Predicted Clinical Outcomes for Patients Treated with Omaveloxolone for Friedreich Ataxia

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OBJECTIVE

- **Estimate treatment-specific mFARS progression over a patient's lifetime, and characterize the functional burden that patients face at different mFARS ranges.**

CONCLUSIONS

- **Using trial and registry data alongside a propensity-matched analysis (demonstrating 55% cumulative reduction in mFARS progression), it was predicted that patients on omaveloxolone have >35% more time before reaching mFARS of 50, 60, and 70, compared to patients on SoC.**
- **Maintaining lower mFARS is shown in registry and trial data to be associated with reduced patient burden.**
- **Once patients reach an mFARS of 50, their gait and stance are severely impacted.**

Introduction

- Friedreich ataxia (FA) is a rare, inherited, neurodegenerative disease that leads to progressive ataxia, dysarthria, sensory loss, and reduced life expectancy.[1,2]
- The modified Friedreich Ataxia Rating Scale (mFARS) measures disease progression in 18 individual items across four domains.[3] It ranges from 0 to 93; higher scores indicate worse disease severity.
- Early age-of-onset in FA patients is a strong predictor of a more severe disease and faster disease progression, as measured by the mFARS.[4]
- The Friedreich's Ataxia Clinical Outcome Measures Study (FACOMS) registry provides 13 years of natural history data for patients with FA.[5]
- Based on the MOXIe part 2 (MOXIe2) study,[6] omaveloxolone added to standard of care (SoC; hereafter referred to as omaveloxolone) is the first approved FA treatment in the US and EU in patients ≥16 years old.[7-9]
- In a propensity-matched comparison with FACOMS registry patients, those on omaveloxolone showed a 55% reduction in mFARS score progression over three years, compared to patients on SoC only.[10]
  - MOXIe open label extension[11] patients were matched to FACOMS patients using logistic regression to estimate propensity scores based on established prognostic covariates—sex, baseline age, age of onset, baseline mFARS, and baseline gait score.

Methods

mFARS Model for Disease Progression

- Data from the FACOMS study was used to model mFARS progression for four established[12] age-of-symptom-onset subgroups (0 to 7, 8 to 14, 15 to 24, ≥25 years), since age of onset is key predictor of disease progression.
  - A multivariate linear model of mFARS progression was developed with the following predictors: time in study, sex, baseline mFARS score, baseline gait subscore, and age of symptom onset.
  - An interaction term between time in study and age of symptom onset allowed different progression rates for each subgroup.
  - While patients were followed in the model by these age-of-onset-subgroups, model outcomes were aggregated based on the overall distribution of these subgroups in the FA population, to obtain population-level results.
  - A naturally extended logistic extrapolation with an mFARS asymptote of 93 was implemented to account for affirmed slower progression as the disease worsens.
- The treatment effect (applied at baseline age, or at 16 years old for minors) of omaveloxolone vs. SoC was applied as a rate ratio of 0.454 from the three-year mFARS change in the propensity-scored matched analyses, which is equivalent to the 55% reported cumulative reduction in mFARS.
- Treatment discontinuation rates (13% in year 1, 2.9% thereafter) were applied equally across subgroups, per the MOXIe2 trial and MOXIe open label extension study.[13]
- Estimates of mortality risks that vary with disease severity were derived from Indelicato and colleagues.[14]
- This model was used to calculate time to mFARS since treatment initiation (i.e., average time to mFARS for each subgroup) for patients ≥16 years old that received omaveloxolone, compared to those that were on SoC.

Functional Burden of mFARS Progression

- Item-level mFARS data from the MOXIe2 and FACOMS studies were analyzed to determine the proportion of patients in each severity level when first entering the following mFARS decile ranges: 40 to 49, 50 to 59, and 60 to 69.
- The patient burden analysis focused on mFARS ranges 40 to 49, 50 to 59, and 60 to 69, since most patients in the MOXIe2 and MOXIe extension studies resided in these mFARS ranges.

Results

mFARS Progression

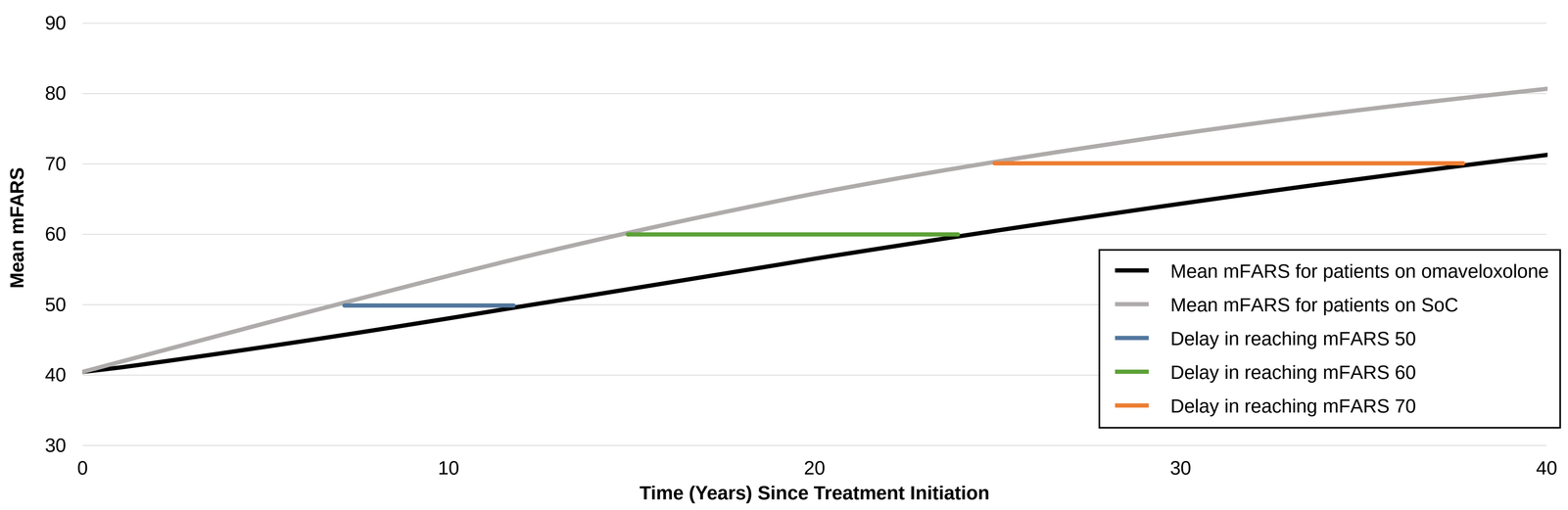
- On average, patients receiving omaveloxolone are predicted to take about 40% longer to reach an mFARS score of 50 than those who are on SoC (11.3 years vs. 8.1 years).
- