Safety and Efficacy of Omaveloxolone in Friedreich’s Ataxia (MOXIe Study)

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Abstract

Objective: Friedreich’s ataxia (FRDA) is a progressive genetic neurodegenerative disorder with no approved treatment. Omaveloxolone, an Nrf2 activator, improves mitochondrial function, restores redox balance, and reduces inflammation in models of FRDA. We investigated the safety and efficacy of omaveloxolone in patients with FRDA.

Methods: We conducted an international, double-blind, randomized, placebo-controlled parallel-group, registrational phase 2 trial at 11 institutions in the United States, Europe, and Australia (NCT02255435, EudraCT2015-002762-23). Eligible patients, 16 to 40 years of age with genetically confirmed FRDA and baseline modified Friedreich’s Ataxia Rating Scale (mFARS) scores between 20 and 80, were randomized 1:1 to placebo or 150 mg per day of omaveloxolone. The primary outcome was change from baseline in the mFARS score in those treated with omaveloxolone compared with those on placebo at 48 weeks.

Results: 155 patients were screened and 103 were randomly assigned to receive omaveloxolone (n=51) or placebo (n=52), with 40 omaveloxolone patients and 42 placebo patients analyzed in the full analysis set. Changes from baseline in mFARS scores in omaveloxolone (−1.55 ± 0.69) and placebo (0.85 ± 0.64) patients showed a difference between treatment groups of −2.40 ± 0.96; p=0.014). Transient reversible increases in aminotransferase levels were observed with omaveloxolone without increases in total bilirubin or other signs of liver injury. Headache, nausea, and fatigue were also more common among patients receiving omaveloxolone.
Interpretation: In the MOXIe trial, omaveloxolone significantly improved neurological function compared to placebo and was generally safe and well tolerated. It represents a potential therapeutic agent in FRDA.
Introduction

Friedreich’s ataxia (FRDA) is a progressive autosomal recessive genetic neurodegenerative disorder affecting approximately 5,000 patients in the US and 22,000 patients globally. In an overwhelming majority of patients, FRDA is caused by a biallelic trinucleotide (GAA) repeat expansion in the first intron of the *FXN* gene, which impairs transcription and significantly reduces the amount of functional frataxin protein.\(^1\,^2\) In 4% of patients, there is a single expanded allele combined with a conventional mutation on the other allele.\(^3\) The pathological consequences of frataxin deficiency include disruption of iron–sulphur cluster biosynthesis, cellular iron dysregulation, mitochondrial dysfunction, and increased sensitivity to oxidative stress *in vitro*,\(^4\,^5\) leading to the clinical features of FRDA.

Ataxia is the most common clinical feature in FRDA, reflecting both proprioceptive loss and cerebellar disease. Patients can also develop spasticity, visual and hearing loss, and non-neurological features such as cardiomyopathy, diabetes and scoliosis. In most patients, symptoms begin between five to fifteen years of age, and patients lose the ability to ambulate by their mid-20s.\(^1\,^2\) FRDA shortens lifespan, most often through consequences of cardiomyopathy; average age of death is 37.5 years. \(^6\,^7\) Currently, there are no approved therapies for FRDA, and over 15 clinical trials have failed to reach their primary endpoints in recent years.\(^7\)
Frataxin deficiency causes dysregulation in antioxidant defenses, which could contribute to disease pathology through a vicious cycle of mitochondrial dysfunction, impaired nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, and decreased adenosine triphosphate (ATP) production. In the healthy state, oxidative stress causes Nrf2 translocation to the nucleus to increase the expression of antioxidant genes, protecting cells from damage. In FRDA, both mitochondrial function and Nrf2 signaling are dysregulated. Cultured cells from patients with FRDA exhibit hypersensitivity to oxidative insults, likely due to impairment in Nrf2 signaling and decreases in Nrf2-mediated endogenous antioxidants such as reduced glutathione, NAD(P)H:quinone oxidoreductase 1 (NQO1), and superoxide dismutase. Moreover, when fibroblasts from FRDA patients are challenged with agents that induce oxidative stress, Nrf2 fails to activate, preventing induction of antioxidant Nrf2 target genes. Since the nervous system is sensitive to changes in cellular redox status, impairment of Nrf2 activation may contribute to neurodegeneration in FRDA.

Omaveloxolone and related triterpenoid analogues are among the most potent known activators of Nrf2. Treatment with omaveloxolone in vitro restores mitochondrial function in fibroblasts from FRDA patients and in neurons from multiple FRDA mouse models. The safety and efficacy of omaveloxolone in patients with FRDA was evaluated in a two-part, multicenter, double-blind, placebo-controlled, randomized trial (MOXIe; NCT02255435). The 12-week, dose-ranging portion of the study (Part 1) identified the optimal omaveloxolone dose for
induction of pharmacodynamic measures of Nrf2. Omaveloxolone also improved selected measures including cardiopulmonary exercise testing and neurological function, as assessed by the modified Friedreich’s Ataxia Rating Scale (mFARS). Part 2 of the trial, described here, aimed to study the effects of omaveloxolone on neurological function, after 48 weeks of treatment in patients with FRDA.
Methods

Study Design

The Part 2 portion of the MOXIe trial was an international, multicenter, double-blind, randomized, placebo-controlled registrational parallel-group phase 2 trial to evaluate the safety and efficacy of omaveloxolone 150 mg per day in patients with FRDA. The trial was conducted at 11 clinical institutions in the United States, Europe, and Australia, and was approved by Institutional Review Boards or Independent Ethics Committees associated with the individual study sites.

