LETTER FROM HEALTHCARE PROVIDERS

Dr. Billy Dunn, Director
Office of Neuroscience,
Center for Drug Evaluation and Research,
Food and Drug Administration,
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002

Dear Dr. Dunn,

We, the undersigned, are specialists knowledgeable about the care of Friedreich Ataxia (FA), a rare genetic disease that affects less than 5,000 individuals in the United States. Many of us are clinician researchers and trialists who have studied the natural history of FA, developed outcome measures and conducted clinical trials. Given the multisystem impact of FA, we are neurologists, medical geneticists, cardiologists, endocrinologists and doctors in physical therapy. All individuals with FA suffer neurological symptoms that are progressive and lead to loss of ambulation and independence with all activities of daily living over two to three decades. The neurological symptoms together with cardiac dysfunction lead to early mortality with the average life expectancy being 35 years. There are no approved disease modifying treatments for FA.

We are writing with regard to the drug Omaveloxolone (Omav) which has completed clinical trials as a potential treatment for FA sponsored by Reata. In support of the Friedreich's Ataxia Research Alliance (FARA) leadership, scientific advisory board, clinical investigators and the individuals with FA in the United States and their families, we write to support FARA's request to Reata to submit a New Drug Application (NDA) on an urgent basis and FDA to exercise the flexibility granted by law and contained in FDA guidance in considering approval of an NDA for Omav in FA based on the existing evidence from clinical trials.

We would like to provide our independent views of the results of MOXIE Part 1 (Phase 2a) and Part 2 (Phase 2b) and why we believe they are persuasive and clinically meaningful by demonstrating that:

- Nrf2 has been validated as a therapeutic target in FA
- Omav has a defined dose-response relationship on both pharmacodynamics markers and clinical benefit (MOXIe Part 1)
- Clinical efficacy in a double blind placebo controlled trial (MOXIe Part 2) has been established
- Additional evidence of clinical benefit is observed in MOXIe Part 2 from the Baseline-Controlled study and
- Omav is generally safe and well-tolerated (MOXIe Part 1 and 2)

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Nrf2 has been validated as a therapeutic target in FA. In multiple academic laboratories it has been demonstrated that a consequence of frataxin deficiency is a maladaptive response that decreases levels and activity of Nrf2. Nrf2 suppression leads to excess oxidative stress, mitochondrial dysfunction and reduced ATP production. In both in vitro and in vivo studies of FA models, Omav rescues these features and increases cell viability and other phenotypes.

We are first impressed by the pharmacodynamic data from both the MOXIe Part 1 and 2 studies. Omav alters a series of Nrf2 targets such as ferritin and GGT and indirectly AST and CK which were measured in both studies. The data from Part 1 and Part 2 not only demonstrate activation of the Nrf2 pathway in a dose-dependent manner but also demonstrate favorable biological effect of the drug in vivo. Of note, individuals with FA have low ferritin levels as a component of the pathophysiology of the disease; in both studies, treatment significantly elevated ferritin levels toward normal levels, consistent with a reversal of the pathophysiology of FA. Another important pharmacodynamic finding is that sub-clinical abnormalities in renal function reversed in the treatment group while the placebo group experienced further decline in function over the 48-week Part 2 study. We believe these biomarkers demonstrate biological evidence that, when considered alongside the clinical data on neurological function, strongly support disease-relevant target engagement by Omav.

MOXIe Part 2 was a randomized, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of 150 mg Omav in FA patients. The primary endpoint was the change from baseline in the modified Friedreich Ataxia Rating Scale (mFARS) at Week 48. 103 individuals with FA, ages 16-40 years, enrolled and randomized 1 to 1 (drug and placebo) and studied for 48 weeks. Individuals with FA treated with Omav (150 mg/day) demonstrated a statistically significant, placebo-corrected 2.40 point improvement in mFARS after 48 weeks of treatment ($p=0.014$). The mFARS is a physician-assessed neurological rating scale used to measure FA disease progression. Improvements were observed in all prespecified subgroups and populations. All subsections of mFARS favored Omav. The data on the secondary endpoints provide evidence of internal consistency and support that what was observed in clinical function as measured by the mFARS was reflected in how patients felt as measured by the PGIC and FA-ADL.

