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RESEARCH ARTICLE

# Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia

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## Abstract

**Objective**: Previous studies have demonstrated that suppression of Nrf2 in Friedreich ataxia tissues contributes to excess oxidative stress, mitochondrial dysfunction, and reduced ATP production. Omaveloxolone, an Nrf2 activator and NF-kB suppressor, targets dysfunctional inflammatory, metabolic, and bioenergetic pathways. The dose-ranging portion of this Phase 2 study assessed the safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia patients (NCT02255435). **Methods**: Sixty-nine Friedreich ataxia patients were randomized 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. Patients were randomized in cohorts of eight patients, at dose levels of 2.5–300 mg/day. **Results**: Omaveloxolone was well tolerated, and adverse events were generally mild. Optimal pharmacodynamic changes (noted by changes in ferritin and GGT) were observed at doses of 80 and 160 mg/day. No significant changes were observed in the primary outcome, peak work load in maximal exercise testing (0.9 ± 2.9 W, placebo corrected). At the 160 mg/day dose, omaveloxolone improved the secondary outcome of the mFARS by 3.8 points versus baseline ($P = 0.0001$) and by 2.3 points versus placebo ($P = 0.06$). Omaveloxolone produced greater improvements in mFARS in patients that did not have musculoskeletal foot deformity (pes cavus). In patients without this foot deformity, omaveloxolone improved mFARS by 6.0 points from baseline ($P < 0.0001$) and by 4.4 points versus placebo ($P = 0.01$) at the 160 mg/day. **Interpretation**: Treatment of Friedreich ataxia patients with omaveloxolone at the optimal dose level of 160 mg/day appears to improve neurological function. Therefore, omaveloxolone treatment is being examined in greater detail at 150 mg/day for Friedreich ataxia.

## Introduction

Friedreich Ataxia (FRDA) is a progressive, life-shortening ataxia caused by mutations in *FXN*, which codes for the protein frataxin.[1–4] The primary features of the disorder include progressive loss of coordination and ambulation, fatigue, cardiomyopathy, and metabolic disturbances. Scoliosis and other skeletal abnormalities are also found in many individuals. The exact mutation is homozygosity for an expansion of an intronic GAA repeat in 96% of patients, with the others having a single expansion with a point mutation in *FXN* on the opposite allele. Although most patients present within the first 15 years, some present later, and in all FRDA is a lifelong disease.[5,6] Although the complete pathophysiology is unclear, there is substantial evidence of mitochondrial dysfunction in FRDA. Frataxin is directed to the mitochondria, where it is thought to play important roles in synthesis of iron sulfur clusters and ATP production. In addition, cells from patients with FRDA are susceptible to reactive oxygen species production. Surprisingly, Nrf2 activation is suppressed in FRDA-derived cells, potentially contributing to oxidative stress, mitochondrial dysfunction, and reduced ATP production in FRDA.[7–10] Augmentation of Nrf2 activation using a variety of compounds increases Nrf2 activation and reverses endogenous antioxidant defense mechanisms in animal and cellular models of FRDA. This makes the Nrf2 pathway a potential therapeutic target in FRDA.

Omaveloxolone (Omav) is a new Nrf2 activator that prevents the ubiquitination of Nrf2 and thus increases its levels. In cell culture, Omav induces Nrf2 as measured by levels of the downstream target NQO1.[11] In cells from patients with FRDA, Nrf2 activation increases mitochondrial function as measured by mitochondrial transmembrane potential and reverses biomarker levels in lymphoblasts.[12,13] In these systems, concentration-response curves demonstrate concentration-dependent increases, followed by a plateau at higher concentrations, and then a decline in effect at still higher concentrations with loss of cell viability.[14] This loss of activity at high concentrations is also observed in other settings with Nrf2 activators, as cellular redox status is tightly regulated to prevent excessive oxidative or reductive stress.[14] In the present study, designated MOXIe, we assessed the pharmacokinetics, safety, pharmacodynamics, and clinical effects of Omav in FRDA over 12 weeks to establish whether it might be a suitable agent for further development in FRDA.

## Methods

### MOXIe study design

The study (NCT02255435) was approved by the Institutional Review Board at the Children's Hospital of Philadelphia and other sites, and written informed consent was obtained from the patient before any study-related procedures were performed. Subjects were enrolled from January 2015 to February 2017 at the Children's Hospital of Philadelphia; the University of California Los Angeles; Ohio State University; Emory University; the University of South Florida; Murdoch Children's Research Institute; University College, London; Medical University, Innsbruck, and the University of Florida. MOXIe was designed as a two-part study. Part 1, presented here, was a Phase 2, double-blind, randomized, placebo-controlled, dose-ranging, multi-center trial (Fig. 1) while Part 2 has been designed to assess efficacy and safety. The sample size for Part 1 was based on a dose-escalation scheme to evaluate initial safety, PK, and PD activity of RTA 408 in this patient population. The small number of patients at each dose in Part 1 was not expected to fully characterize safety, efficacy, or PD, but rather inform the DSMB and Sponsor of the appropriate doses to select for Part 2. In Part 1, cohorts of 8 patients at ascending dose levels were screened, randomized 3:1 to Omav or placebo, and treated for 12 weeks. Two cohorts were enrolled at 160 mg/day (12 Omav and 4 Placebo), and two cohorts were enrolled at 300 mg/day with the final cohort enrolling only five patients (resulting in 10 Omav and 3 Placebo in the 300 mg/day cohort; discontinued due to sufficient safety data being obtained). Safety was overseen by a Data Safety and Monitoring Board. Multiple clinical assessments of muscular and neurological function were assessed in Part I including neuromuscular endpoints (peak work during exercise testing, the primary endpoint, assessed at baseline and 12 weeks); neurological abilities (assessed by the mFARS, a key secondary endpoint, assessed at baseline 4 and 12 weeks); performance measures (the timed 25 foot walk test, nine hole peg test, low contrast vision, assessed at baseline and 12 weeks); health related quality of life (SF-36 Health Survey Update, assessed at baseline and Week 12); and laboratory testing for safety and biochemistry, assessed at baseline, 1, 2, 4, 8, and 12 weeks during the study.