Participants

Eligible patients were 16 to 40 years of age with genetically confirmed FRDA, had baseline mFARS scores between 20 and 80, and could complete maximal exercise testing on a recumbent stationary bicycle. These mFARS scores represent individuals just after the time of presentation at the mildest and several years after loss of ambulation at the most severe. Patients were excluded if they had uncontrolled diabetes, clinically significant cardiac disease, active infections, significant laboratory abnormalities, or interfering medical conditions. Patients who developed diabetes or cardiac disease (such as arrhythmias) remained in the study unless the subject chose to withdraw. All patients provided written informed consent.

Randomization and Masking
Patients were randomly assigned in a 1:1 ratio to receive placebo or 150 mg per day of omaveloxolone. A 1:1 ratio was chosen in order to maximize the statistical power of comparisons between treatment groups and to allow a balanced comparison of safety and efficacy. Randomization was generated using a centralized interactive web response system, and stratified by pes cavus status (with pes cavus and without pes cavus) based on findings from a previous study. Moreover, patients with severe pes cavus have a musculoskeletal foot deformity and may represent a subtype of FRDA with subtly different clinical phenotypes, so patients with pes cavus were included in the study but limited to 20% of subjects enrolled. In this study, pes cavus was systematically defined by the visualization of a flashlight on the medial aspect of the foot when shown from the lateral aspect. This confirms the inability of the foot to flatten completely, a component (along with high arches) necessary for the diagnosis of pes cavus. If the test was positive on one foot, the individual was categorized as having pes cavus. The sponsor, investigators, and patients were unaware of group assignments. Study medications and packaging were identical in appearance to ensure adequate masking.

Procedures

Following randomization on Day 1, patients self-administered study drug for 48 weeks. Neurological function assessments (mFARS) and maximal exercise testing were conducted during screening and at Weeks 4, 12, 18, 24, 36, and 48 (Figure 1A). Other efficacy measures were also assessed during screening and either once every 12 weeks (Patient Global Impression
of Change (PGIC), Clinician Global Impression of Change (CGIC), or once every 24 weeks (9-hole peg test (9-HPT), timed 25-foot walk test [T25-FW], Activities of Daily Living [FA-ADL] score). Routine laboratory testing was performed at all scheduled visits and analyzed by a central laboratory. During the study, subjects maintained their typical exercise routine. A follow-up safety visit occurred at Week 52 (four weeks after last dose).

Outcomes
The primary outcome was the change from baseline in mFARS compared with placebo, at 48 weeks. The mFARS, which was generally administered by the lone investigator at each site, provides a quantifiable measure of neurological function in FRDA patients, and has four subsections (bulbar, upper limb coordination, lower limb coordination, and upright stability). Scores range from 0 to 99, with lower scores indicating better neurological function. To minimize potential bias, examiners performing neurological assessments were blinded to all other results, including laboratory values. Key secondary outcome measures included the PGIC and CGIC, 9-HPT, T25-FW, frequency of falls, peak work during maximal exercise testing, and FA-ADL scores (using FA-validated ADL questionnaire), all evaluated at Week 48 as change from baseline, and performed as previously described.\textsuperscript{18-20} We also recorded vital signs, electrocardiograms, and the frequency and severity of adverse events at each visit. Echocardiograms were also performed during screening, and at Weeks 24 and 48. Patient safety was monitored by an independent data and safety monitoring committee.
Statistical Analysis

We calculated that with 80 patients, a longitudinal analysis would provide approximately 85% power to test a mean (± SD) difference in the change from baseline in the mFARS of 2.0 ± 3.5 points between those randomized to omaveloxolone and those randomized to placebo, assuming a two-sided Type I error rate of 0.05.

A full analysis set (FAS) was used for primary analysis of efficacy and limited to patients without pes cavus who had at least one post-baseline measurement. Safety analyses included all randomized patients (ARP). We used mixed models repeated-measures (MMRM) to analyze the primary outcome. The MMRM used site (degrees of freedom [df]=10) and baseline mFARS (df=1) as covariates and the following fixed factors: treatment group (df=1), time (df=4), the interaction between treatment and time (df=5), the interaction between baseline and time (df=5). The analysis used post-baseline mFARS values collected through 48 weeks as the response (6 repeated measurements at Weeks 4, 12, 18, 24, 36, and 48) as the response. We assumed an unstructured covariance matrix to model the within-subjected variance-covariance errors and did not impute for missing data in the primary analysis of efficacy.

We analyzed secondary endpoints using a hierarchical approach to maintain the family-wise overall Type I error rate of 0.05. Several additional functional measures served as secondary endpoints that were analyzed using a fixed-sequence hierarchical approach to maintain the family-wise
overall Type I error rate of 0.05: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), 9-hole peg test (9-HPT), timed 25-foot walk test (T25-FWT), frequency of falls, peak work, and FA-ADL. The hierarchy order was prespecified in the statistical analysis plan based on natural history and Part 1 Study data. Natural history data in published literature showed the annual rates of change for the secondary endpoints of 9-HPT and 25-FWT to be very small (-0.001 ± 0.003 and -0.01 ± 0.04, respectively)\textsuperscript{20}. Multi-year follow-up and/or large sample sizes would have been necessary to show statistically significant between-group differences, based on an assumption of zero annual change from baseline (i.e., halting progression) in the omaveloxolone cohort. Therefore, these endpoints were not expected to show statistical significance and were placed lower in the hierarchy. It was hypothesized that PGIC and CGIC might improve from baseline, although these endpoints were not assessed in Study Part 1.

