

RESEARCH ARTICLE

Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXle Extension

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ABSTRACT: Background: MOXle was a two-part study evaluating the safety and efficacy of omaveloxolone in patients with Friedreich's ataxia, a rare, progressive neurological disease with no proven therapy. MOXle part 2, a randomized double-blind placebo-controlled trial, showed omaveloxolone significantly improved modified Friedreich's Ataxia Rating Scale (mFARS) scores relative to placebo. Patients who completed part 1 or 2 were eligible to receive omaveloxolone in an open-label extension study.

Objective: The delayed-start study compared mFARS scores at the end of MOXle part 2 with those at 72 weeks in the open-label extension period (up to 144 weeks) for patients initially randomized to omaveloxolone versus those initially randomized to placebo.

Methods: We performed a noninferiority test to compare the difference between treatment groups (placebo to omaveloxolone versus omaveloxolone to omaveloxolone)

using a single mixed model repeated measures (MMRM) model. In addition, slopes of the change in mFARS scores were compared between both groups in the open-label extension.

Results: The noninferiority testing demonstrated that the difference in mFARS between omaveloxolone and placebo observed at the end of placebo-controlled MOXle part 2 (-2.17 ± 1.09 points) was preserved after 72 weeks in the extension (-2.91 ± 1.44 points). In addition, patients previously randomized to omaveloxolone in MOXle part 2 continued to show no worsening in mFARS relative to their extension baseline through 144 weeks.

Conclusions: These results support the positive results of MOXle part 2 and indicate a persistent benefit of omaveloxolone treatment on disease course in Friedreich's ataxia. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

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Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 26 April 2022; **Revised:** 29 September 2022; **Accepted:** 24 October 2022

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29286

Introduction

Friedreich's ataxia (FRDA) is a rare genetic neurodegenerative disorder affecting an estimated 5000 patients in the USA and 22,000 patients globally.¹ People with FRDA develop progressive difficulty with ambulation, coordination, and speech, losing the ability to walk, on average, 10 to 15 years after disease onset.^{2,3} Ultimately, FRDA shortens life expectancy; the average age of death is approximately 37.5 years.^{4,5} Currently, no approved disease-modifying therapy is available for the treatment of FRDA.

The pathophysiology of FRDA reflects mitochondrial dysfunction, impaired Nrf2 signaling, and decreased energy (adenosine triphosphate) production.⁶⁻⁹ Omaveloxolone, a potent activator of Nrf2, restores mitochondrial function *ex vivo* in fibroblasts from people with FRDA.¹⁰ Clinical data from the MOXIE study (ClinicalTrials.gov: NCT02255435) demonstrated that omaveloxolone treatment induces Nrf2 and exhibits pharmacological activity based on Nrf2-inducible biomarkers such as ferritin in those with FRDA.^{1,11} This study includes two placebo-controlled parts and an open-label extension for patients who completed part 1 or part 2. Part 1 was a placebo-controlled, dose-ranging study that enrolled 69 individuals, whereas part 2 was a multicenter, randomized, placebo-controlled clinical trial that enrolled 103 people at 11 study sites in the USA, Europe, and Australia.^{1,11} The open-label extension enrolled 149 patients (87% of those enrolled in part 1 or part 2) and remains ongoing.

In the prespecified primary analysis population for MOXIE part 2, treatment with omaveloxolone significantly improved neurological function, as measured by modified Friedreich's Ataxia Rating Scale (mFARS) scores, by -2.40 points relative to placebo at week 48 ($P = 0.014$; $n = 82$).¹ To evaluate the persistence of omaveloxolone's treatment effect, we performed a delayed-start analysis comparing the difference in mFARS scores at the end of the 48-week placebo-controlled period with the difference after 72 weeks in the open-label extension.

Subjects and Methods

Participants

People in MOXIE were 16 to 40 years of age with genetically confirmed FRDA and baseline mFARS scores between 20 and 80. Individuals were excluded if they had uncontrolled diabetes, clinically significant cardiac disease, active infections, significant laboratory abnormalities, or interfering medical conditions. Those who developed diabetes or cardiac morbidity, such as arrhythmias, remained in the study unless they chose to withdraw. Subjects who completed MOXIE part

2, including 48 weeks of treatment and a follow-up safety visit at 52 weeks (4 weeks after last dose), could enroll in the open-label extension study (up to 144–168 weeks at March 24, 2022 database lock).