### Eligibility criteria

Patients were required to have genetically confirmed Friedreich's ataxia with an mFARS score $\geq$10 and $\leq$80, be

 

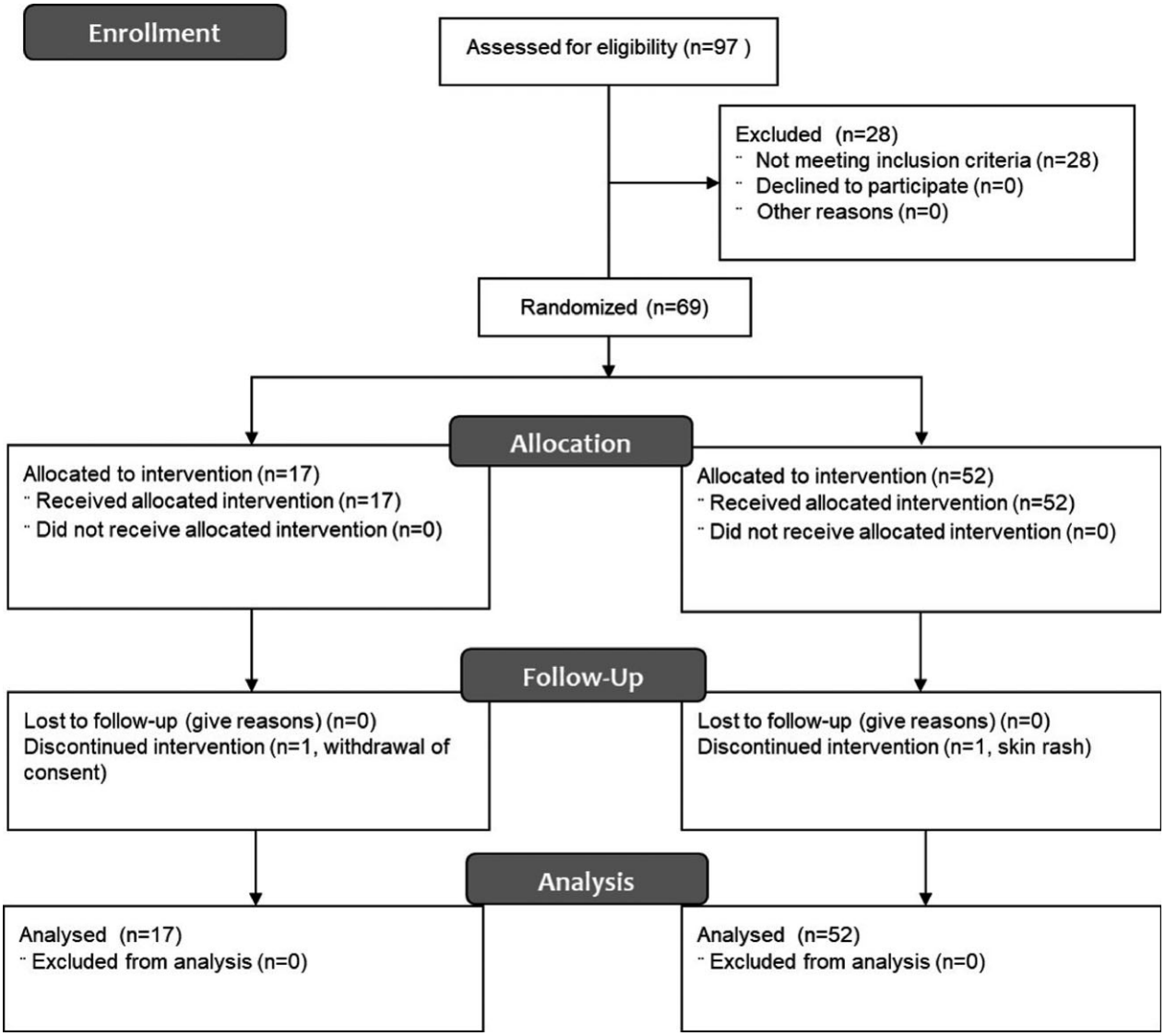


**Figure 1.** Consort diagram of MOXie, part 1.

≥16 years of age, and ≤40 years of age. They also needed the ability to complete maximal exercise testing, defined by being able to ride an exercise ergometer at approximately 60 rpm against no added resistance for 3 min. Patients were excluded if they had uncontrolled diabetes (HbA1c >11.0%), B-type natriuretic peptide (BNP) level >200 pg/mL, or a history of clinically significant cardiac disease. They were required to discontinue all antioxidant supplements at least 14 days prior to baseline.

## Randomization and masking

When subjects met inclusion criteria, they were randomized by computer generated program at 3:1 for each dose group. Subjects and all study staff were masked to subject assignment. Fifty-two patients were randomized to Omav at doses of 2.5–300 mg/day, and 17 patients were randomized to placebo.

