Update on MOXIe

A Study of Omaveloxolone in Friedreich's Ataxia

EURO-ATAXIA Conference 2021

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Bardoxolone methyl and omaveloxolone are investigational drugs, and their safety and efficacy have not been established by any agency.

Disclaimers

Omaveloxolone is an investigational drug. Safety and efficacy have not been established by any regulatory agency.

This presentation is for informational purposes only and is not intended to promote a product or study.

More information can be found on www.ReataPharma.com

Overview of Friedreich's Ataxia

Friedreich's Ataxia (FA) effects an estimated ~22,000 people globally[1-6]

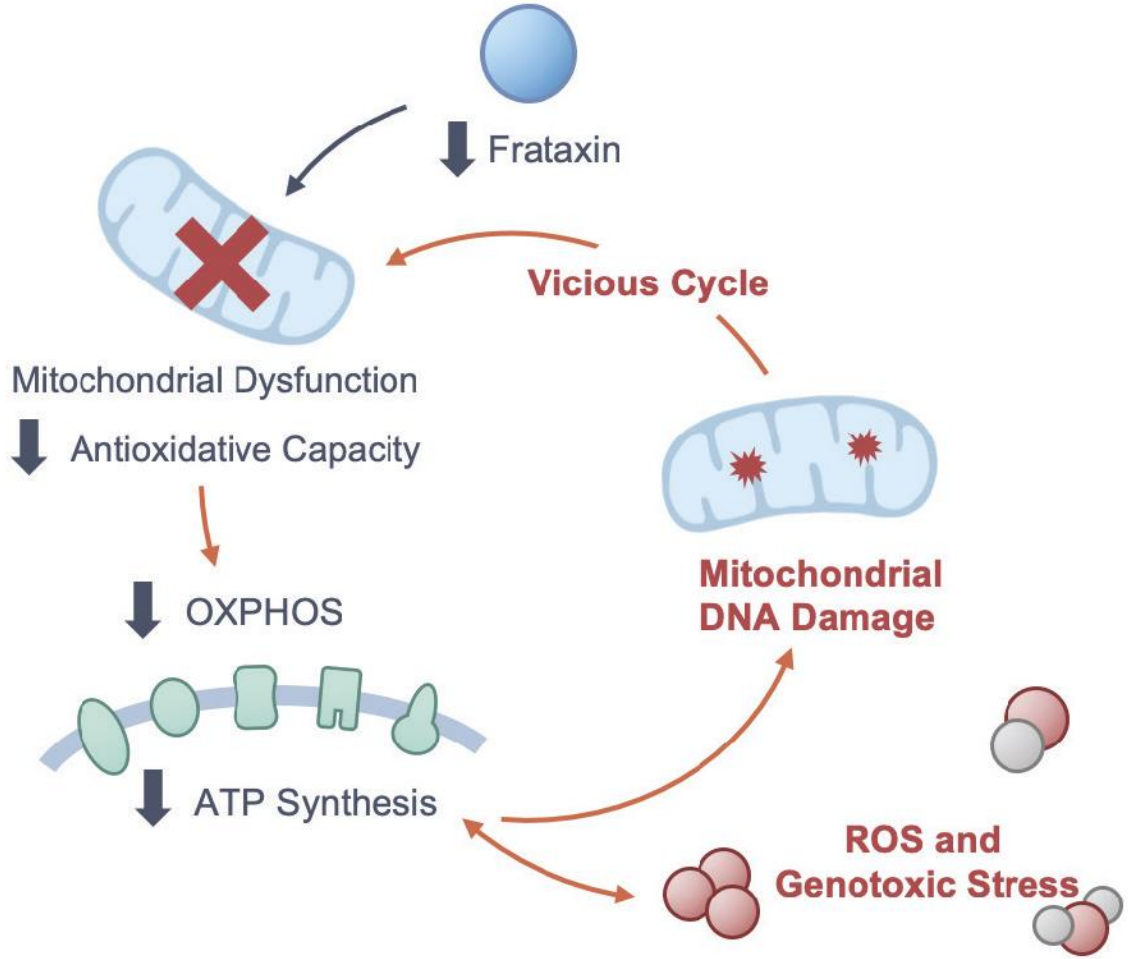
Numerous failed trials with no approved therapies

