiving Treatment and mFARS Assessment by Study Week**

| **Treatment Group** | **Study 1402 Part 2** | | | | | **Study 1402 Extension** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | **4** | **12** | **24** | **36** | **48** | **0** | **24** | **48** | **72** | **96** | **120** | **144** |
| Number of Patients Receiving Study Drug | | | | | | | | | | | | |
| Omav-Omav | 40 | 36 | 34 | 35 | 35 | 34 | 32/33 | 29/33 | 29/33 | 33 | 14/32 | 1/32 |
| Placebo-Omajv | 42 | 41 | 40 | 40 | 40 | 39 | 30/33 | 28/32 | 29/31 | 27/31 | 14/31 | 0/31 |
| Number of Patients with mFARS Assessments | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Omav-Omav | 40 | 40 | 36 | 35 | 34 | 34 | 28 | 20 | 17 | 21/22 | 11/27 | 0/17 |
| Placebo-Omav | 42 | 42 | 41 | 41 | 41 | 39 | 27 | 22 | 14 | 13/15 | 11/24 | 0/15 |

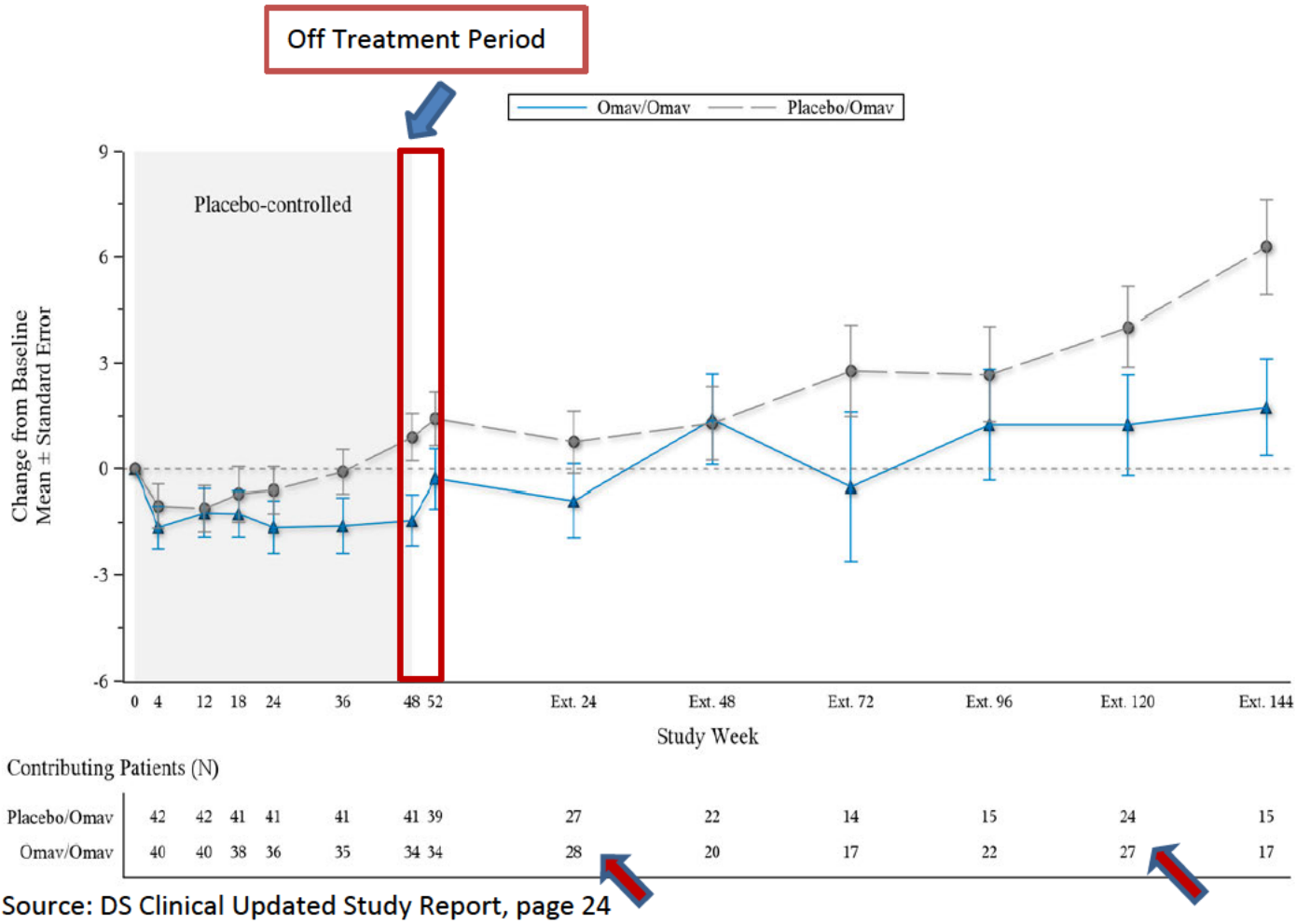
Source: Source: DS Study Report, page 15
Note: Numbers in red are updated patient numbers at each time point based on the March 2022 cutoff date

The following analyses were performed: (1) a noninferiority test (2) an evaluation of mFARS trajectory over time (slope) in the extension, by treatment group as based on patients' Study 1402 Part 2 randomized treatment.

***Reviewer's comment:***
*The Delayed-start analyses appear uninterpretable in many aspects. Many patients discontinued the study and several did not have mFARS assessment due to the COVID pandemic. The Applicant's analysis shows that noninferiority was only demonstrated at Extension Week 72 and 120 but not at Weeks 96 and 144, where Week 144 in fact had the same number of patients as Week 72, suggesting concerns with the analyses/interpretation. The statistical analyses and assumption associated with such analyses to evaluate non-inferiority in a post hoc setting are complicated and not considered reliable by the FDA statistician due to large number of missing data, and therefore not included in this review.*

*I only include the Applicant's figure on the Mean Change from Baseline versus Study Week profile in this review and discuss its relevance related to efficacy findings (Figure 19).*

**Figure 19 Applicant's Change from Baseline in mFARS (Full Analysis Set) March 2022 cut off**



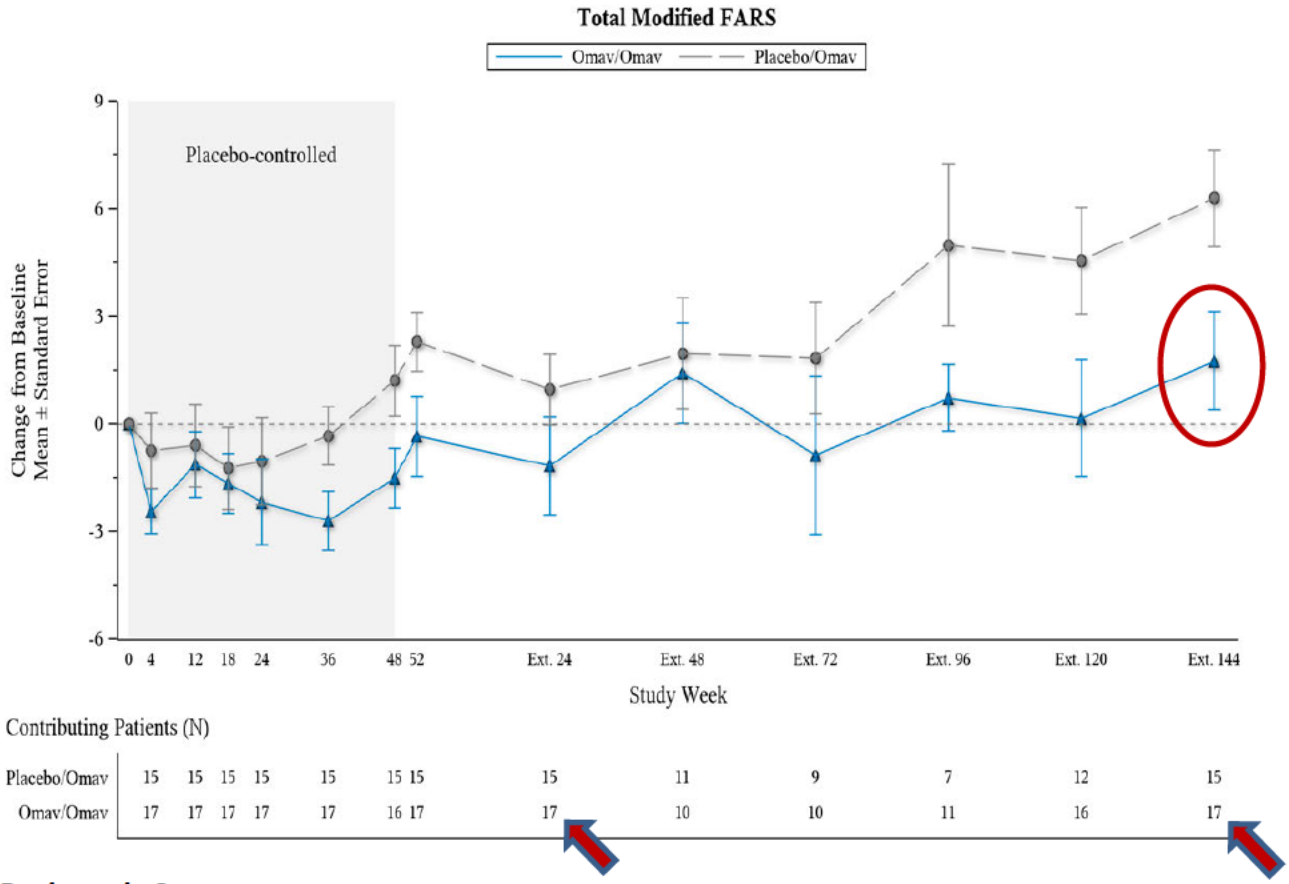

Source: DS Clinical Updated Study Report, page 24

***Reviewer's Comment:***

*The off-treatment period shown by the red bar at Week 48-Week 52 in Figure 19, shows that after discontinuing omaveloxolone at Week 48, the mFARS scores increased and further decreased after Week 52 upon reinitiating treatment suggestive of a pharmacodynamic effect indicating worsening on treatment discontinuations.*

Additionally, the Applicant reports the mean change from baseline in just the patients that completed Week 144 assessment (15 patients in the Placebo-Omav group and 17 in the Omav-Omav group) (Figure 20).

**Figure 20 Change from Baseline in mFARS (Extension Week 144 mFARS Completers in the Full Analysis Set, March 2022 cut off)**




***Reviewer's Comments:***

*Although the delayed start analysis is largely uninterpretable, as discussed above, I note based on these Figures that the patients that have been on Omaveloxolone for the entire duration in the Omav-Omav group (N=17) (48 weeks double blind plus 144 weeks in the extension phase) have deviated from the natural history. Natural history patients would have shown a mean increase in the mFARS score of approximately 8 points in 4 years. However, patients treated with Omav (N=17) have shown a mean increase of <2 points in 4 years. In a duration of 120 weeks of the extension phase (Ext Week 24 and Ext Week 144 the mFARS score has increased by <2-points as shown by the red arrows (Figure 20). There has been missing data due to the COVID-19 pandemic; however, just comparing patients in the extension phase at different timepoints suggests a slower decline in the Omav-Omav group. Similarly, the Placebo-Omav patients also appear to have deteriorated at a slower pace after initiating Omaveloxolone showing a mean increase in mFARS of ~4-points over 3 years (N=15).*

*Figure 19 also shows a mean increase of <2 points at Week 120 in the Omav-Omav group (N=27) and the Placebo-Omav group showing a mean increase in mFARS of 4-points over 3 years (N=24). These mean changes in mFARS appear consistent with change in total number of patients evaluated as shown by red arrows* (Figure 19). *This is compared to FA-COMS natural history that shows a mean increase of about 6-points in mFARS over 3 years and 8-points over 4 years in mFARS.*

# 7. Integrated Review of Effectiveness

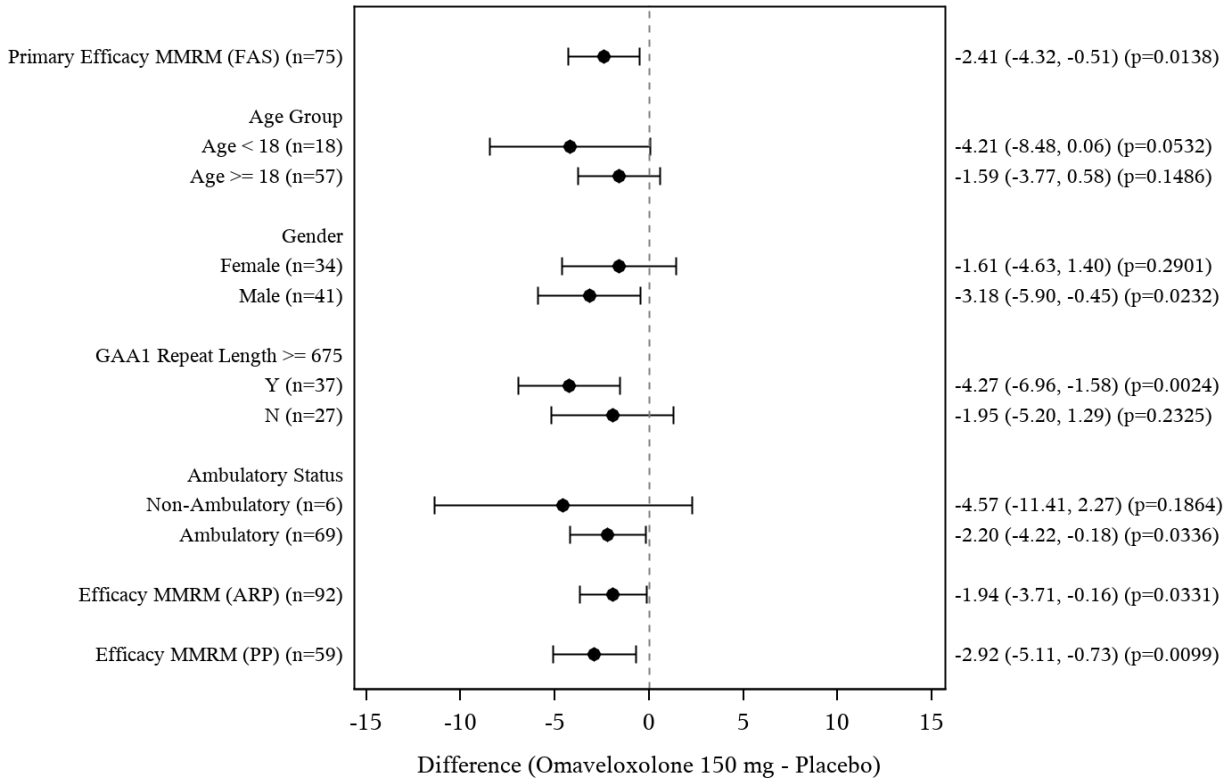
## 7.1. Assessment of Efficacy Across Trials

There is only one study RT-1408 and its extension, therefore assessment of effectiveness across trials is not performed.

### 7.1.1. Subpopulations

There are a small number of patients in each subgroup evaluated to have interpretable assessment of subpopulations. However, the results favored omaveloxolone in each subpopulation. Applicant's assessment is shown in Table 23.

**Table 23 Analysis of mFARS Change from Baseline at Week 48 Across Subgroups in the Full Analysis Set and in Other Prespecified Analysis Populations**




***Reviewer's Comment:*** *According to Dr. Jinnan Liu (Statistic Reviewer), the Applicant has used a different statistical method to calculate the treatment differences between omaveloxolone and placebo arms in this analysis compared to the primary analysis method. Please refer to Dr. Liu's review for the correct analysis method for the subgroup analyses. Subgroup analyses are descriptive in nature without p-values due to the small number of patients in each subgroup that causes a concern for inflation of Type 1 error. Therefore, differences between the subgroups are not interpretable.*

### 7.1.2. Dose and Dose-Response

Only one dose was evaluated in the randomized phase Part 2. Part 1 was a dose-ranging phase, however, no interpretable assessment of efficacy can be drawn due to small number of patients at each dose.

## 7.2. Integrated Assessment of Effectiveness

The Applicant is seeking approval of omaveloxolone for the treatment of Friedreich's ataxia

based on a single study and confirmatory evidence.

Under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug's effectiveness must be established by "substantial evidence." In section 115(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress amended section 505(d) of the FD&C Act to make it clear that the Agency may consider "data from one adequate and well controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.

The Applicant submitted a 48-Week Study 1402 (MOXIe) Part 2 as one adequate, and well-controlled study. For confirmatory evidence, the Applicant submitted post hoc propensity matched analyses of the long term 144-week open label extension of Study 1402 compared to FA-COMS natural history study in FA patients. In addition, the Application has provided mechanistic biological markers of Nrf2 activation as supportive confirmatory evidence.

As described in the FDA draft guidance on "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products", reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible". The guidance further suggests factors when a single study plus confirmatory evidence will be adequate to support an application. "These factors may include the persuasiveness of the single trial; the robustness of the confirmatory evidence; the seriousness of the disease, particularly where there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation". The guidance further suggests that "the strength of the single trial will affect the extent of confirmatory evidence required."

Considering these regulatory standards for approval, the following assessment can be made on how the data included in this Application meets the requirement for approval based on a single study plus confirmatory evidence or single study alone.

Friedreich's ataxia is a serious disease with unmet need. There is no approved treatment for FA. FA patients have loss of motor skills and speech as major disease burdens that lead to the loss of ambulation and becoming wheelchair-dependent by their mid-20s. Ultimately, FA leads to a shortened life expectancy, with the average age of death being 37.5 years of age.

**Study 1402 Part 2 as a single adequate well controlled study:**

Study Part 2 was randomized, double-blind, placebo-controlled study that was intended to serve as the primary basis of assessing effectiveness of omaveloxolone.

Primary Endpoint: The Applicant's prespecified primary endpoint analysis in the 'Full Analysis Population' that consisted of FA patients without pes cavus (N=82) was positive, with a statistically significant improvement in mFARS at Week 48 of -2.41 points in the omaveloxolone arm compared to placebo (p=0.0138). In the 'All-Randomized Population' that consisted of FA patients both with or without pes cavus (N=103), a nominally significant improvement in mFARS at Week 48 of -1.94 points in the omaveloxolone arm compared to placebo (p=0.0331) was also observed. Lower scores on mFARS indicate improvement.

The Applicant is seeking approval of omaveloxolone in the treatment of FA and not for the treatment of FA in patients without pes cavus only. The initial protocol for Study 1402 intended to include all patients enrolled in the analysis, however the protocol was amended after a post hoc analysis of Part 1 of the study where a small subset of patients without pes cavus (4 on omaveloxolone and 7 on placebo) demonstrated a greater improvement on mFARS likely due to the ability the perform the "Upright Stability" component of the mFARS. There is no clinical reason that patients with pes cavus will not benefit from omaveloxolone treatment if substantial evidence of effectiveness was established in patients without pes cavus. It is only the ability to perform the mFARS to assess effectiveness would be impacted. Therefore, a nominally significant improvement in mFARS in "All Randomized Patients" is assuring of treatment benefit in patients with FA, with or without pes cavus.

Secondary endpoints:

The key secondary endpoint mean PGIC and CGIC scores at Week 48 numerically favored omaveloxolone arm but were not statistically different from placebo in the FAS population. LS Mean treatment difference between treatment groups for PGIC was -0.43 (p=0.1300) and that for CGIC was -0.13 (p=0.5259) in the prespecified 'Full Analysis Population'. Higher scores in PGIC and CGIC indicate worsening.

In the 'All-Randomized population', a nominally positive p-value was observed with PGIC (p=0.0282), however CGIC remained negative in this population (p=0.1328).

Omaveloxolone treatment did not statistically significantly improve the other secondary endpoints including 9-HPT, 25-foot timed walk test, frequency of falls, or peak work relative to placebo. Numerically, frequency of falls favored omaveloxolone. During the 48-week treatment period, omaveloxolone patients reported a median of 3.0 falls (range, 1 to 89), while placebo patients reported a median of 8.5 falls (range, 0 to 131).

ADL scores at Week 48 were last in the hierarchy of statistical testing and showed improvement from baseline with LS mean difference between treatment groups was -1.30 points reached nominal statistical significance relative to placebo (p = 0.04).

Overall, the single small study, with lack of adequate support from secondary endpoints, does not appear robust enough to independently provide substantial evidence of effectiveness; therefore, additional confirmatory evidence is needed for establishing substantial evidence of effectiveness in this Application. The FDA draft guidance on "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, suggests that such confirmatory evidence could come from data on well-documented natural history of the disease or compelling mechanistic evidence in the setting of a well-understood disease pathophysiology (e.g., pharmacodynamic data). The Applicant has included such data to provide confirmatory evidence of effectiveness of omaveloxolone as discussed below.

Confirmatory evidence:

A post hoc 'Propensity Matched Analysis' of the ongoing long-term, open-label extension Study 408-C-1402 data of up to 3 years duration was compared to an external control, the mFARS data from a natural history study "Clinical Outcome Measures in Friedreich's Ataxia" (FA-COMS; NCT0309078), to provide additional confirmatory evidence of effectiveness for this application. Propensity score matching was based on: sex, baseline age, age of FA onset, baseline mFARS score, and baseline gait score. The goal of a propensity score analysis was to mimic randomization by creating groups that were balanced on important covariates that may affect the outcome of any efficacy analysis.

The primary efficacy endpoint of this external comparator analysis was the change from baseline in mFARS at Year 3 for Study 1402 Extension patients compared to the propensity score-matched FA-COMS patients, analyzed using mixed model repeated measures (MMRM) analysis. The secondary endpoints were the change from baseline in mFARS at Year 1 and Year 2.

Applicant's primary endpoint analysis at Year 3 shows a mFARs change from baseline difference between Study 1402 Extension and FA-COMS of -3.354 points in favor of Study 1402 extension for the primary pooled analysis (Match 1 (p=0.0002)), -4.096 points in favor of Study 1402 extension for the primary placebo-omav population analysis (Match 2 (p=0.0001)), and -4.240 points in favor of Study 1402 extension for the primary Omav-omav population analysis (Match 3 (p=0.0190)).

Natural history comparisons are generally difficult to interpret due to selection biases of patients for comparisons from the natural history database, comparability of patient's selection of patients due to missing information on known or unknown prognostic factors of disease progression, attrition of patients during the comparison duration in both treated and natural history groups. These are just a few key elements that complicate the interpretation of such comparisons. All of these factors were limitations with this analysis as well. Despite all these

limitations, an assuring point of consideration was the magnitude of change in mFARS score each year in the FA-COMS data versus the omaveloxone study. The magnitude of change observed in patients receiving omaveloxolone treatment appeared to have deviated from that observed in the FA-COMS natural history study. These data are also published by Patel et. al in a larger number of FA patients between the ages 16-40 years (inclusion criteria for the omaveloxolone Study) showing an approximately 2-point average increase in mFARS each year. i.e., a change of approximately 6-points average increase at 3 years. In comparison to this worsening in mFARS observed in natural history study, the omaveloxolone treated patient showed a slower worsening, which was consistent in any subset of patients evaluated. Patients who were treated with omaveloxone for the longest duration showed an average increase of 2-points in mFARS at 3 years, thus suggesting a clinically meaningful deviation from the observed natural history predicted increase of 6 points in 3 years. This pattern was consistent in various subgroups of patients evaluated in either the FA-COMS patients or omaveloxolone treated patients matched for covariates that could affect efficacy analyses. Therefore, despite the limitations of a post-hoc analysis that may be confounded by known or unknown biases as discussed in this review, these analyses do provide confirmatory evidence of effectiveness of omaveloxolone.