## Outcome measures

The primary outcome measure was the peak work attained during maximal exercise testing, along with the safety and tolerability of Omav. Key secondary outcome measures included the mFARS score.[5,15] Exploratory measures included the SF-36 Health Survey Update score; the Fatigue Severity Scale score, 9-hole peg test, the timed 25-foot walk test, low-contrast letter visual

 

**Table 1.** Demographic and clinical features of cohort.

| | Placebo | Omav | All |
|---|---|---|---|
| *N* | 17 | 52 | 69 |
| Sex (% Female) | 10 (59%) | 27 (52%) | 37 (54%) |
| Age (years) | 24.4 ± 6.7 (16–37) | 25.9 ± 6.4 (16–37) | 25.6 ± 6.5 (16–37) |
| BMI (kg/m$^2$) | 22.4 ± 3.7 (16.2–31.5) | 24.2 ± 4.9 (17.4–38.7) | 23.7 ± 4.7 (16.2–38.7) |
| Race(% White) | 16 (94%) | 51 (98%) | 67 (97%) |
| Age at Onset (years) | 16.6 ± 4.7 (11–27) | 14.8 ± 4.8 (6–30) | 15.3 ± 4.8 (6–30) |
| Duration (years) | 7.7 ± 3.5 (0–10) | 11.1 ± 5.3 (0–16) | 10.3 ± 5.1 (0–16) |
| GAA1 repeat length | 863 ± 278 (333–1300) | 700 ± 277 (216–1350) | 741 ± 285 (216–1350) |
| GAA2 repeat length | 620 ± 304 (19–1050) | 714 ± 274 (200–1333) | 690 ± 282 (19–1333) |
| Ambulatory | 16 (94%) | 46 (89%) | 62 (90%) |
| Pes cavus | 10 (59%) | 22 (42%) | 32 (46%) |
| Areflexia | 13 (77%) | 42 (81%) | 55 (80%) |
| Scoliosis surgery | 3 (18%) | 6 (12%) | 9 (13%) |
| Modified FARS | 40.5 ± 10.0 (22.5–53.8) | 41.3 ± 12 (10.7–59.5) | 41.1 ± 11.5 (10.7–59.5) |

Values are mean + SD with quartile ranges in parentheses where indicated.

acuity test, and peak oxygen utilization during maximal exercise testing.[15] Pharmacodynamic markers included protein and enzyme (AST, GGT, CK, and ferritin) levels in serum samples, and assessment of platelet metabolism with $^{13}$C-isotopologues.[16] Isotopologue analysis was performed only in subjects evaluated at the primary site (CHOP). Safety measures included weight, BMI, vital sign measurements, physical examinations, laboratory test results (clinical chemistry, hematology, and urinalysis), concomitant medications, adverse events, and serious adverse events. Pharmacokinetic measures included Omav plasma concentration levels. Disease features such as the presence of pes cavus were ascertained by physical examination.

### Maximal exercise test

Cycle ergometry using a recumbent stationary bicycle was used to conduct maximal exercise testing. Maximal exercise testing assessments included peak work and peak oxygen utilization. On study days where multiple assessments were completed, the maximal exercise test was the first functional assessment performed.

### Neurological testing

The FARS was used as the neurological measure. This includes five sections that measure upper and lower limb coordination, upright stability, bulbar function, and peripheral nervous system function. The mFARS used here omits the peripheral nervous system components so that all remaining assessments are functional tests. The testing was performed as described previously.[5,17–19] The timed 25 foot walk (T25W), SF36, low contrast letter acuity, and the 9 hole peg test (9HPT) were performed as described previously.[17]

### Statistical analysis

Peak work, mFARS, percent change from baseline in laboratory parameters, and the 25-foot timed walk test were analyzed using repeated measures analysis of variance. Analysis visits at baseline, week 4, week 8, and week 12 were used in the repeated measures analysis, with an unstructured covariance structure. Adjustment for baseline weight was utilized in the analysis of peak work. The pairwise dose group comparisons with placebo were estimated using the difference in adjusted means and 95% confidence intervals for the difference in changes from baseline to Week 12. Significance of Week 12 median change from baseline in creatine kinase was evaluated using a one-way ANOVA. For isotopologue analysis, cohorts were pooled into placebo ($n$ = 3), cohorts 1 and 2 ($n$ = 8) and cohorts 3–8 ($n$ = 13) due to the small number of participants in each individual cohort.

## Results

### Patient features

Sixty-nine patients were enrolled, with baseline characteristics generally balanced across treatment groups. The mean age at study entry was 25.6 years and at diagnosis was 15.3 years. Ninety percent of patients were ambulatory, and the cohort had a mean mFARS of 41.1 (Table 1). Examining the age at onset and other features, this cohort is slightly less affected than average in large natural history studies.[17]

 

## Safety, tolerability, pharmacokinetics, and pharmacodynamics

Omav was well-tolerated with only a single discontinuation, which occurred in a 40 mg/day patient who developed a skin rash. One placebo patient discontinued prematurely due to withdrawal of consent. Overall, adverse events were generally mild in severity, and most prominently included an increased number of upper respiratory tract infections and nasopharyngitis (Table 2). A limited number of subjects demonstrated ALT and AST increases. However, these were not associated with any signs or symptoms of liver injury (increased direct bilirubin, decreased albumin, changes in total protein) and are expected as isolated pharmacological effects of Nrf2 activation.[20,21] Two serious adverse events were reported, both of which occurred in placebo patients (benzodiazepine withdrawal and 3rd degree burns).

Pharmacokinetic testing demonstrated generally dose-dependent, linear increases in exposure (Fig. 2). The $C_{max}$ at 300 mg/day was in the concentration range where decreased Nrf2 induction and mitochondrial function have been observed in vitro.[22–25] Pharmacodynamically, Omav commonly alters a series of Nrf2 targets such as ferritin and GGT in vitro and in other human studies.[20–25] Thus we monitored these targets during the present study. Dose-dependent changes in these were observed with Omav, with the most robust changes occurring at 80 -300 mg/day; such changes were maximal after 4 weeks of administration (Fig. 3). Similarly aspartate amino transferase (AST) and creatine kinase (CK) are indirectly regulated by Nrf2.[20,21] AST variably increased at lower doses and was maximal at 160 mg/day while optimal CK decreases were observed at 80–160 mg/day with reduced improvement at 300 mg/day.