We defined the analysis populations for the present analysis in a manner consistent with MOXIE part 2; the full analysis set (FAS) included individuals without pes cavus, and the all-randomized population (ARP) included all who enrolled in part 2 of the trial.¹ Omaveloxolone-omaveloxolone refers to those who were randomized to omaveloxolone in MOXIE part 2 and then continued with omaveloxolone in the open-label extension. Placebo-omaveloxolone refers to the set of people originally randomized to placebo in part 2 who then initiated treatment with omaveloxolone in the open-label extension. Thus, people in the placebo-omaveloxolone group began treatment with omaveloxolone 52 weeks after those in the omaveloxolone-omaveloxolone group (Fig. 1).

All subjects provided written informed consent.

General Design

Day 1 of the extension was the same as the last visit in MOXIE part 2 (week 52). All people in the open-

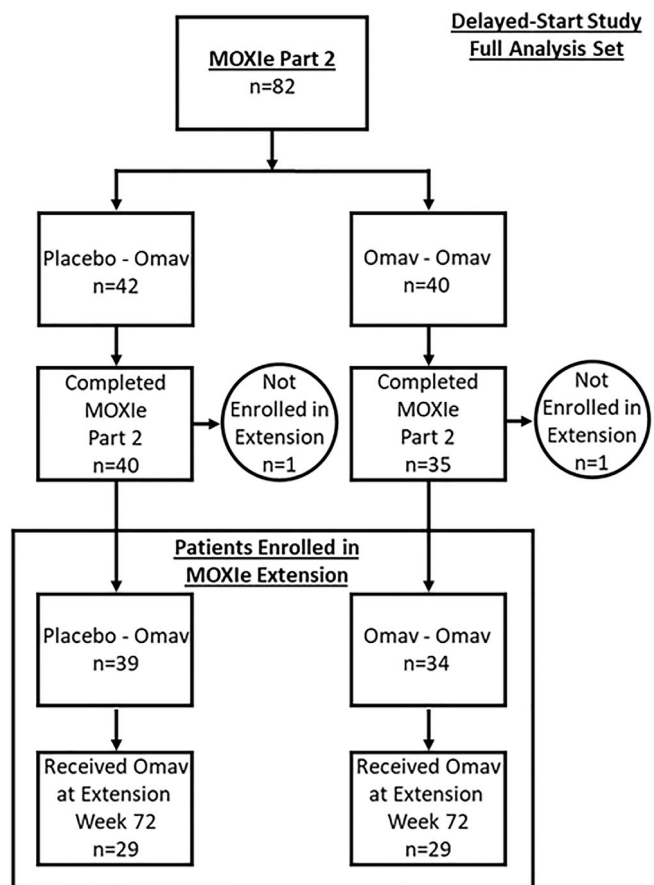


FIG. 1. Consort diagram. Omav, omaveloxolone.

label extension received 150 mg omeveloxolone once daily. Subjects were scheduled for mFARS assessments in the extension at day 1 and every 24 weeks during treatment thereafter. Both subjects and examiners remained blinded to their original treatment group in the randomized and placebo-controlled part 2 throughout the open-label extension; thus, no difference in expectation bias should occur. Data were accrued through March 2022.

The primary endpoint was the difference in the initial placebo and initial omeveloxolone groups in the “delayed-start period” (extension week 72 change from baseline mFARS values) versus the initial omeveloxolone – placebo difference in the “placebo-controlled period” (MOXIe part 2 week 48 change from baseline mFARS values). This analysis used the

FAS. As a sensitivity analysis, efficacy was assessed using the ARP.

We performed a noninferiority analysis using a single mixed model repeated measures (MMRM) model that included all available data from both the 48-week placebo-controlled period (part 2) and the open-label, delayed-start period (open-label extension) through extension week 144 (total follow-up week 196).^{12,13} Analysis using MMRM without imputation assumes data are missing at random. This MMRM included treatment, time, and the interaction of treatment and time as fixed factors, as well as baseline mFARS (from part 2), study site, and the interaction of baseline mFARS and time as covariates. The difference between treatment groups (omeveloxolone-omeveloxolone versus placebo-omeveloxolone) was estimated using the

TABLE 1 Demographics and baseline characteristics for the primary analysis population (full analysis set)