In addition, the Applicant included mechanistic data from pharmacodynamic biomarkers that provide additional support for omaveloxolone treatment effects observed in Study 1402. Frataxin deficiency in FA patients is thought to result in alterations in iron sulfur cluster biogenesis, mitochondrial iron homeostasis. Nrf2 regulates iron metabolism pathway in response to oxidative and electrophilic stress by directly increasing the expression of several genes involved in iron handling, including genes involved in iron buffering and sequestration [eg, ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL), which combine to form ferritin]. Excess free iron generates reactive oxygen species, impairs mitochondrial function, and initiates ferroptosis. Therefore, the regulation of the pool of free iron within the cell is warranted. 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. In vitro data supports a conclusion that omaveloxolone is a Nrf2 activator in animal models. The Office of Clinical Pharmacology review also concludes that the increase in ferritin in the plasma may be related to Nrf2 activation, however, further points out that the increase in ferritin due to Omaveloxolone mediated cell damage could not be ruled out.

Based on this mechanistic biological plausibility of ferritin increase with Nrf2 activation, omaveloxolone treatment has shown dose dependent increase in ferritin observed in Part 1 of the study (doses 5 mg to 300 mg) (Table 24). Therefore, this mechanistic increase in ferritin can be considered a pharmacodynamic effect of omaveloxolone suggestive of Nrf2 activation that provides additional confirmatory evidence of effectiveness of omaveloxolone.

**Table 24 Ferritin Levels Across Doses**

| Parameter | Visit | Omaveloxolone | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5 mg (N=6) | 10 mg (N=6) | 20 mg (N=6) | 40 mg (N=6) | 80 mg (N=6) | 160 mg (N=12) | 300 mg (N=10) | Placebo (N=17) |
| Ferritin (µg/L) | Week 4 | -6.35 (11.243) | -17.87 (21.355) | 4.22 (13.570) | 15.38 (15.233) | 21.33 (16.870) | 34.23 (41.524) | 43.49 (62.560) | -4.86 (10.776) |

However, the magnitude of increase in ferritin that may have an optimal effect on mitochondrial iron homeostasis remains unclear.

Conclusion: Overall, given the unmet need in FA, with no currently available therapies, I consider the observed evidence of effectiveness from a single adequate and well-controlled study, Study 1402, in the pre specified FA population without pes cavus, the observed effect in all randomized population consisting of patients with or without pes cavus, with confirmatory evidence from the natural history comparison, in addition to the pharmacodynamic data supporting the biologic plausibility of the treatment effect, adequate to provide substantial evidence of effectiveness of omaveloxolone in the treatment of FA.

# 8. Review of Safety

The safety population consisted of all randomized patients who received at least 1 dose of omaveloxolone.

The clinical safety profile of systemic dosing of omaveloxolone has been studied in approximately 400 patients and healthy subjects, including 4 pharmacokinetic studies and 6 clinical studies in FA, mitochondrial myopathy, and oncology. The FA development program included 3 individual parts to Study 1402 (Study 408-C-1402 Part 1, Part 2 and Extension) that enrolled 172 patients and included a total of 33 patients greater than 16 and less than 18 years of age.

The evidence of safety of omaveloxolone in the FA population at the to-be marketed dose of 150 mg is based on:

- 48-Week controlled Study 408-C-1402 Part 2 (referred to as Study 1402 Part 2)
- Open label extension Study 408-C-1402 (referred to as Study 1402 Extension)

In addition, the safety data from the following studies was reviewed to look for adverse events that were not observed in Study 1402 Part 2 and its extension:

- 12-Week controlled Dose escalating Study 408-C-1402 Part 1 (referred to as Study 1402 Part 1)
- Serious Adverse events and deaths in studies with omaveloxolone in other indications

Overall safety will be assessed in the following groups:

**Analysis Set A**: Primary placebo-controlled analysis set at the proposed dose Omaveloxolone 150 mg. This analysis set is also utilized for the basis of proposed labeling (Table 25).

**Table 25 Placebo-Controlled Safety Assessment from Study 1402-PT2 (Analysis Set A)**

| Study Number | Study Design | Omaveloxolone 150 mg | Placebo | Total |
|---|---|---|---|---|
| 408-C-1402-PT2 | Double-blind, randomized, placebo-controlled | 51 | 52 | 103 (Final DBL 12 Nov 2019) |
| **Total Patients** | | **51** | **52** | **103** |

**Analysis Set E:** This set provides safety data on open-label, long term exposure to omaveloxolone at 150 mg. This set consists of patients with ≥48 weeks exposure to omaveloxolone 150 mg, ≥96 weeks exposure to omaveloxolone 150 mg, and ≥144 weeks exposure to omaveloxolone 150 mg. This set also included patients from Study 408-1402-PT1. Part 1 patients had a gap in time of up to four years before enrolling into the extension study after completion of Part 1, and are therefore considered treatment naïve in the extension study, where all patients received omaveloxolone 150 mg. Patients in 408-C-1402 Part 2 could go directly from the double blind to the extension study with a gap of 4 weeks after Week 52.

**Table 26 Long-Term Safety Assessment from Study 1402 PT-1 and PT2 extension (Analysis Set E)**

| | >=48 Weeks | >=96 Weeks | >=144 Weeks |
|---|---|---|---|
| 408-C-1402-PT1 | 50 | 41 | 0 |
| 408-C-1402-PT2 | 87 | 71 | 37 |
| **Total Patients** | **137** | **112** | **37** |

In addition, the following sets were reviewed for additional information on safety and time trends in adverse events.

**Analysis Set B:** This adds placebo and omaveloxolone 160 mg dose for 12 weeks duration from Study 1402 Part 1 to the Analysis Set A.

**Table 27 Placebo-Controlled Safety Assessment from Study 1402-PT1 (160 mg) and Study 1402-PT2 (Analysis Set B)**

| Study Number | Study Design | Omaveloxolone 150/160 mg | Placebo | Total |
|---|---|---|---|---|
| 408-C-1402-PT2 | Double-blind, randomized, placebo-controlled | 51 | 52 | 103 |
| 408-C-1402-PT1 | Double-blind, dose-ranging, randomized, placebo-controlled | 12 | 17 | 29 |
| | **Total Patients** | **63** | **69** | **132** |

**Analysis Set D:** This analysis set (Long term Safety Study Subgroup) includes all omaveloxolone-treated patients (no placebo-treated patients) from Study 1402 Part 2 who were randomized to omaveloxolone and enrolled into the open-label extension. Patients in the OLE who had completed Study 1402 Part 1 and patients who were randomized to placebo in Study 1402 Part 2 are not included in this subgroup. This analysis set was assessed to confirm the long-term safety of omaveloxolone 150 mg treatment from start of Study 1402 Part 2 to the end of extension phase. However, Analysis set E also includes these patients, therefore no new information will likely be observed from this set.

**Table 28 Long-Term Safety Assessment in Only Omaveloxolone Treated Patients (Analysis Set D)**

| Study Number | Study Design | Omaveloxolone 150 mg |
|---|---|---|
| 408-C-1402-PT2 | Double blind, randomized, placebo-controlled | 51 |
| 408-C-1402 Extension | Double blind, dose-ranging, randomized, placebo-controlled | 43 |
| | **Total Patients** | **51** |

**120-Day Safety Update:**

The original interim database lock date was August 17, 2021. The 120-day safety update reported additional safety data from August 18, 2021 to March 24, 2022 from the ongoing Study 1402 Extension.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

In ongoing and completed clinical studies across all indications and diseases, approximately 392 patients and healthy subjects have been exposed to omaveloxolone capsules (Table 29).

**Table 29 Overall Exposure to Capsule Formulation of Omaveloxolone Across Studies (Unique Patients)**

| Clinical Trial Group | Studies Included | Omaveloxolone N=392 | Placebo |
|---|---|---|---|
| Placebo-controlled studies conducted in patients with FA | Study 1402 Part 2<br>Study 1402 Part 1 | 51*<br>52* | 52<br>17 |
| Open-label studies conducted in patients with FA | Study 1402 Extension | 62* | |
| Placebo-controlled studies conducted in patients with mitochondrial myopathies | 408-C-1403 | 40 | 13 |
| Open-label studies conducted in patients with oncologic indications | 408-C-1303<br>408-C-1401 | 11<br>41 | |

| | | | |
|---|---|---|---|
| Clinical pharmacology studies conducted in healthy volunteers | 408-C-1703<br>408-C-1804<br>408-C-1805<br>408-C-1806 | 34<br>32<br>8<br>61 | |

*Unique patients: includes placebo subjects that went to the open label extension study to received Omaveloxolone 150 mg (49 placebo patients from PT2+13 placebo patients from PT1).

The overall exposure on omaveloxolone in FA is summarized in Table 30.

**Table 30 Omaveloxolone Enrollment for Pivotal and Supportive Clinical Studies in Friedreich's Ataxia**

| Study | Treatment | | Number of Patients |
|---|---|---|---|
| **Study 1402 Part 1** | Placebo<br>Omav | <br><br>**Total Patients** | 17<br>52<br>**69** |
| | 2.5/5 mg<br>10 mg<br>20 mg<br>40 mg<br>80 mg<br>160 mg<br>300 mg | | 6<br>6<br>6<br>6<br>6<br>12<br>10 |
| **Study 1402 Part 2** | Placebo<br>Omav 150 mg | <br><br>**Total Patients** | 52<br>51<br>**103** |
| **Study 1402 Extension** | <u>From Part 1</u>:<br>Placebo/Omav 150 mg<br>(Initially randomized to Placebo)<br>Omav/Omav 150 mg<br>(Initially randomized to Omav) | | 57 out of 69<br>13<br><br>44 |
| | <u>From Part 2</u>:<br>Placebo/Omav 150 mg<br>Omav 150 mg/Omav 150 mg<br><br>**Total Patients** | | 92 out of 103<br>49<br>43<br><br>**149** |

The duration of exposure in FA patients at omaveloxolone 150 mg is show in Table 31.

**Table 31 Duration of exposure in FA patients**

| Duration | Omaveloxolone 150 mg |
|---|---|
| ≥48 Weeks Omaveloxolone Exposure | 137 |
| ≥96 Weeks Omaveloxolone Exposure | 125 |
| ≥144 Weeks Omaveloxolone Exposure | 69 |
| ≥168 Weeks Omaveloxolone Exposure (120-Day Safety Update) | 11 |
| **Total Patients** | **137** |

### 8.2.2. Relevant characteristics of the safety population:

The baseline demographics of the safety population (Analysis Set A) are shown in Table 32. Overall, the mean age at screening was 23.4 years and 24.1 years for the omaveloxolone-treated and placebo-treated groups, respectively, and patients ranged from 16 to 40 years of age. A total of 24 adolescent patients (≥16 and less than 18 years) were randomized into the study. In the randomized patient population, 53% (55/103) patients were male and 47% (48/103) were female, with a higher proportion of patients randomized to the omaveloxolone treatment group being female (31/51 [61%]) compared to placebo group (17/52 [33%]). The majority of patients were White (100/103 [97%]), with 5% (5/103) Hispanic or Latino patients and 95% (98/103) not Hispanic or Latino.

**Table 32 Baseline Demographics for Safety Population (Analysis Set A)**

| Parameter (units) | Statistics | Safety Population | |
|---|---|---|---|
| | | Placebo (N = 52) n (%) | Omaveloxolone 150 mg (N = 51) n (%) |
| Age at Screening (Years) | n | 52 | 51 |
| | Mean (SD) | 24.1 (7.85) | 23.4 (6.08) |
| | Median | 21.0 | 22.0 |
| | Min, Max | 16, 40 | 16, 39 |
| Age Group at Screening (Years) | <18 | 15 (28.8) | 9 (17.6) |
| | ≥18 | 37 (71.2) | 42 (82.4) |
| Sex | Female | 17 (32.7) | 31 (60.8) |
| | Male | 35 (67.3) | 20 (39.2) |
| Ethnicity | Hispanic or Latino | 3 (5.8) | 2 (3.9) |
| | Not Hispanic or Latino | 49 (94.2) | 49 (96.1) |
| Race | White | 50 (96.2) | 50 (98.0) |
| | Other | 2 (3.8) | 1 (2.0) |

Source: Reviewer verification

The baseline demographics by patient age <18 and ≥ 18 years (Analysis Set A) is shown in Table 33.

**Table 33 Baseline Demographics by Age (Analysis Set A)**

| Category (Statistic) | <18 Years of Age | | ≥18 Years of Age | |
|---|---|---|---|---|
| | Omaveloxolone 150 mg N=9 | Placebo N=15 | Omaveloxolone 150 mg N=42 | Placebo N=37 |
| Age (years) at Screening | | | | |
| Mean (SD) | 16.6 (0.53) | 16.5 (0.52) | 24.9 (5.71) | 27.1 (7.34) |
| Median (min, max) | 17.0 (16, 17) | 17.0 (16, 17) | 23.0 (18, 39) | 26.0 (18, 40) |
| Sex (n,%) | | | | |
| Male | 3 (33.3%) | 10 (66.7%) | 17 (40.5%) | 25 (67.6%) |
| Female | 6 (66.7%) | 5 (33.3%) | 25 (59.5%) | 12 (32.4%) |
| Race (n,%) | | | | |
| White | 9 (100%) | 15 (100%) | 41 (97.6%) | 35 (94.6%) |
| Non-White | 0 | 0 | 1 (2.4%) | 2 (5.4%) |
| Ethnicity (n,%) | | | | |
| Not Hispanic or Latino | 9 (100%) | 14 (93.3%) | 40 (95.2%) | 35 (94.6%) |
| Hispanic or Latino | 0 | 1 (6.7%) | 2 (4.8%) | 2 (5.4%) |
| Region (n,%) | | | | |
| United States | 8 (88.9%) | 12 (80.0%) | 28 (66.7%) | 23 (62.2%) |
| Other | 1 (11.1%) | 3 (20.0%) | 14 (33.3%) | 14 (37.8%) |

Source: Reviewer verification

### 8.2.3. Adequacy of the safety database:

Patient exposure of 137 patients with omaveloxolone 150 mg for >48 weeks is adequate given the rare nature of the disease and is generalizable to the US population. Of the 24 adolescent patients, 14 (63.6%) had 48 weeks of treatment, and 11 (50.0%) had >96 weeks, supporting the extended exposure of omaveloxolone in adolescents ≥16 years of age. Drug compliance was >90% in >90% of the patients.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall, the safety database was adequate in format and quality for review.

### 8.3.2. Categorization of Adverse Events

Pre-planned elective procedures (surgeries or therapies) that were performed to manage/treat conditions that existed prior to the patient's enrolling in the trial (e.g., elective periodontal

surgery, elective hernia repair) were not recorded as AEs, but were documented in the patient's source documents. If a pre-planned procedure was performed early (e.g., as an emergency) because the pre-existing condition worsened, the worsening condition was captured as an AE.

The verbatim terms were manually reviewed for accuracy of coding. The Applicant's coding resulted in appropriate translation of verbatim terms to preferred terms. However, TEAEs were often coded to multiple different equivalent Preferred Terms. The grouping of some closely related terms or pooling of preferred terms (AEDECOD) by the Applicant may have led to potential splitting of like terms, which may decrease the ability to identify a safety signal. These were regrouped by the reviewer to avoid splitting and pool similar preferred terms together as shown in Table 34. The regrouped dataset was used in the AE analyses summarized in the review.

**Table 34 Pooling of Preferred Terms and Re-grouping of Terms**

| **Groupings for AEDECOD** | **AEDECOD as** |
|---|---|
| Abdominal discomfort<br>Abdominal pain<br>Abdominal distension<br>Abdominal pain lower<br>Abdominal pain upper | Abdominal pain |
| Blood pressure abnormal<br>Blood pressure increased | Blood pressure abnormal |
| Depression<br>Depressed mood | Depression |
| Dizziness<br>Dizziness postural | Dizziness |
| Eczema<br>Eczema Eyelids | Eczema |
| Dyspnea<br>Dyspnea exertional | Dyspnea |
| Diarrhea<br>Fecal volume increased<br>Frequent bowel movements | Diarrhea |
| Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Hepatic enzyme increased<br>Hepatic function abnormal<br>Gamma-glutamyltransferase increased<br>Liver function test increased | Elevated Liver enzymes |

| | |
|---|---|
| Hepatic steatosis | |
| Gastroenteritis<br>Gastroenteritis viral<br>Gastrointestinal viral infection | Gastroenteritis |
| Glucose urine present<br>Glycosuria | Glycosuria |
| Hypercholesterolemia<br>Hypertriglyceridemia<br>Lipids increased | Hypercholesterolemia |
| Influenza<br>Influenza Like Illness | Influenza |
| Initial insomnia<br>Middle insomnia<br>Insomnia | Insomnia |
| Asthenia<br>Fatigue | Fatigue |
| Muscle spasms<br>Muscle Spasticity<br>Muscle twitching | Muscle spasms |
| Musculoskeletal chest pain<br>Musculoskeletal discomfort<br>Musculoskeletal pain<br>Musculoskeletal stiffness<br>Myalgia<br>Non cardiac chest pain<br>Muscle strain | Musculoskeletal pain |
| Pain<br>Pain in extremity<br>Pain in Jaw<br>Neck Pain<br>Back Pain<br>Oropharyngeal pain<br>Arthralgia | Pain |
| Pruritus<br>Pruritus generalized | Pruritus |
| Ovarian Cyst<br>Ovarian Cyst ruptured | Ovarian Cyst |
| Rash<br>Rash Macular<br>Rash erythematous<br>Rash generalized | Rash |

| | |
|---|---|
| Rash maculo-papular<br>Dermatitis allergic<br>Dermatitis contact | |
| Rhinitis<br>Rhinitis allergic | Rhinitis |
| Tooth disorder<br>Tooth ache | Tooth disorder |
| Upper respiratory tract infection<br>Upper respiratory tract congestion<br>Lower respiratory tract congestion<br>Lower respiratory tract infection<br>Sinusitis<br>Sinus congestion<br>Viral infection<br>Viral upper respiratory tract infection<br>Respiratory tract infection<br>Respiratory tract infection viral<br>Bronchitis | Respiratory tract infection |
| Suicidal behavior<br>Suicidal ideation | Suicidal ideation |
| Sinus tachycardia<br>Tachycardia | Sinus tachycardia |
| Temperature intolerance<br>Temperature regulation disorder<br>Feeling hot<br>Hot Flush | Temperature intolerance |
| Urinary incontinence<br>Incontinence<br>Micturition urgency | Urinary incontinence |
| Vertigo<br>Vertigo positional | Vertigo |
| Vitamin D decreased<br>Vitamin D deficiency | Vitamin D deficiency |
| Abnormal Weight loss<br>Weight decreased | Weight decreased |

### 8.3.3. **Routine Clinical Tests**

Safety parameters in both Part 1 and Part 2 of Study 1402 include results of echocardiogram,

ECG, vital sign measurements, weight, BMI, physical examination, concomitant medications, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, assessment of BNP and NT-Pro BNP, and pregnancy tests [as indicated]). Safety parameters in the extension study include vital sign measurements, physical examination results, AEs, SAEs, weight, and assessment of B-Type Natriuretic Peptide (BNP) and N-Terminal Prohormone of B-Type Natriuretic Peptide (Pro-BNP).

## 8.4. Safety Results

The overall summary of fatal and serious TEAEs (SAEs) in the controlled and open-label phases of the study are tabulated in Table 35 and will be elaborated in subsequent sections of this review.

**Table 35 Overall Safety Summary**

**Analysis Set A (placebo-controlled Study 1408-PT2)**

| Preferred Terms | Omaveloxolone 150 mg (N = 51) | Placebo (N = 52) |
|---|---|---|
| Subjects Who Had Drug Withdrawn Due to a TEAE | 4 ( 7.8%) | 2 ( 3.8%) |
| Subjects Who Had Drug Withdrawn Due to a SAE | 1 ( 2.0%) | 1 ( 1.9%) |
| Subjects With Serious TEAE | 5 ( 9.8%) | 3 ( 5.8%) |
| Subjects With Fatal TEAE | 0 | 0 |

**Analysis Set E (long-term open label extension)**

| Preferred Terms | Omaveloxolone 150 mg (N = 137) |
|---|---|
| Subjects With Fatal TEAE | 0 |
| Subjects With Serious TEAE | 13 ( 9.5%) |
| Subjects Who Had Drug Withdrawn Due to a Serious TEAE | 0 |
| Subjects Who Had Drug Withdrawn Due to a TEAE | 1 ( 0.7%) |

Source: Reviewer verification

**Analysis Set A**: No deaths were reported.
**Analysis Set E**: No deaths were reported.

Other indications: There were 7 deaths reported in the oncology study that were related to

disease progression. Omaveloxolone treatment was <85 days in these patients.

### 8.4.2. Serious Adverse Events

**Analysis Set A:**

Eight (8) patients, (5 [9.8%] omaveloxolone; 3 [5.8%] placebo) experienced serious TEAEs. No serious TEAEs were reported by more than 1 patient during the 48-week treatment period except atrial fibrillation, which was reported in 1 patient in each treatment group. None of the SAEs occurred in the pediatric subgroup (Table 36).

**Table 36 SAEs in Analysis Set A**

| Treatment | Patient Sex/Age (Years) | Preferred Term | Onset Day/Severity | Action Taken with Study Drug Outcome |
|---|---|---|---|---|
| **Placebo** | Male/21 | Gallbladder disorder | Day 55/Moderate | Dose not changed<br>Resolved |
| | Female/33 | Ankle fracture | Day 273/Moderate | Dose not changed<br>Resolved |
| | Male/22 | Atrial fibrillation | Day 38/Moderate | Drug withdrawn<br>Resolved |
| **Omaveloxolone** | Male/18 (b) (6) | Atrial fibrillation | Day 52/Moderate | Dose not changed<br>Resolved |
| | Female/21 (b) (6) | Laryngitis | Day 166/Moderate | Dose not changed<br>Resolved |
| | | Viral upper respiratory tract infection | Day 166/Moderate | Dose not changed<br>Resolved |
| | | Palpitations | Day 227/Moderate | Drug interrupted<br>Resolved |
| | | Musculoskeletal pain | Day 309/Moderate | Drug interrupted<br>Resolved |
| | | Sinus tachycardia | Day 311/Moderate | Drug interrupted<br>Resolved |
| | | Palpitations | Day 340/Moderate | Dose not changed<br>Resolved |

| | | | | |
|---|---|---|---|---|
| | Male/29 (b) (6) | Anemia | Day 346/Mild | Dose not changed Resolved |
| | Female/30 (b) (6) | Ventricular tachycardia[a] | Day 29/Mild | Drug withdrawn Resolved |
| | Male/23 (b) (6) | Craniocerebral injury[a] | Day 349/Moderate | Dose not changed Resolved |

Patient narratives of these SAEs are summarized below for those on omaveloxolone:

**Patient (b) (6) (Atrial fibrillation):**
This patient (18 years, male) had a history of cardiomyopathy. The patient experienced the SAE of atrial fibrillation on (b) (6) (Study Day 52). The last dose of study medication prior to the event was administered on Study Day 51 (b) (6)

On Study Day 52 (b) (6), the patient woke up in the morning and, upon standing, felt as if his heart were racing. Upon arrival to the emergency department, the patient reported palpitations, lightheadedness, generalized weakness, and shortness of breath described as constant and moderate; however, he denied chest pain, cough, dyspnea, nausea, or vomiting. Vital signs revealed a blood pressure of 125/60 mm Hg, heart rate of 162 bpm, and respiratory rate of 17 breaths per minute. An ECG revealed atrial fibrillation with rapid ventricular response (heart rate of 154 bpm) and inferolateral ST-T segment changes without ST elevation. The patient was treated with diltiazem. After diltiazem was stopped, results of an ECG revealed rate-controlled atrial fibrillation (heart rate of 92 bpm) with improved inferolateral ST segment changes.