**Table 2.** Adverse events.

| Adverse events occurring in ≥10% patients | | |
|---|---|---|
| AE | All doses ($n$ = 52) | Placebo ($n$ = 17) |
| Upper respiratory tract infection | 21 (40%) | 1 (6%) |
| Headache | 9 (17%) | 3 (18%) |
| Ligament sprain | 1 (2%) | 2 (12%) |
| Abdominal pain upper | 1 (2%) | 3 (18%) |
| Nasopharyngitis | 7 (14%) | 0 (0%) |
| Fatigue | 4 (8%) | 2 (12%) |
| Diarrhea | 6 (12%) | 1 (6%) |
| Alanine aminotransferase increased | 6 (12%) | 0 (0%) |
| Aspartate aminotransferase increased | 6 (12%) | 0 (0%) |
| Constipation | 1 (2%) | 2 (12%) |
| Nausea | 5 (10%) | 1 (6%) |
| Arthralgia | 5 (10%) | 0 (0%) |

Individuals with FRDA also have altered metabolism, which can be quantified with *ex vivo* isotopologue analysis in isolated platelets.[16,19] Such analysis reveals an increased conversion of $^{13}$C-palmitate to HMG-CoA. In subgroup at the primary site, isolated platelets revealed lower conversion of $^{13}$C-palmitate to HMG-CoA as Omav dose increased (Fig. 4). As for other pharmacodynamic markers, this effect was maximal and significant at 160 mg alone (data not shown), and significant when cohorts were pooled (Fig. 4). No changes were seen in metabolism to beta-hydroxy-butyrate or acetate, and no changes in metabolism of $^{13}$C-glucose were noted.

## Effect of Omav on clinical testing in FRDA

### Exercise and mFARS testing

No statistical difference in peak workload (the primary outcome measure) was found with Omav treatment versus placebo or relative to baseline ($P$ = 0.77 vs. placebo for all Omav dose groups) (Table 3). A nonsignificant increase in peak work occurred at 160 mg/day compared to baseline. In contrast, Omav significantly improved mFARS scores from baseline in a dose-dependent manner ($P < 0.001$) (Fig. 5; Table 4). Overall, dose-dependent improvements at Week 12 were maximal at 160 mg/day. When compared to the placebo-corrected change at 160 mg/day (−2.3), the improvement in mFARS approached statistical significance ($P$ = 0.06) and was equivalent to an improvement of about 1 year of progression in FRDA based on comparisons to natural history data.[15,17] The improvements in mFARS were time dependent, as the mFARS improved by week 4 and further improved by week 12. In addition, the improvement compared to placebo increased over this time. Interestingly, mFARS changes mirrored AST induction and isotopologue results, since all responses were maximal at doses of 80–160 mg/day and decreased between 160 and 300 mg/day.

After 12 weeks of treatment, patients treated with Omav 160 mg/day did not show improvements versus placebo in 9-hole peg test time for dominant ($P$ = 0.20) or nondominant hand ($P$ = 0.89), 25-foot timed walk test ($P$ = 0.64), 1/25-foot timed walk test ($P$ = 0.85), low-contrast letter acuity test ($P$ = 0.93), or SF-36 ($P$ = 0.19).

## Association of OMAV response with disease features in FRDA

We then sought to ascertain if any features of FRDA predicted a greater response to Omav. Patients with FRDA can develop pes cavus, also referred to as neuromuscular foot deformity. In the present study, the absence of pes cavus was associated with larger improvements in mFARS exam, including a placebo-corrected change in mFARS in

 