Parameter (units)	Statistic/ Category	Placebo-omeveloxolone (n = 42)	Omeveloxolone-omeveloxolone (n = 40)
Baseline age (y)	Mean (SD)	23.6 (7.8)	24.2 (6.5)
	Median	21.0	23.0
	Q1, Q3	17.0, 27.0	19.0, 28.5
Baseline age group, n (%)	<18 years	13 (31%)	7 (18%)
Age at FRDA onset (y)	Mean (SD)	15.1 (5.3)	15.9 (5.7)
	Median	15.0	15.0
	Q1, Q3	12.0, 18.0	12.0, 19.5
Sex, n (%)	Male	28 (67%)	16 (40%)
Ethnicity, n (%)	Non-Hispanic/Latino	39 (93%)	39 (98%)
Race, n (%)	White	40 (95%)	40 (100%)
Weight (kg)	Mean (SD)	66.3 (17.9)	68.9 (18.4)
	Median	64.7	65.8
	Q1, Q3	51.5, 78.1	53.1, 80.9
mFARS	Mean (SD)	38.8 (11.0)	40.9 (10.4)
	Median	35.7	39.2
	Q1, Q3	32.5, 47.0	31.1, 51.7
FA-ADL	Mean (SD)	9.9 (4.8)	10.7 (4.8)
	Median	10.0	11.5
	Q1, Q3	6.0, 13.5	7.50, 13.8
GAA1 repeat length	n	36	31
	Mean (SD)	693.8 (277.2)	739.2 (214.9)
	Median	684.5	700.0
	Q1, Q3	500.0, 899.5	570.0, 933.0
Ambulatory status, n (%)	Ambulatory	39 (93%)	37 (93%)
History of cardiomyopathy, n (%)	Yes	12 (29%)	19 (48%)

Abbreviation: SD, standard deviation; mFARS, modified Friedreich’s Ataxia Rating Scale. FA-ADL, Friedreich Ataxia Activities of Daily Living Scale.

MMRM model estimates at the end of the placebo-controlled period (Δ_1 ; part 2, week 48) and in the open-label, delayed-start period (Δ_2 ; extension week 72). A decrease in mFARS represents improved function. Therefore, negative values for Δ_1 and/or Δ_2 represent improved function in the omaveloxolone-omaveloxolone versus placebo-omaveloxolone groups. The noninferiority test used a noninferiority margin equal to 50% of Δ_1 ($H_0: \Delta_2 - \Delta_1 \geq -0.5\Delta_1$ versus $H_a: \Delta_2 - \Delta_1 < -0.5\Delta_1$).^{12,13} The alternative hypothesis is equivalent to $\Delta_2 < 0.5\Delta_1$, which implies that the treatment effect at the end of the delayed-start period (Δ_2) preserved more than 50% of the treatment effect after the placebo-controlled period (Δ_1) or Δ_2 did not lose more than 50% of Δ_1 . The upper bound of a one-sided 90% confidence interval [CI] was used for the noninferiority test. For this analysis, we first considered an unstructured covariance structure; however, the model did not converge. Therefore, a Toeplitz covariance structure, which assumes mFARS change from baseline values within a subject are correlated over time, was used.

To further characterize the rate of change in mFARS during open-label treatment, we used a random coefficients mixed model to fit change from baseline mFARS using all available data from the extension study through extension week 144 to estimate annualized slopes based on the part 2 randomized treatment group. The model included terms for baseline (day 1 of the extension), treatment, time, the interaction between treatment and time, and a random intercept.

All statistical analyses were performed using SAS (v9.4; SAS Institute, Cary, NC, USA). For safety data, the assessment of relation to drug is defined by the investigator, based on known effects of drug, temporal relationship to drug, and other factors.

Data Sharing

Data collected for the study, including individual patient data, will not be made available.