The Investigator considered the event of atrial fibrillation serious, moderate in intensity, and unlikely related to the study medication. The Investigator reported FA as a probable etiology of the event.

**Patient (b) (6) (Palpitations, musculoskeletal pain and sinus tachycardia):**
A 21-year-old white female enrolled in Study 1402 Part 2 and received omaveloxolone 150 mg from Study Day 1 (b) (6) until Study Day 338 (b) (6) The patient's ongoing medical history included cardiac tachycardia since (b) (6).

The patient developed palpitations described as intermittent in nature and occurring on and off for several weeks. The palpitations would resolve with rest, and some episodes were associated with lightheadedness and postural changes. On Study Day 115 (b) (6) she experienced a moderate TEAE of palpitations for which a Holter monitor was prescribed; no change in study drug was made, and the TEAE was resolved on Study Day 170 (b) (6)

On Study Day 169 (b) (6), laboratory testing revealed a BNP level of 222 ng/L (NR: <100 ng/L) and NT-proBNP level of 1674 ng/L (NR: ≤97 ng/L). The BNP and NT-proBNP remained high even though the TEAE of palpitations and sinus tachycardia resolved on Day 170.

On Study Day 181 (b) (6), the patient presented to the hospital and was admitted for evaluation and treatment of viral URTI and laryngitis. That same day, laboratory testing revealed a BNP level of 127 ng/L. The patient's troponin levels were 0.29 µg/L, 0.4 µg/L, and 0.3 µg/L (NR: <0.040 µg/L), and her white blood cell count was increased.

On Study Day 181 (b) (6), a second moderate TEAE of palpitations was reported; study drug was not changed, and the event was resolved on Study Day 186 (b) (6). The investigator considered these events possibly related to study drug.

On Study Day 183 (b) (6), results of an echocardiogram revealed a small left ventricular cavity with normal systolic function, normal ejection fraction at 55%, no obvious regional wall motion abnormalities, **a moderate concentric increase in left ventricular wall thickness**, normal right ventricular size with normal systolic function, normal atrial dimensions, trivial circumferential pericardial effusion without signs of constrictive physiology, and no evidence of significant valvular dysfunction by Doppler ultrasonography. Results of an ECG revealed sinus tachycardia. The treating physician believed that myocarditis might have been the cause for the patient's palpitations.

On Study Day 227 (b) (6), the patient experienced a moderate serious TEAE of recurrent palpitations (reported third event), a moderate serious TEAE of noncardiac chest pain on Study Day 309 (b) (6), and a moderate serious TEAE of worsening sinus tachycardia on Study Day 311 . The last dose of study drug administered prior to these events was on Study Day 227 (b) (6) Study drug was **interrupted**, and the event of recurrent palpitations was reported as resolved on Study Day 260 (b) (6) and the events of noncardiac chest pain and sinus tachycardia were reported as resolved on Study Day 321 (b) (6) . All 3 TEAEs were considered by the investigator to be possibly related to study drug.

On Study Day 338 (b) (6), the study medication was discontinued.

The events of palpitations, noncardiac chest pain, and sinus tachycardia reported in 1 omaveloxolone-treated patient were the only SAEs considered by the Investigator to be possibly related to the study drug.

***Reviewer's comment:*** *This patient had a low diastolic blood pressure of 65 and 56 mmHg on Day 169 and Day 339 with normal systolic pressures of 90 mmHg and 98 mmHg on Day 169 and Day 339 around the time palpitations were experienced. The hospital diagnosis of palpitations was considered secondary to viral URTI and laryngitis. This patient also had elevated BNP and*

*NT pro-BNP at the time of one of his events of palpitations, but an echocardiogram did not show any clinically significant evidence of heart failure at the time. There appears to be many confounders limiting attribution to study drug.*

**Patient (b) (6) (Anemia):** Patient (29 years, male) received omaveloxolone 150 mg from (b) (6) until (b) (6) On Study Day 172 (b) (6), the subject developed worsening of anemia. This patient had a history of iron deficiency anemia on a background of hiatus hernia with associated gastric reflux and esophagitis. Worsening of anemia was considered serious but mild in intensity.

On Study Day 346 (b) (6), the patient was admitted to the hospital and underwent an elective esophagogastroduodenoscopy procedure to further investigate the cause of his worsening anemia and was kept overnight as a safety procedure. Findings revealed nonerosive gastritis and poorly visualized fundus, a sliding hiatus hernia 3 cm in length, esophagitis (Grade C)/reflux, mild erythematous change in the antrum, and normal duodenum. On Study Day 347 (b) (6), the event of worsening of anemia was considered resolved, and the patient was discharged with instructions to follow up in 8 weeks to ensure healing of the esophagus. The patient continued in the study. The Investigator considered the event of worsening of anemia serious, mild in intensity, and unlikely related to study drug.

***Reviewer's Comment:*** *This patient had a history of iron deficiency anemia on a background of hiatus hernia with associated gastric reflux and esophagitis worsening of anemia may not be related to study drug.*

**Patient (b) (6) (Ventricular tachycardia):** Patient (30 years, female) received omaveloxolone 150 mg from (b) (6) until (b) (6). Her medical history included acne. On Study Day 29 (b) (6) the patient experienced the SAE of ventricular tachycardia. The last dose of study drug prior to the event was administered on Study Day 17 (b) (6) due to subject withdrawal of consent. Therefore, this SAE occurred 2 weeks after the last drug administration.

On (b) (6), baseline transthoracic echocardiography revealed normal left ventricular cavity size and wall thickness, normal systolic and diastolic function, ejection fraction of 62%, normal right ventricular size and systolic function, normal bi-atrial size, no hemodynamically significant valvulopathies, mild tricuspid regurgitation, right ventricular systolic pressure of 21 mm Hg, and no evidence of pericardial effusion. A baseline ECG revealed low voltage and diffuse repolarization abnormalities; however, they were not considered clinically significant. ECG results revealed no clinically significant abnormalities on Day 15. Study drug was interrupted on the same day. Elevated liver enzymes were reported as a nonserious AE, and transaminase levels returned to within normal limits on Study Day 29. The following laboratory testing were reported abnormal.

| Day | ALT (U/L) | AST (U/L) | TBL (µmol/L) | Lactate dehydrogenase (U/L) | GGT (U/L) |
|---|---|---|---|---|---|
| Day 15 | 132 | 69 | 4 | 174 | 11 |
| Day 17 | 170 | 85 | 5 | 222 | 13 |

On the same day, a week-4 exercise test done per protocol revealed trace ventricular tachycardia of 175 beats per minute (resting rate, 90 beats per minute) at peak exercise. The patient remained asymptomatic and had a normal recovery without treatment, and the event of ventricular tachycardia was considered resolved on the same day. The patient was evaluated by a cardiologist on Study Day 50 (b) (6), and an ECG revealed sinus rhythm, a normal QTc interval, and widespread repolarization abnormalities. An ECG revealed low to normal left ventricular ejection fraction but was otherwise unremarkable. The patient underwent a 24-hour Holter monitor analysis; results were unremarkable and showed sinus rhythm throughout with a maximum heart rate of 113 beats per minute. The cardiologist concluded that the findings suggest a mild FA cardiac phenotype, and a low-dose β-blocker was recommended.

On Study Day 57 (b) (6), cardiac magnetic resonance imaging revealed normal right and left ventricle volumes, an aberrant origin of the right subclavian artery with retro-esophageal course to right, suspicion of subepicardial fibrosis in the left ventricle lateral wall, and no left ventricular hypertrophy or myocardial inflammation, edema, or infarction. This new information was evaluated by the cardiologist, who then considered the event of non-sustained ventricular tachycardia to be out of keeping with the phenotype and unexpected and therefore recommended the patient not re-start the study medication. The study drug was not restarted and was **permanently discontinued** due to the SAE. The Investigator identified a possible cause of the event as underlying cardiac disease.

***Reviewer's Comment:*** *Ventricular tachycardia occurred 2 weeks after the last study drug administration, therefore it is less likely due the omaveloxolone treatment.*

**Reviewer's Comment:** *This reviewer notes that clinical determination of cardiac involvement due to investigational treatment is often complicated by comorbidities in FA patients. The walls of the left ventricle become thickened, and different phenotypic manifestations are seen, including concentric or asymmetric hypertrophy and (less commonly) dilated cardiomyopathy. Dilated cardiomyopathy and arrhythmia are associated with mortality in patients with FA. Cardiomyopathy tends to be correlated with the clinical neurologic age of onset and the nucleotide triplet repeat length (i.e., markers of phenotypic disease severity) rather than the duration of disease or the severity of neurologic symptoms. Shortness of breath or palpitations are the most common signs of heart disease in FA patients.*

**Patient (b) (6) (Craniocerebral injury):** Patient (23 years, male) in Study 1402 Extension had a serious TEAE of craniocerebral injury requiring hospitalization starting on

Study Day 349 (b) (6) that resolved on Study Day 350 (b) (6). On Study Day 349 (b) (6), the patient experienced a fall down the stairs at school, which was unwitnessed. The patient had fallen onto the left side of his head, left shoulder, and left side of the chest and may have lost consciousness. When first found, the patient displayed retrograde amnesia and impaired vigilance and was subsequently taken to the emergency services department. The patient's last dose of study drug was 15 days prior to the event on (b) (6) (last day of dosing in Study 1402 Part 2). The craniocerebral injury event was assessed as moderate in severity and unrelated to study drug by the investigator; study drug was unchanged. This patient continued in the Study 1402 Extension on (b) (6).

***Reviewer's Comment**: Craniocerebral injury appears to be related to the fall, which is likely related to FA, and unlikely omaveloxolone related.*

**Analysis Set E:**

Thirteen patients (9.5%) experienced a serious TEAE in the extension phase as shown in Table 37.

**Table 37 Serious TEAEs in the Open label extension Phase (≥ 48 weeks of treatment)**

| Preferred Terms | Omaveloxolone 150 mg (N = 137) |
|---|---|
| Total Subjects with any Adverse Events | 13 ( 9.5%) |
| Sinus tachycardia* (b) (6) | 2 ( 1.5%) |
| Suicide attempt (b) (6) | 2 ( 1.5%) |
| Depression (b) (6) | 2 ( 1.5%) |
| Acute left ventricular failure * (b) (6) | 1 ( 0.7%) |
| Anemia* | 1 ( 0.7%) |
| Corona virus infection | 1 ( 0.7%) |
| Craniocerebral injury* | 1 ( 0.7%) |
| Facial bones fracture | 1 ( 0.7%) |

| Preferred Terms | Omaveloxolone 150 mg (N = 137) |
|---|---|
| Gastroenteritis norovirus (b) (6) | 1 ( 0.7%) |
| Hip fracture | 1 ( 0.7%) |
| Laryngitis* | 1 ( 0.7%) |
| Musculoskeletal pain* | 1 ( 0.7%) |
| Pain (b) (6) | 1 ( 0.7%) |
| Palpitations* | 1 ( 0.7%) |
| Pilonidal cyst (b) (6) | 1 ( 0.7%) |
| Sepsis (b) (6) | 1 ( 0.7%) |
| Troponin increased (b) (6) | 1 ( 0.7%) |
| Viral upper respiratory tract infection* | 1 ( 0.7%) |

*Events that occurred in the same patient in the double-blind PT2 phase. One additional sinus tachycardia was observed.

**Patient (b) (6) - Patient (b) (6) (Depression and Suicide Attempt)**
A 38-year-old patient who was initially on placebo received omaveloxolone in the extension phase on (b) (6). The patient's relevant medical history included abdominal pain(with vinegar containing food), muscle spasms, and insomnia (since (b) (6)); Friedreich's ataxia (since (b) (6)); arthralgia, joint stiffness, and back pain (mild, since (b) (6)); vasectomy (since (b) (6)); depression and fatigue (since (b) (6)); periodic limb movement disorder (since (b) (6)); non-cardiac chest pain and heart rate increased (since (b) (6)); pyrexia, nephrolithiasis, nausea, and neck pain (since (b) (6)). Concomitant medications: atenolol, cyanocobalamin 500 mg, duloxetine 120 mg, ibuprofen, melatonin 3 mg, paracetamol 500 mg, tramadol, and Vitamin B12.

This patient had two episodes of major depression and 2 suicide attempts on Study Day 213 and 268 that required hospitalization. While hospitalized, the patient reported marital issues,

medical issues, inability to work, and concerns for family and children as contributing factors. The patient reported intermittent and missed doses of duloxetine prior to admission. The study drug dose was not changed. Associated signs and symptoms included: depressed mood, poor appetite, decreased energy, unintentional weight loss, anhedonia, pretense to isolate, hopelessness, and passive thoughts of death. On Study Day 217 and 273 respectively, both episodes Major depression was recovered/resolved. The dose of omaveloxolone was not changed.

***Reviewer's Comment:*** *The episodes of depression and suicide attempts appear to be due to the patient's underlying conditions.*

**Patient (b) (6) (Sinus tachycardia and Acute left ventricular failure)**

A 28-years old female patient who was initially on omaveloxolone enrolled in the extension phase on (b) (6) and treatment is ongoing.
The patient's relevant medical history included headache (intermittent, since (b) (6)), diabetes mellitus type 1 (since (b) (6)), heart rate increased (since (b) (6), depression (since (b) (6)), Friedreich's ataxia (since (b) (6), also reported as (b) (6)), migraine (since , foot operation (right, ligament repair, since (b) (6)), and musculoskeletal pain and pain in extremity (right arm pain, right shoulder pain, since (b) (6)).

On Study Day 167 (b) (6), the patient experienced the SAE of sinus tachycardia (Inappropriate sinus node tachycardia) and was hospitalized on the same day. Symptoms included shortness of breath and severe fatigue which had been progressive and occurred with little activity. Additional signs included: blood pressure 102/55 mmHg; heart rate was 50-55 "seconds" (reported as seconds per MedWatch not beats per minute). Chest x-ray revealed pulmonary vascular congestion. On Study Day 167, the patient underwent a planned, combined endocardial and epicardial ablation of the sinus node with insertion of a chest tube. Post-operatively, the patient experienced hypotension (blood pressure not provided) which required norepinephrine infusion. Her blood pressure became stable. On Study Day 168 (b) (6), the chest tube was removed. The study drug dose was not changed. The SAE of Sinus tachycardia was considered recovered/resolved the following day, on Study Day 169 (b) (6) and the patient was discharged from the hospital on the same day. Upon discharge vital signs included: blood pressure 118/96 mmHg, respiratory rate 18 (units not reported; NR not provided), and heart rate 62 "seconds" (reported as seconds per MedWATCH not beats per minute).

On Study Day 173, the patient then experienced the SAE of cardiac failure congestive (Acute diastolic congestive heart failure). Laboratory test results included: troponin 0.111 ng/mL NR 0.000-0.034 ng/mL) and white blood cell (WBC) count 14.60 x 10*3/uL (NR 4.5-11.0 x 10*3/uL).

On Study Day 174 (b) (6), laboratory testing results revealed troponin 0.093 ng/mL and the patient was released from the hospital. On Study Day 177 (b) (6), the patient presented to the ED with shortness of breath, orthopnea with lying flat, dyspnea while lying down and on exertion, increased body wide edema especially in the lower extremities, mild non-productive cough, and wheezing. She reported the feeling of a marble moving around in her chest. Laboratory test results included: troponin 0.057 ng/mL; n-terminal pro-brain natriuretic peptide (proBNP) **961.0 pg/mL** (NR less than 125 pg/mL); blood urea nitrogen (BUN) 16 mg/dL (NR 7-20 mg/dL); and creatinine 0.6 mg/dL (NR 0.7-1.5 mg/dL). Electrocardiogram revealed probable sinus rhythm versus a junctional rhythm and nonspecific ST-T wave changes.

Day 178 (b) (6), echocardiogram revealed an ejection fraction of 62%, normal left ventricular and right ventricular systolic function, mildly dilated left atrium, inter-atrial septal aneurysm without evidence of shunting, mild tricuspid regurgitation, and trace aortic, pulmonic, and mitral regurgitation. The treating physician considered the lower extremity edema and total body volume overload as possibly a residual effect of fluid infusions around the time of ablation procedure and afterwards. The treating physician also noted the elevated proBNP level may reflect congestive heart failure but may also be due to the ablation procedure. The patient reported much of her symptoms resolved; the swelling in her legs completely resolved. The patient was discharged from the hospital with the SAE of Cardiac failure congestive considered recovered/resolved. Upon discharge, vital signs included: blood pressure 92/59 mmHg, heart rate 55 “seconds” (seconds reported in MedWATCH not beat per minute), and respiratory rate 18.

***Reviewer’s Comment:*** *Patient experienced sinus tachycardia requiring ablation. Subsequently, she had signs of elevated pro-BNP and fluid overload, but her echocardiogram did not show significant signs of cardiac failure. It is possible that the elevation of proBNP and fluid overload were secondary to the ablation procedure or underlying cardiac disease related to FA. The role of omaveloxolone in these symptoms is unclear, but as the symptoms occurred after 179 days on treatment and resolved while on drug makes it less likely the primary cause of the symptoms.*

**Patient (b) (6) (Troponin increased)**

Patient (21 years, female) enrolled in the extension study is receiving omaveloxolone since (b) (6). On Study Day 215 (b) (6), the patient experienced an SAE of Troponin increased (Elevated troponins) and was hospitalized on the same day.

Computerized tomography (CT) scan revealed no evidence of acute intracranial abnormality. Chest x-ray revealed no acute cardiopulmonary findings. Electrocardiogram revealed sinus tachycardia (heart rate (HR) 116 beats per minute [bpm]) and left atrial enlargement. Within a few hours, the non-serious AE of Non-cardiac chest pain was recovered/resolved. Laboratory

test results revealed: serial troponin 1 values of 22 pg/mL, 54 pg/mL and 80 pg/mL (normal range [NR] 15 pg/mL). The patient was hospitalized to rule out acute coronary syndrome. During the hospitalization, troponin 1 values began to trend downward (21 pg/mL and 16 pg/mL). On Study Day 216 (b) (6), CT angiogram of chest and transthoracic echocardiography were non-contributory.

The SAE of Troponin increased, and the non-serious AE of Migraine were considered moderate in severity and unrelated to study drug by the clinical investigator. The clinical investigator reported Friedreich's ataxia as the probable etiology of the SAE of Troponin increased.

***Reviewer's Comment:*** *The elevated troponin that resolved on its own within one day after 215 days of treatment make it unlikely drug related.*

120-Day Safety Update reported a SAE of epilepsy in a 21-year-old male patient (b) (6) 9 months after starting Omaveloxolone treatment. Patient had a history of epilepsy. The patient had been taking anticonvulsants regularly. The patient's study treatment was not interrupted due to the SAE.

### 8.4.3. Dropouts and/or Discontinuations and Treatment Interruptions Due to Adverse Effects

**Analysis Set A:**

Overall, 7 (13.7%) omaveloxolone-treated patients and 2 (3.8%) placebo-treated patients discontinued the study. Four (7.8%) omaveloxolone-treated patients and 2 (3.8%) placebo-treated patients discontinued the study drug because of TEAEs. There were no TEAE Preferred Terms leading to study drug discontinuation that occurred in greater than 1 omaveloxolone- or placebo-treated patient. No pediatric patients <18 years of age discontinued treatment due to a TEAE or had a treatment interruption due to an TEAE (Table 38).

The proportion of patients who interrupted study drug administration because of a TEAE (but ultimately continued with treatment) was greater in the omaveloxolone-treated patients (17.6%) compared to placebo-treated patients (1.9%).

**Table 38 Summary of Patient Discontinuations (Analysis Set A)**

| Study 1402 Part 2 Patient Disposition | Omaveloxolone 150 mg (N=51) | Placebo (N=52) |
|---|---|---|
| Number (%) of patients who completed double-blind treatment[a] | 44 (86.3%) | 50 (96.2%) |
| Number (%) of patients who discontinued treatment | 7 (13.7%) | 2 (3.8%) |
| Primary reason for early withdrawal from treatment | | |
| Adverse event | 4 (7.8%) | 2 (3.8%) |
| Withdrawal by patient | 3 (5.8%) | 0 |

List of TEAEs that led to permanent treatment discontinuation are shown in Table 39. None of AEs that led to treatment discontinuation occurred in the pediatric subgroup.

**Table 39 Patients Who Discontinued Treatment due to TEAE (Analysis Set A)**

| Treatment | Patient sex/age (years) | Preferred Term | Action taken Outcome |
|---|---|---|---|
| Placebo | Male/22 | Atrial fibrillation | Withdrawn Resolved |
| | Female/40 | Atrial fibrillation | Withdrawn Resolved |
| Omaveloxolone | Male/20 | Aspartate aminotransferase increased Alanine aminotransferase increased | Withdrawn Resolved |
| | Male/28 | Muscle spasms | Withdrawn Resolved |
| | Female/30 | Ventricular tachycardia | Withdrawn Resolved |
| | Female/20 | Rosacea | Withdrawn Resolved |

The narrative of patients that discontinued from the omaveloxolone arm is discussed below:

**Patient** (b) (6) **(ALT and AST increased):** Patient (20 years, male) enrolled in Study 1402 Part 2 and began treatment with omaveloxolone 150 mg on (b) (6). On Study Day 17 (b) (6), he experienced TEAEs of ALT and AST increased.

The patient had an ALT value of 586 U/L (13.6× upper limit of normal ULN]) and an AST value of 167 U/L (4.6× ULN) on Study Day 17 and did not have a corresponding elevation in total bilirubin or any signs or symptoms of liver injury. Study drug was ***discontinued permanently*** on Study Day 21 (b) (6). The event of AST increased was considered resolved on Study Day 35 (b) (6) with the patient's AST value at 33 U/L (<ULN), and the event of ALT increased was considered resolved on Study Day 78 (b) (6), with the patient's ALT value at 41 U/L (<ULN).