\textit{Post-hoc Sensitivity Analyses}

Because randomization was stratified by presence of pes cavus, the prespecified model included pes cavus as a covariate. However, some baseline characteristics consistent with more advanced disease (e.g., longer GAA1 repeat length, and history of cardiomyopathy; Table 1) were more prevalent in the patients randomized to omaveloxolone than in patients randomized to placebo, and were not included in the prespecified model. Although all demographic and baseline characteristics were explored in a post-hoc manner for inclusion as covariates in the repeated
measures model, history of cardiomyopathy and GAA1 repeat length provided the best overall model fit. Accordingly, additional post-hoc sensitivity analyses were also performed to assess the impact of controlling for the imbalances in these baseline disease characteristics between the randomized cohorts.

Additionally, we also conducted post-hoc sensitivity analyses to assess the impact of analysis methodology on the primary outcome. An analysis of covariance (ANCOVA) included the same covariates as the MMRM analysis (i.e., baseline mFARS and site, as well as history of cardiomyopathy and GAA1 repeat length).

To evaluate the consistency of findings across primary and secondary outcomes, post-hoc analyses were conducted to evaluate whether patients were improved, stable, or worsened from baseline in mFARS scores, FA-ADL scores, and/or PGIC after 48 weeks. The categorical thresholds for determining improvements or worsening in mFARS or FA-ADL were based on published annual rates of change for these measures and defined as follows: Improvements were defined as changes from baseline ≤-1.9 points for mFARS scores, ≤-0.4 points for FA-ADL scores, and PGIC scores < 4; stable scores were defined as changes from baseline between >-1.9 and <1.9 points for mFARS scores, >-0.4 and <0.4 for FA-ADL scores, and PGIC scores = 4; worsening was defined as changes from baseline ≥1.9 points for mFARS scores, ≥ 0.4 points for FA-ADL scores, and PGIC scores > 4.
All statistical analyses were performed using SAS (version 9.4).

**Results**

Between October 20, 2017 and November 5, 2018, 155 patients were screened in the United States (n=71), Italy (n=7), United Kingdom (n=8), Austria (n=9), and Australia (n=8). Of the patients screened, primarily reasons for not being eligible to participate in the study included inability to compete maximal exercise testing and screening mFARS scores. A total of 103 met entry criteria, with 82 patients included in the FAS, with 40 patients who were randomly assigned to receive omaveloxolone and 42 patients who were randomly assigned to receive placebo. A total of 94 (91%) patients completed treatment through Week 48, including 44/51 (86%) randomized to omaveloxolone and 50/52 (96%) randomized to placebo (Figure 1B). One patient randomized to omaveloxolone did not have any post-baseline assessments and was excluded from the FAS population. Significance testing of baseline differences were not performed, but baseline characteristics were generally similar across the FAS and ARP populations (Table 1). While the distribution of baseline characteristics was generally similar between treatment groups, the omaveloxolone cohort had slightly more advanced disease, with higher average baseline mFARS scores, longer GAA1 repeat lengths, and a greater proportion of patients with a history of cardiomyopathy. Nearly all patients (92%) were ambulatory. Patients with pes cavus had a shorter GAA1 repeat length, but otherwise were similar to other subjects in the study (Table 1).
Patients randomized to omaveloxolone (n=40) experienced a mean (± SEM) decrease from baseline in mFARS of \(-1.55 \pm 0.69\) (95% CI: \(-2.93, -0.18\); df=72.6) points at Week 48 (Figure 2A). In contrast, patients randomized to placebo (n=42) had a mean increase in mFARS of \(0.85 \pm 0.64\) (95% CI: \(-0.43, 2.13\); df=67.8) points, resulting in a difference between treatment groups of \(-2.40 \pm 0.96\) (95% CI: \(-4.31, -0.5\) points (p=0.014; Figure 2A).

Within the mFARS assessment, omaveloxolone improved each component (bulbar, upper limb coordination, lower limb coordination, and upright stability) relative to placebo though the greatest effects were on the upright stability (Figure 2B). Upright stability scores in placebo patients consistently worsened over time, with no observed placebo effect. Prespecified sensitivity analyses of the primary endpoint in the ARP (n=103), including those with pes cavus, confirmed the primary analysis in the FAS population, with a difference between omaveloxolone and placebo groups of \(-1.93 \pm 0.90\) (95% CI: \(-3.7, -0.15\) points (n=103; p=0.034; Figure 2C).

The improvements in mFARS with omaveloxolone were consistent across subgroups, including stratifications by age and sex (Figure 2C). The greatest improvements in mFARS occurred in patients < 18 years of age; pediatric patients randomized to placebo worsened by \(+2.52 \pm 1.18\) points at Week 48 while pediatric patients randomized to omaveloxolone improved by \(-1.63 \pm 1.78\) points, resulting in a placebo-corrected improvement of \(-4.16 \pm 2.15\) points (n=20;
p=0.057) (Figure 2C). In addition, although numerical improvement was noted in every subgroup examined, the greatest treatment effects were observed in men and in subjects enrolled in sites in the United States.