Results

Disposition and Baseline Characteristics

From the FAS ($n = 82$), 73 individuals enrolled in the extension study, including 39 people who were randomized to placebo in MOXIe part 2 (placebo-omaveloxolone group) and 34 randomized to omaveloxolone in MOXIe part 2 (omaveloxolone-omaveloxolone group). At extension week 72, subjects completed a combined total follow-up of up to 124 weeks (2.4 years) when accounting for the initial 52 weeks of follow-up in the double-blind study (Fig. 1). Within the FAS, 75 subjects had mFARS assessments at week 48 in MOXIe part 2, and 31 had mFARS assessments at extension week 72. A notable number of

mFARS values were missing at weeks 48 and 72 of the extension study, primarily because of coronavirus disease 2019 (COVID-19) pandemic-related interruptions in on-site clinic visits. However, most patients remained in the study and in the extension study beyond week 72 and subsequently returned to the clinic for mFARS assessments in greater numbers. Only 10 patients in the FAS discontinued treatment during the extension study, including 8 in the placebo-omaveloxolone group and 2 in the omaveloxolone-omaveloxolone group.

Demographics and baseline characteristics were generally similar across treatment groups. Select demographic and baseline characteristic data for the FAS are summarized in Table 1. The mean baseline age \pm standard deviation (SD) was 23.6 ± 7.8 years in the placebo-omaveloxolone group and 24.2 ± 6.5 years in the omaveloxolone-omaveloxolone group. The majority of subjects were non-Hispanic/Latino white individuals in both treatment groups. In the placebo-omaveloxolone group, 28/42 (67%) subjects were male, and 13/42 (31%) were less than 18 years old at baseline. These values are approximately two times higher than the values summarizing the number of male (16/40, 40%) and pediatric (7/40, 18%) individuals in the omaveloxolone-omaveloxolone group. The mean age \pm SD at FRDA onset was 15.1 ± 5.3 years in the

TABLE 2 Primary efficacy results: noninferiority testing for mFARS change from baseline

Description	Period	
	Placebo controlled ^a (Δ_1)	Delayed start ^b (Δ_2)
Full analysis set		
Difference (LS mean \pm SE) ^c	-2.17 ± 1.089 $P = 0.0471$	-2.91 ± 1.437 $P = 0.0433$
Estimate (\pm SE) = $\Delta_2 - 0.5 \times \Delta_1$	-1.826 ± 1.3535	
Upper limit of 1-sided 90% CI for estimate	-0.090	
All-randomized population		
Difference (LS Mean \pm SE) ^c	-1.81 ± 1.057 $P = 0.0878$	-2.17 ± 1.382 $P = 0.1172$
Estimate (\pm SE) = $\Delta_2 - 0.5 \times \Delta_1$	-1.264 ± 1.2637	
Upper limit of 1-sided 90% CI for estimate	0.357	

^aPart 2 week 48 (primary endpoint time point for MOXIe part 2).

^bMOXIe extension week 72 (represents 124 weeks of total follow-up).

^cDifference is omaveloxolone - placebo, based on MOXIe part 2 randomized treatment assignment.

Abbreviations: mFARS, modified Friedreich's Ataxia Rating Scale; SE, standard error; CI, confidence interval.