***Reviewer's Comment:*** *The ALT and AST increase is reversible upon treatment discontinuation and was not associated with an increase in total bilirubin. The recovery time for ALT was longer (62 days) and that for AST shorter (18 days) and could be related to the magnitude of increase over ULN (14x vs 5x respectively). Monitoring of liver enzyme levels should be recommended accordingly (See Section 8.4.6).*

**Patient** (b) (6) **(Muscle Spasm):** Patient (28 years, male) enrolled in Study 1402 Part 2 and began treatment with omaveloxolone 150 mg on (b) (6). On Study Day 25 (b) (6), he experienced a TEAE of muscle spasms (verbatim: intermittent right gastrocnemius muscle cramps), and on Study Day 53 (b) (6) he experienced a second TEAE of muscle spasms (verbatim: intermittent left leg muscle cramps); both events were assessed as moderate in severity and possibly related to study drug. Study drug was ***interrupted*** temporarily for these TEAEs, and both events were considered resolved on Study Day 68 (b) (6). On Study Day 84, he again experienced 2 TEAEs of muscle spasms (verbatim: left gastrocnemius muscle cramps and right gastrocnemius muscle cramps); both events were assessed as moderate in severity and possibly related to study drug. Study drug was ***discontinued permanently*** on Study Day 85 (b) (6); both muscle spasms events were reported as resolved on Study Day 90 (b) (6)

***Reviewer's Comment:*** *Muscle spasm is not uncommon in FA patients, especially in late onset patients. However, it occurred it greater number of omaveloxolone-treated patients (13.7%) compared to placebo patients (5.8%).*

**Patient** (b) (6) **(Rosacea)**: Patient (20 years, female) enrolled in Study 1402 Part 2 and began treatment with omaveloxolone 150 mg on (b) (6). On Study Day 109 (b) (6), she experienced a TEAE of rosacea that was assessed by the investigator as mild in severity and probably related to study drug. A skin biopsy revealed perivascular and perifollicular dermatitis and focal junctional vasculopathy. Study drug was ***discontinued permanently*** on Study Day 131 (b) (6), and the rosacea was considered resolved as of Study Day 355 (b) (6)

**Patient** (b) (6) **(Ventricular tachycardia):** The narrative of this patient is discussed in the previous section of the review under Serious TEAEs.

Table 40 list TEAEs that lead to treatment interruptions in both treatment arms.

**Table 40 TEAEs Leading to Treatment Interruptions (Analysis Set A)**

| Preferred Term | Omaveloxolone 150 mg (N=51) | Placebo (N=52) |
|---|---|---|
| **Number (%) of Patients with TEAEs Resulting in Study Drug Interruption** | **9 (17.6%)** | **1 (1.9%)** |
| Alanine aminotransferase increased | 6 (11.8%) | 0 |
| Aspartate aminotransferase increased | 3 (5.9%) | 0 |
| Gamma-glutamyltransferase increased | 2 (3.9%) | 0 |
| Diarrhea | 1 (2.0%) | 0 |
| Nausea | 1 (2.0%) | 0 |
| Palpitations* | 1 (2.0%) | 0 |
| Sinus tachycardia* | 1 (2.0%) | 0 |
| Musculoskeletal pain* | 1 (2.0%) | 0 |
| Muscle spasms** | 1 (2.0%) | 0 |
| Somnolence | 1 (2.0%) | 0 |
| Rash erythematous | 0 | 1 (1.9%) |

*These events occurred in the same patient. Narrative of this patient is discussed under Serious TEAEs section of the review.
** Narrative of this patient is discussed in the previous section on Treatment discontinuation

**Patient** (b) (6) **(Somnolence)**: Patient (22 years, female) enrolled in Study 1402 Part 2 experienced a mild TEAE of somnolence that occurred from Study Day 284 until an unknown date that led to study drug interruption. No additional details were provided.

Elevation in liver enzymes is discussed in a separate section 8.4.6 in this review.

**Analysis Set E:**

Only one patient discontinued during the extension phase due to a TEAE (abdominal pain and diarrhea).

A total of 15 patients (13.7%) had dosing interruptions in the extension phase, where 8 (7.1%) were related to elevated liver enzymes and one patient each for deep vein thrombosis, influenza, sepsis, somnolence, tonsilitis, vomiting and toothache.

In the 120-Day Safety Report one additional patient discontinued due to the TEAE of constipation.

### 8.4.4. Significant Adverse Events

### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Common TEAEs occurring in ≥5% of omaveloxolone-treated patients and with a difference in incidence of ≥1% between omaveloxolone-treated patients and placebo-treated patients in Analysis Set A is shown in (Table 41). TEAES that occurred in ≥20% of omaveloxolone-treated patients elevated liver enzyme, headache, nausea, abdominal pain, skin abrasion, fatigue.

**Table 41 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%) |

| Preferred Terms | Omaveloxolone 150 mg (N = 51) | Placebo (N = 52) |
|---|---|---|
| Musculoskeletal pain | 10 ( 19.6%) | 8 ( 15.4%) |
| Oropharyngeal pain | 9 (17.6%) | 3 (5.8%) |
| Influenza | 8 ( 15.7%) | 3 ( 5.8%) |
| 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 Table 34 in this review. For example:
PT terms pooled under Elevated Liver Enzymes include Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Gamma-glutamyltransferase 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

The Applicant asserts that increase in liver enzymes are related to the pharmacologic mechanism of omaveloxolone rather than drug-induced liver injury. All of these TEAEs were resolved. One (1) patient in the omaveloxolone group was permanently discontinued from study drug due to the increases in ALT and AST. The breakdown of incidences of each liver enzyme from Analysis set A is given in Table 42.

**Table 42 TEAEs of Increases in Liver Enzymes and Hepatic TEAEs (Analysis Set A)**

| System Organ Class | Omaveloxolone 150 mg (N=51) | Placebo (N=52) |
|---|---|---|
| **Investigations** | | |
| Alanine aminotransferase increased | 19 (37.3%) | 1 (1.9%) |
| Aspartate aminotransferase increased | 11 (21.6%) | 1 (1.9%) |
| Gamma-glutamyltransferase increased | 3 (5.9%) | 0 |
| **Hepatobiliary disorders** | | |
| Cholelithiasis | 1 (2.0%) | 0 |
| Gallbladder disorder | 0 | 1 (1.9%) |
| Hepatic steatosis | 1 (2.0%) | 0 |

*Reviewer's comment: It appeared that most cases were occurring earlier in the trial, so I correspondingly looked at Hepatic TEAEs that occurred in the first 12 weeks of treatment. Most of the cases of increased liver enzymes occurred in the first 12 weeks of omaveloxolone treatment (Table 43). This suggest increased frequency of monitoring should be recommended in the first 12 weeks of initiating treatment with omaveloxolone.*

**Table 43 Hepatic TEAEs occurring in the first 12 weeks of Treatment**

| Laboratory Test | Omaveloxolone 150 mg (N = 51) n (%) | Placebo (N = 52) n (%) |
|---|---|---|
| Alanine aminotransferase | 14 (27.5%) | 0 |
| Aspartate aminotransferase | 10 (19.6) | 0 |
| γ-glutamyl transferase increased | 3 (5.9) | 0 |

One patient (2%) had an elevation of ALT or AST in association with moderate or severe nausea, vomiting, and one (2%) had in association with moderate or severe vomiting.

It should be noted that there were more female patients overall in the omaveloxolone treatment group (60.8% vs. 32.7% placebo; and more omaveloxolone-treated patients had a medical history of dysmenorrhea (19.6% vs. 5.8% placebo). Dysmenorrhea (3 [5.9%] omaveloxolone, 0 placebo) and in addition, ovarian cyst (2 [3.9%] omaveloxolone, 0 placebo) were observed only in the omaveloxolone-treated patients.

Overall, the incidence of many of the TEAEs occurred was greater in the first 12 weeks of the study.

**Analysis Set E (long term):**

The TEAEs occurring in ≥5% of patients with long term use of omaveloxolone (≥48 weeks) is similar to the double-blind phase within 48 weeks. Additional common TEAEs included influenza, nasopharygitis, cough, pyrexia, covid, dizziness, depression, insomnia, dyspepsia, gastroesophageal reflux disease, and epistaxis.

**Table 44 Common TEAEs Occurring in ≥5% of Omaveloxolone-treated Patients for ≥ 48 weeks**

| Preferred Terms | Omaveloxolone 150 mg (N = 137) |
|---|---|
| Total Subjects with any Adverse Events | 134 ( 97.8%) |
| Pain | 46 ( 33.6%) |
| Respiratory tract infection | 40 ( 29.2%) |
| Headache | 37 ( 27.0%) |
| Elevated liver enzymes | 36 ( 26.3%) |
| Nausea | 30 ( 21.9%) |
| Contusion | 29 ( 21.2%) |
| Abdominal pain | 27 ( 19.7%) |
| Skin abrasion | 27 ( 19.7%) |
| Fatigue | 26 ( 19.0%) |
| Diarrhea | 22 ( 16.1%) |
| Musculoskeletal pain | 22 ( 16.1%) |
| Ligament sprain | 21 ( 15.3%) |
| Influenza | 20 ( 14.6%) |
| Muscle spasms | 20 ( 14.6%) |
| Skin laceration | 17 ( 12.4%) |
| Vomiting | 17 ( 12.4%) |

| Preferred Terms | Omaveloxolone 150 mg (N = 137) |
|---|---|
| Nasopharyngitis | 16 ( 11.7%) |
| Cough | 10 ( 7.3%) |
| Depression | 9 ( 6.6%) |
| Insomnia | 9 ( 6.6%) |
| Rash | 9 ( 6.6%) |
| Urinary incontinence | 9 ( 6.6%) |
| Urinary tract infection | 9 ( 6.6%) |
| Decreased appetite | 8 ( 5.8%) |
| Dizziness | 8 ( 5.8%) |
| Limb injury | 8 ( 5.8%) |
| Pyrexia | 8 ( 5.8%) |
| Corona virus infection | 7 ( 5.1%) |
| Dyspepsia | 7 ( 5.1%) |
| Epistaxis | 7 ( 5.1%) |
| Gastroesophageal reflux disease | 7 ( 5.1%) |
| Joint injury | 7 ( 5.1%) |
| Tooth disorder | 7 ( 5.1%) |

Pain included PTs: Arthralgia, Back Pain, Neck Pain, Oropharyngeal Pain, Pain, Pain in extremity and Pain in Jaw

TEAEs occurring in ≥5% of patients with long term use of omaveloxolone (≥96 weeks) in 112 patients was same as the above Table. However, those occurring in ≥5% of patients with long term use of omaveloxolone (≥144 weeks) in 37 patients that did not occur at earlier times is summarized in Table 45.

**Table 45 Common TEAEs Occurring in ≥5% of Omaveloxolone-treated Patients for ≥ 144 weeks**

| Preferred Terms | Omaveloxolone 150 mg (N = 37) |
|---|---|
| Eczema | 3 ( 8.1%) |
| Ovarian cyst | 3 ( 8.1%) |
| Acne | 2 ( 5.4%) |
| Alopecia | 2 ( 5.4%) |
| Bronchitis | 2 ( 5.4%) |
| Coccydynia | 2 ( 5.4%) |
| Constipation | 2 ( 5.4%) |
| Dyspnea | 2 ( 5.4%) |
| Eye contusion | 2 ( 5.4%) |
| Gait disturbance | 2 ( 5.4%) |
| Hemorrhoids | 2 ( 5.4%) |
| Hyperhidrosis | 2 ( 5.4%) |
| Joint swelling | 2 ( 5.4%) |
| Ligament rupture | 2 ( 5.4%) |
| Menstruation irregular | 2 ( 5.4%) |
| Mood swings | 2 ( 5.4%) |
| Nasal congestion | 2 ( 5.4%) |
| Neuropathy peripheral | 2 ( 5.4%) |
| Pharyngitis streptococcal | 2 ( 5.4%) |
| Presyncope | 2 ( 5.4%) |
| Pruritus | 2 ( 5.4%) |
| Restless legs syndrome | 2 ( 5.4%) |
| Rhinorrhea | 2 ( 5.4%) |
| Scoliosis | 2 ( 5.4%) |
| Suicidal ideation | 2 ( 5.4%) |

| Preferred Terms | Omaveloxolone 150 mg (N = 37) |
|---|---|
| Syncope | 2 ( 5.4%) |

The laboratory parameters that showed a change (worsening) in omaveloxolone treated patients compared to placebo patients are discussed below:

**Liver Laboratory Results (ALP, ALT, AST, GGT and Total BILI or TBL) in Analysis Set A:**

The following number and percentage of patients met the prespecified threshold criteria for abnormal liver function tests at any time during the study:

- Sixteen (31.4%) patients in the omaveloxolone group exceeded the threshold criterion of ALT or AST ≥3× the ULN.
- Eight (15.7%) patients in the omaveloxolone group exceeded the criterion of ALT or AST ≥5× the ULN.
- Two (3.9%) patients in the omaveloxolone group exceeded the criterion of ALT or AST ≥10× the ULN.
- One (1) patient in the placebo group met the criteria for AST ≥3× the ULN (Upper Limit of Normal).

Mean increases in ALT, AST and GGT induced by omaveloxolone were observed that were maximal at Week 2 and then gradually decreased. Following withdrawal of omaveloxolone, aminotransferase levels typically returned to baseline within 2 to 4 weeks. Increases in aminotransferases were not associated with increases in total bilirubin (TBL) or alkaline phosphatase (ALP). Omaveloxolone patients had a small decrease from baseline in mean TBL relative to placebo.

Per the Study 1402 Part 2 protocol, patients discontinued or interrupted study drug (per investigator's evaluation) if any of the following occurred:

- ALT or AST were >8× ULN
- ALT or AST >5× ULN for more than 2 weeks
- ALT or AST >3× ULN and total bilirubin >2× ULN or
- ALT or AST >3× ULN with the appearance of other clinical symptoms (e.g., fatigue, nausea, and vomiting).

A total of 2.0% of the omaveloxolone-treated patients in Analysis Set A discontinued study drug

due to an increase in either 1 or both of the aminotransferases.

Alanine Aminotransferase:

The shift Tables summarizing the shift from baseline to the worst post-treatment assessment are shown in Table 46. A total of 14/51 patients on omaveloxolone had peak ALT levels ≥3xULN compared to none in the placebo group.

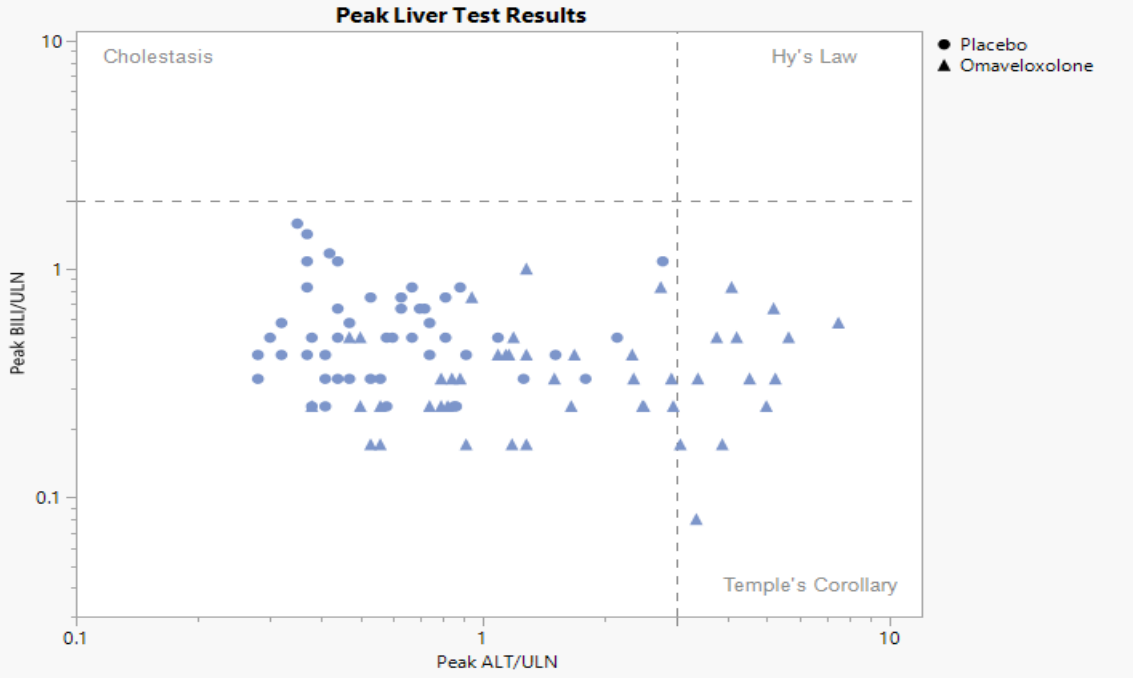
**Table 46 Shift Tables for ALT**

| | | ALT (Maximum) - ULN | | | | |
|---|---|---|---|---|---|---|
| **Grouping Variable** | **ALT (Baseline)** | **<= 1X ULN** | **>1X ULN- <3X ULN** | **>=3X ULN- <= 5X ULN** | **>5X ULN- <= 10X ULN** | **>10X ULN** |
| Omaveloxolone 150 mg (N = 50, 1 missing) | <= 1X ULN | 15 (30%) | 20 (40%) | 7 (13.7%) | 6 (11.8%) | 1 (2%)[a] |
| | 1X ULN < x <= 3X ULN | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) |
| | 3X ULN < x <= 5X ULN | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | 5X ULN < x <= 10X ULN | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | >10X ULN | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Placebo (N = 52) | <= 1X ULN | 46 (88.46%) | 4 (7.69%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | 1X ULN < x <= 3X ULN | 0 (0%) | 2 (3.85%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | 3X ULN < x <= 5X ULN | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | 5X ULN < x <= 10X ULN | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | >10X ULN | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Source: OCS Analysis Studio, Shift Table Tool.
[a] Patient [redacted] (b) (6) discontinued based on protocol criteria

No patients in the study met Hy's law criteria (ie, ALT ≥3× ULN and total bilirubin >2× ULN). There was no associated increase in ALP or TBL in any patients with increased ALT (Figure 21).

**Figure 21 Peak Liver Test Results (Analysis Set A)**

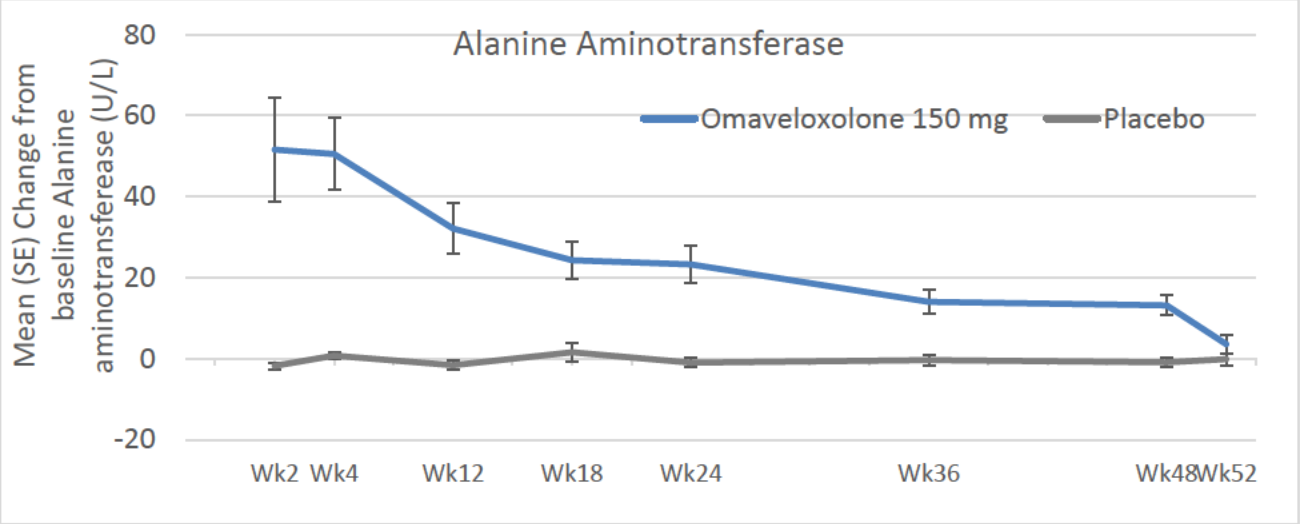



Source: Reviewer Analysis: N=14 fell in the Temple's corollary (ALT>3xULN)

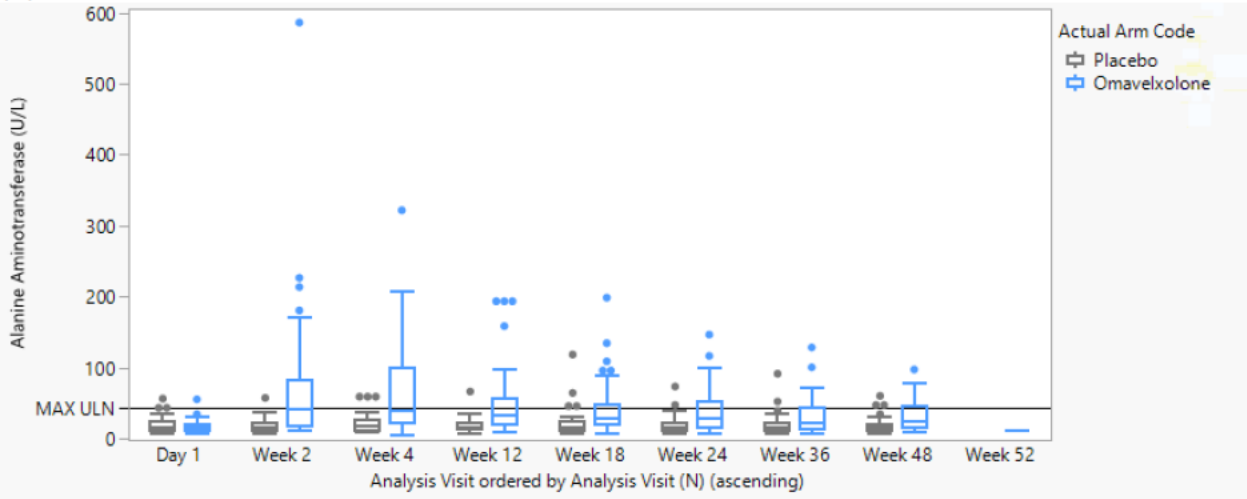
The mean changes in liver enzymes over time and observed ALT values in both treatment arms are shown in Figure 22 A and B. The Figure shows that serum ALT level increases are generally maximal within 2 to 4 weeks after initiation of omaveloxolone treatment and were generally higher in the first 12 weeks of treatment. Increases in ALT with omaveloxolone treatment were reversible, with mean serum ALT concentrations declining to baseline values within 4 weeks following drug withdrawal. ALT levels in placebo treated patients remained unchanged throughout.

**Figure 22 (A) Mean Change from Baseline (B) Observed Serum ALT Concentrations**

(A)




(B)



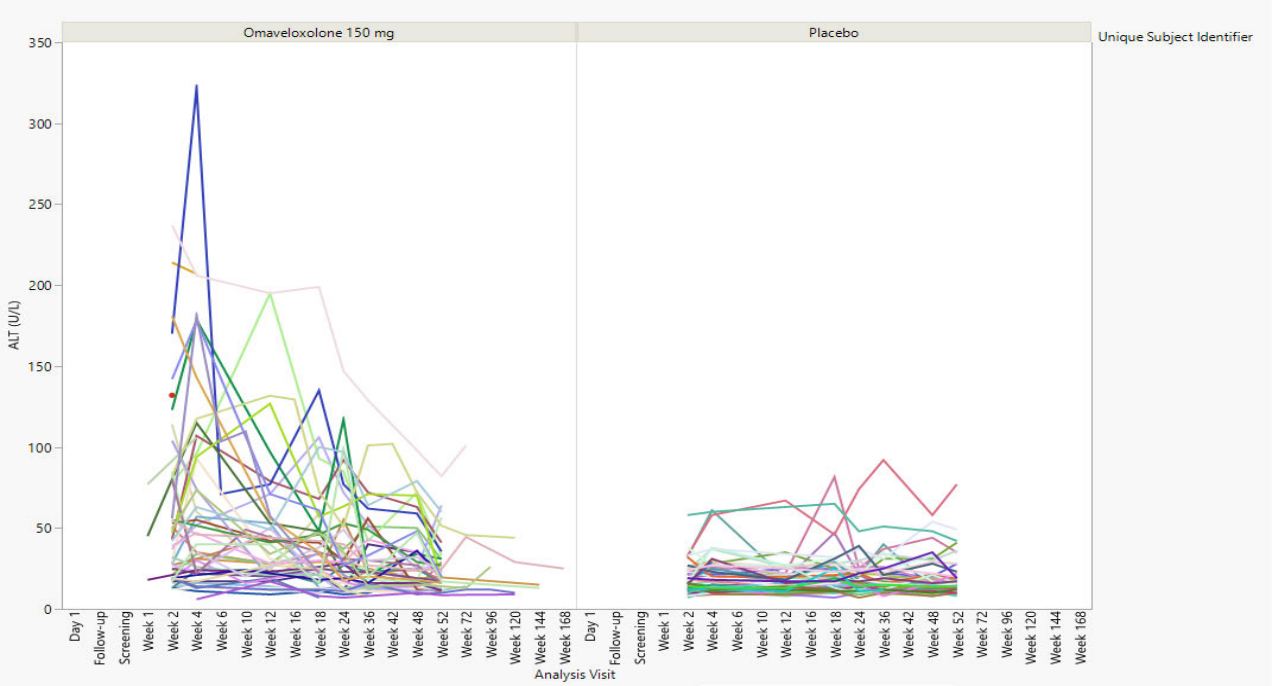

Source: Reviewer Analysis

The ULN for ALT was either 34 or 43 U/L across labs. Five Patients (10%) had ALTs >ULN-3 X ULN during the 4-week withdrawal phase. Individual profiles for ALT are shown in Figure 23.