Nrf2 is a transcription factor which promotes the resolution of inflammation and restores mitochondrial function

Mutations in frataxin gene in FA result in vicious cycle of mitochondrial dysfunction and paradoxically reduced Nrf2[7]

Nrf2 suppression further contributes to oxidative stress, mitochondrial dysfunction and reduced ATP production[8]

Omaveloxolone (Omav) appears to restore Nrf2 activity in FA cellular models and improves mitochondrial function[9]



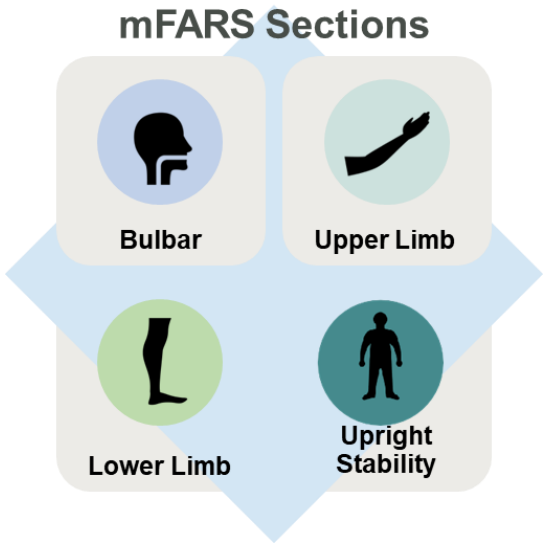
[1]Friedreich's Ataxia Research Alliance; [2]Vankan P, J Neurochem (2013); [3]Zheng J, J Neurol Sci (2015); [4]Sasaki H, J Neurol Sci (2000); [5]Mariño T, Clin Genet (2010); [6]Fussiger H, Cerebellum (2019); [7]Paupe V, PloS One (2009); [8]Tai G, Neurol Neurochir Pol (2018); [9]Abeti R, Front Cell Neurosci (2018)

Clinical Measures of FA: Modified Friedrich's Ataxia Rating Scale (mFARS)

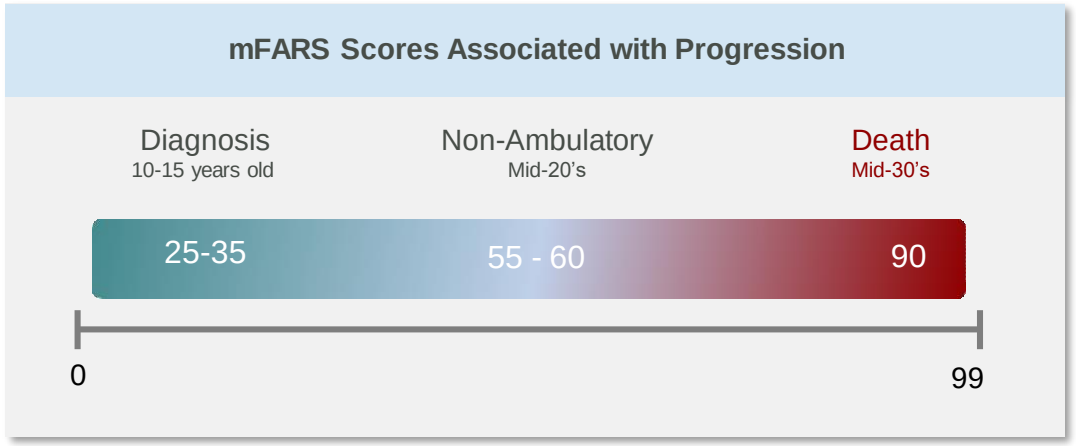
mFARS validated using 1,000-patient natural history study called the Friedreich's Ataxia Clinical Outcomes Measures Study (FA-COMS)[1]

mFARS: Physician-Assessed Neurological Exam that Tracks Progression of FA

mFARS has four sections that are considered clinically meaningful



In FA patients, mFARS worsens (increases) on average one to two points annually[1]