Omav also significantly improved activities of daily living and other efficacy measures in some analysis populations. Finally, the change in mFARS scores on Omav was more than 2.5 times the yearly change in placebo or matched natural history groups, suggesting that the drug provides an improvement of more than 2.5 years of progression in the study. These values are certainly meaningful in the daily lives of patients.

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A baseline-controlled study was designed to help assess the strength and certainty of the positive primary endpoint findings in MOXIe Part 2 from MOXIe Part 3, the Open Label Extension (OLE). Patients considered treatment-naïve prior to initiation of Omav treatment in MOXIe Part 3 OLE (i.e., MOXIe Part 1 patients and MOXIe Part 2 placebo patients) served as their own controls. The primary efficacy endpoint of the baseline-controlled study was the paired difference in annualized mFARS slope in the treatment period relative to the pre-treatment period (48 weeks). All treated populations reversed their disease course and improved. The p-value for primary analysis was 0.0022. Multiple sensitivity and other analyses confirmed the robustness of the results. Of note, the baseline-controlled study maintained operational and analytical rigor given that mFARS assessments were conducted in a systematic manner, and investigators and patients remained blinded to prior treatment assignments in Part 1 and 2. Furthermore, the quantitative level of improvement has been consistent in magnitude across all of the studies, even before accounting for subtle differences in subject cohorts. This provides evidence of the reproducibility of treatment effect.

Omav has been generally safe and well-tolerated in FA in three clinical studies with few discontinuations or serious adverse events.

FARA has supported a prospective, longitudinal natural history and outcome-measure study conducted by the Collaborative Clinical Research Network in FA (CCRN) since 2003 which has enrolled more than 1,000 FA patients. There have been more than 15 publications generated from this study including several providing rationale and evidence for clinically relevant outcome measures that are sufficiently sensitive for conducting FA clinical trials in a practical manner. In addition, we have worked with FDA to identify the modified version of the FARS neurological scale (mFARS) to be an acceptable primary endpoint clinical trials. This approach has been acceptable to sponsors and several FA trials have been or are being conducted using the mFARS as the primary end point.

We believe that the mFARS data along with the FA-ADL data (which was nominally statistically significant despite being underpowered in MOXIe) from MOXIE Part 2, supported by the pharmacodynamic effect and the baseline-controlled study, provide strong evidence of the treatment effect of Omav in slowing disease progression and possibly improving neurological function. Our experience from the natural history study and other clinical trials, in which we have demonstrated mFARS to be a sensitive and predictive measure of neurological progression and clinical function and have observed that individuals with FA consistently progress as measured by the mFARS, informs the strength of our conviction that, in this well-controlled study over 48 weeks, improvement in mFARS is clinically meaningful and likely predictive of longer-term benefit. In addition, as we have now had patients taking Omav in an open label extension study for about 2 years, we have observed and heard from patients that they “have not worsened or progressed” since initiating Omav, an outcome that is of the highest priority to patients given relentless progression of FA.

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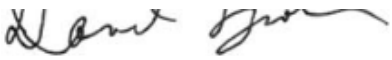
Our community understands that it may take many years to show unequivocal long-term benefits on disease progression. In the meantime, with no available treatment, patients and physicians know they will only continue to lose function, ability to do activities, their independence, and ultimately their lives. Therefore, the small uncertainty of an ultimate positive treatment effect can be tolerated. What would devastate this community is if a safe treatment that showed an impact on those earlier indicators was not permitted to go forward in an accelerated fashion while the long-term benefits are confirmed.

Further, we don't believe it is feasible to conduct additional placebo-controlled trials of Omav in the United States due to complications of the current pandemic and the limited number of patients available as there are multiple trials ongoing. We are eager to work with Reata to conduct an ex-US, controlled, post-marketing, confirmatory study to evaluate longer-term clinical benefit.

In conclusion, as healthcare professionals, familiar with and in many cases actively treating patients with FA, relying upon our best ability and medical judgment of the clinical and basic science data collected to date, we want the option to prescribe Omav as a treatment for our patients with FA. We therefore ask you to encourage the sponsor to submit a new drug application for Omav for the treatment of Friedreich ataxia, and that you undertake to promptly review that application.

We also want to take this opportunity to whole-heartedly thank you and your colleagues at the FDA for all the work you are doing through the current crisis to respond to the urgent demands the pandemic has imposed. We admire and thank you for your continued commitment to the patients affected by Friedreich ataxia, even as you battle a broader public health crisis.

Sincerely,



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