In one patient [redacted] (b) (6), drug was withdrawn that had an ALT increase up to 586 U/L (14x ULN) on Day 15. This patient did not have elevation in TBL. The ALT increase was resolved by Day 78 when the ALT value decreased to 41 U/L.

In another patient [redacted] (b) (6) drug was temporarily discontinued due to an increase in ALT/AST.

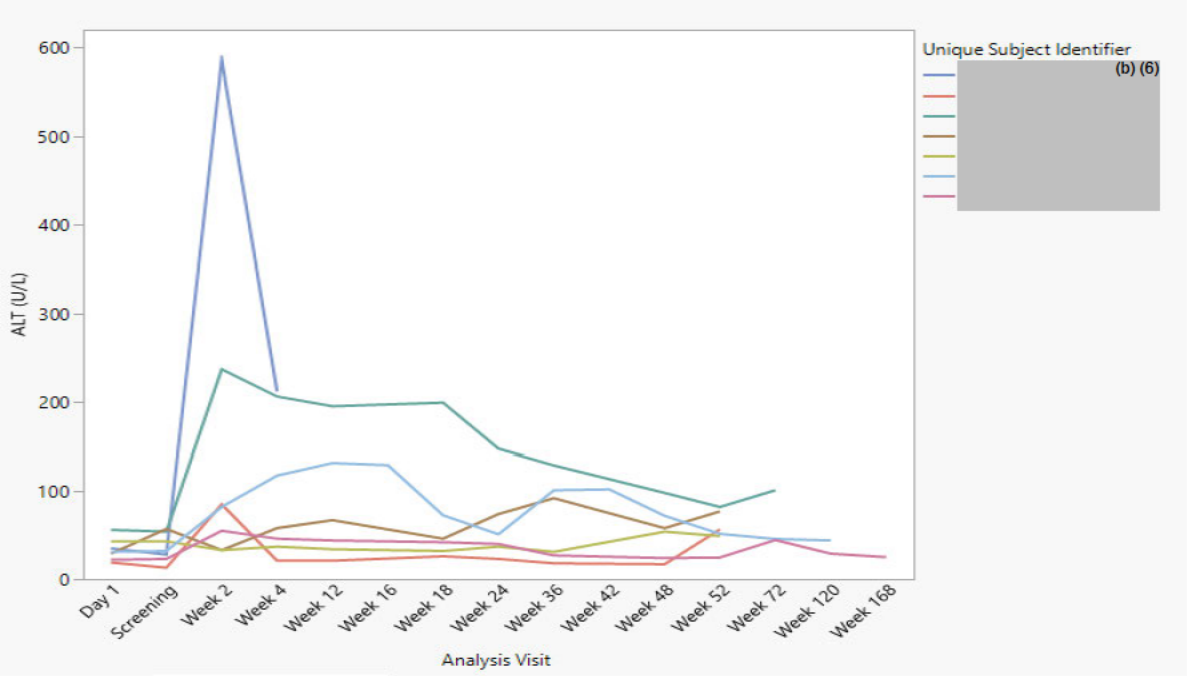
**Figure 23 Individual ALT Time-Profile**




Note: This Figure does not include one time point of one subject [redacted] (b) (6) that had an increase of 586 U/L at Week 2 to expand the time profiles for other subjects.

Seven subjects continued to have greater than ULN to less than 3xULN of ALT values during the Week 52 when omaveloxolone was withdrawn as shown in Figure 24.

**Figure 24 ALT that Remained >ULN through Week 52 and beyond**




Note: Subject (b) (6) with ALT of 586 U/L is shown in the Figure

Adolescents aged ≥16 to < 18 years showed similar changes, although a lower magnitude of increase was observed.

Aspartate Aminotransferase

The shift Tables summarizing the shift from baseline to the worst post-treatment assessment are shown in Table 46 Shift Tables for  A total of 4/51 (7.8%) omaveloxolone-treated patients had maximum AST values ≥3× ULN at some time during the treatment period. All these patients also had increases in ALT. No patients had a shift of ≥5x ULN AST value during the dosing

period.

**Table 47 Shift Tables for AST**

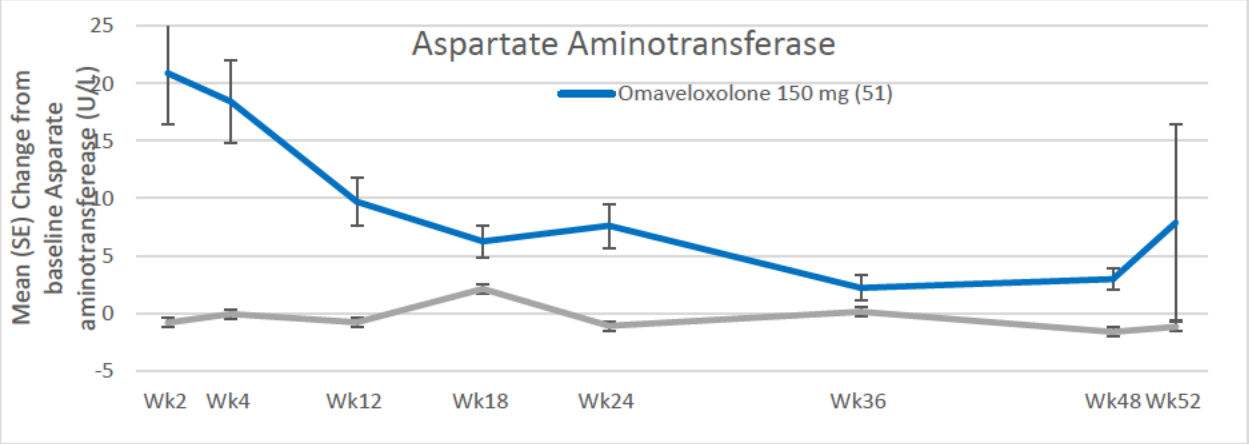
| | | AST (Maximum) | | |
|---|---|---|---|---|
| **Grouping Variable** | **AST (Baseline)** | **<= 1X ULN** | **1X ULN - < 3X ULN** | **≥3X ULN** |
| Omaveloxolone 150 mg (N = 50, 1 missing) | <= 1X ULN | 22 (44%) | 24 (48%) | 4 (8%) |
| | 1X ULN < x <= 3X ULN | 0 (0%) | 0 (0%) | 0 (0%) |
| | >3X ULN | 0 (0%) | 0 (0%) | 0 (0%) |
| Placebo (N = 52) | <= 1X ULN | 47 (90.38%) | 4 (7.69%) | 1 (1.92%) |
| | 1X ULN < x <= 3X ULN | 0 (0%) | 0 (0%) | 0 (0%) |
| | >3X ULN | 0 (0%) | 0 (0%) | 0 (0%) |

Source: OCS Analysis Studio, Shift Table Tool.

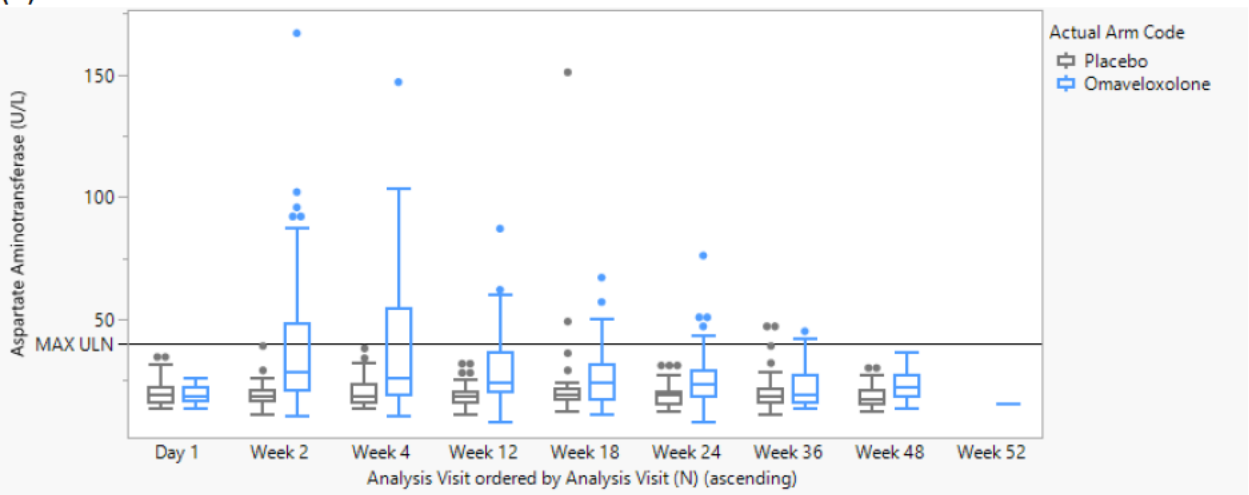
In omaveloxolone-treated patients, peak elevations in serum AST were observed at Week 2, with values decreasing toward baseline values through Week 48. Placebo-treated patients remained unchanged throughout the 48-week treatment period (Figure 25).

**Figure 25 (A) Mean Change from Baseline (B) Observed Serum AST Concentrations**

(A)




(B)




Only one patient had ≥10x ULN of AST during the withdrawal period at Week 52 (>10 half-lives after drug cessation). This patient's Week 48 AST was 19 U/L. On Study Day 365, the patient's AST level had spiked to 397 U/L with no TEAE reported. On Study Day 394, the patient's AST values had returned to 23 U/L. No reason for the abrupt increased AST value was provided. It is unclear if this was a laboratory error (not shown in the Figure).

Adolescents aged ≥16 years to < 18 years showed similar changes, although a lower magnitude of increase was observed.

Gamma-Glutamyl Transferase:

The shift Tables summarizing the shift from baseline to the worst post-treatment assessment are shown in Table 48.

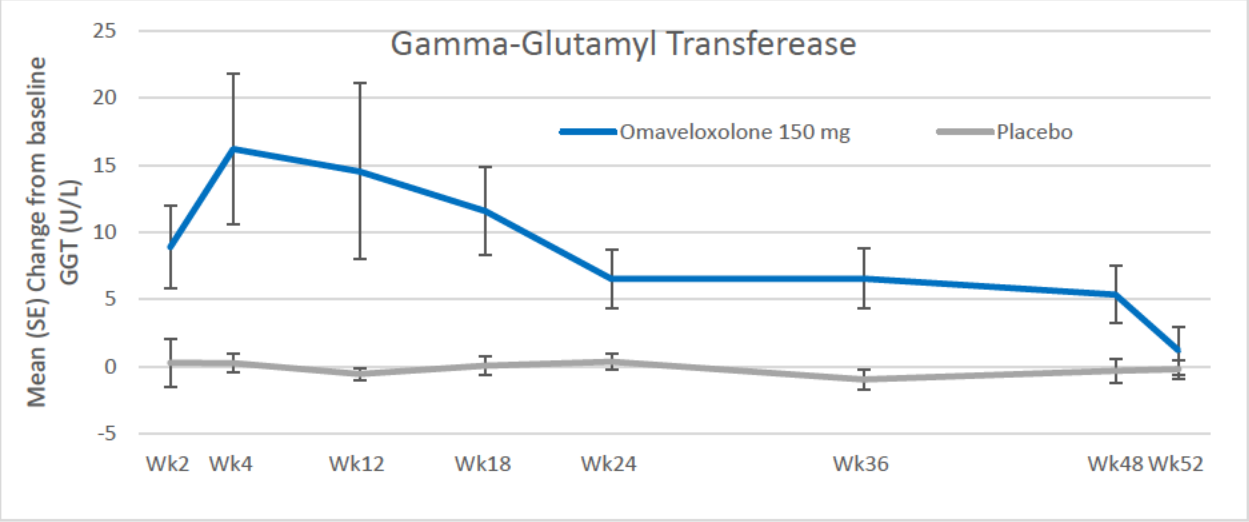
**Table 48 Shift Table for GGT**

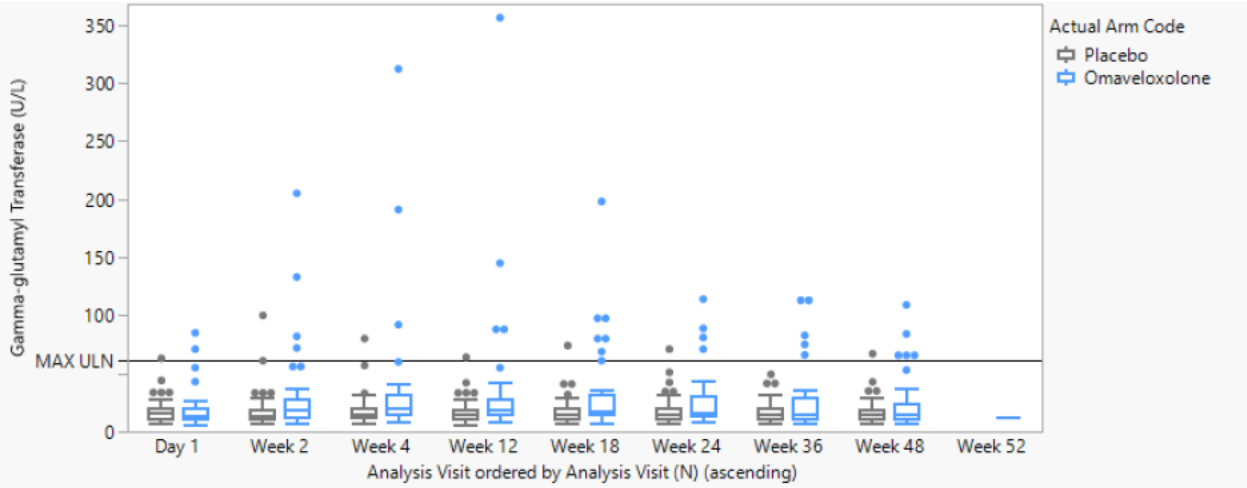
| | | GGT (Maximum) | | |
|---|---|---|---|---|
| **Grouping Variable** | **ALP (Baseline)** | **<= 1X ULN** | **1X ULN < x <5X ULN** | **≥5X ULN** |
| Omaveloxolone 150 mg (N = 50, 1 missing) | <= 1X ULN | 43 (84.3%) | 6 (9.8%) | 0 (0%) |
| | 1X ULN < x <= 5X ULN | 1 (2%) | 2 (4%) | 2 (3.9%) |
| | >5X ULN | 0 (0%) | 0 (0%) | 0 (0%) |
| Placebo (N = 52) | <= 1X ULN | 49 (94.2%) | 2 (3.8%) | 0 (0%) |
| | 1X ULN < x <= 5X ULN | 0 (0%) | 1 (1.9%) | 0 (0%) |
| | >5X ULN | 0 (0%) | 0 (0%) | 0 (0%) |

Source: OCS Analysis Studio, Shift Table Tool.

Serum GGT increase were observed beginning at Week 2 that remained elevated between 25 and 35 U/L throughout Week 48 of therapy.

**Figure 26 Mean Change from Baseline in Serum GGT Concentrations**






Adolescents showed similar changes in, although a lower magnitude of increase was observed.

Total Bilirubin

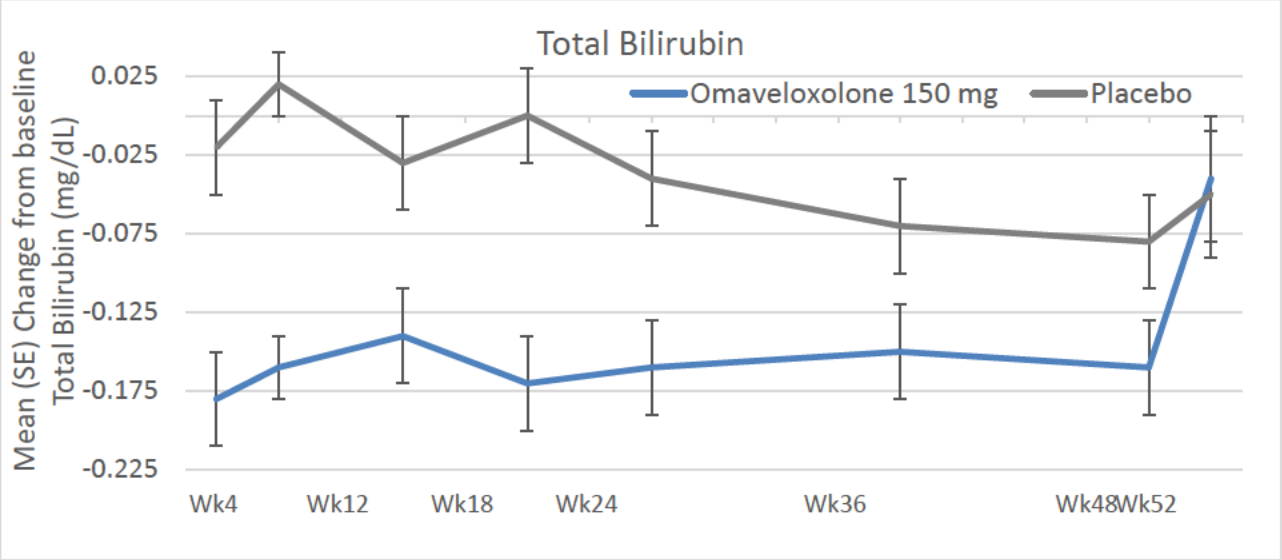
The shift Tables summarizing the shift from baseline to the worst post-treatment assessment are shown in Table 49.

**Table 49 Shift Table for TBILI**

| | | BILI (Maximum) | | |
|---|---|---|---|---|
| **Grouping Variable** | **BILI (Baseline)** | **<= 1X ULN** | **1X ULN < x <= 2X ULN** | **>2X ULN** |
| Omaveloxolone 150 mg (N = 50, 1 missing) | <= 1X ULN | 49 (98%) | 0 (0%) | 0 (0%) |
| | 1X ULN < x <= 2X ULN | 0 (0%) | 1 (2%) | 0 (0%) |
| | >2X ULN | 0 (0%) | 0 (0%) | 0 (0%) |
| Placebo (N = 52) | <= 1X ULN | 46 (88.46%) | 3 (5.77%) | 0 (0%) |
| | 1X ULN < x <= 2X ULN | 0 (0%) | 3 (5.77%) | 0 (0%) |
| | >2X ULN | 0 (0%) | 0 (0%) | 0 (0%) |

The mean change from baseline in TBILI concentrations is shown in Figure 27.

**Figure 27 Mean Change from Baseline in TBILI Concentrations**




One (2.0%) omaveloxolone-treated patient had maximum bilirubin values > ULN at some point during the treatment period, none exceeded 2× ULN. One omaveloxolone-treated patient in Analysis Set A had total bilirubin levels that exceeded 1.5× ULN. Patient (b) (6), had total bilirubin levels >1.5× ULN (1.80 mg/dL) at Day 136, an increase from baseline value of 1.40 mg/dL. No TEAE was reported, and the patient's total bilirubin value decreased to 0.5 mg/dL on Day 165. On Day 333 (last on-treatment value), the patient's bilirubin level was 0.60 mg/dL.

Alkaline Phosphatase

The shift Tables summarizing the shift from baseline to the worst post-treatment assessment are shown in Table 50. There were no shifts in ALP values.

**Table 50 Shift Table for ALP**

| | | ALP (Maximum) | | |
|---|---|---|---|---|
| **Grouping Variable** | **ALP (Baseline)** | **<= 1X ULN** | **1X ULN < x <1.5X ULN** | **≥1.5X ULN** |
| Omaveloxolone 150 mg (N = 50, 1 missing) | <= 1X ULN | 46 (92%) | 1 (2%) | 0 (0%) |
| | 1X ULN < x <= 1.5X ULN | 1 (2%) | 2 (4%) | 0 (0%) |
| | >1.5X ULN | 0 (0%) | 0 (0%) | 0 (0%) |
| Placebo (N = 52) | <= 1X ULN | 51 (98.08%) | 1 (1.92%) | 0 (0%) |
| | 1X ULN < x <= 1.5X ULN | 0 (0%) | 0 (0%) | 0 (0%) |
| | >1.5X ULN | 0 (0%) | 0 (0%) | 0 (0%) |

There were no differences between placebo- and omaveloxolone-treated patients in alkaline phosphatase.

Study 1402 Part 1: In Part 1 of the Study as well five patients treated with omaveloxolone (3 in the 160 mg group and 2 in the 300 mg group) exceeded the threshold criterion of ALT or AST > 5x the upper limit of normal during the study. In all 5 patients, the increases occurred early in the study (on or before Week 4), and ALT and AST values were below this threshold limit by Week 8. In 3 of these patients (1 in the 160 mg group and 2 in the 300 mg group), the increases in ALT and AST (as well as increased GGT) were reported as TEAEs. Hy's Law criteria was not met by any patient in the study.

The Hepatic TEAEs are discussed at length in the Common TEAE section of the review.

According to the Applicant, aminotransferase increase is postulated to be a pharmacodynamic effect of omaveloxolone. Increase in aminotransferase is hypothesized to be related to restoration of mitochondrial function. Nrf2 is activated by omaveloxolone. Genetic manipulation of Nrf2 is thought to regulate the induction of aminotransferase genes and the serum activity of ALT and AST. 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. ALT and AST are thought to play key roles in several metabolic processes including amino acid metabolism, glycolysis, glucogenesis, and the tricarboxylic acid (TCA) cycle. In addition, these enzymes influence redox balance and

mitochondrial metabolism by contributing to glutathione production (Ellinger, 2011)[14]. Elevations in serum GGT, a protein involved in glutathione synthesis and is also postulated to be controlled by Nrf2 (Zhang, 2006).

Based on these, the Applicant concludes that changes in GGT, ALT and AST observed in this study are not associated with liver injury but are consistent with Nrf2-mediated increases in enzymes involved in glutathione synthesis and support the hypothesis that aminotransferase elevations reflect an increased demand for glutamate to support increased glutathione production.