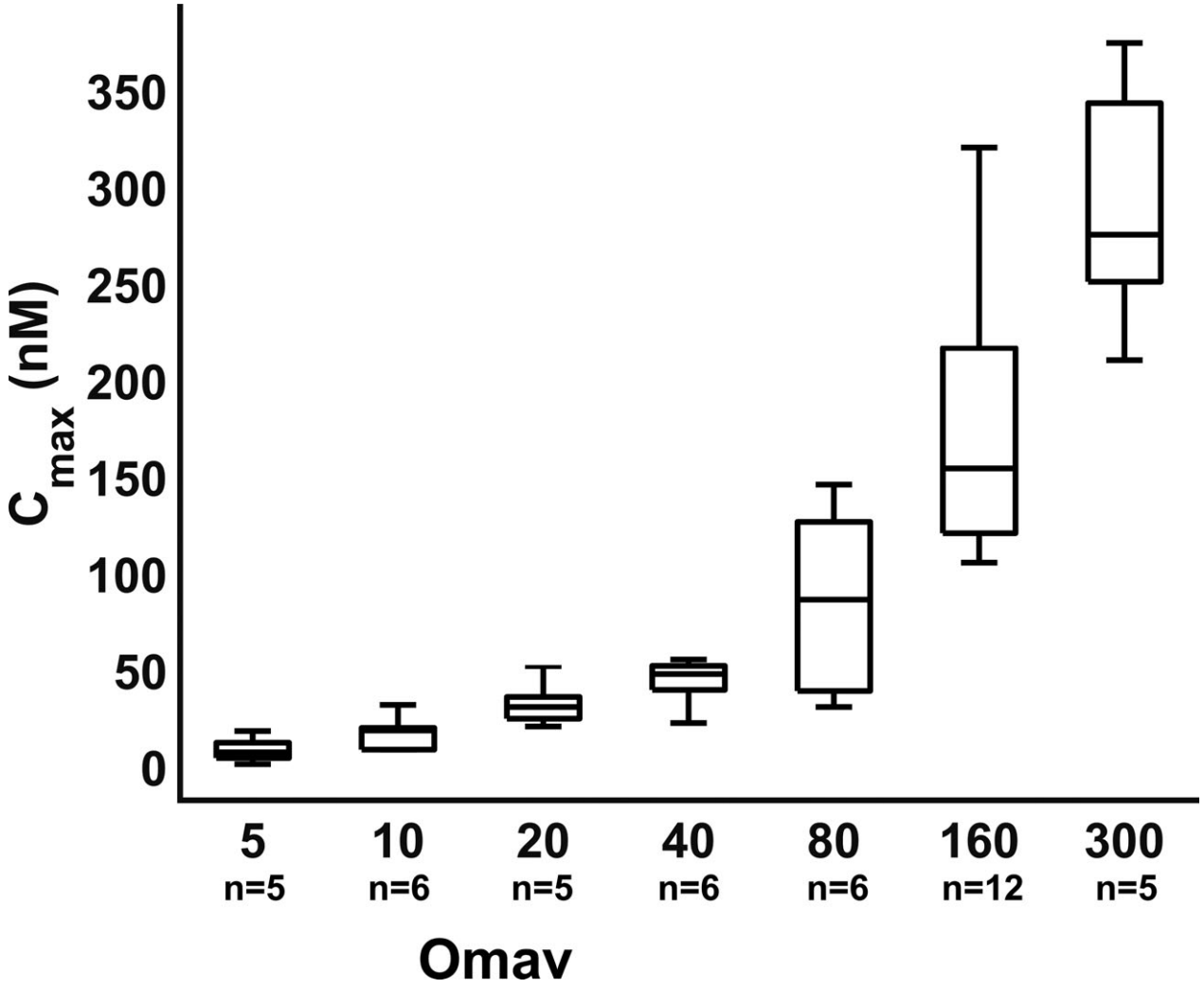


**Figure 2.** Pharmacokinetics of Omav. Maximal concentration of Omaveloxolone $C_{max}$ levels are shown at different doses. Data are presented as a Box and whisker plot. Plasma concentrations increased exponentially over the dose range of the study.

patients without pes cavus of −4.4 points ($P = 0.01$) at Omav 160 mg/day (Fig. 6). Placebo-related change in mFARS was unaffected by the presence of pes cavus. In exercise testing in patients on 160 mg/day who did not have pes cavus, peak workload increased 11.5 W (95% CI 1.1, 21.9), which was significant vs. baseline ($P = 0.03$). In addition, absence of pes cavus was associated with a greater improvement in the 25-ft walk test and exercise testing compared with placebo.

We also examined the relation of a series of other disease features to responsiveness to Omav, including age of onset, disease duration, GAA1 (shorter) and GAA2 (longer) repeat length, sex, ambulation assist type, prior scoliosis surgery, and age. In contrast to the association with pes cavus, none had a clear relationship to response on Omav. Age of onset, age, disease duration, GAA1 repeat length and GAA2 repeat length did not correlate with improvements in mFARS in Omav-treated patients. Omav-treated patients also showed no significant difference in mFARS as a function of ambulation status ($P = 0.97$), sex ($P = 0.71$), prior scoliosis surgery ($P = 0.86$), and ambulation assist type ($P = 0.51$).

## Discussion

The present study demonstrates that Omav remains a viable therapeutic agent for ongoing development in FRDA, as it was well tolerated and associated with relatively few adverse events. In addition, although it had no effect on the primary outcome of measure of peak work

 