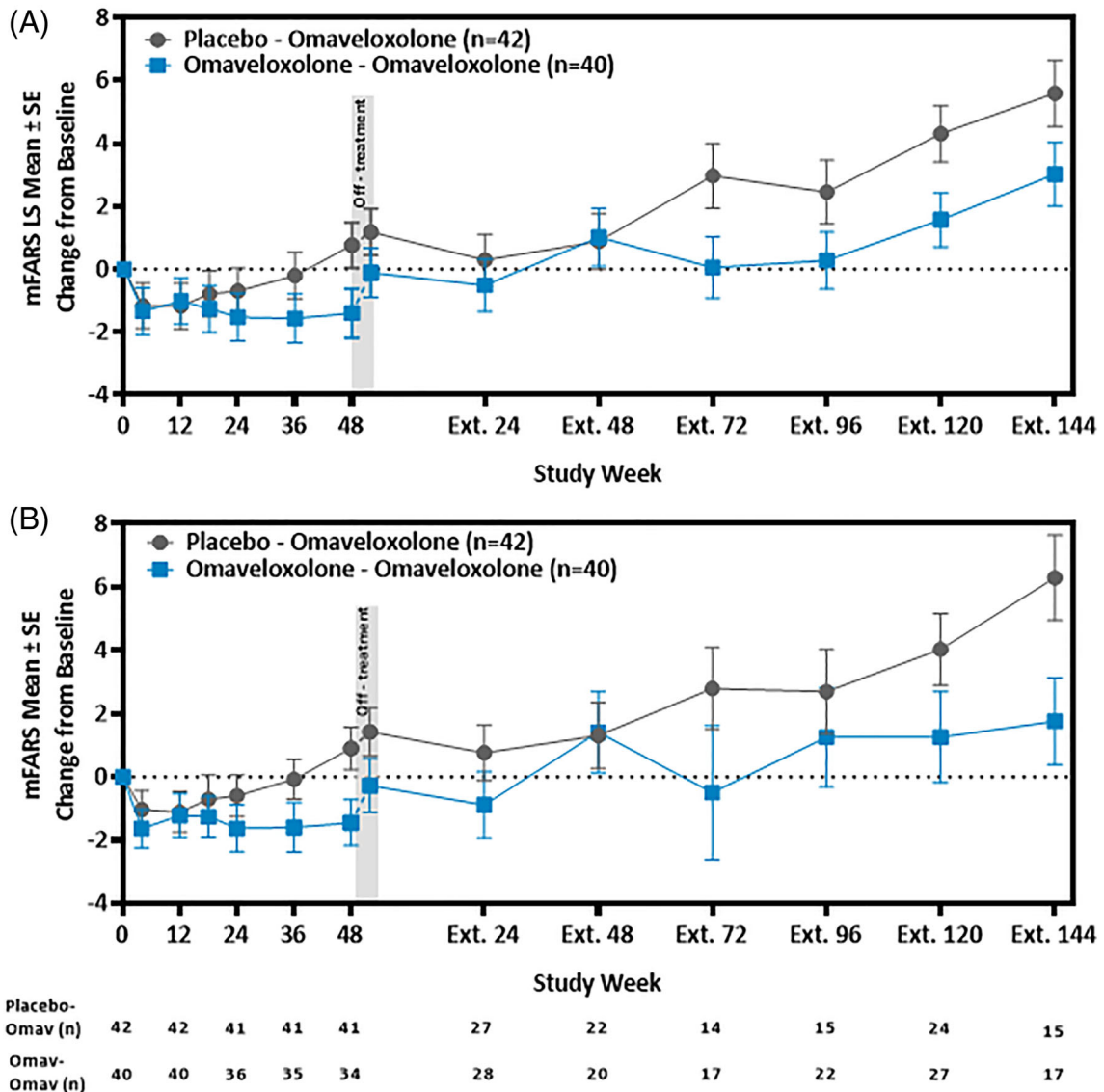


FIG. 2. Change from baseline in modified Friedrich's Ataxia Rating Scale (mFARS; full analysis set [FAS]). **(A)** Mean changes from baseline in mFARS score over time in the FAS for subjects in the omaveloxolone-omaveloxolone ($n = 40$) or placebo-omaveloxolone ($n = 42$) group estimated using mixed models repeated measures (MMRM) analysis. **(B)** Observed mean changes from baseline in mFARS score over time in FAS for subjects in the omaveloxolone-omaveloxolone ($n = 40$) or placebo-omaveloxolone ($n = 42$) groups. LS, least squares; Omav, omaveloxolone; SE, standard error. [Color figure can be viewed at wileyonlinelibrary.com]

placebo-omaveloxolone treatment group and 15.9 ± 5.7 years in the omaveloxolone-omaveloxolone treatment group. The majority of subjects were ambulatory in both the placebo-omaveloxolone (93%) and the omaveloxolone-omaveloxolone (93%) treatment groups.

The mean baseline mFARS score was 38.8 in the placebo-omaveloxolone group and 40.9 in the omaveloxolone-omaveloxolone group. The mean GAA1 (shorter of the two FXN intron 1 GAA repeats) repeat length (with longer repeat length associated with worse disease severity) at baseline was 694 in the placebo-omaveloxolone group and 739 in the omaveloxolone-omaveloxolone group. More omaveloxolone-omaveloxolone subjects (19/40 [48%])

had a history of cardiomyopathy than those in the placebo-omaveloxolone group (12/42 [29%]). Thus, although the distribution of most baseline characteristics was similar between treatment groups, compared with the placebo-omaveloxolone group, the omaveloxolone-omaveloxolone group had slightly more advanced disease, with higher average baseline mFARS scores, longer GAA1 repeat lengths, and a greater proportion of individuals with a history of cardiomyopathy.