***Reviewer's Comment:***
*Dimethyl fumarate (TECFIDERA) is also an Nrf2 activator approved for the treatment of relapsing forms of multiple sclerosis. This drug also showed increases in transaminases without increase in bilirubin. In addition, omaveloxolone analogue Bardoxolone methyl, with similar mechanism of action has shown similar increases without increase in bilirubin.*

***Drug Induced Liver Injury (DILI) Team Consultation (Drs. Ling Lan and Paul Hayashi):(Refer to detailed consult review for the Application):***

*Given the observations of transaminase elevations, the DILI team was consulted to evaluate the safety signal and to provide recommendations for monitoring and labeling. DILI Team concludes that the non-clinical data do not suggest a high risk for DILI and suggest the possibility of benign increase ALT and AST gene expression. Clinical data indicates that there were no cases of jaundice, Hy's law, or cholestatic liver injury. However, the trials for FA are quite small (less than 60 patients in the placebo-controlled study phase), so the NDA is under-powered to detect a significant DILI signal. There were more aminotransferase elevations seen with omaveloxolone. Close examination of the cases suggests that benign off-target ALT and AST gene expression and DILI with adaptation are the main competing etiologies for these transient increases in aminotransferases. The enzyme elevation patterns are consistent with rapid gene expression followed by decline while on drug. In cases where omaveloxolone was stopped, ALT and AST tended to fall rapidly which would be more consistent with gene expression rather than DILI. Bardoxolone produced similar aminotransferase patterns. If off-target gene expression is not explanatory, then DILI is the most likely etiology. Fortunately, all the cases recovered, and most had enzyme declines without stopping omaveloxolone, suggesting adaptation and a benign course if there was DILI. Nevertheless, prescribers should not presume benign gene induction or adaptation will always be explanatory when enzymes rise. Lastly, the lack of return to baseline of ALT while on omaveloxolone could also be due to gene expression or chronic, low-level DILI. Post market acute and chronic studies can be considered to further assess DILI. Adequate labeling for monitoring should be recommended that includes liver enzyme and bilirubin*

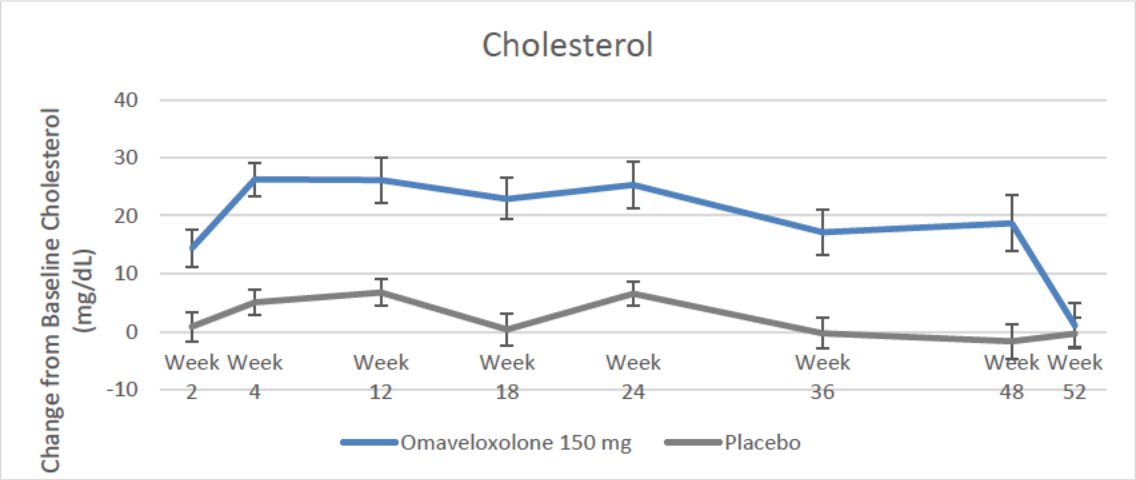
[14] Ellinger et. al. 2011; Role of aminotransf erases in glutamate metabolism of human Erythrocytes; J Biomol NMR (2011) 49:221-229

*monitoring monthly for the first three months and as clinically indicated thereafter. If liver enzymes do not fall substantially or bilirubin rises, omaveloxolone should be stopped.*

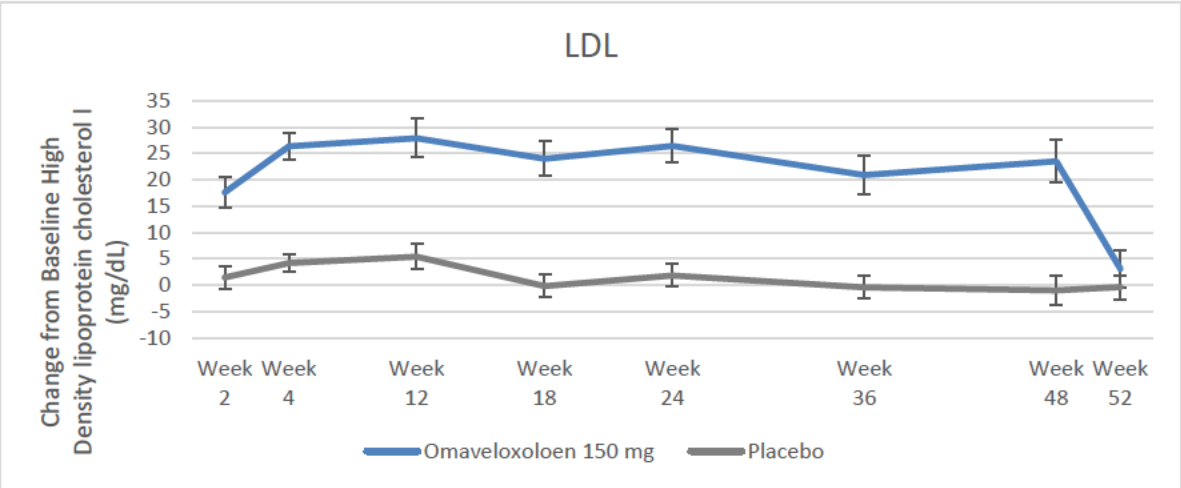
**Lipids in Analysis Set A:**

Mean increases in cholesterol and Low-Density Lipoprotein Cholesterol (LDL-C) and decreases in High-Density Lipoprotein Cholesterol (HDL-C) was observed within 2 weeks in the omaveloxolone arm compared to placebo arm as shown in the time trend plots Figure 28 A, B and C. Although, for most patients the values remained within the reference range. Values approached baseline within 4 weeks of discontinuing treatment.

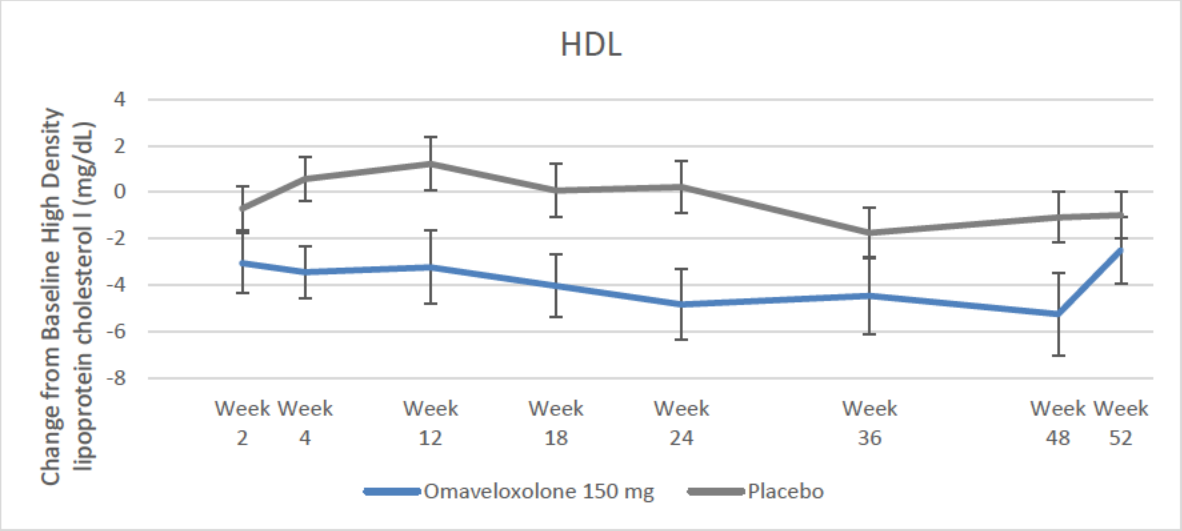
**Figure 28 (A, B, C) Mean Change from Baseline in Lipids over Time**




(B)




(C)




A total of 15 (29%) Omaveloxolone treated patients and 3 (6%) placebo patients had a shift from normal to high (above the ULN) cholesterol at one or more time points. There were 8 (16%) Omaveloxolone treated patients and 4 (8%) placebo patients who had a shift from normal to high LDL-C at one or more time points. A total of 3 (6%) Omaveloxolone treated patients and 2 (4%) placebo patients had a shift from normal to low HDL-C at one or more time points (Table 51).

**Table 51 Treatment Emergent Abnormal Cholesterol Values (Analysis Set A)**

| Laboratory Parameter | Abnormality Category | Omaveloxolone 150 mg (N=51) | Placebo (N=52) |
|---|---|---|---|
| Cholesterol (mg/dL) | Normal to high | 15 (29%) | 3 (6%) |
| | ≥240 mg/dL[a] | 9 (17%) | 3 (6%) |
| HDL cholesterol (mg/dL) | Normal to low | 3 (6.0%) | 2 (4%) |
| | <40 mg/dL | 19 (37%) | 14 (27%) |
| LDL cholesterol (mg/dL) | Normal to high | 8 (16%) | 4 (8%) |
| | ≥190 mg/dL | 2 (4%) | 1 (2%) |

Note: [a]Some labs had ULN of 264, 265 and 280. Only shifts from normal to high were counted.

There were 3 patients (6%) in the omaveloxolone group and 1 (2%) in the placebo group that reported a TEAE of hypercholesteremia in Part 2 of the Study. (#'s (b) (6) )

Adolescent patients showed lower increases in cholesterol and LDL cholesterol compared to adults. Reductions on HDL cholesterol was similar to adults.

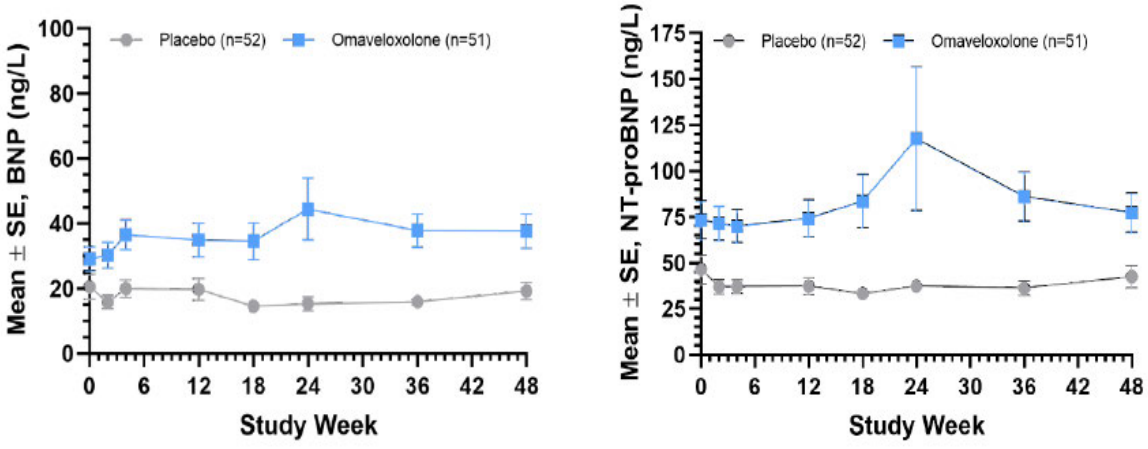
Increases in serum lipid parameters are also postulated by the Applicant to be related to PD activation of Nrf2. According to the Applicant, the reversibility of the total cholesterol increases suggests that the increases in total cholesterol are associated with PD effects of omaveloxolone.

**Reviewer's Comment:** *The Applicant asserts beneficial effects of omaveloxolone on lipid metabolism, glucose utilization, and mitochondrial function. The mechanism of increased cholesterol and it being related to pharmacodynamic effect of Nrf2 activation appear contradictory to an assertion of beneficial effect on lipid metabolism. Monitoring for Lipid abnormalities should be recommended in the label/Warnings and Precautions.*

**B-Type Natriuretic Peptide (BNP) and N-Terminal Prohormone of B-Type Natriuretic Peptide (Pro-BNP) in Analysis Set A**

Mean increases in BNP and NT-Pro BNP were observed in the omaveloxolone treated patients compared to placebo patients. There were several patients that had greater increases in BNP and NT-Pro-BNP in omaveloxolone treated patients; however, BNP values and NT-Pro-BNP values remained within the normal range (<100 pg/mL; normal values, and < 125 pg/mL; normal values, respectively) for the majority of the patients (Figure 29).

**Figure 29 B-Type Natriuretic Peptide and N-Terminal Prohormone of B-Type Natriuretic Peptide over Time**

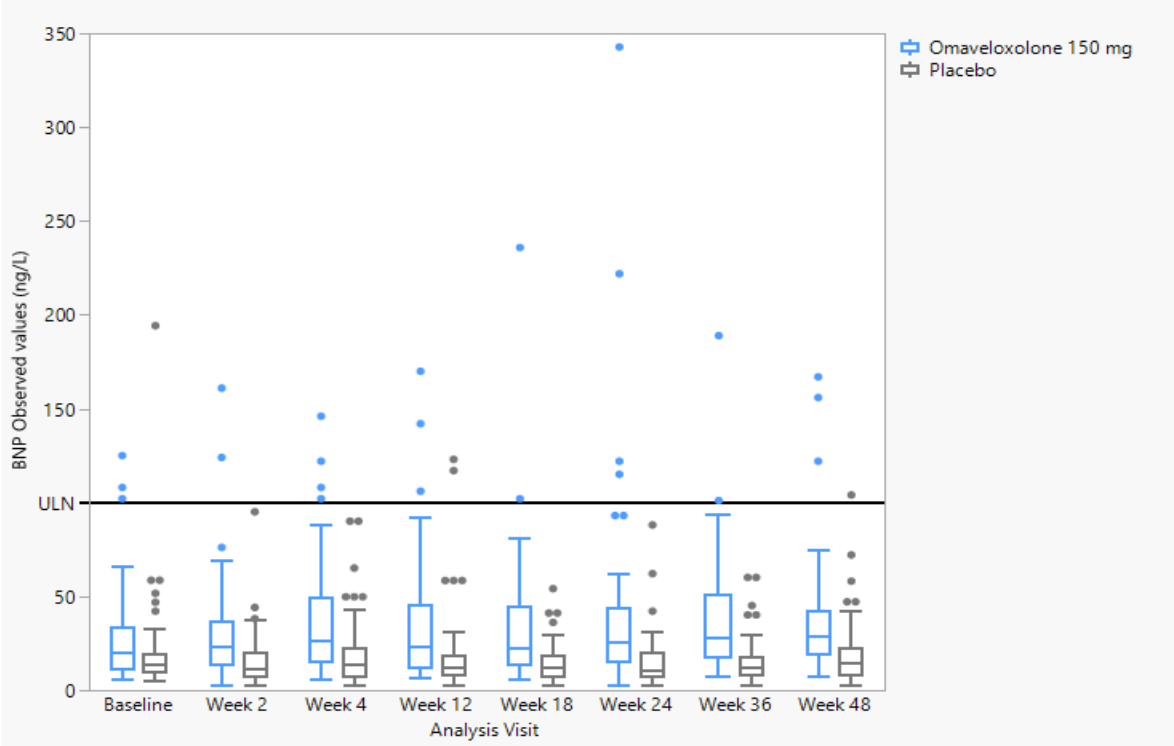



Source: Clinical Study Report, page 106 (pg/mL=ng/L)

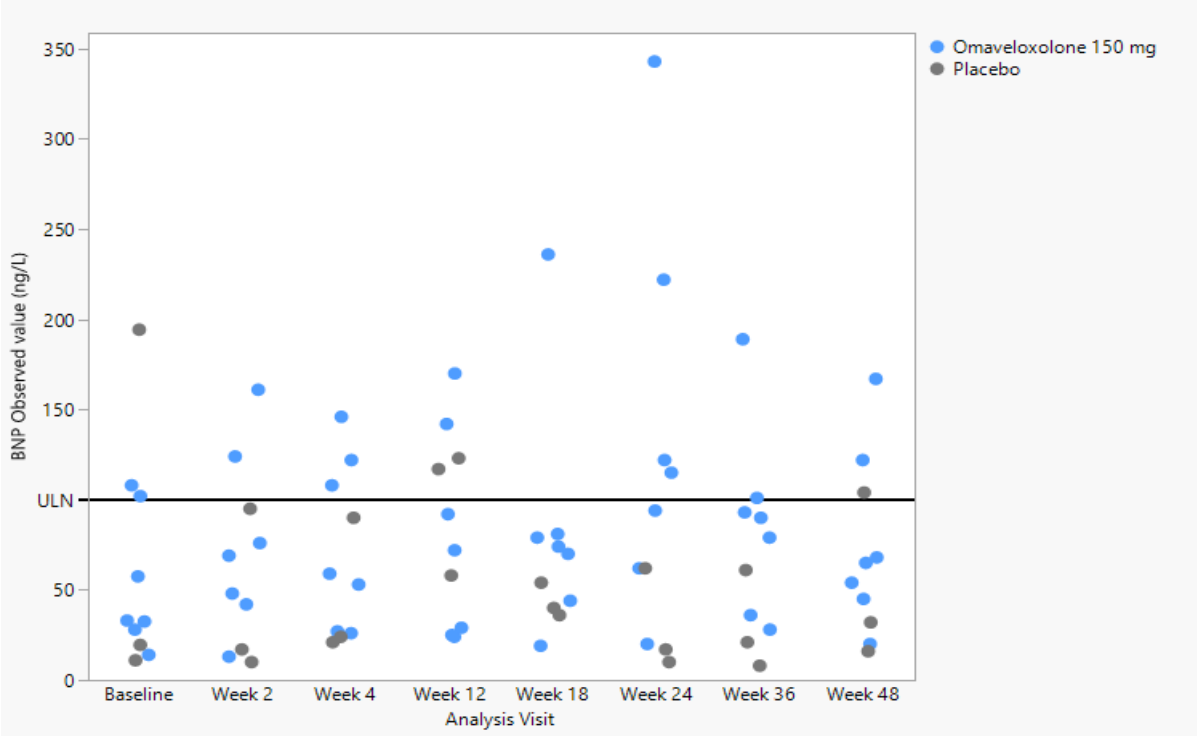
BNP values were >100 pg/mL in 8 (16%) of the omaveloxolone treated patients compared to 2 (4%) of the placebo treated patients at one or more time points (Figure 30 A), however 3 (6%) of omaveloxolone treated patients had high BNP at baseline as well compared to none of placebo treated patients (Figure 30B). A total of 5 omaveloxolone-treated patients that had an increase in BNP had a history of cardiomyopathy. None of the placebo patients with increase BNP values had a history of cardiomyopathy. **Two patients receiving omaveloxolone had levels >200 pg/mL at Week 24: Patient (b) (6) (16 years, female) had levels of 236 and 342 pg/mL at Week 18 and 24, and Patient (b) (6) (21 years, female) had a level of 222 pg/mL at Week 24.** No patients had BNP levels that were >350 pg/mL.

**Figure 30 (A) Observed BNP Values (B) Observed Values in Patients with >100 pg/mL at Any Timepoint**

(A)



(B)

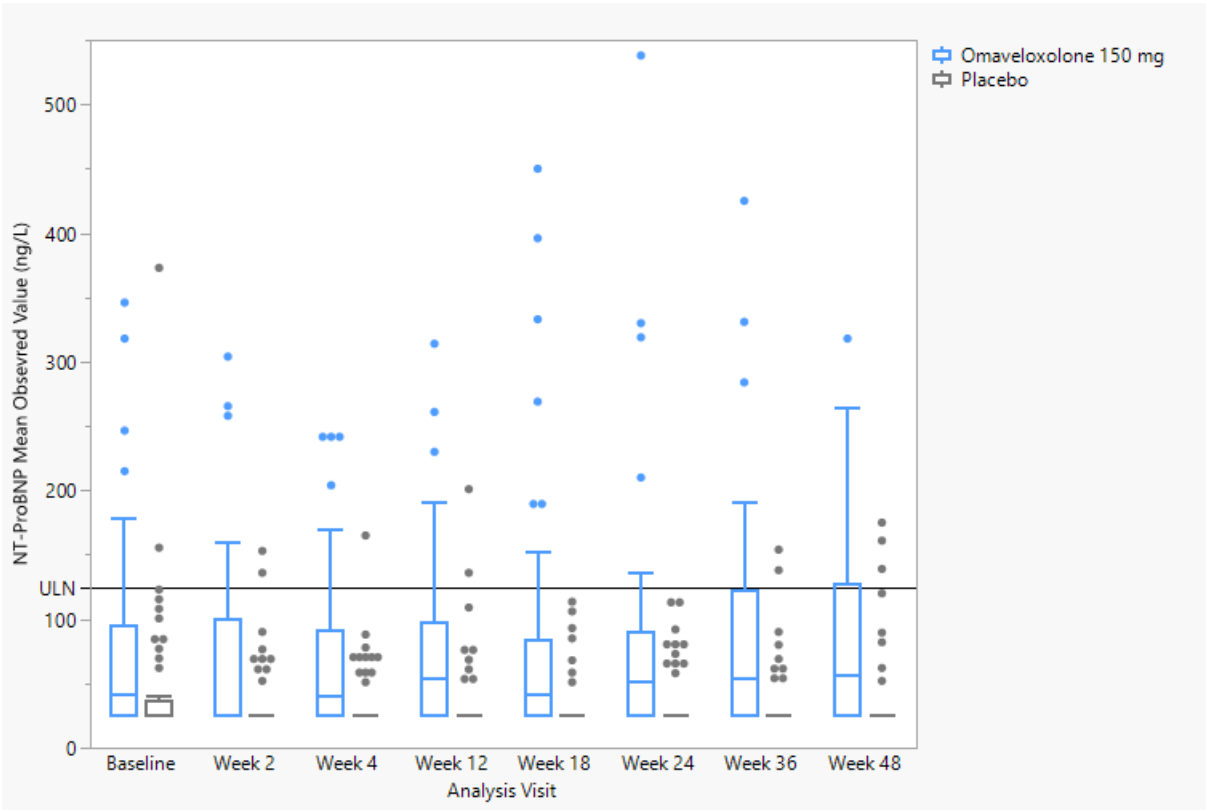



***Reviewer's note:*** *I note that in the open label phase, two patients from Part 1 who switched to the extension phase also had increase in BNP of >200 pg/mL: Patient* (b) (6)*, 201 pg/mL at Week 4, and Patient* (b) (6)*, 244 pg/mL at Week 144.*

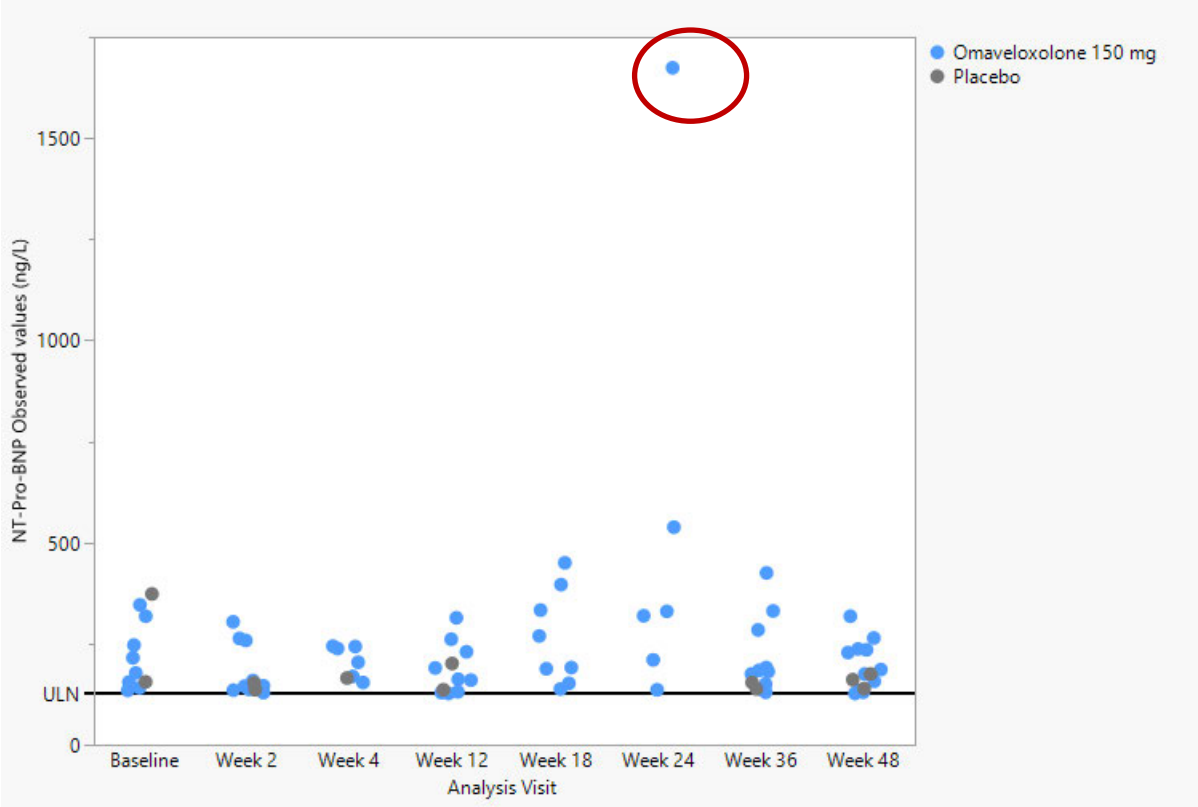
NT-Pro-BNP values were >125 pg/L in 24 (47%) of the omaveloxolone treated patients. compared to 6 (11.5%) of the placebo treated patients at one or more time points (Figure 31 A), however, 8 (16%) of omaveloxolone treated patients and 2 (4%) of placebo treated patients had high NT-Pro-BNP at baseline as well (Figure 31 B). A total of 17/24 omaveloxolone treated patients that had an increase in NT-Pro-BNP had a history of cardiomyopathy. A total of 4/6 of the placebo treated patients who had an increase in NT-Pro-BNP had a history of cardiomyopathy. **Two patients had levels >450 pg/mL at Week 24 with omaveloxolone treatment: Patient** (b) (6)**; 16 years, female) and Patient** (b) (6) **(21 years, female) had levels 538 and 1674 pg/mL, respectively.** These are the same two patients that had increases above 200 pg/mL for BNP.