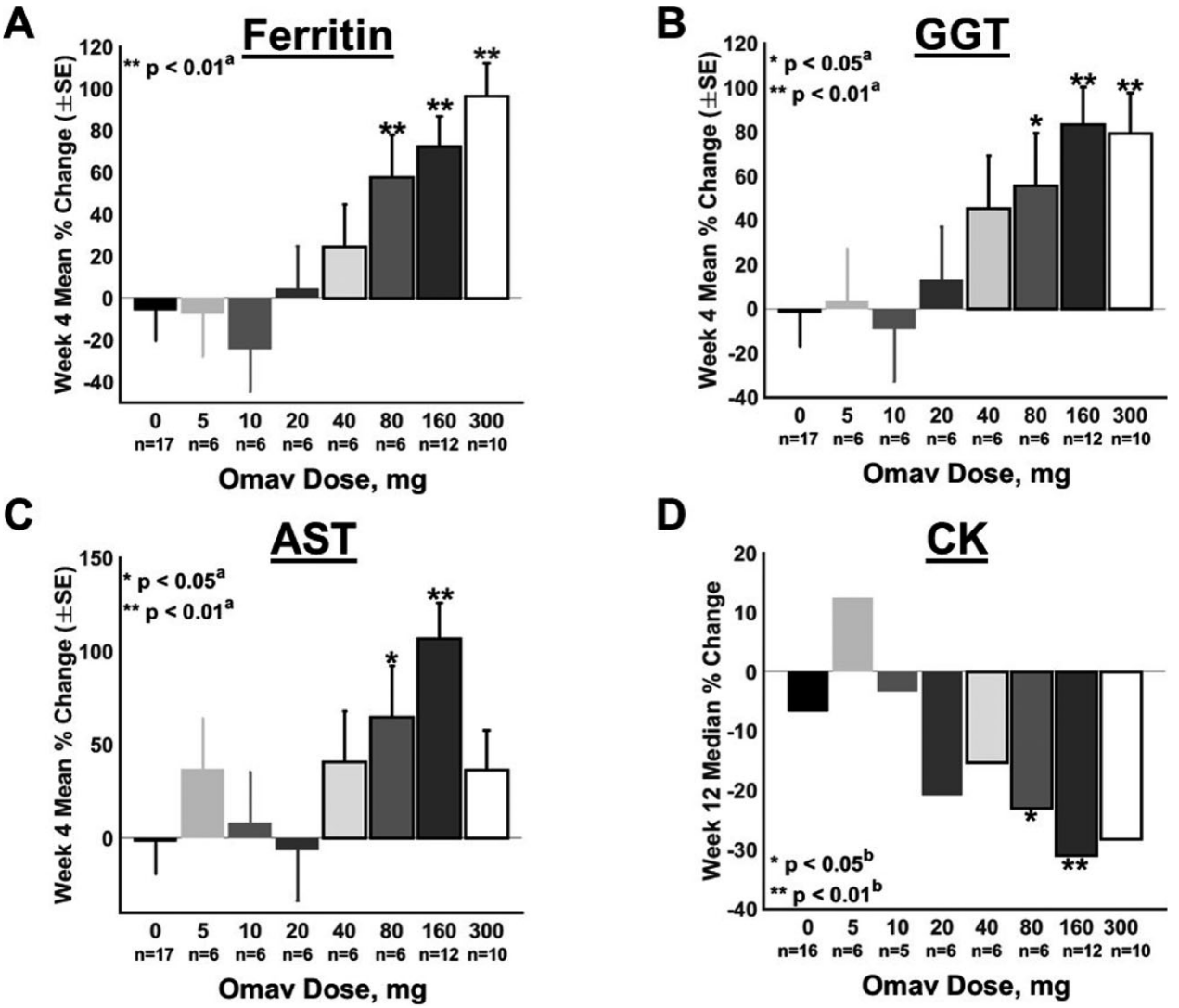


**Figure 3.** Pharmacodynamic effects of Omav. Omav had dose dependent effects on Ferritin (A), GGT (B), AST (C) and creatine kinase (D). In general, effects of Omav increased through doses of 180 mg, then were blunted at the highest dose (300 mg).

in exercise testing, Omav led to a dose-dependent improvement in pharmacodynamic measures and neurological function as measured by the mFARS exam. Finally, Omav improved selected other measures to a modest degree in this short study. The dose dependence of Omav was concordant across clinical and pharmacodynamic measures, and was in the range expected based on in vitro studies. Consequently, the present data create a solid rationale for further clinical trials of Omav.

The present data correspond with the proposed role of Nrf2 suppression in FRDA. Nrf2 fails to undergo nuclear translocation in cellular models of FRDA, and in mice with FRDA, downstream targets of Nrf2 are decreased, consistent with downregulation of the pathway.[7–10] This may reflect increases in Keap1, which regulates ubiquitination of Nrf2 and thus its turnover. In addition, several different Nrf2 targets are downregulated in patients with FRDA, including ferritin, whose levels are at the lower end of normal in FRDA.[26,27] There have been previous suggestions that topical Nrf2 application could reverse Nrf2 suppression and improve frataxin levels in FRDA.[7] Nrf2, its downstream pathways, and frataxin were not directly measured in the present study, but other Nrf2 targets including GGT and AST were altered by Omav, demonstrating the activation of Nrf2. Although other Nrf2 related agents are clinically approved for other diseases, their relative tolerability is modest and in vitro potency lower.[28] Thus Omav is likely to provide superior results in clinical studies in FRDA compared with other available Nrf2 activators. In the present study, the

 

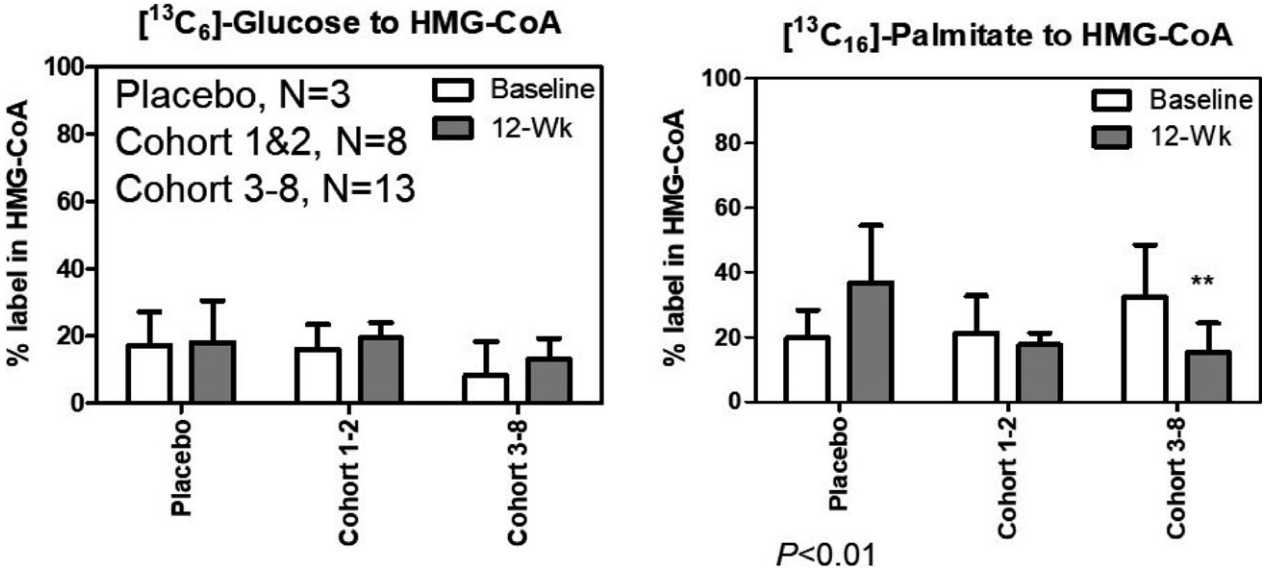


**Figure 4.** Platelet isotopologue analysis. Isotopic incorporation from [$^{13}C_6$] glucose (A) and [$^{13}C_{16}$] palmitate (B) to HMG-CoA (%) was determined in subjects at different dose of Omav. Cohorts were pooled into placebo ($n$ = 3), cohorts 1 and 2 ($n$ = 8) and cohorts 3-8 ($n$ = 13) for analysis due to the small number of participants in each individual cohort.