Efficacy

Results of the noninferiority testing using a single MMRM model demonstrated that the difference in

TABLE 3 Summary of treatment-emergent adverse events

Adverse Event	Placebo – omaveloxolone (n = 106)	Omaveloxolone – omaveloxolone (n = 43)	Total (N = 149)
Patients with at least one adverse event, n (%)	103 (97.2%)	40 (93.0%)	143 (96.0%)
Patients with a serious adverse event, n (%)	8 (7.5%)	5 (11.6%)	13 (8.7%)
Patients with a related serious adverse event, n (%)	0	0	0
Patients with a serious adverse event leading to drug discontinuation, n (%)	0	0	0
Common adverse events reported in ≥10% of patients in either group, n (%)			
Alanine aminotransferase increased	24 (22.6%)	4 (9.3%)	28 (18.8%)
Coronavirus infection	20 (18.9%)	8 (18.6%)	28 (18.8%)
Headache	20 (18.9%)	7 (16.3%)	27 (18.1%)
Upper respiratory tract infection	15 (14.2%)	10 (23.3%)	25 (16.8%)
Nausea	17 (16.0%)	7 (16.3%)	24 (16.1%)
Fatigue	14 (13.2%)	6 (14.0%)	20 (13.4%)
Diarrhea	15 (14.2%)	4 (9.3%)	19 (12.8%)
Excoriation	16 (15.1%)	2 (4.7%)	18 (12.1%)
Contusion	14 (13.2%)	4 (9.3%)	18 (12.1%)
Arthralgia	13 (12.3%)	5 (11.6%)	18 (12.1%)
Ligament sprain	14 (13.2%)	3 (7.0%)	17 (11.4%)
Abdominal pain	9 (8.5%)	7 (16.3%)	16 (10.7%)
Vaccination complication	9 (8.5%)	6 (14.0%)	15 (10.1%)
Muscle spasms	12 (11.3%)	2 (4.7%)	14 (9.4%)
Nasopharyngitis	6 (5.7%)	7 (16.3%)	13 (8.7%)
Vomiting	7 (6.6%)	5 (11.6%)	12 (8.1%)
Back pain	6 (5.7%)	5 (11.6%)	11 (7.4%)
Depression	4 (3.8%)	5 (11.6%)	9 (6.0%)
Constipation	3 (2.8%)	5 (11.6%)	8 (5.4%)
Treatment-emergent serious adverse events			
Cardiac failure congestive	0	1 (2.3%)	1 (0.7%)
Sinus tachycardia	0	1 (2.3%)	1 (0.7%)
Myocarditis	1 (0.9%)	0	1 (0.7%)
Constipation	0	1 (2.3%)	1 (0.7%)
Pilonidal cyst	0	1 (2.3%)	1 (0.7%)
Upper respiratory tract infection	0	1 (2.3%)	1 (0.7%)
Gastroenteritis norovirus	1 (0.9%)	0	1 (0.7%)
Sepsis	1 (0.9%)	0	1 (0.7%)
Viral upper respiratory tract infection	1 (0.9%)	0	1 (0.7%)
Facial bones fracture	1 (0.9%)	0	1 (0.7%)

(Continues)

TABLE 3 Continued

Adverse Event	Placebo – omaveloxolone (n = 106)	Omaveloxolone – omaveloxolone (n = 43)	Total (N = 149)
Hip fracture	1 (0.9%)	0	1 (0.7%)
Troponin increased	1 (0.9%)	0	1 (0.7%)
Back pain	0	1 (2.3%)	1 (0.7%)
Epilepsy	1 (0.9%)	0	1 (0.7%)
Suicide attempt	2 (1.9%)	0	2 (1.3%)
Major depression	1 (0.9%)	0	1 (0.7%)
Depression	1 (0.9%)	0	1 (0.7%)
Dyspnea	0	1 (2.3%)	1 (0.7%)

mFARS between omaveloxolone and placebo observed at the end of the placebo-controlled portion (LS mean difference = -2.17 ± 1.09) was preserved at the end of the delayed-start period (LS mean difference = -2.91 ± 1.44). The upper limit of the 90% CI for the test statistic ($\Delta_2 - 0.5 \times \Delta_1$) was less than zero (-0.09), demonstrating significant evidence of noninferiority (Table 2). Similar trends were observed in the ARP, although the noninferiority criteria were not met (Table 2).