*Sensitivity Analyses of Primary Mixed Model for Repeated Measures (MMRM) Efficacy Results*

In order to diminish the possibility that the primary results represent an aberration, post-hoc analyses using ANCOVA were conducted to assess the impact of analysis methodology on the primary outcome. These analyses showed an even greater treatment effect with omaveloxolone at Week 48, with an improvement in mFARS relative to placebo of -2.83 points (p=0.0068). In addition, small differences in baseline characteristics were noted between the randomized omaveloxolone and placebo populations. Accounting for history of cardiomyopathy as a covariate in the model resulted in an improvement in mFARS of -2.65 points at Week 48 for omaveloxolone relative to placebo (p=0.0064; Figure 3A). In addition, although all patients had genetic confirmation of FRDA, not all randomized patients had baseline GAA1 repeat length data. Inclusion of GAA1 repeat length as a covariate in the longitudinal model for the patients with available data (n=31 for omaveloxolone and n=36 for placebo) also improved the treatment effect on mFARS with omaveloxolone, resulting in a difference between treatment groups of -3.37 points (p=0.0017). Finally, inclusion of both cardiomyopathy and GAA1 repeat lengths into the longitudinal model further improved the treatment effect with omaveloxolone.
(difference of -3.48 points relative to placebo; p=0.0012). Similar trends were observed when including the baseline covariates using an ANCOVA analysis (Figure 3B).

**Secondary outcome measures**

Mean PGIC and CGIC scores at Week 48 numerically improved in patients randomized to omaveloxolone (3.90 and 3.93, respectively), but did not statistically differ between treatment groups (Table 2). The PGIC and CGIC values at Week 48 correlated positively with changes in mFARS (Pearson’s correlation for mFARS versus PGIC: r = 0.47, p<0.0001; CGIC: r = 0.44, p<0.0001). Since the first secondary endpoint in the hierarchy did not demonstrate statistically significant evidence of efficacy, omaveloxolone did not significantly improve any secondary efficacy measures relative to placebo. Nevertheless, all secondary endpoints numerically favored omaveloxolone. Omaveloxolone improved FA-ADL scores relative to baseline and achieved nominal statistical significance relative to placebo at Week 48 (‒0.17 ± 0.45 and 1.14 ± 0.42, respectively; p=0.042; Table 2). All 9 sections of the FA-ADL score numerically favored omaveloxolone. Finally, a post-hoc analysis of FA-ADL change employing additional covariates to account for imbalances in baseline characteristics (i.e., baseline mFARS and history of cardiomyopathy) showed an even greater treatment effect with omaveloxolone at Week 48, with an improvement in FA-ADL relative to placebo of -1.50 points (p=0.020).
To reconcile the differences between the primary and secondary outcomes, we examined the number of subjects responding to different measures. A greater proportion of omaveloxolone patients had improvements and fewer omaveloxolone patients had worsening of mFARS, FA-ADL, or PGIC (Table 2). Moreover, a greater proportion of omaveloxolone patients had improvements in mFARS, FA-ADL, and PGIC while a smaller proportion of patients experienced worsening in all three independent measures. Collectively, the data demonstrate that the improvements with omaveloxolone treatment were concordant across several clinical measures assessing how patients felt and functioned in daily life. This shows the internally consistent nature of the overall data despite lack of the statistical significance in the hierarchy of secondary measures.

**Adverse events**

The rates of adverse events were similar in the omaveloxolone (100% of patients) and placebo groups (100%). Most adverse events were mild to moderate in intensity. The most common adverse events occurring more frequently in patients who received omaveloxolone than those who received placebo included headache, nausea, increased alanine and aspartate aminotransferase (ALT and AST, respectively), fatigue, diarrhea, and abdominal pain (Table 3).

Apart from increases in aminotransferases, the excess occurrence of adverse events in patients receiving omaveloxolone was limited to the first 12 weeks of treatment as patients adjusted to treatment and developed improved drug tolerability. Patients reported adverse events less
frequently between Weeks 12 and 48, and they generally occurred with similar frequency across omaveloxolone and placebo groups (data not shown).

Increases in aminotransferase levels in patients receiving omaveloxolone were maximal within the first 12 weeks of treatment and trended back toward baseline as therapy continued (Figure 4A and B). Such increases were reversible, with mean serum ALT and AST concentrations declining to baseline values within four weeks following drug withdrawal. Fifteen (29%) omaveloxolone patients, but no placebo patients, had maximum ALT elevations ≥ 3× the upper limit of normal (ULN). Of those patients, nearly all (12/15) had serum ALT concentrations that returned to normal within four weeks after drug discontinuation; similar trends were observed for AST. Increases in aminotransferases were not associated with increases in total bilirubin, and patients treated with omaveloxolone had small, but statistically significant, decreases in total bilirubin relative to baseline and to patients on placebo (Figure 4C). None of the patients who received omaveloxolone met potential Hy’s law criteria, had clinical symptoms, or other testing to suggest hepatic injury (Figure 4D).

Patients in both cohorts had mean decreases from baseline in systolic and diastolic blood pressure through Week 48 (not shown). No changes were noted on echocardiograms in either group (not shown). On average, patients receiving omaveloxolone had mean decreases in weight relative to baseline and to patients receiving placebo at Week 48. Such decreases were limited to
adults and were more pronounced in overweight patients (baseline BMI > 25 kg/m²; not shown).

 Serious adverse events were reported in three omaveloxolone and two placebo patients while receiving study drug (Table 3). Two additional omaveloxolone patients reported serious adverse events approximately two weeks after receiving the final dose. Four patients receiving omaveloxolone and two patients receiving placebo discontinued treatment due to the occurrence of an adverse event. Three additional patients receiving omaveloxolone withdrew consent for personal reasons. None of the serious adverse events or adverse events that led to treatment discontinuations occurred in the pediatric subgroup.