**Figure 31 (A) Observed NT-Pro-BNP Values (B) Observed Values in Patients with NT-Pro-BNP >125 pg/mL**

(A)




(B)

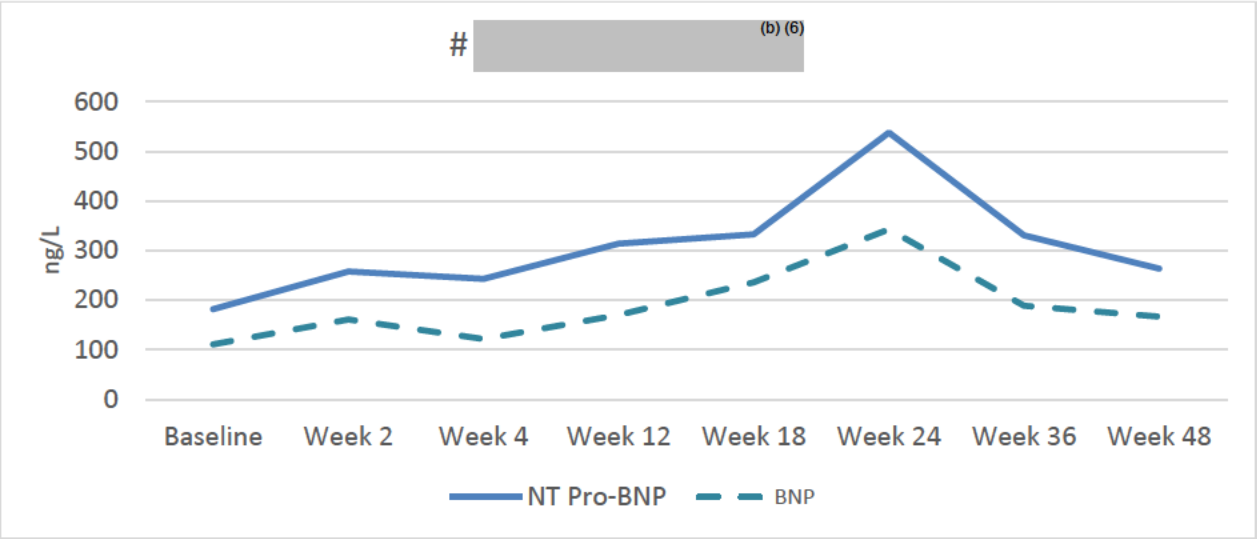



Note: The figure 31A deletes one outlier time point in one patient # (b) (6) on omaveloxolone that had a value of 1674 ng/L at Week 24 to expand the other datapoints.

One adolescent patient with a history of cardiomyopathy (# (b) (6)) had values higher than 100 pg/mL (mentioned above as well) but the normal reference range for this patient was 200 ng/L based on the patient's laboratory reference range. TEAEs reported in this patient include back pain, contusion, dyspnea, excoriation, fatigue, non-cardiac chest pain, scoliosis, syncope.

The same adolescent patient with a history of cardiomyopathy (# (b) (6)) had high values of NT-Pro BNP as well, but the reference ULN for this patient was 206 ng/L. This patient showed a similar pattern of increase in both BNP and NT-ProBNP at multiple timepoints.

**Figure 32 BNP and NT-ProBNP in a single patient with values higher than ULN**

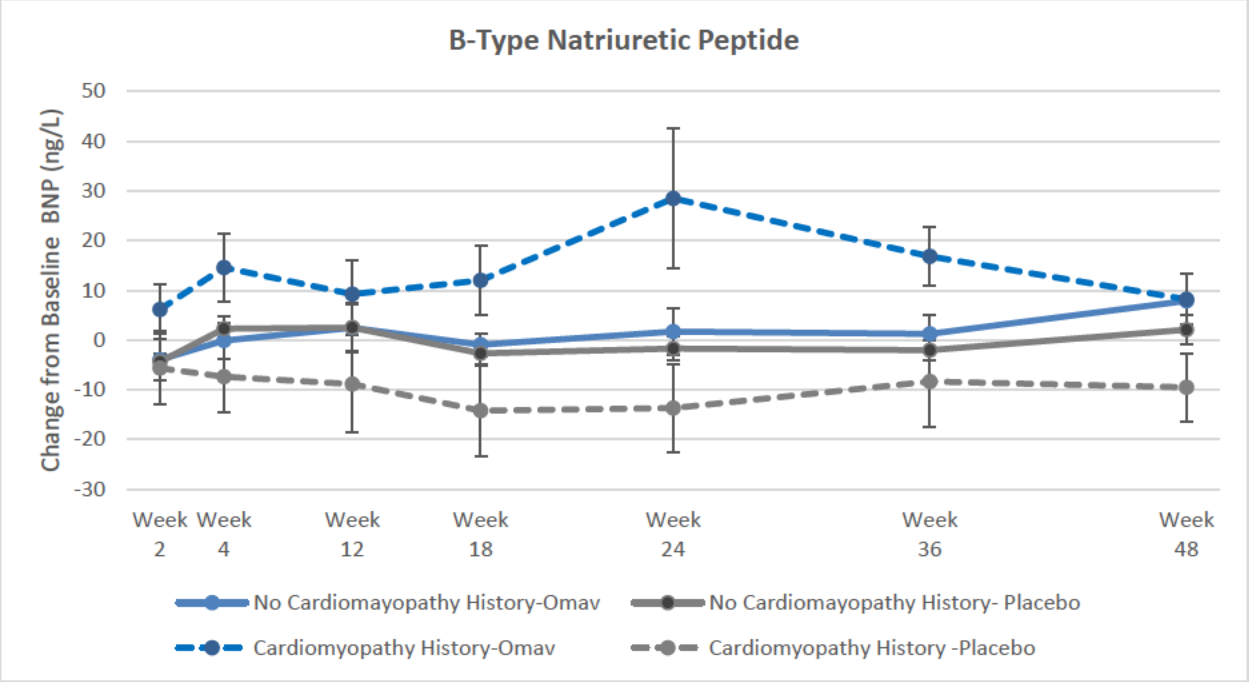



Note: The reference limit for this patient was 200 ng/L and 206 ng/L for BNP and NT-ProBNP is which is higher than the normal reference range of 100 and 125 respectively.

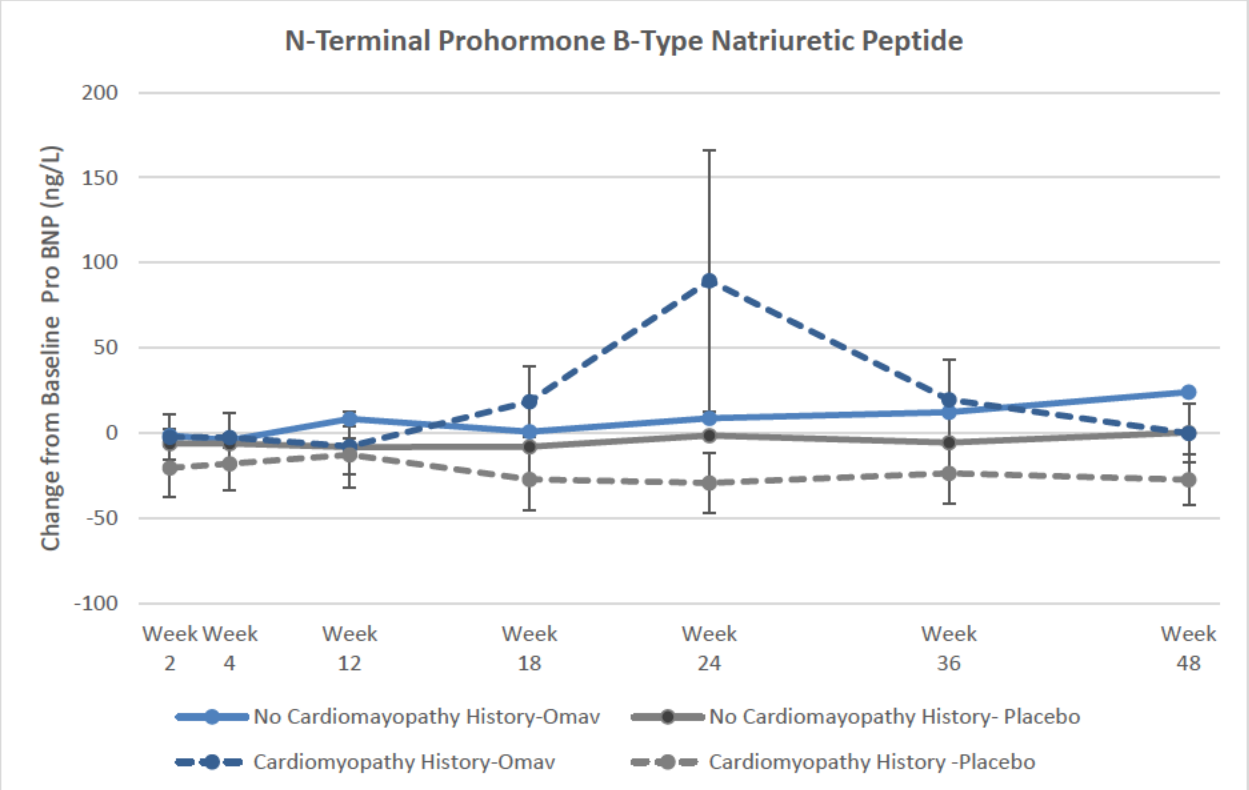
Both BNP and NT-proBNP are released in response to changes in pressure inside the heart. These changes can be related to heart failure and other cardiac problems. Therefore, the overall mean changes in these in patients with and without a history of cardiomyopathy was explored.

Mean change from baseline was higher in omaveloxolone-treated patients with a history of cardiomyopathy. By week 48 it reached similar values to patients without cardiomyopathy (Figure 33)

**Figure 33 Mean Change from Baseline in B-Type Natriuretic Peptide and N-Terminal Prohormone of B-Type Natriuretic Peptide over Time by Cardiomyopathy History**




**(B)**



No TEAE of cardiac failure was observed; however, patients with clinically significant cardiac disease were excluded (See exclusion criteria).

The Clinical Study report indicates that no fluid overload was observed in any phase of the clinical trials. However, this reviewer noted the following preferred terms related to fluid overload were observed in Study 1402 Part 2 and the extension study with omaveloxolone 150 mg (Table 52). These patients were not reported to have an increase in BNP or NT-Pro BNP.

**Table 52 Preferred Terms Related to Fluid Overload**

| Preferred Term | AE Start Day | AE End Day |
|---|---|---|
| Edema Peripheral (edema of legs) | 906 | - |
| Edema Peripheral (edema of legs) | 231 | - |
| Peripheral swelling (Swelling of fingers) | 121 | 131 |
| Edema of Eyelid | 67 | 68 |

BNP was considered a pharmacodynamic marker by the Applicant. According to the Applicant, BNP is thought to regulate energy expenditure by influencing several metabolic processes, such as triglyceride lipolysis in adipocytes, fatty acid oxidation by skeletal muscle, mitochondrial biogenesis, and mitochondrial respiration, which are processes associated with Nrf2 activation.

***Reviewer's Comment:*** *BNP and NT-Pro-BNP were higher in the omaveloxolone treated patients compared to placebo patients. Given that a larger number of patients had a history of cardiomyopathy and/or had an increase of these markers at baseline, the risk of omaveloxolone contributing to these elevated levels is unclear; however, there were a few patients without the baseline history of cardiomyopathy that also showed increases in either BNP or NT-Pro-BNP making a drug effect more likely. Note that at baseline 49% omaveloxolone-treated patients vs. 29% placebo-treated patients had cardiomyopathy; the risk for the increase in BNP and or NT-Pro-BNP with omaveloxolone remains unclear. Some patients also had NT-Pro-BNP levels ≥300 ng/L, indicating these patients are at risk for cardiac failure. FA patients generally die from cardiac failure, but whether the risk is increased with omaveloxolone if difficult to establish given the small number of patients in the study. Further pharmacovigilance will be required to assess the cardiac risk with omaveloxolone in this patient population.*

***Division of Cardiology and Nephrology Consultation (Drs. DeConti and Southworth)*** *(Refer to the detailed consult review)*

*Given the findings of increased BNP and NT-Pro-BNP, the Division of Cardiology and Nephrology was consulted to evaluate the potential safety signal and make recommendations for*

*monitoring and labeling. The consultants concluded that the safety database is too small to characterize omaveloxolone CV safety. A greater baseline history of CV events and cardiomyopathy in the omaveloxolone group than placebo and a high background rate of cardiomyopathy and arrhythmias in FA further complicate interpretation. However, the elevations in BNP levels in the omaveloxolone-treated raise concern for adverse cardiac effects due to the similarities to bardoxolone[15], which shares a similar mechanism and chemical structure, whose phase 3 study in chronic kidney disease patients was discontinued early due to a signal for heart failure-related hospitalizations and death. Labeling recommendations included to advise patients of the signs and symptoms of fluid overload, such as sudden weight gain (≥ 3 lb of weight gain in one day, or ≥ 5 lb of weight gain in a week), peripheral edema, palpitations, and shortness of breath. If signs and symptoms of fluid overload develop, worsen, or require hospitalization, evaluate cardiac function and manage appropriately. Management of fluid overload and heart failure may require discontinuation of treatment.*

**Ferritin in Analysis Set A**

Mean increases in ferritin were seen in the omaveloxolone group relative to baseline and placebo that were not clinically concerning from the safety perspective Figure 34 Mean Change from Baseline in Ferritin over Time (Figure 34)). Although there were increases in ferritin seen with omaveloxolone treatment, the levels were still within the reference range of normal. Higher levels of Ferritin are a non-specific marker of inflammation. Levels over 300 ng/mL can suggest inflammation.

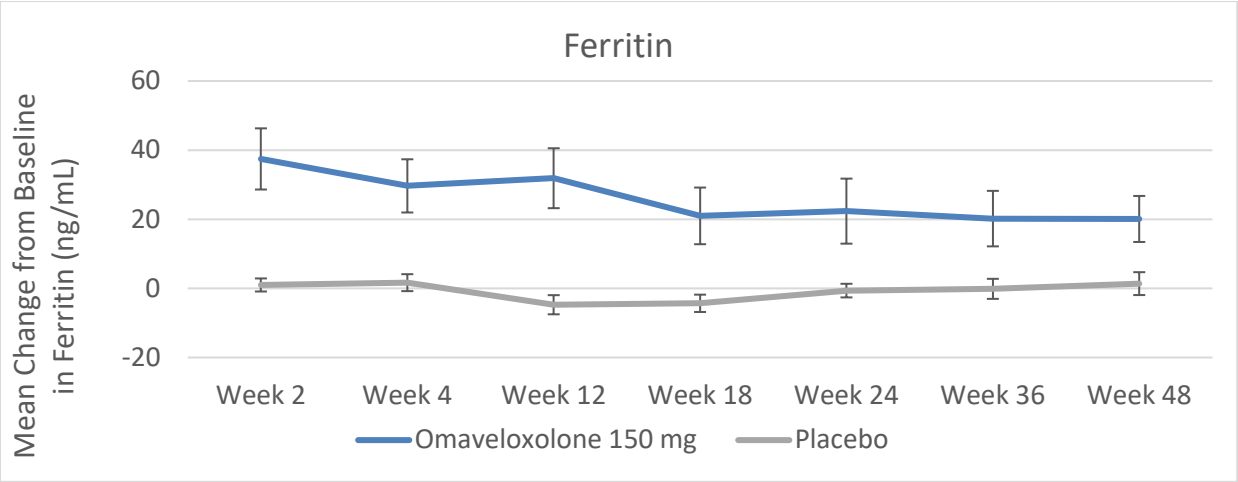
There was only one patient (# (b) (6) ) that had ferritin levels above the ULN in the omaveloxolone arm in the range of 414-569 ng/mL at various visits. No clinical signs of inflammation were observed.

The Applicant postulates ferritin to be a pharmacodynamic marker for omaveloxolone, as Nrf2 induces the expression of the genes that encode the components of the ferritin complex, thus, increases in ferritin likely reflect activation of Nrf2 (Tsuji, 2005[16]). A dose dependent increase in ferritin was observed in Part 1 of the Study (to include data on Part 1) that has been discussed Section 6.1.2 of the review under pharmacodynamic markers.

[15] Bardoxolone methyl, NDA 215484, received a Complete Response on February 25, 2022. DARRTS Reference ID: 4943446

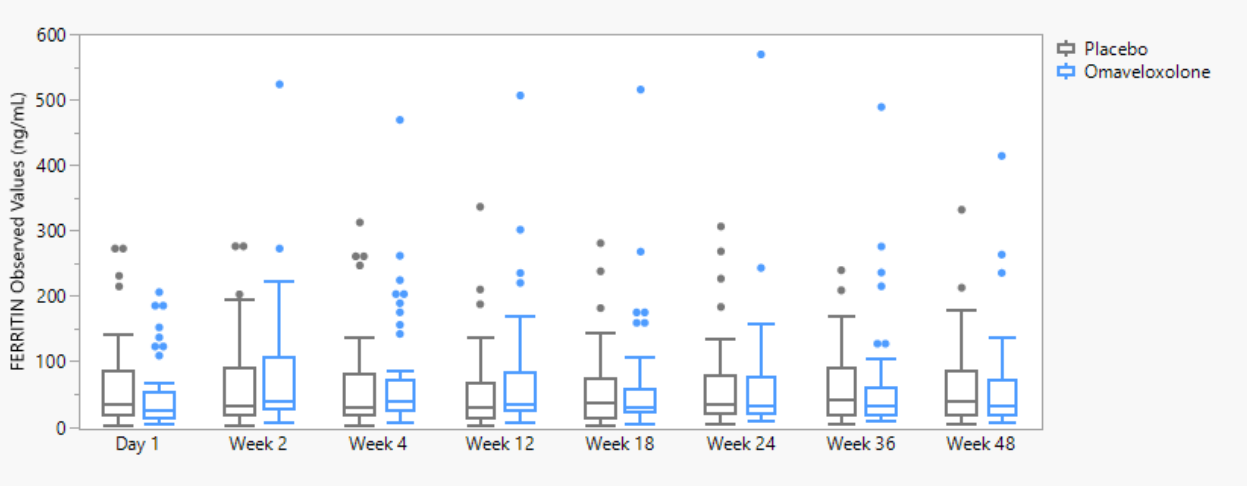
[16] Tsuji, 2005, JunD activates transcription of the human ferritin H gene through an antioxidant response element during oxidative stress; Oncogene. 2005 November 17; 24(51): 7567–7578.

**Figure 34 Mean Change from Baseline in Ferritin over Time**




Although mean increase in Ferritin was observed as shown above, it is driven by one single patient, as shown in Figure 35.

**Figure 35 Observed Ferritin Values (Analysis Set A)**




***Reviewer's comment:***
*Ferritin is also a marker for disturbed iron metabolism. Increased ferritin may cause stomach pain, palpitations, unexplained weakness/fatigue, and joint pain. These were all TEAEs that were observed in the clinical study. Ferritin levels greater than 200 ng/mL in women and greater than 300 ng/mL in men are abnormal. Although levels remained with the normal reference range for most patients, with one exception, an increase in ferritin can have associated symptoms in patients.*

**Others:**

There were no clinically meaningful changes in other laboratory parameters that were outside the reference range and clinically meaningful.

**Estimated glomerular filtration rate:**
Slight increase in mean eGFR were observed in the omaveloxolone arm compared to placebo arm that were not clinically meaningful.

**Hemoglobin and Hematocrit:**
Slight decreases from baseline in hemoglobin and hematocrit were observed in the omaveloxolone arm compared to placebo arm that were also not clinically meaningful. All values returned to baseline within 4 weeks after discontinuing treatment. Decreases >1.5 g/dL from baseline in hemoglobin values were not observed in any patients.

**Creatine Kinase:**
Decreases in creatine kinase were observed in the omaveloxolone arm that also went back to baseline. The Applicant postulates this to be a reflection of improved cellular metabolism and mitochondrial function as creatine kinase catalyzes the reversible transfer of high-energy phosphate from adenosine triphosphate to creatine.