[1]*Patel M, Ann Clin Transl Neurol (2016)*

MOXIe: A Study of Omaveloxolone in FA

MOXIe Part 1

- 69 patients around the globe
- 3 Omav : 1 Placebo
- Designed to assess multiple endpoints across a range of doses
- 12-week treatment duration

MOXIe Part 2

- 103 patients around the globe
- 1 Omav : 1 Placebo
- Designed to confirm safety and efficacy of 150mg dose
- 48-week treatment duration

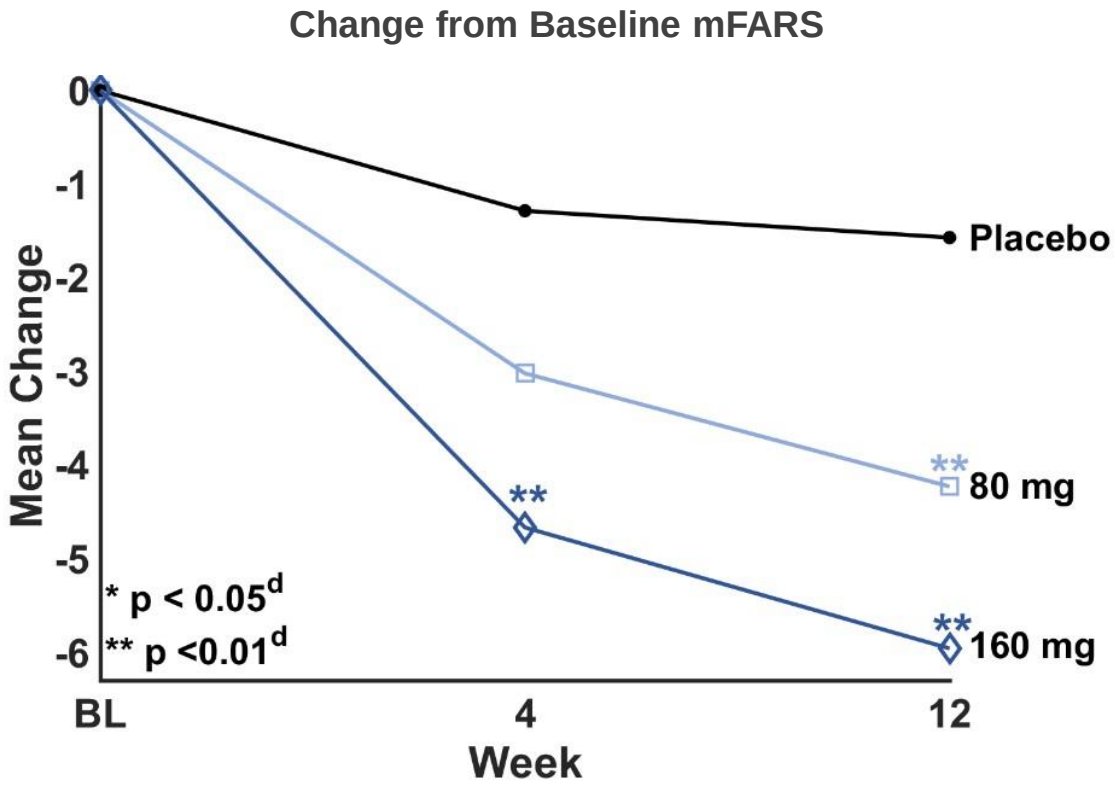
Open-Label Extension (Baseline-Crossover Study)

- Patients who completed Part 1 or Part 2 are eligible
- Every patient receives Omav
- Data available on Baseline-Crossover Study for 34 patients

MOXIe Part 1 Highlights

Study details
- 69 patients included
- Omav doses ranging from 5mg – 300 mg
- 3:1 ratio of Omav to placebo
- 12-week treatment duration

Results
- 160mg determined to be the optimal dose
- No change in peak-work
- Improvement in mFARS from baseline compared to placebo (greater improvements seen in patients without pes cavus than patients with pes cavus)



[d] Change from baseline comparison to zero and LSMEAN estimates at Week 12 using mixed-model repeated measures

Lynch D, Ann Clin Transl Neurol (2018)