The graphical representation of changes from baseline in mFARS for omaveloxolone and placebo groups shows that the separation at the end of the placebo-controlled period is maintained in the open-label period (through extension week 144). Apart from the data at extension week 48, which had many missing mFARS assessments because of COVID-19 pandemic-related interruptions, nearly parallel trajectories were seen between the placebo-omaveloxolone group and the omaveloxolone-omaveloxolone group (Fig. 2). The difference at extension week 72 persisted through week 120 and in the limited number of subjects who have presently returned for week 144. In addition, the mFARS scores of people in the omaveloxolone-omaveloxolone group were maintained relative to their extension baseline through extension week 120.

Annualized slopes during the open-label period using all available data from the extension study through week 144 for the omaveloxolone-omaveloxolone group was 0.45 ± 0.63 (95% CI: $-0.82, 1.71$) and the placebo-omaveloxolone group was 0.76 ± 0.28 (95% CI: $0.21, 1.31$). There was no evidence of a significant difference between the two groups (difference: -0.31 ± 0.71 , 95% CI: $-1.72, 1.10$; $P = 0.66$). There was no evidence of convergence between the two groups. The annual slope for each group in MOXIE Extension is less than the expected worsening of about two points per year based on natural history data.¹⁴

The resulting parallel trajectories between both treatment groups demonstrate a lack of convergence between the groups that is consistent with omaveloxolone treatment altering disease course.

Safety

The longer-term safety profile of omaveloxolone in the extension study was similar to that seen in MOXIE Parts 1 and 2, and omaveloxolone was generally well tolerated in the extension study. No deaths were reported. Serious adverse events were reported in 13 (8.7%) patients; of these, 8 (7.5%) individuals were in the placebo-omaveloxolone group and 5 (11.6%) were in the omaveloxolone-omaveloxolone group. All of the serious adverse events were considered by the investigator to be unrelated to study drug, and none resulted in permanent discontinuation of study drug (Table 3). An increased number of upper respiratory infections was noted in part 1, but not part 2, of MOXIE and were not clearly noted in the extension cohort, although there was no clear control group to precisely define this. The most common treatment-emergent adverse events were increased alanine aminotransferase and coronavirus infection. Other adverse events occurring in $\geq 10\%$ of patients in either group and treatment-emergent serious adverse events are shown in Table 3. Elevations in aminotransferase increases were not associated with elevations in total bilirubin, and no subject met Hy’s law criteria.

Discussion

The results of the delayed-start analyses indicate a persistent benefit of omaveloxolone treatment on disease course. Those who received omaveloxolone during the placebo-controlled, double-blind period (MOXIE part 2) experienced a sustained benefit that could not

be recovered by individuals initially randomized to placebo who began omaveloxolone in the extension study, implying a benefit of starting omaveloxolone treatment earlier. In addition, patients previously randomized to omaveloxolone in the controlled, double-blind period continue to show slowed disease progression, as assessed with mFARS, over more than 2.5 years of treatment in the extension; mean mFARS values for these individuals were maintained from extension baseline through extension week 144. The -2.17 difference at week 48 in part 2 results from the same model used for the pivotal analysis in Study 1402 part 2, for which a -2.4 difference was described; the small difference in these values (-2.17 and -2.4) reflects the additional visits being included in the delayed-start model; however, they describe the same time point. The Study 1402 part 2 analysis included data through part 2 week 48. The delayed-start analysis includes that part 2 data plus the data from all visits through extension week 144 as of the database lock. In addition, the delayed-start analysis suggests that the improvement in neurological function persists to some degree with ongoing therapy, suggesting that earlier treatment with omaveloxolone might provide greater benefit than delayed therapy in this study population. The ongoing difference in groups in the later time points of the delayed-start analysis supports this idea.

A challenge in conducting studies of investigational therapies for mitochondrial diseases is the complicating factor of hope bias. Although the possible presence of such bias existed in the placebo-omaveloxolone group during the extension study (an early placebo effect in mFARS was observed in MOXIe part 2 that was maximal by week 12 but resolved by week 36), the noninferiority criterion was still met using the MMRM, which included all data up through 144 weeks of the extension study. The 72-week duration of the delayed-start period for the primary noninferiority analysis also allowed those with a delayed start enough time to experience potential symptomatic effects of omaveloxolone, because the maximal effects of omaveloxolone on subjects in the placebo-controlled MOXIe part 2 occurred at week 24.

