Abstract # 2514

Kidney Effects in the MOXIe Trial: A Study of Omaveloxolone in Patients with Friedreich's Ataxia

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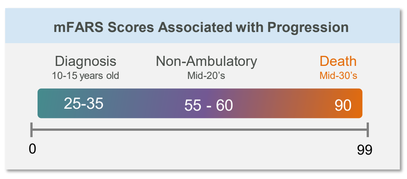
FRIEDREICH'S ATAXIA

Friedreich's Ataxia (FA) is a rare, progressive, and debilitating genetic disorder caused by epigenetic silencing of frataxin

Most patients are diagnosed in childhood, surviving into their mid-30's, and typically become wheelchair-dependent within 10 – 15 years after diagnosis. There are approximately 22,000 FA patients globally.[1-3]

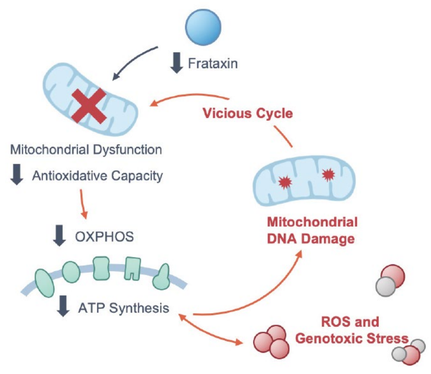
FA progression is measured by the modified FA Rating Scale (mFARS), a physician-administered neurological exam that tracks bulbar function, upper and lower limb mobility, and upright stability. On average, mFARS scores increase (i.e. disease worsens) by 1-2 points per year.[4]

FA is driven by mitochondrial dysfunction, which affects multiple organ systems and manifests in many ways:[5]



Molecular implications of frataxin deficiency:[5]
- Dysfunctional iron handling
- Impaired antioxidative defense mechanisms
- Excessive reactive oxygen species (ROS) production
- Mitochondrial dysfunction (i.e., reduced energy production)
- Dysregulation of Nrf2 activity

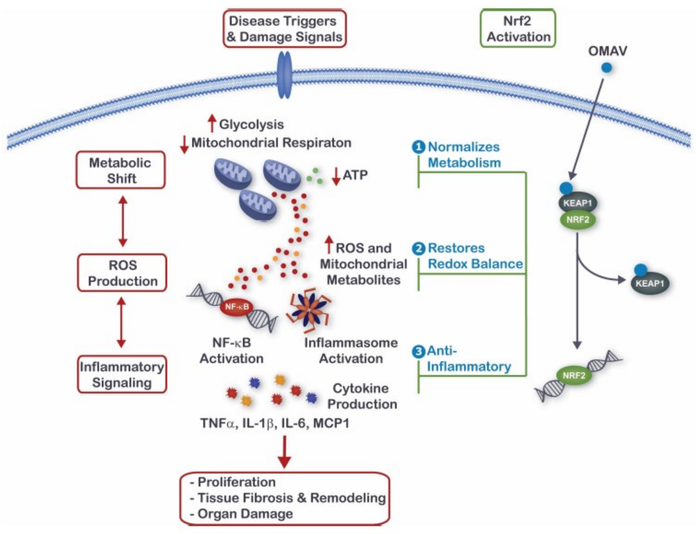
Clinical manifestations of FA:[1]
- Ataxia
- Chronic fatigue and reduced exercise capacity
- Heart disease, vision loss, and diabetes
- Loss of independence and reduced quality of life



There are no approved therapies for the treatment of FA

OMAVELOXOLONE MECHANISM OF ACTION

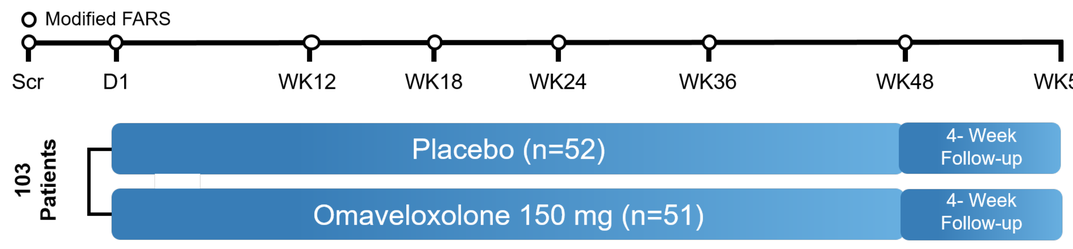
Activation of Omaveloxolone target, Nrf2, restores mitochondrial function and improves ATP production
- Omaveloxolone is a potent Nrf2 activator[6]
- Nrf2 is a transcription factor that improves mitochondrial metabolism, restores redox balance, and suppresses pro-inflammatory gene expression[7-9]
- Restoration of Nrf2 activity can normalize mitochondrial function and therefore address progressive muscle weakness and ataxia experienced by FA patients
- Omaveloxolone improved mFARS in FA patients in the 12-week, dose-ranging portion of the study[10]



