

## FA Community Response to Reata and FDA

### **FDA & Reata Pharmaceuticals: Allow Individuals with Friedreich Ataxia Access to Omaveloxolone**

We, the Friedreich Ataxia (FA) community, are at a point where our investments in building this community, tools for drug development (such as our patient registry, natural history study, cell and animal models, and clinical network), and investments in research are translating into a pipeline of treatments. One important result is that as these drug development programs are maturing, we have reached the point where the companies developing the drugs, the regulators at the Food and Drug Administration (FDA), and we stakeholders in the process need to achieve clarity on sound guidance regarding pivotal issues such as what the bar for approving new drugs for FA should entail. How many clinical trials are needed? How robust of a finding in those trials must there be? As we know from having seen other trials fail, not all drugs make it this far. However, we have arrived at this decision point for omaveloxolone (omav), an experimental drug being developed by Reata Pharmaceuticals, which has been shown to improve neurological function in people with FA in well-controlled clinical trials. Omav has the potential to prevent long-term consequences, slow progression of the disease and improve FA symptoms by addressing the underlying pathologic processes associated with inflammation, mitochondrial dysfunction, and oxidative stress. Two placebo- controlled clinical trials, along with pre-clinical studies in FA cellular and animal models provide the evidence for these claims.

Why are we sharing this, and why now? It is because we come to you with a call to action. The voice of the patient is critical to the drug development process and FDA has been a strong advocate for identifying opportunities for the “patient voice” to inform and guide drug development. The 21<sup>st</sup> Century Cures Act requires sponsors to include and FDA to consider the patient perspective in making approval decisions for new drugs. The FA community contributed its patient voice in June 2017, when we hosted the externally-led Patient Focused Drug Development meeting on FA for FDA which revealed that nearly 100% of people with FA experience neurological symptoms including loss of balance and difficulty walking, loss of coordination of movement in the upper and lower limbs and fatigue. We described to FDA that these neurological symptoms have an enormous effect on quality of life as they lead to lost ability to perform activities of daily living and loss of independence. Many of these neurological symptoms (balance, gait, upper limb function, and speech) are measured in the clinic with a structured functional exam called the modified Friedreich Ataxia Rating Scale (mFARS). Data from an ongoing, large, prospective, longitudinal, FA natural history study has demonstrated that neurological symptoms as assessed by mFARS get progressively worse over time and that the mFARS score is highly correlated to activities of daily living in FA. We worked with FDA to improve this scale and ensure it is included in clinical trials in FA.

This brings us to where we are today. There are currently no approved treatments for FA. However, recently a well-controlled clinical trial of omav in 103 individuals with FA demonstrated a statistically significant, placebo-corrected 2.40-point improvement in

mFARS after 48 weeks of treatment ( $p=0.014$ ). In addition, individuals in the treatment arm reported improvements in activities of daily living, such as walking, quality of sitting position and swallowing compared to the placebo group. Given the positive clinical trial results, favorable safety profile of omav, and difficulty conducting clinical trials in FA especially during the current pandemic environment, we are asking FDA and Reata to work together to provide access to omav for people with FA as soon as possible. We hope you will read the information below, which will explain what omav is and the evidence that we have from it being tested in clinical trials. We ask you to review this information and, if you consider this information sufficient for individuals living with FA (and their doctors) to decide whether it is a good choice for them, to sign on to join us in this request.

### **Background on Omaveloxolone (Omap)**

FA is caused by mutations in the FXN gene which results in decrease of the essential mitochondrial protein frataxin. Decreased frataxin in the cell leads to several maladaptive responses, including down regulation of Nrf2 which is an important transcription factor (signal for activating specific genes) and regulator of mitochondrial biogenesis. Omap is an activator of Nrf2 and suppressor of NF- $\kappa$ B. Based on data in cell and animal models, omap was identified as a potential treatment for FA.

### **Omap Pre-Clinical Data**

Several research labs have demonstrated in both human FA cell models and mouse FA models that Nrf2 is downregulated. Treatment of FA cell and animal models with omap have demonstrated activation of Nrf2 and improvements in the mitochondrial function of these models. Treatment with omap reduced pathologic levels of oxidative stress, restored antioxidative response, restored complex 1 activity, decreased lipid peroxidation, decreased mitochondrial ROS, and omap prevented cell death following pro-oxidant challenge.<sup>1</sup>

### **Studies to Evaluate the Efficacy, Safety, and Pharmacodynamics of Omap in the Treatment of People with FA**

MOXle Part 1 was a study designed to test the safety and potential efficacy of different doses of omap in FA. This study was needed to establish a safe dose of omap that was then used in Part 2, the larger, longer study designed to test if the drug improved symptoms of FA. The MOXle Part 1 results provided evidence that omap positively affected the expression of specific genes, as well as neurological function in a dose dependent manner. Omap was also safe and well tolerated.