**Table 3.** Mean change in peak workload (W)[1].

| Treatment | *N* | ΔWeek 12 (±SE)[2] (95% confidence interval) | PBO-corrected (±SE)[3] (95% confidence interval) |
|---|---|---|---|
| All Placebo | 17 | 3.7 ± 2.5 (−1.3, 8.7) $P$ = 0.15 | – |
| All Omav | 52 | 2.8 ± 1.4 (0.0, 5.6) $P$ = 0.046 | −0.9 ± 2.9 (−6.7, 4.9) $P$ = 0.77 |

[1]Values are least-squared means from mixed effect model repeat measurement (MMRM) analysis, adjusted for baseline weight, and treatment group, time, and the interaction between treatment and time as fixed factors.
[2]Change from baseline at Week 12 compared to zero.
[3]Change from baseline at Week 12 in Omav patients compared to placebo subjects.

pharmacodynamic, pharmacokinetic, and beneficial responses all maximized at the 160 mg dose, suggesting it may provide the appropriate dose in future studies.

In this study, a variety of commonly measured clinical laboratory values served as pharmacodynamic markers of Nrf2 activation. The increase in ferritin is particularly interesting, as ferritin levels are relatively suppressed in FRDA. Changes in AST and GGT are initially perplexing, but most likely do not represent liver dysfunction. Transaminases are not liver-specific, but is expressed in other tissues, and also play a role in glucose metabolism by catalyzing the conversion of α-ketoglutarate to glutamate.[20] The profile of transaminase increases with Omav is similar to those reported in response to a high-carbohydrate, high-calorie diet in healthy volunteers.[20] Thus, the increases in transaminases with Omav may reflect improvements in glucose metabolism. Still, such changes have the potential for unblinding study staff. In the present study, laboratory results were delivered days after evaluations were performed and were only viewed by staff monitoring adverse events, minimizing the chance of unblinding. In the ongoing study of Omav, neurological evaluators specifically remain blinded by specifically not viewing laboratory studies.

In the present study, individuals without pes cavus showed greater improvement in mFARS as well as several other measures, while other disease features such as GAA repeat length, disease duration and age were not associated with greater improvements in mFARS. Although the relationship with pes cavus was not absolute (subjects with pes cavus improved overall, but not as much as those without this finding) and the size of the overall cohort was modest, the effect of pes cavus did occur across multiple measures. There are several possible explanations for this phenomenon. First, pes cavus might interfere with some of the measures (particularly exercise testing), making it more difficult to appreciate a response. Alternatively, as pes cavus affects the majority of FRDA patients and is largely developmental in nature, its presence might identify a subgroup with a relatively large fixed dysfunction that does not improve in short term

 

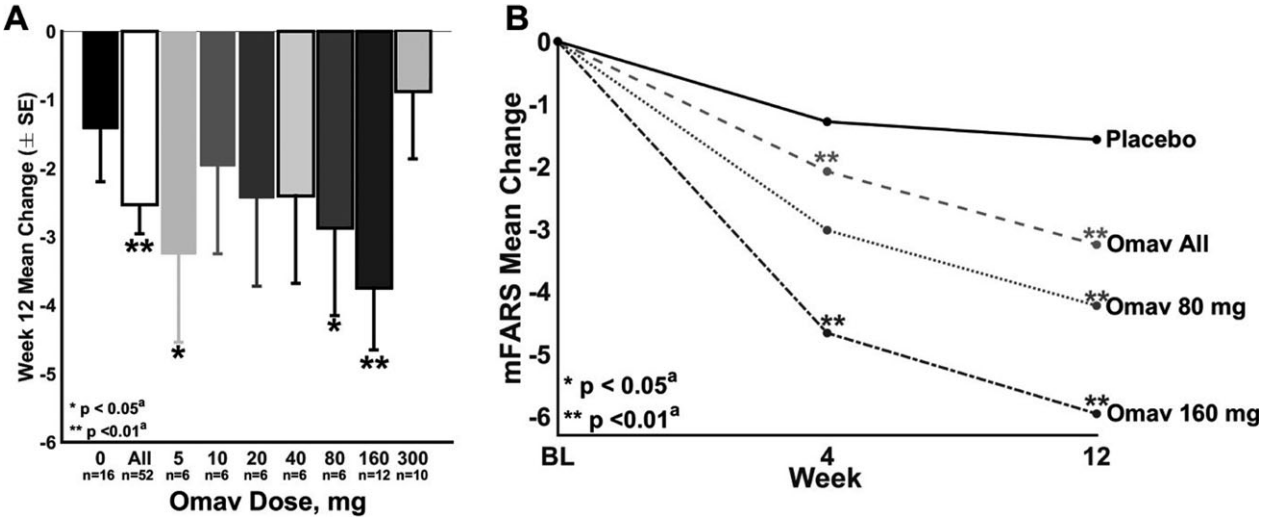


**Figure 5.** Effect of Omav on mFARS exam results. Omav produced a dose dependent improvement in mFARS score. The difference was more apparent at the higher doses in the study, with less benefit at 300 mg, consistent with AST, ferritin, GGT and CK changes at 300 mg.