MOXIe Part 1 Safety Summary

Adverse events were generally mild in severity

Included increased upper respiratory tract infections and nasopharyngitis, which were generally mild in severity

ALT and AST increases are expected pharmacological effects of Nrf2 activation and were not associated with any signs or symptoms of liver injury

Only two SAEs (benzodiazepine withdrawal and 3rd degree burns) were reported, both of which occurred in placebo patients

Summary of AEs from MOXIe Part 1*

Adverse Event	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%)

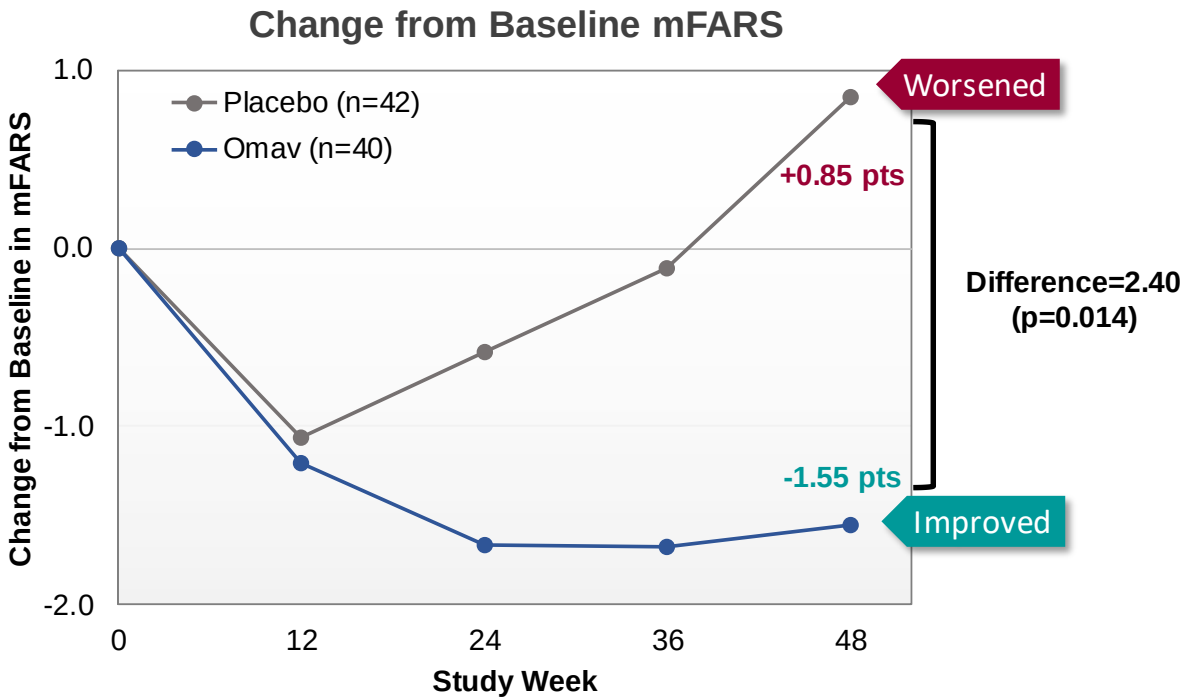
AEs reported in ≥10% of patients

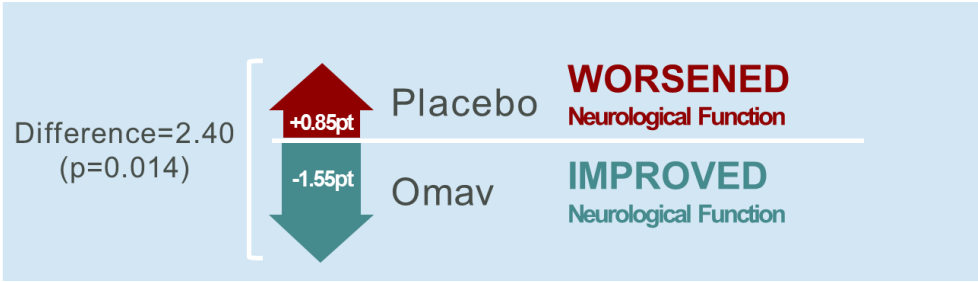
Lynch D, Ann Clin Transl Neurol (2018)