MOXIe STUDY DESIGN

MOXIe STUDY (NCT02255435)
- International, multicenter, double-blind, randomized, and placebo-controlled phase 2 study
- Enrolled 103 patients 16 to 40 years of age with genetically-confirmed FA
- Patients were orally administered either placebo or omaveloxolone (150 mg) daily for 48 weeks
- Key eligibility criteria: baseline mFARS score > 20 and < 80 and ability to complete maximal exercise testing on a recumbent stationary bike
- Key exclusion criteria: clinically significant cardiovascular disease, brain natriuretic peptide (BNP) levels > 200 ng/L

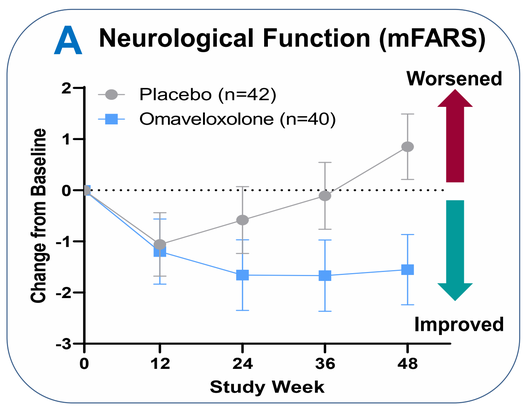
STUDY DESIGN
- Primary endpoint: mean change from baseline in mFARS at 48 weeks as compared to placebo in prespecified full analysis set (patients without pes cavus)
- Safety assessments: estimated glomerular filtration rate (eGFR), blood pressure (BP), BNP, hepatic enzymes, and weight changes

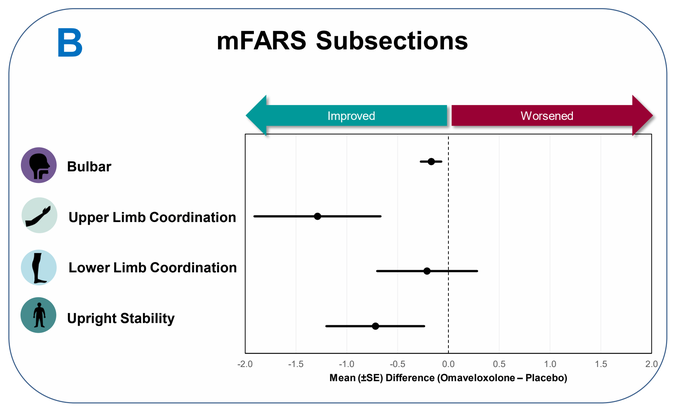


BASELINE CHARACTERISTICS

Characteristic		Placebo	Omaveloxolone
N		52	51
Age, years (Mean, SD)		24.1 (7.8)	23.4 (6.1)
< 18 (n, %)		15 (29%)	9 (18%)
Sex	**Female (n, %)**	17 (33)	31(61)
	Male (n, %)	35 (67)	20 (39)
Body Mass Index (BMI), kg/m² (Mean, SD)		22.8 (4.8)	23.2 (5.1)
mFARS (Mean, SD)		37.9 (10.8)	40.8 (10.2)
eGFR, mL/min/1.73m² (Mean, SD)		109.2 (21.7)	113.4 (14.7)
BNP, ng/L (Mean,SD)		20.5 (27.8)	29.2 (26.4)

NEUROLOGICAL FUNCTION RESULTS



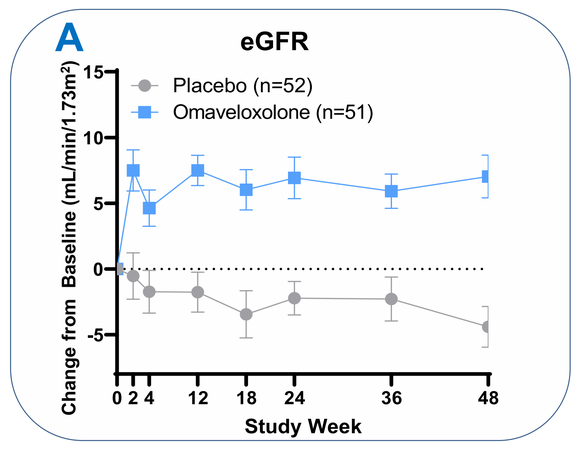


Panel A: Mean (± SEM) changes in mFARS from baseline score over time for the full analysis set (n=82)
Panel B: Mean (± SEM) changes in mFARS subsections from baseline at 48-week timepoint

Key Finding:
Forty-eight weeks of omaveloxolone treatment led to a significant improvement relative to placebo in neurological function as assessed by mFARS (-2.40; p=0.014). Improvement was time-dependent and observed through all mFARS subsections.