In the open-label phase, the safety profile was similar to that seen in MOXIe Parts 1 and 2, without any new safety risks identified.^{1,11} The later portion of the extension study was conducted during the global COVID-19 pandemic. Because the mFARS examination is an in-person assessment, this led to a large number of missed mFARS assessments. This primarily impacted study visits occurring at or beyond 48 weeks in the extension study, but a substantial majority of subjects had at least one in-person visit during the later time points. In addition, one major reason for loss of visits was the inability to travel to the primary site, a reason that most likely is random. Thus, missing visits most likely lead to a loss of sensitivity but are unlikely to systematically bias the study.

Limitations of the study include missing mFARS data, small sample size, and the possibility of unmeasured confounding effects. Collectively, the safety and efficacy results of this study support that omaveloxolone is generally safe and well tolerated and indicate a persistent effect of omaveloxolone on disease course in FRDA. ■

Acknowledgments: We acknowledge the supportive role of J. Farmer and the Friedreich's Ataxia Research Alliance, as well as all MOXIe investigators, support staff, and patients. We appreciate the work of clinical trial coordinators T. Alexander, M. Amprosi, G.T. Black, L. Campbell, A. Castaldo, A. Clay, A. Cowser, A. Eigentler, A. Fisher, Z. Fleszar, M. Green, L. Hauser, S. Heintzman, E. Indelicato, C. McDaniel, M. McGriff-Baxter, L. Mezache, A. Mongelli, Dr L. Nanetti, S. Norman, C. Park, B. Sharot, E. Sperin, G. Tai, M. Tellez, and M. Wells. We thank Drs. S. Pitts and S. Natarajan of Reata Pharmaceuticals for administrative assistance in coordinating author responses, forms, and biographical information for electronic submission.

Data Availability Statement

Following publication and regulatory review, no plans are yet made for making data available.

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D.R.L., C.J.M., and M.P.C. conceived and designed the study and drafted the initial manuscript. A.G., M.O., D.R.L., M.P.C., C.M., M.B.D., S.H.S., J.C.H., S.B., W.N., C.J.M., K.D.M., P.G., G.W., T.Z., and S.P. helped collect data, analyzed data, and revised the manuscript.

Financial Disclosures

M.P.C., C.M., A.G., and M.O. are employees of Reata Pharmaceuticals. D.R.L. receives grants from FARA, the Muscular Dystrophy Association, the National Institutes of Health, Reata Pharmaceuticals, and Retrotope. S.B. reports grants from European Friedreich's Ataxia Consortium for Translational Science and NICOFA E-rare (FWF I 3352-B28), AbbVie, Ipsen, and Grünenthal. M.B.D., J.C.H., and C.M. report funding from Reata Pharmaceuticals during the conduct of the study. J.C.H. also reports funding from FARA. K.D.M. reports grants from Reata Pharmaceuticals during the conduct of the study, a personal fee for consultancy from VICO Therapeutics, and grants from Takeda and FARA. S.H.S. reports grants from Reata Pharmaceuticals, Biohaven Pharmaceuticals, Takeda Pharmaceutical, PTC Therapeutics, Retrotope, Acceleron Pharmaceuticals, National Institutes of Health, US Food and Drug Administration, Muscular Dystrophy Association, Wyck Foundation, Friedreich's Ataxia Research Alliance (FARA), Stealth, AveXis, and Dyne Therapeutics. T.Z. has received compensation for serving on the advisory boards of Boston Scientific, Reata Pharmaceuticals, and Steminent Biotherapeutics; has received personal compensation as senior editor for Neurodegenerative Disease Management and as a consultant for Steminent Biotherapeutics; has received royalty payments as co-inventor of varenicline for treating imbalance (patent number 9,463,190) and non-ataxic imbalance (patent number 9,782,404); has received research/grant support as principal investigator/investigator for studies from AbbVie, Biogen, Biohaven Pharmaceuticals, Boston Scientific, Bukwang Pharmaceutical Co, Ltd, Cala Health, Cavion, FARA, Houston Methodist Research Institute, National Institutes of Health (READISCA U01), Retrotope, and Takeda Development Center Americas. P.G., S.B., and G.W. report no conflicts or relevant disclosures.