MOXIe Part 2 Highlights

Study details
- 103 patients enrolled (20 with pes cavus)
- 1:1 ratio of Omav (150mg) to Placebo for 48-week treatment duration
- Primary endpoint = change in mFARS at week 48

Results
- Omav treatment significantly improved mFARS by 2.40 points relative to placebo in patients without pes cavus (n=82; p=0.014)
- In all patients, including those with pes cavus, Omav treatment improved mFARS by 1.93 points relative to placebo (n=103; p=0.034)





Lynch D, Annals of Neurology (2020)

MOXIe Part 2 Summary of Safety

Adverse events (AEs) generally mild to moderate in intensity

- 4 (8%) Omav-treated patients and 2 (4%) placebo-treated patients discontinued study due to AEs
- ALT and AST increases are a pharmacological effect of other Nrf2 activators[1]
  - Not associated with liver injury
  - Coincide with decreases in total bilirubin
  - May reflect improvements in mitochondrial metabolism

Few serious AEs (SAEs)

- SAEs in 3 (6%) Omav patients and 3 (6%) placebo patients while receiving study drug
- Two additional Omav patients reported SAEs approximately 2 weeks after receiving final dose

89% of patients chose to enroll in the long-term extension study

Summary of AEs from MOXIe Part 2*

Adverse Event	Placebo (n=52)	Omav (n=51)
Contusion	19 (37%)	17 (33%)
Headache	13 (25%)	19 (37%)
Upper respiratory tract infection	15 (29%)	14 (28%)
Excoriation	12 (23%)	13 (26%)
Nausea	7 (14%)	17 (33%)
ALT increased	1 (2%)	19 (37%)
Fatigue	7 (14%)	11 (22%)
Abdominal pain	3 (6%)	11 (22%)
AST increased	1 (2%)	11 (22%)

**AEs reported in >20% of patients*

[1]*Lewis J, Clin Transl Sci (2020); Lynch D, Annals of Neurology (2020)*

Open-Label Extension Highlights

Patients that completed Part 1 or Part 2 of MOXIe were eligible to enter Open-Label Extension

89% of eligible Part 2 patients elected to enter extension study

All patients in the Extension study receive Omav and continue to complete mFARS assessments

Patients and investigators remained blinded to Omav vs. placebo assignment during Part 1 and Part 2

Data from the MOXIe Open-Label Extension Study includes

- Baseline-Controlled Study
- Delayed-Start Analysis
- Safety

Baseline-Controlled Study

Objective: MOXIe Part 1 and Part 2 treatment-naïve patients served as their own controls to assess changes in mFARS in MOXIe Extension

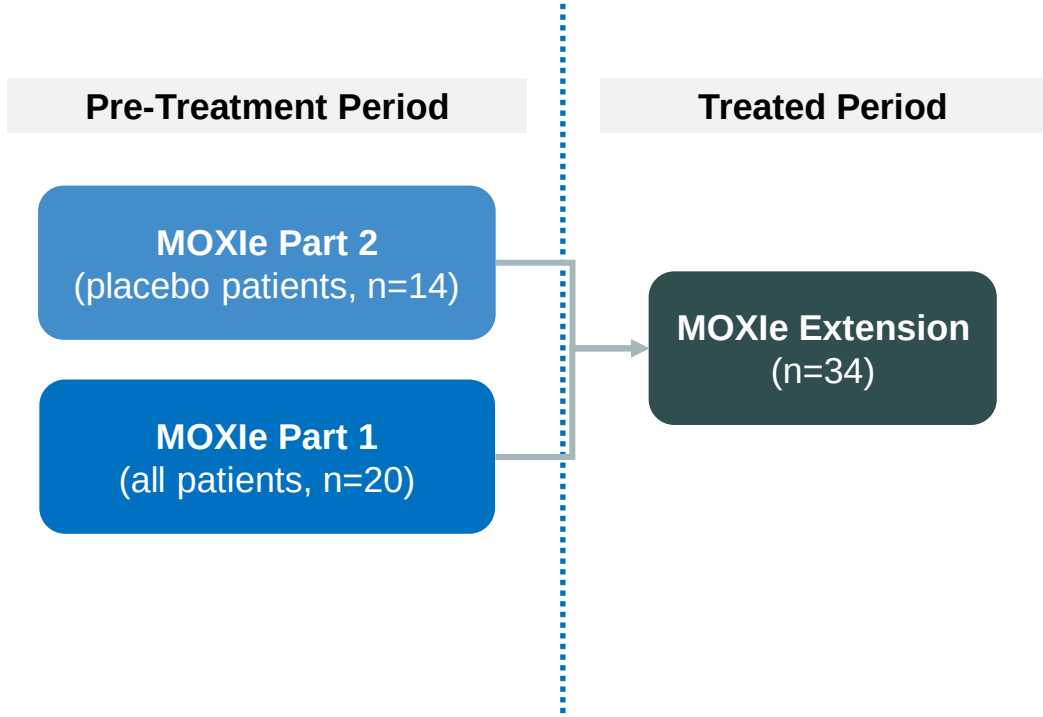
Primary efficacy endpoint: paired difference in annualized mFARS slope for treatment period vs pre-treatment period

Primary analysis population:

- All Part 1 patients (at least 21 months off treatment before Extension)
- Part 2 placebo patients
- Excludes patients with pes cavus
- Only included patients with 48 weeks of mFARS data in MOXIe Extension (as of July 2020)

Methods:

- mFARS assessments conducted in similar and rigorous manner throughout MOXIe Part 1, Part 2, and Extension
- Investigators and patients remained blinded to prior treatment assignments



Baseline-Controlled Study: Significant Treatment Effect on mFARS Across All Analysis Populations

Primary Efficacy Analysis: -3.76 improvement in mFARS (p-value=0.0022)

Across all analysis populations:

- Statistically significant treatment effect on mFARS rate of change using patients as their own control
- Worsening during pre-treatment period
- Reversal of disease course and improvement during the treatment period

Annualized Rate of Change in mFARS, Mean (SE)

Analysis Population	Pre-treatment	Treatment	Paired Difference	p-value
Primary Population (n=34)	2.28 (0.49)	-1.47 (0.96)	-3.76 (1.13)	0.0022
Part 2 Placebo (n=14)	2.84 (1.05)	-1.79 (1.56)	-4.62 (1.89)	0.029
Part 1 (n=20)	1.90 (0.40)	-1.26 (1.25)	-3.15 (1.43)	0.040

Baseline-Controlled Study Responder Analysis vs Matched Natural History Cohort (FA-COMS)

Categorical summary of annualized mFARS slopes in the treatment period versus the pre-treatment period

- "Stable or improved": mFARS slope of ≤ 0
- "Worsening": mFARS slope of > 0

Baseline-Controlled Study vs FA-COMS

- 8/34 (24%) of patients were stable or improved during the pretreatment period, consistent with FA-COMS
- 21/34 (62%) of patients were stable or improved in the treatment period

Status	Baseline-controlled Study		Natural History Study*
	Pre-treatment (n=34)	Treatment (n=34)	
Stable or Improved**	8 (24%)	21 (62%)	45 (30%)
Worsened***	26 (76%)	13 (38%)	103 (70%)

** Data from patients in the Clinical Outcome Measures in Friedrich's Ataxia (FA-COMS) natural history study matching baseline age and mFARS requirements defined for MOXIe*