**Table 4.** Mean mFARS change[1].

| Treatment | *N* | ΔWeek 12 (±SE)[2] (95% confidence interval) | PBO-Corrected (±SE)[3] (95% confidence interval) |
|---|---|---|---|
| Without Pes Cavus | | | |
| All | 7 | −1.6 ± 1.1 (−3.9, 0.7) | – |
| Placebo | | *P* = 0.17 | |
| All Omav | 30 | −3.3 ± 0.5 (−4.4, −2.1) | −1.7 ± 1.3 (−4.2, 0.9) |
| | | *P* < 0.001 | *P* = 0.19 |
| 80 mg | 4 | −4.2 ± 1.3 (−6.9, −1.6) | −2.7 ± 1.6 (−6.0, 0.7) |
| | | *P* = 0.003 | *P* = 0.11 |
| 160 mg | 4 | −6 ± 1.3 (−8.6, −3.3) | −4.4 ± 1.6 (−7.7, −1.1) |
| | | *P* < 0.0001 | *P* = 0.01 |
| Treatment with Pes Cavus | | | |
| All | 10 | −1.2 ± 1.0 (−3.4, 0.9) | – |
| Placebo | | *P* = 0.25 | |
| All Omav | 22 | −1.5 ± 0.7 (−2.9, −0.2) | −0.3 ± 1.2 (−2.9, 2.2) |
| | | *P* = 0.03 | *P* = 0.81 |
| 80 mg | 2 | −0.2 ± 2.3 (−4.9, 4.6) | 1.2 ± 2.5 (−4.1, 6.4) |
| | | *P* = 0.94 | *P* = 0.65 |
| 160 mg | 8 | −2.7 ± 1.2 (−5.0, −0.3) | −1.3 ± 1.6 (−4.5, 2.0) |
| | | *P* = 0.03 | *P* = 0.42 |

[1]Values are least-squared means from mixed effect model repeat measurement (MMRM) analysis, adjusted for treatment group, time, and the interaction between treatment and time as fixed factors.
[2]Change from baseline at Week 12 compared to zero.
[3]Change from baseline at Week 12 in Omav patients compared to placebo patients.

studies. Another possibility that the true variable is not pes cavus but another related entity not assessed in the present study. Within the present analysis, pes cavus was one of a variety of potential stratifiers that were tested and its presence was not balanced between placebo and active agent, leading to potential artifactual associations. Longer duration studies including larger cohorts may better address these possibilities and assess whether this differentiation persists with longer Omav administration.

The present study is limited slightly by the cohort features, including its small size at any given dose and in individual subgroups. The subjects were largely ambulatory and included no children, thus not directly addressing some subgroups of FRDA patients. In addition, although the cohort in general resembled large natural history populations, the mean GAA repeat length was slightly shorter than that of other cohorts.[5]

In the past 10 years, a variety of agents (particularly antioxidants) have been moderately successful in early studies in FRDA yet failed in phase III studies.[29–36] The reasons for this have included the paroxysmally small placebo response in initial studies, the absence of a placebo group in initial studies, and the short duration of initial studies. The present study noted a placebo effect consistent with previous studies, yet benefit was seen above that level. In addition, the 3 month duration of the present study is longer than in several other early studies. As with other proposed agents in FRDA (idebenone, interferon gamma, A0001) that have shown some short term response, the anatomical site of action of Omav is not entirely clear, Mitochondrial abnormalities that might be ameliorated by Omav exist in skeletal muscle, a location in which rapid metabolic improvement could occur. However, Omav may also be able to enter the CNS and peripheral nerve, where longer term slowing of neurodegeneration might be possible and immediate effects are

 

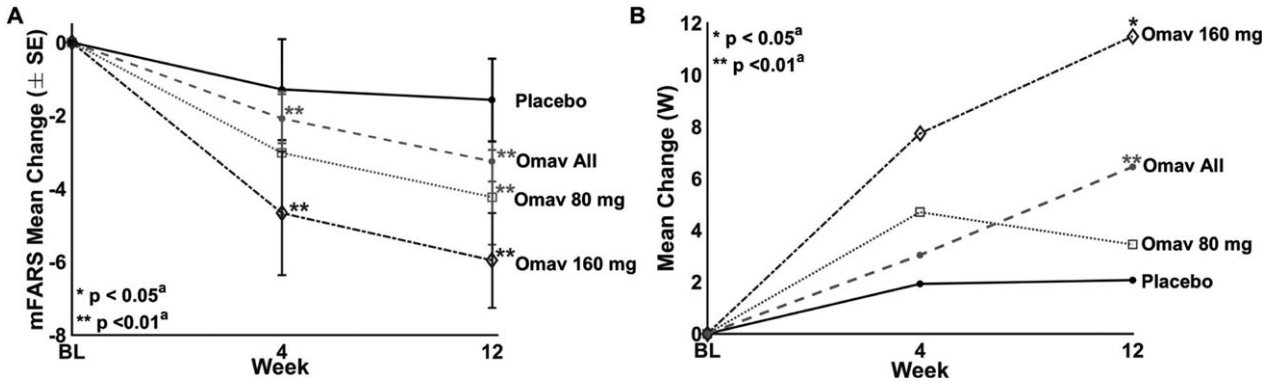


**Figure 6.** Pes cavus is associated with less response to Omav. The magnitude of improvement from Omav was higher on the mFARS exam in subjects without pes cavus compared with those with pes cavus. Similarly, a benefit of Omav on cardiac exercise stress testing was noted in the subgroup without pes cavus, whereas there was minimal effect in the overall cohort. Without pes cavus: $n = 30$ Omav, $n = 7$ placebo. With pes cavus: $n = 22$ Omav, $n = 10$ placebo

not as readily explained. Consequently, although the effect of Omav in longer term studies must be tested and its site of action identified, the present study provides a solid rationale for optimism in future studies.

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## Author Contributions

All authors have seen and approved the final text.

David Lynch, M.D., aided in design of the experiments and protocol, performed investigations, wrote the first draft, interpreted data, and revised the manuscript.

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Susan Perlman, M.D., interpreted data, perfomed investigations, and revised the manuscript.

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Nathaniel Snyder, PhD, aided in design of the experiments, interpreted data, and revised the manuscript.

## Conflict of Interest

None.

 

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