#### **Details**

MOXle Part 1: Randomized, placebo-controlled, double-blind, dose escalation study to evaluate the safety of omap at various doses, designed to identify optimal dose for use in Part 2.

- 69 individuals enrolled and randomized 3 to 1 (drug to placebo) and studied for 12 weeks.
  - Cohorts of 8 individuals studied at doses ranging from 2.5-300mg.
  - Results<sup>2</sup>:
    - Omav dose-dependently increased Nrf2 target genes ferritin and GGT
    - Omav improved neurological function, as assessed by mFARS
    - Dose-dependent trends observed and optimal dose identified for Part 2
- Omav had a favorable safety profile in patients with FA in MOXIe Part 1

MOXIe Part 2 was designed to study the longer term effects on safety and function or FA symptoms in FA patients. This is the part of the trial that was designed to establish the effectiveness of the investigational drug. Again, omav was generally well tolerated. In addition, when compared to the placebo group, patients receiving omav showed improvement in both a clinical exam scale (mFARS) as well as in assessments of activities of daily living and other clinical endpoints.

### **Details**

MOXIe Part 2: 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 change from baseline in 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
- Results<sup>3</sup>:
  - 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.
  - Omav also significantly improved activities of daily living and other efficacy measures.
  - Omav was generally well tolerated in patients with FA.

MOXIe Part 3, open-label extension (OLE) allowed previously enrolled patients who completed MOXIe Parts 1 and 2 to enter into a new study where they would be getting omav at 150 mg once daily (no placebo). Patients will not be unblinded to study treatment in Part 1 or Part 2 upon entering the extension study. This study is still ongoing however some of the data has been made available. The goal of Part 3/OLE is to demonstrate longer term safety and efficacy. Reata has shared results assessing the therapeutic benefit of the drug by comparing the function of patients while on drug to their function at the beginning of the study (baseline).

## **Details**

MOXle Part 3/Open Label Extension – Baseline-Controlled Study Baseline-Controlled Study - The baseline-controlled study was designed to help assess the strength and certainty of the positive primary endpoint findings in MOXle Part 2.

- Results:
  - Patients served as their own controls to assess changes in mFARS and included patients considered treatment-naïve prior to initiation of omav treatment in MOXle Part 3 OLE (i.e., MOXle Part 1 patients and MOXle Part 2 placebo patients). All treated populations showed reversal of disease course and improvement P-value for primary analysis is 0.0022.

## **Rationale**

FA is a devastating, progressive and life-shortening rare genetic condition that affects children and adults and for which there are no approved treatments. All individuals with FA suffer neurological symptoms which include loss of coordination of movement in the upper and lower limbs, loss of balance and gait ataxia leading to loss of ambulation and loss of independence in performing activities of daily living (eating, writing, dressing, bathing, etc.). Other common symptoms include dysarthria (speech difficulty), fatigue, cardiomyopathy, arrhythmia, and diabetes. The average life expectancy for individuals with FA is about 35 years.

*Omaveloxolone targets a specific cellular dysfunction in FA and has been demonstrated in clinical trials to improve disease specific biomarkers and meaningful neurological clinical outcomes and activities of daily living. Omav has also been demonstrated to be safe and well-tolerated.*

Given the clinical trial results, FA patient families and clinicians strongly encourage Reata and the FDA to work together promptly to give people with FA, who currently have no other choice for treatment, access to omav as soon as possible. FDA has emphasized the importance of the patient voice, especially for rare conditions without FDA-approved treatment options. As summarized in the report on [The Voice of the Patient: Friedreich Ataxia](#), people with FA experience severely compromised quality of life, loss of independence and early mortality due to symptoms of FA. The majority of patients reported that balance/walking, upper limb function and fatigue have the highest impact on quality of life and treating even one of these individual symptoms would be meaningful. Ninety-five percent (95%) of individuals indicated that slowing or stopping disease progression would be extremely meaningful to them when considering a drug therapy.

The patients and clinicians of the FA community are fully aware of the clinical trial results evaluating the use of omav in FA and are convinced that the results demonstrate meaningful benefit and low risk. More than 95 percent of eligible individuals who



participated in the clinical trials elected to enter the open-label extension study to continue their access to omav while awaiting formal analysis of the trial data and regulatory review. We ask 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.

References:

1. [Novel Nrf2-Inducer Prevents Mitochondrial Defects and Oxidative Stress in Friedreich's Ataxia Models](#)
2. [MOXle Part 1 trial results - Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia](#)
3. [MOXle Part 2 trial results - Safety and Efficacy of Omaveloxolone in Friedreich Ataxia \(MOXle Study\)](#)