**Magnesium**
Decreases in serum magnesium from baseline were observed in the omaveloxolone arm compared to the placebo arm. No patients reported magnesium values below the lower limit of normal. All patients had on-treatment serum magnesium levels ≥1.4 mg/dL throughout treatment. The reductions in serum magnesium were reversible, trending back toward baseline values after stopping the study drug. No TEAEs of hypomagnesemia were reported in omaveloxolone-treated patients.

**Laboratory abnormalities as TEAEs:** In addition, laboratory abnormalities (other than liver enzymes, which is reported in the Common TEAE section of the review) reported as TEAEs that occurred in two or more patients are summarized in Table 53. All TEAEs related to laboratory findings were related to chemistry and none related to hematology laboratory tests. All of the TEAEs related to laboratory values were mild to moderate in severity, except, 1 event of blood creatine phosphokinase increased which was considered severe.

**Table 53 Laboratory abnormalities as TEAEs**

| Laboratory Test | Placebo (N = 52) n (%) | Omaveloxolone 150 mg (N = 51) n (%) |
|---|---|---|
| Blood creatine phosphokinase | 2 (3.8) | 3 (5.9) |
| Hypercholesteremia* | 1 (1.9%) | 3 (5.9%) |

*Preferred Terms: Hypercholesterolemia, Hypertriglyceridemia, Lipids increased, very low-density lipoprotein increased.

### 8.4.7. Vital Signs

Blood pressure: Mean decreases in diastolic blood pressure of <3 mmHg were seen in the omaveloxolone arm from baseline through Week 48. Mean decrease in the placebo group was -0.4 mm Hg. No patient had a diastolic blood pressure <50 mmHg. Mean decreases in systolic blood pressure of <3 mmHg were seen in both the omaveloxolone and placebo arm from baseline through Week 48. No patient had a systolic blood pressure <90 mmHg.

Changes of similar magnitude were observed in patients greater than 16 and less than 18 years of age.

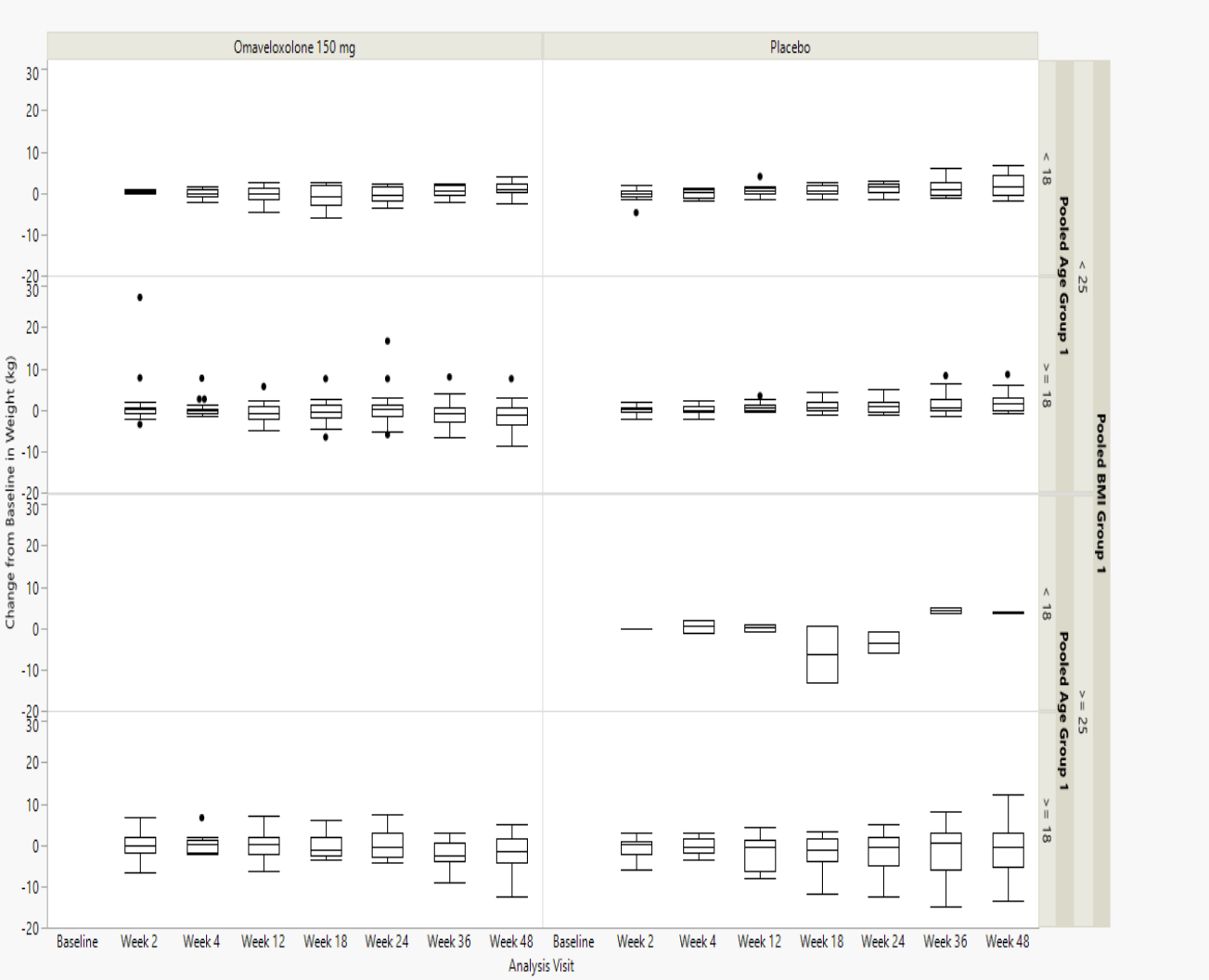
***Division of Cardiology and Nephrology Consult Reviewer's Comments (Drs. DeConti and Southworth)*** *(Refer to the detailed consult review)*

*The lack of observed BP effects of omaveloxolone is not reassuring of no cardiac risk with omaveloxolone, given this trial was not powered to detect small, but potentially clinically meaningful increases in BP. The Applicant used clinic measurements which cannot capture BP changes that occur naturally throughout the day and clinic monitoring is associated with measurement error and increased variability. The Agency recommends ambulatory blood pressure monitoring (ABPM) for drugs intended for chronic use, if a large BP effect is not detected by clinical measurements in early, small trials. ABPM provides more accurate measurements of BP throughout the day and can detect small changes in BP (nocturnal).*

Weight: Applicant reports that the omaveloxolone patients had mean decreases in weight relative to baseline and relative to placebo that were apparent only at Weeks 36 and greater. In Analysis Set A, a mean decrease of -0.95 ± 3.585 kg in weight relative to baseline was observed in omaveloxolone-treated patients over 48 weeks. A mean increase of 1.34 ± 4.053 kg in weight relative to baseline was observed with placebo-treated patients over 48 weeks.

Additional analysis of weight change by age and baseline BMI subgroups showed that the mean decreases in weight occurred in adult patients and were more pronounced in patients that were overweight at baseline (BMI >25 kg/m2) in both treatment groups (Figure 36).

**Figure 36 Weight loss by BMI and age**




Pooled age group 1: <18 years, Pooled age group 2: >18 years

A total 34% omaveloxolone treated patients had a weight loss of at least 5% compared to 19% of placebo patients, but weight loss of at least 7% were similar across treatment groups as shown in Table 54. This could suggest the apparent weight loss may be attributed to other factors for example adverse events observed such as decreased appetite, nausea, vomiting and

diarrhea that were more in the omaveloxolone treated patients compared to placebo patients.

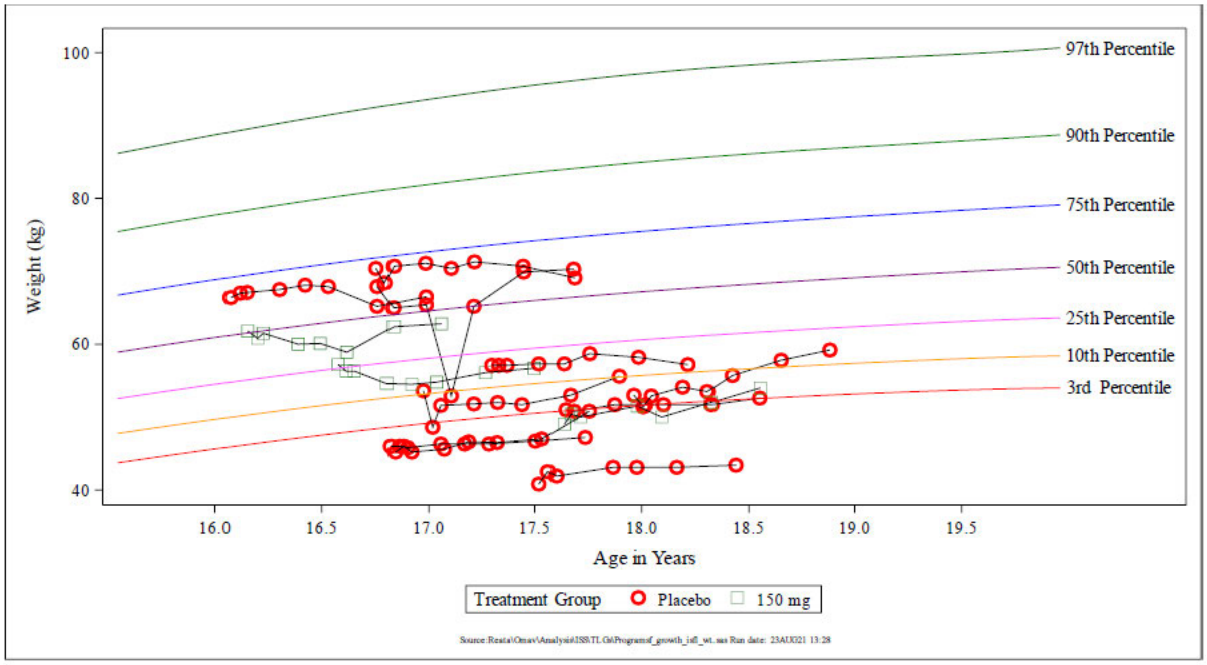
**Table 54 Weight Loss Relative to Baseline (Analysis Set A)**

| | Omaveloxolone 150 mg (N = 51) n (%) | Placebo (N = 52) n (%) |
|---|---|---|
| Weight Loss of at least 5% or more | 17 (34%) | 10 (19%) |
| Weight Loss of at least 7% or more | 6 (12%) | 7 (13.5%) |

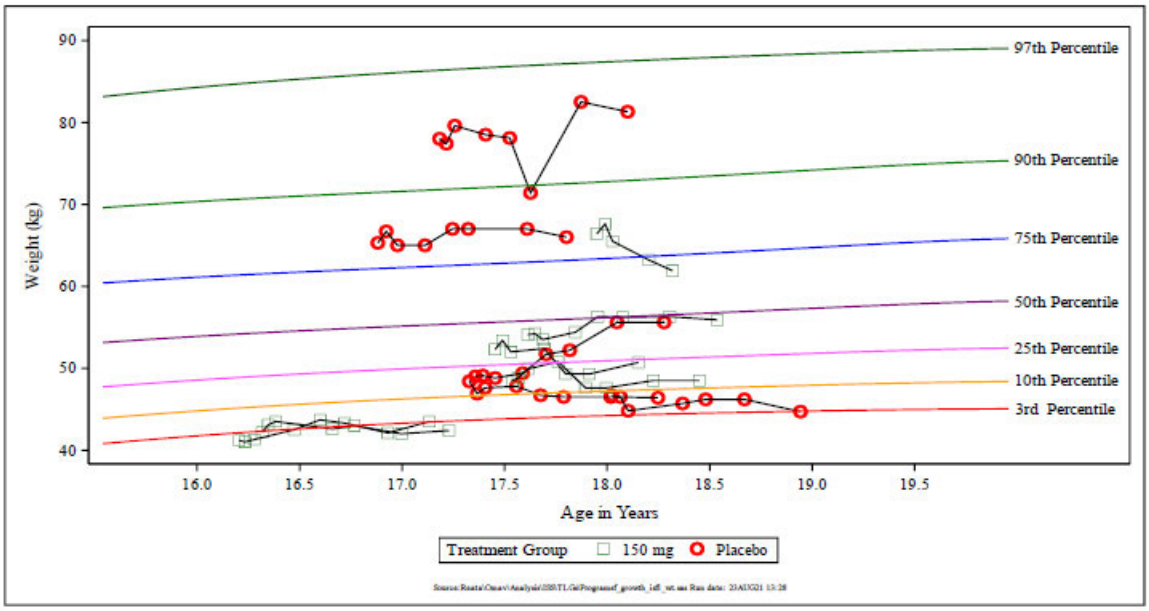
Mean weight did not decrease in patients <18 years of age. Male adolescent patients continued on their growth curves (Figure 37). Growth trajectory in the female adolescent patients is less clear due to overlap of profiles, however, a couple trajectories show a decline in weight. Overall, pediatric patients (<18 years of age) treated with omaveloxolone had mean increases in weight at Week 48.

**Figure 37 Scatter Plot of Weight (kg) for Adolescent Patients (Analysis Set A)**

Male Adolescent Patients




Female Adolescent Patients




Source: Applicant's ISS page 155

Patients that were not overweight at baseline had, on average, generally unchanged weight through Week 48.

One patient in each treatment group (omaveloxolone and placebo) reported a TEAE of weight decreased in Analysis Set A; however, there was also 1 TEAE reported in each treatment group of weight increased. Therefore, the effect of omaveloxolone treatment on weight is unclear.

***Reviewer's Comment:***
*The Applicant includes* (b) (4) *This does not appear warranted.* (b) (4)

### 8.4.8. Electrocardiograms (ECGs)

Omaveloxolone-treated patients did not show meaningful changes in ECG parameters relative to baseline or compared with placebo-treated patients.

### 8.4.9. QT

*The effect of omaveloxolone on the QTc interval has not been adequately characterized. The submitted clinical ECG data are not sufficient to exclude a 10-msec mean increase in the QTc interval. There is not a concerning proarrhythmic signal in the clinical and nonclinical data, but the data cannot be used to exclude a small increase in the QTc interval. We still*

*recommend that the Applicant conducts their planned TQT study.*

## 8.5. Analysis of Submission-Specific Safety Issues

### 8.5.1. Treatment-Emergent Adverse Events Related to Depression, Suicide, and Self-Injury

Depression is known to occur in 9 to 36% of the FA population (Nieto, 2018[17]). Suicidality in these patients become a greater risk. Five omaveloxolone-treated patients reported TEAEs related to suicide: One TEAE occurred in Study 1402 Part 2, and 4 TEAEs occurred in the Study 1402 Extension. Patient narratives revealed that all 5 patients had a medical history of depression. No actions were taken with the study drug on these patients, and they continued in the study.

### 8.5.2. Treatment-Emergent Adverse Events Related to Infections and Infestations

There is a hypothetical concern that the anti-inflammatory effects associated with Nrf2 activation may lead to a decreased innate immune response. Therefore, TEAEs related to Infections and Infestations SOC were reviewed to explore drug related trends for decreased immune response.

The number of patients reporting Infections and infestations TEAEs were generally similar between treatment groups. Influenza (15.7% vs 5.8%), urinary tract infection (7.8% vs 0%), gastroenteritis (5.9% vs 3.8%) and conjunctivitis (3.8% vs 0%) occurred in 2 or more patients and occurred more in the omaveloxolone-treated patients compared to placebo. Several other infection-related TEAEs occurred in a single patient in either treatment group (Table 55).

**Table 55 Summary of Infections and Infestations Treatment-Emergent Adverse Events**

| Preferred Terms | Omaveloxolone 150 mg (N = 51) | Placebo (N = 52) |
|---|---|---|
| Total Subjects with any Adverse Events | 34 ( 66.7%) | 33 ( 63.5%) |
| Respiratory tract infection | 16 ( 31.4%) | 20 ( 38.5%) |
| Influenza | 8 ( 15.7%) | 3 ( 5.8%) |

[17] Nieto A, Hernández-Torres A, Pérez-Flores J, Montón F. Depressive symptoms in Friedreich ataxia. Int J Clin Health Psychol. 2018 Jan-Apr;18(1):18-26.

| Preferred Terms | Omaveloxolone 150 mg (N = 51) | Placebo (N = 52) |
|---|---|---|
| Nasopharyngitis | 7 ( 13.7%) | 11 ( 21.2%) |
| Urinary tract infection | 4 ( 7.8%) | 0 ( 0.0%) |
| Gastroenteritis | 3 ( 5.9%) | 2 ( 3.8%) |
| Conjunctivitis | 2 ( 3.9%) | 0 ( 0.0%) |
| Furuncle | 1 ( 2.0%) | 0 ( 0.0%) |
| Hordeolum | 1 ( 2.0%) | 0 ( 0.0%) |
| Laryngitis | 1 ( 2.0%) | 0 ( 0.0%) |
| Nail bed infection | 1 ( 2.0%) | 0 ( 0.0%) |
| Oral herpes | 1 ( 2.0%) | 0 ( 0.0%) |
| Pharyngitis streptococcal | 1 ( 2.0%) | 1 ( 1.9%) |
| Pilonidal cyst | 1 ( 2.0%) | 0 ( 0.0%) |
| Pneumonia | 1 ( 2.0%) | 0 ( 0.0%) |
| Rash pustular | 1 ( 2.0%) | 0 ( 0.0%) |
| Tinea pedis | 1 ( 2.0%) | 0 ( 0.0%) |
| Tonsillitis | 1 ( 2.0%) | 0 ( 0.0%) |
| Cellulitis | 0 ( 0.0%) | 1 ( 1.9%) |
| Cystitis | 0 ( 0.0%) | 1 ( 1.9%) |
| Ear infection | 0 ( 0.0%) | 1 ( 1.9%) |
| Otitis externa | 0 ( 0.0%) | 1 ( 1.9%) |
| Pharyngitis | 0 ( 0.0%) | 1 ( 1.9%) |
| Rhinitis | 0 ( 0.0%) | 2 ( 3.8%) |

Most infections were mild in symptoms. Moderate TEAEs related to infections were seen in 27% of omaveloxolone and 8% of placebo treated patients. Serious TEAEs included Influenza pilonidal cyst, laryngitis, coronavirus (SARS-CoV2), and respiratory tract infection that occurred in the omaveloxolone treated patients. Treatment was only interrupted for coronavirus infection. Laryngitis and respiratory tract infection occurred in the same patient. The time of onset of TEAE was generally similar between treatment arms. The mean time to onset of a reported TEAE in the Infections and infestations SOC was 106.5 (±16.50) days for omaveloxolone-treated patients and was similar to that for placebo-treated patients (105.3 ± 20.93 days).

### 8.5.3. Cardiac Disorders

Evaluation of cardiac safety has been a concern in this Application given the findings of increased cardiac failure observed in a large clinical trial with bardoxolone methyl in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease, although patients with type 2 diabetes mellitus and stage 4 chronic kidney disease are at higher risk of cardiac failure.

Nevertheless, patients with FA have background cardiomyopathy and arrythmia and often die of cardiac failure too. Therefore, evaluating the possibility of an increase in risk of cardiac failure is complicated in small studies such as this Application.

The TEAEs in the cardiac disorder SOC were not different in the two groups, rather TEAES were greater in the placebo-treated patients (13.5%) compared to omaveloxolone-treated patients (9.8%) (Table 56)

**Table 56 Summary of Cardiac Disorders Treatment-Emergent Adverse Events**

| Preferred Terms | Omaveloxolone 150 mg (N = 51) | Placebo (N = 52) |
|---|---|---|
| Total Subjects with any Adverse Events | 5 ( 9.8%) | 7 ( 13.5%) |
| Angina pectoris | 1 ( 2.0%) | 1 ( 1.9%) |
| Atrial fibrillation | 1 ( 2.0%) | 1 ( 1.9%) |
| Atrioventricular block first degree | 1 ( 2.0%) | 0 ( 0.0%) |
| Cardiomyopathy | 1 ( 2.0%) | 0 ( 0.0%) |
| Palpitations | 1 ( 2.0%) | 2 ( 3.8%) |
| Tachycardia | 1 ( 2.0%) | 1 ( 1.9%) |
| Ventricular tachycardia | 1 ( 2.0%) | 0 ( 0.0%) |
| Left ventricular hypertrophy | 0 ( 0.0%) | 1 ( 1.9%) |
| Ventricular extrasystoles | 0 ( 0.0%) | 2 ( 3.8%) |

Other parameters that could affect cardiac safety (BNP, NT-ProBNP, lipids, blood pressure, echocardiograms and QTc) are discussed in other sections of the review.

## 8.6. Safety Analyses by Demographic Subgroups

**Age:**

- Adolescent patients ≥16 years and < 18 years of age were enrolled in the study.
- Adverse events were similar in patients ≤18 years (9 on Omaveloxolone and 15 on placebo) or age or >18 years of age.
- Increase in ALT/AST/GGT in patients ≤18 years were similar to adults but the magnitude of increase was much less.
- Increases in cholesterol and LDL cholesterol was lower in magnitude in patients ≤18 years than adults. Decrease in HDL cholesterol was similar to adults.
- Increases in BNP and NT-Pro-BNP were observed in patients ≤18 years.

- Pediatric patients (<18 years of age) treated with omaveloxolone had mean increases in weight at Week 48 and patients that were not overweight at baseline had, on average, generally unchanged weight through Week 48. Adolescent patients generally continued along their growth curves for weight during treatment with omaveloxolone.

**Gender:** No gender related differences were observed.

**Race:** 97% of the patients in the study were White.

## 8.7. Specific Safety Studies/Clinical Trials

None

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

[Insert text here.]

### 8.8.2. Human Reproduction and Pregnancy

Effect of omaveloxolone on human fetal development is not known. Pregnant and lactating women were excluded from the clinical trials.

### 8.8.3. Pediatrics and Assessment of Effects on Growth

No clinical studies to assess the effect on growth was conducted. However, no obvious effects were observed.

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of overdose were observed. No evidence of abuse potential was observed in clinical studies. No clinical studies were conducted to assess withdrawal or rebound effects of omaveloxolone.

## 8.9. Safety in the Postmarket Setting

Omaveloxolone is not approved for any indication. There is no postmarket safety data available.

## 8.10. Integrated Assessment of Safety

An integrated assessment of safety was not performed given the small sample size of the safety database.

In summary, common TEAES that occurred in ≥20% of omaveloxolone-treated patients elevated liver enzymes, headache, nausea, abdominal pain, skin abrasion, and fatigue.

Laboratory increases in ALT, AST, GGT, BNP and lipids were observed. These will be included in the Warnings/Precautions section of the label. Enhanced pharmacovigilance for ALT/AST and BNP will be required.

# 9. Advisory Committee Meeting and Other External Consultations

None.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

Labeling is reviewed separately.

# 11. Risk Evaluation and Mitigation Strategies (REMS)

There are no REMS required for the Application.

# 12. Postmarketing Requirements and Commitments

The following PMRs are recommended:

PMR 1: 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 2: 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 3: A clinical trial to assess the risk of QT prolongation with omaveloxolone to exclude mean QTc effects greater than 10 ms.

# 13. Appendices

## 13.1. References

Given throughout the Review.

## 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number):**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 110 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR | | |

| | | |
|---|---|---|
| 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

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/s/

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