KIDNEY FUNCTION RESULTS

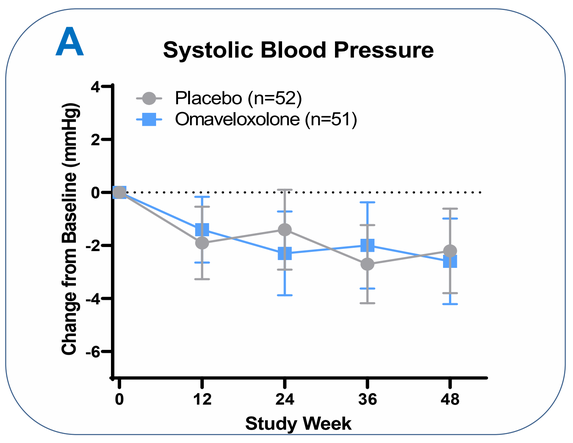
	Mean (SD) Week 48 Change in eGFR (ml/min/1.73 m²)		
	Overall	**<18 years of age**	**≥18 years of age**
Omaveloxolone	+7.0 (10.7)	+5.5 (14.5)	+7.4 (9.9)
Placebo	-4.4 (11.0)	-11.3 (14.3)	-1.5 (7.9)

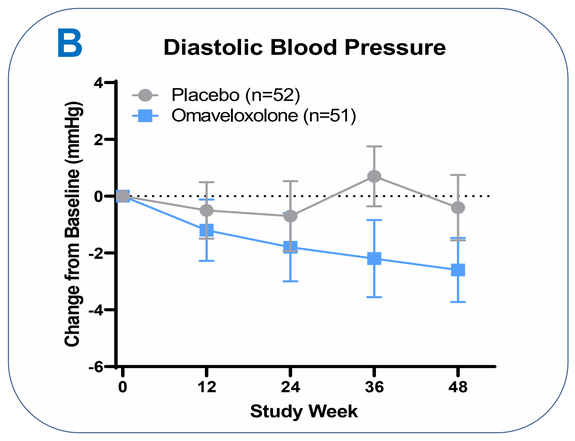


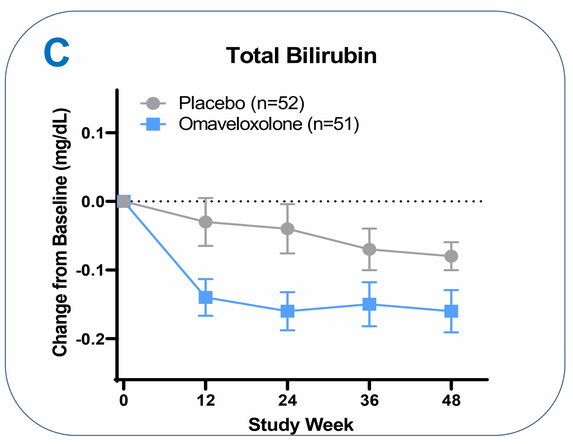
Key Summary:
- At Week 48, mean eGFR in the omaveloxolone group significantly increased +7.0 mL/min/1.73 m² from baseline (p<0.001) while mean eGFR in the placebo group declined -4.4 ml/min/1.73 m²
- In pediatric patients (16-17 years old), a mean eGFR difference of +16.8 mL/min/1.73 m² was observed between treatment groups at Week 48
- Four weeks post-treatment, a mean eGFR difference of +5.4 mL/min/1.73 m² was observed between treatment groups

Panel A: Mean (± SEM) changes in estimated glomerular filtration rate (eGFR) from baseline

SAFETY ASSESSMENTS







Key Summary:
- Common adverse events reported more frequently in omaveloxolone patients were headache, nausea, and alanine aminotransferase (ALT) increases
- Increases in ALT were not associated with signs of liver injury and total bilirubin decreased
- There were no significant increases in either systolic or diastolic blood pressure

Panel A: Mean (± SEM) changes in systolic blood pressure from baseline **Panel B:** Mean (± SEM) changes in diastolic blood pressure from baseline **Panel C:** Mean (± SEM) levels of total bilirubin

CONCLUSION
- Forty-eight weeks of omaveloxolone treatment improved total and all mFARS subsection scores in FA patients
- Omaveloxolone treatment for 48 weeks was associated with an increase in eGFR. These increases were durable and sustained throughout one year of treatment, similar to results observed with its analog, bardoxolone methyl, in clinical trials for various forms of CKD.[11-13] In contrast, in the placebo group a rapid, continuous eGFR decline was observed, similar to that seen in patients with rapidly progressing forms of CKD
- Omaveloxolone treatment was not associated with increases in blood pressure
- Most common adverse events in omaveloxolone patients were headache, nausea, and ALT increases, which were not associated with liver injury

DISCLOSURES

CJM, MPC, AG, and MO are employees of Reata Pharmaceuticals. DRL and SHS received grants from Reata Pharmaceuticals. TZ and SP received personal compensation for serving on the advisory board of Reata Pharmaceuticals.

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