 Other Changes in Laboratory Parameters
 In a previous study, omaveloxolone lowered minimally elevated creatine kinase levels and restored minimally lowered ferritin levels in FRDA. Both of these effects are consistent with normalization of subclinical but abnormal laboratory values. Thus here, we examined not only effects on ferritin, but also eGFR (as an index of kidney function) and bilirubin (as an index of liver function). Over the course of 48 weeks, omaveloxolone increased ferritin levels, eGFR and lowered total bilirubin, consistent with restoration of biochemical abnormalities (Figure 4C and Figure 5) in FRDA.
Discussion

In our study, omaveloxolone treatment significantly improved neurological function relative to placebo after 48 weeks of treatment. Unlike patients treated with placebo, whose mFARS scores worsened, patients treated with omaveloxolone had improvements in neurological function after 48 weeks. This occurred not only in the primary analysis but also in post hoc analyses accounting for additional baseline covariates that were meaningfully different across randomized cohorts. Moreover, the magnitude of observed improvements is equivalent to approximately two years of FRDA disease progression, as judged by similar cohorts based on age in a natural history (FACOMS) study. Although a small placebo response was noted during the first 12 weeks of the study, the two treatment groups steadily diverged thereafter, and the rate of disease progression between Weeks 12 and 48 for patients randomized to placebo was similar to natural history data. More importantly, the improvements in upright stability with omaveloxolone relative to placebo demonstrate an effect on the mFARS component that defines important clinical milestones in FRDA, including loss of ambulation.

Overall, the results correspond well with the Part 1 of the MOXIe trial with respect to the temporal course and magnitude of improvement with omaveloxolone treatment. As in Part 1, omaveloxolone improved mFARS in subjects with pes cavus to a lesser degree than those without pes cavus. The replication of this finding suggests that it is real, though the immediate explanation is not obvious. Pes cavus is reported in about 50-70% of individuals with FRDA in...
natural history studies, its characterization does not usually reflect the systematic approach in the present study.\textsuperscript{22,23} Using the specific criteria in the present study, individuals with particularly severe foot deformity were excluded. In natural history studies it is more common among more severely affected individuals, while in the present study GAA1 length was shorter among those with pes cavus. While the reason is not entirely clear, pes cavus could identify a subgroup of FRDA patients with fixed deficits that do not readily reverse, a subgroup of individuals without abnormalities in functions targeted by omaveloxolone, or a subgroup not reproducibly assessed by the present protocol. Alternatively, the lower response may simply reflect that as assessed here, the participants designated as having pes cavus represent a more severely affected set of individuals with FRDA. From an anatomical perspective, a variety of neuroanatomic locations are affected in FRDA (e.g., dorsal root ganglia, cerebellar dentate nuclei, sensory systems, corticospinal tracts); however the sites at which omaveloxolone acts are unclear, suggesting that pes cavus may mark neuronal substrates for which omaveloxolone benefit is lower.\textsuperscript{24} Still, no matter the exact biology of the effect of pes cavus, it represents a pre-specified marker of those with less measurable improvement in response to omaveloxolone. This result may deserve further study.

The relative response to omaveloxolone treatment in mFARS subscores and specific subpopulations with FRDA also supports the potential global benefit of omaveloxolone. Improvement in the treatment groups reflected improvements observed in each of the individual
components of the mFARS assessment (bulbar function, upper limb coordination, lower limb coordination, and upright stability) relative to placebo, though of greater magnitude in the upright stability and upper limb subscores. While this could reflect a preferential effect on those items, it may also result from the greater maximum score in those subscores. In addition, the greater response to omaveloxolone treatment in younger subjects and those with longer GAA repeat lengths suggests that omaveloxolone targets the most severe biochemical abnormalities in FRDA and may address deficits in those with more severe or most rapidly changing disease.