***Stable or improved defined as annualized changes from baseline ≤ 0 points for mFARS scores*

****Worsened defined as annualized changes from baseline > 0 for mFARS scores*

Delayed-Start Analyses Support Disease-Modifying Profile

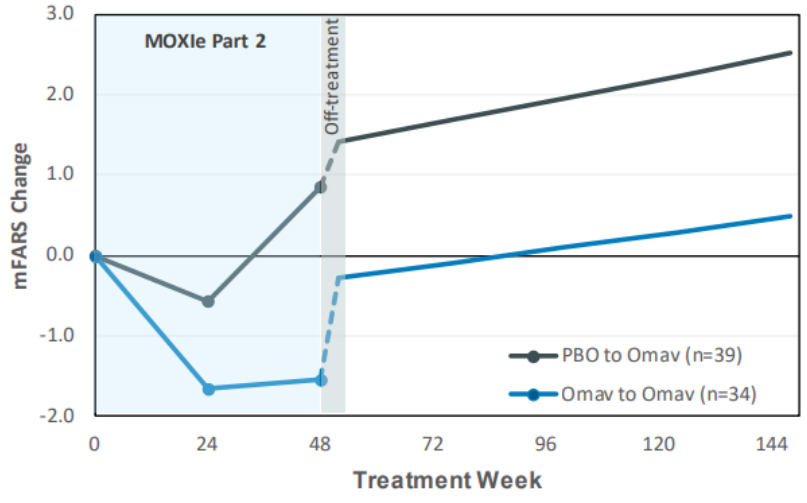
Data from MOXIe extension study were analyzed as “Delayed-Start” analyses

- Comparison of mFARS during the Open-Label Extension for patients randomized to Omav or placebo during MOXIe Part 2
- Annualized slopes using all data from the MOXIe extension study showed similar slopes in mFARS for both groups
- 89% of eligible Moxie Part 2 patients enrolled in the extension study and were included in the analysis

Parallel trajectories in annualized slopes between both treatment groups is consistent with disease-modifying activity

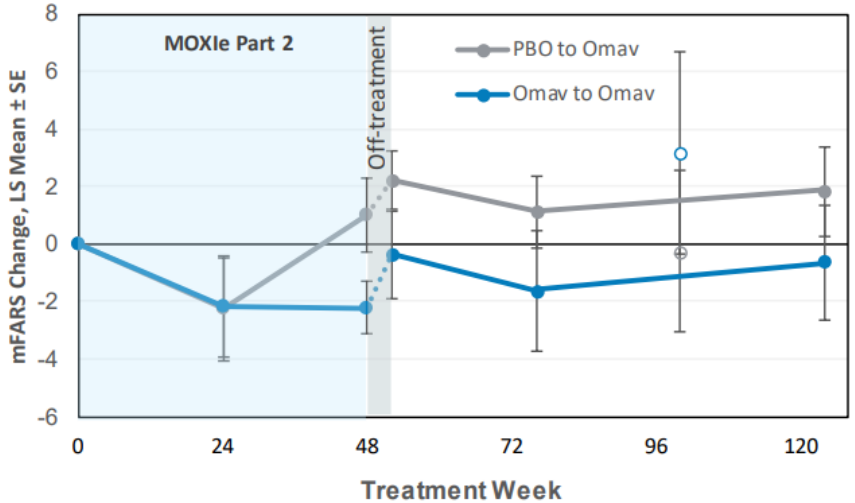
Omav prevented worsening of neurological function in 11 patients who have completed 2.5 years of treatment

All Extension Patients (Annualized Slope)



PBO-Omav (n)	42	41	41	27	22	9	3
Omav-Omav (n)	41	36	34	28	18	11	6

Week 124 Completers (Mean Change from Baseline)



PBO-Omav (n)	9	9	9	9	9	5	9
Omav-Omav (n)	11	11	11	11	11	3	11

PBO = placebo;
Omav = omaveloxolone

MOXIe Extension Summary of Safety

AEs generally mild to moderate in intensity
- 8 (5.4%) patients discontinued study due to AEs
- Common AEs similar to MOXIe Part 2

SAEs reported in 9 (6.1%) patients that were considered treatment-emergent

No new safety signals have been observed in the Extension study to date

Summary of AEs from MOXIe Extension*

Preferred Term	Omav (n=148)
ALT increased	26 (18%)
Headache	22 (15%)
Upper respiratory tract infection	23 (15%)
Nausea	22 (15%)
Fatigue	15 (10%)
Abdominal pain	15 (10%)

**AEs reported in >10% of patients; data is through 02/22/2021 and includes all patients enrolled in the Extension study, including 114 patients that did not meet criteria for inclusion in the primary analysis population of the baseline-controlled study (i.e. patients with pes cavus, not treatment naïve prior to Extension, and/or missing an mFARS assessment at Week 48 in Extension)*

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