Overall, secondary endpoints did not demonstrate a benefit of omaveloxolone. Patients randomized to omaveloxolone had improvements in FA-ADL scores that achieved nominal significance compared to patients randomized to placebo, but other secondary endpoints did not differ significantly between treatment groups. Available natural history data demonstrate that many of the secondary endpoints assessed here are insensitive to change, typically reaching significant changes without intervention over the course of years. Given the small magnitude of annual changes and the small sample size, the study was not powered to detect a statistical difference between treatment groups in these secondary endpoints. Nevertheless, there were also improvements in selected secondary outcome measures including the PGIC and FA-ADL scores. Collectively, the improvements across multiple measures suggest that the improvements in neurological function with omaveloxolone translated to improvements in how patients felt (PGIC) and functioned (FA-ADL).
Consistent with prior studies, omaveloxolone was generally well tolerated in this study with few discontinuations or serious adverse events. Importantly, given the presence of cardiomyopathy in FRDA, omaveloxolone did not increase blood pressure and was not associated with adverse effects on electrocardiogram or echocardiogram parameters, including ventricular heart rate, QTcF, wall thicknesses, or ejection fraction. Treatment with omaveloxolone was associated with asymptomatic, transient, reversible increases in aminotransferases without liver injury. Such changes could represent a consequence of reactivation of hepatic function in FRDA. While the liver is normal for clinical care in FRDA, liver frataxin levels are among the highest in the body and are decreased in animal models of FRDA. Patients have subclinical decreases in a variety of hepatically synthesized proteins including Apo A1 and ferritin, and hepatic knockout of frataxin is toxic to the liver in mice. Activation of Nrf2 induces aminotransferase genes and serum activity of ALT and AST in some situations. Exposure of liver cells to omaveloxolone or its analogue, bardoxolone methyl, results in concentration-dependent increases in both ALT and AST mRNA levels. Omaveloxolone also increases ALT and AST protein levels in cell lines derived from non-hepatic tissues, such as colon, skeletal muscle, and kidney, indicating that omaveloxolone regulates transcription of ALT and AST genes in multiple organs. ALT and AST catalyze the reversible transfer of amino groups between alanine or aspartate, respectively, and \(\alpha\)-ketoglutarate to form pyruvate or oxaloacetate and glutamate. Thus, these enzymes play key roles in metabolic processes including the tricarboxylic acid cycle. In addition, these
enzymes influence redox balance and mitochondrial metabolism through glutathione production\textsuperscript{32} and regulate the NAD\textsuperscript{+}/NADH ratio via the malate-aspartate shuttle.\textsuperscript{33} Accordingly, changes in aminotransferase levels may reflect physiological adaptations to restoration of Nrf2 levels in FRDA.\textsuperscript{31} Similarly, elevations in serum gamma-glutamyl transferase (GGT), a protein involved in glutathione synthesis and also controlled by Nrf2, were observed in omaveloxolone-treated patients in the present study (data not shown). Collectively, changes in GGT, ALT, AST, and total bilirubin observed with omaveloxolone do not appear to be associated with liver injury but are consistent with Nrf2-mediated increases in enzymes of glutathione synthesis and mitochondrial bioenergetics, and thus an appropriate physiological response to Nrf2 activation. Longer-term safety data collected from an open-label extension study with omaveloxolone in patients with FRDA can help confirm this finding.

Furthermore, the response of plasma markers of renal and hepatic function, match the role of Nrf2 in multiple organs. Both eGFR and total bilirubin levels improved in the FRDA subjects given omaveloxolone, even though baseline levels were nominally in the normal range. This response essentially provides a biomarker of omaveloxolone activity in unaffected tissue, emphasizing its global effects on the FRDA phenotype.

Although potential unblinding can be a concern with side effects or the need for unplanned or additional laboratory testing (for example, if necessitated by aminotransferase increases),
confounding factors such as concomitant medications and disease progression may also influence parameters so treatment assignment is not truly known. Although nausea was reported more frequently in patients randomized to omaveloxolone, it was also reported in 14% of placebo participants. Second, the occurrence of adverse events was not temporally associated with the observed treatment effect on efficacy; adverse events tended to occur within the first 12 weeks after treatment initiation while improvements in mFARS with omaveloxolone occurred beyond Week 24. Third, to minimize potential bias, assessment of the primary outcome (mFARS), was conducted by a neurologist who was blinded to laboratory values in almost all cases and several sections of the exam (e.g., upright stability subscore) included timed components that are objective measures and not readily altered by subject effort. Collectively, though there are limitations, the data support that the observed benefit with omaveloxolone noted in the present study is unlikely reflective of any potential participant unblinding.

Limitations of the present study include the small sample size, modest duration and possible limitations of the generalizability of the results. FRDA is a rare, progressive disease that precludes enrollment of a larger cohort or longer duration that could more robustly assess the effects of omaveloxolone in certain subpopulations, including pediatric patients. In particular, the recent set of outcome measures focuses on individuals at the mid-stages of disease when patients can perform an exercise test and almost all patients are ambulatory. This is not the most rapidly progressing group based on natural history studies, but is the most readily studied subgroup.\textsuperscript{20,22}
Thus, as other efficacy assessments, including the 9-HPT and T25-FW were unimproved but underpowered, further studies may require cohorts with more advanced disease and longer-term follow-up to reliably determine the effect of omaveloxolone on such groups. Nevertheless, as Nrf2 dysfunction is found diffusely in FRDA and because change is more easily demonstrated in patients with earlier stages of the disease, it seems likely that at least some benefit will be noted throughout the course of the illness. Thus, omaveloxolone may be a potential therapeutic agent in many if not all stages of FRDA.

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Author Contributions

DL, CM and MC conceived and designed the study and drafted the initial manuscript. AG, MO, DL, MC, CM, MD, SS, CH, SB, WN, CM, KM, PG, GW, TZ, and SP helped collect data, analyzed data, and revised the manuscript.

Potential Conflicts of Interests

This work was sponsored and funded by Reata Pharmaceuticals, which is developing omaveloxolone for clinical applications. Drs. Chin, Meyer, O’Grady, and Goldsberry are employees of Reata Pharmaceuticals.
References

Figure legends

Figure 1
Study Schema for the MOXIe Part 2 Trial and CONSORT Diagram

Figure 2
Panel A shows the mean changes from baseline in modified Friedrich’s Ataxia Rating Scale (mFARS) score over time in the full analysis set (FAS) for patients randomized to omaveloxolone (n=40) or placebo (n=42). The change from baseline in mFARS and p-value were estimated using mixed models repeated measures (MMRM) analysis. Significant differences in the change from baseline in mFARS in the omaveloxolone group, as compared with the placebo group, were observed at Week 48 (p=0.014). The error bars indicate standard errors.

Panel B shows mean changes from baseline in the upright stability scores (Section E) of mFARS over time estimated using MMRM analysis.

Panel C shows a forest plot representing the difference between omaveloxolone and placebo treatment groups for the change from baseline in mFARS score at Week 48 for the following pre-specified analysis populations: FAS (n=82), all randomized patients (ARP) (n=103), and pre-specified subgroups. The change from baseline at Week 48 was estimated using MMRM analysis and each p-value was estimated from a test comparing the difference in means between the omaveloxolone and placebo groups.
Figure 3.

Post-hoc analyses of change from baseline in mFARS at Week 48 with additional baseline covariates (FAS Population). Data are presented as bar graphs comparing mean changes from baseline in mFARS at Week 48 for patients randomized to omaveloxolone (n=40) or placebo (n=42) using the primary mixed model repeated measures (MMRM) methodology (Panel A) or ANCOVA (Panel B) with the inclusion of history of cardiomyopathy, GAA1 repeat length, or history of cardiomyopathy and GAA1 repeat length included as covariates. Note that the model with GAA1 repeat length as a covariate includes only those patients with baseline GAA1 repeat length data (n=31 for omaveloxolone and n=36 for placebo).

Figure 4.

Mean (± SEM) alanine aminotransferase (ALT) (Panel A), aspartate aminotransferase (AST) (Panel B), and total bilirubin values (Panel C) for all randomized patients in the omaveloxolone (n=51) or placebo (n=52) groups through 48 weeks of treatment. Post-treatment values collected at Week 52, 4 weeks after the last dose of study drug was administered, are also shown. Panel D shows an evaluation of drug-induced hepatotoxicity (eDISH) plot. Vertical lines correspond to 3 x ULN for ALT. Horizontal lines correspond to 2 x ULN for total bilirubin. No patients met potential Hy’s criteria in the upper-right quadrant.
Figure 5

Data shown are mean (±SEM) changes in serum ferritin (μg/L) and eGFR (mL/min/1.73 m²) over time for patients randomized to omaveloxolone or placebo.
Table 1. Baseline and Demographic Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Full Analysis Set (FAS)</th>
<th>All Patients (ARP)</th>
<th>Pes Cavus Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=42)</td>
<td>Omaveloxolone (n=40)</td>
<td>Placebo (n=52)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>14 (33)</td>
<td>24 (60)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Age at Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.6 (7.8)</td>
<td>24.2 (6.5)</td>
<td>24.1 (7.8)</td>
</tr>
<tr>
<td>Median</td>
<td>21.0</td>
<td>23.0</td>
<td>21.0</td>
</tr>
<tr>
<td>&lt;18, N (%)</td>
<td>13 (31)</td>
<td>7 (18)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Race White, N (%)</td>
<td>40 (95.2)</td>
<td>40 (100)</td>
<td>50 (96.2)</td>
</tr>
<tr>
<td>mFARS, Mean (SD)</td>
<td>38.8 (11)</td>
<td>40.9 (10.4)</td>
<td>37.9 (10.8)</td>
</tr>
<tr>
<td>Peak Work (W/kg), Mean (SD)</td>
<td>1.2 (0.6)</td>
<td>1.1 (0.5)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>ADL, Mean (SD)</td>
<td>9.9 (4.8)</td>
<td>10.7 (4.8)</td>
<td>9.9 (4.7)</td>
</tr>
<tr>
<td>Age at Onset (years), Mean (SD)</td>
<td>15.1 (5.3)</td>
<td>15.9 (5.7)</td>
<td>15.3 (5.3)</td>
</tr>
<tr>
<td>Duration (years), Mean (SD)</td>
<td>4.7 (4.7)</td>
<td>4.8 (4.0)</td>
<td>4.4 (4.4)</td>
</tr>
<tr>
<td>GAA1 Repeat Length, Mean (SD)</td>
<td>693.8 (277.2)</td>
<td>739.2 (214.9)</td>
<td>676.2 (267.9)</td>
</tr>
<tr>
<td>Ambulatory, (%)</td>
<td>39 (93)</td>
<td>37 (93)</td>
<td>49 (94)</td>
</tr>
<tr>
<td>History of Cardiomyopathy, N (%)</td>
<td>12 (29)</td>
<td>19 (48)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>History of Scoliosis, N (%)</td>
<td>32 (76)</td>
<td>29 (73)</td>
<td>37 (71)</td>
</tr>
<tr>
<td>Scoliosis Surgery, N (%)</td>
<td>7 (17)</td>
<td>12 (30)</td>
<td>10 (19)</td>
</tr>
</tbody>
</table>
Table 2. Secondary Endpoints and Post-hoc Analyses of Proportion of Patients that Improved or Worsened in Primary and Secondary Measures at Week 48

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Week 48 Change from Baseline</th>
<th>Mean Difference ± SEM Between Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=42)</td>
<td>Omaveloxolone (n=40)</td>
</tr>
<tr>
<td>PGIC</td>
<td>4.33</td>
<td>3.90</td>
</tr>
<tr>
<td>CGIC</td>
<td>4.06</td>
<td>3.93</td>
</tr>
<tr>
<td>9-HPT (1/s)ᵇ</td>
<td>-0.0001 ± 0.0006 (p=0.82)</td>
<td>-0.0014 ± 0.0007 (p=0.04)</td>
</tr>
<tr>
<td>T25-FW (1/s)ᶜ</td>
<td>-0.0226 ± 0.0053 (p&lt;0.001)</td>
<td>-0.0169 ± 0.0056 (p=0.004)</td>
</tr>
<tr>
<td>Frequency of Fallsᵈ (Median (Min, Max))</td>
<td>8.5 (0, 131)</td>
<td>3.0 (1, 89)</td>
</tr>
<tr>
<td>Peak Work (W/kg)</td>
<td>0.090 ± 0.033 (p=0.005)</td>
<td>0.03 ± 0.035 (p=0.33)</td>
</tr>
<tr>
<td>FA-ADL</td>
<td>1.14 ± 0.42 (p=0.009)</td>
<td>-0.17 ± 0.450 (p=0.71)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>mFARS Scores</th>
<th>Placebo</th>
<th>Omaveloxolone</th>
<th>Ratio (Omav/PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvedᵈ</td>
<td>11 (27%)</td>
<td>16 (47%)</td>
<td>1.75</td>
</tr>
<tr>
<td>Worsenedᶠ</td>
<td>18 (44%)</td>
<td>7 (21%)</td>
<td>0.47</td>
</tr>
<tr>
<td>FA-ADL Score</td>
<td>41</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Improvedᵈ</td>
<td>8 (20%)</td>
<td>13 (36%)</td>
<td>1.85</td>
</tr>
<tr>
<td>Worsenedᶠ</td>
<td>27 (66%)</td>
<td>17 (47%)</td>
<td>0.72</td>
</tr>
<tr>
<td>PGIC</td>
<td>41</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Improvedᵈ</td>
<td>11 (27%)</td>
<td>16 (44%)</td>
<td>1.66</td>
</tr>
<tr>
<td>Worsenedᶠ</td>
<td>17 (42%)</td>
<td>11 (31%)</td>
<td>0.74</td>
</tr>
<tr>
<td>mFARS, FA-ADL, PGIC</td>
<td>41</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>All Improved</td>
<td>1 (2%)</td>
<td>5 (15%)</td>
<td>6.03</td>
</tr>
<tr>
<td>None Worsened</td>
<td>7 (17%)</td>
<td>13 (38%)</td>
<td>2.24</td>
</tr>
</tbody>
</table>

ᵃ Mean changes for PGIC and CGIC responses and p-values were analyzed using an analysis of covariance (ANCOVA), with treatment group and site as fixed factors and Week 48 values as the outcome with multiple imputation for missing Week 48 values based on the treatment group to which the subject is assigned. Mean changes and p-values for 9-HPT, T25-FW, Peak Work, and FA-ADL were estimated using a mixed-model repeated measures analysis.

ᵇ Analysis based on reciprocal of average time, non-dominant hand

c Analysis based on reciprocal of average walk time

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

e Improvements were defined as changes from baseline ≤-1.9 points for mFARS scores, ≤-0.4 points for FA-ADL scores, and PGIC scores < 4.

f Worsening was defined as changes from baseline ≥1.9 points for mFARS scores, ≥0.4 points for FA-ADL scores, and PGIC scores > 4.
Table 3. Overall Summary of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=52)</th>
<th>Omaveloxolone (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>52 (100%)</td>
<td>51 (100%)</td>
</tr>
<tr>
<td>Any Serious Adverse Event</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Discontinuation due to Adverse Event</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>

### Adverse Events (occurring in >20% of patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Omaveloxolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contusion</td>
<td>19 (37%)</td>
<td>17 (33%)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (25%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>15 (29%)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Excoriation</td>
<td>12 (23%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (14%)</td>
<td>17 (33%)</td>
</tr>
<tr>
<td>Alanine Aminotransferase Increased</td>
<td>1 (2%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (14%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (10%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3 (6%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase Increased</td>
<td>1 (2%)</td>
<td>11 (22%)</td>
</tr>
</tbody>
</table>

### Serious Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Omaveloxolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Ankle fracture</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Cranioencephalic Injury(^b)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Gallbladder disorder</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Laryngitis(^a)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Non-cardiac chest pain(^a)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Palpitations(^a)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Sinus tachycardia(^a)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Ventricular tachycardia(^b)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection(^b)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

\(^a\) Multiple SAEs reported in a single patient
\(^b\) SAEs were reported in patients approximately two weeks after last dose of study drug administration.
A

Modified FARS

Scrn D1 WK12 WK18 WK24 WK36 WK48 WK52

103 Patients

Placebo (n=52) 4-Week Follow-up

Omaveloxolone 150 mg (n=51) 4-Week Follow-up

B

Enrollment

Assessed for eligibility (n=155)

Excluded (n=52)
- Not meeting inclusion criteria (n=52)
- Declined to participate (n=0)
- Other reasons (n=0)

Randomized (n=103)

Allocated to Placebo (n=52)
- Safety Population (n=52)
- Full Analysis Set (n=42)
- Did not receive allocated intervention (n=0)

Allocated to Omaveloxolone (n=51)
- Safety Population (n=51)
- Full Analysis Set (n=40)
- Did not receive allocated intervention (n=0)

Follow-Up

Patients with a post-baseline efficacy assessment (n=51)

Completed treatment through Week 48 (n=50)

Discontinued study treatment (n=2)
- Adverse event (n=2)

Completed study follow-up through Week 52 (n=51)
- Completed study follow-up through Week 52 and completed treatment (n=49)

Discontinued the study (n=1)
- Withdrawal by patient (n=1)

Patients with a post-baseline efficacy assessment (n=51)

Completed treatment through Week 48 (n=44)

Discontinued study treatment (n=7)
- Adverse event (n=4)
- Withdrawal by subject (n=3)

Completed study follow-up through Week 52 (n=45)
- Completed study follow-up through Week 52 and completed treatment (n=40)

Discontinued the study (n=6)
A

B

C

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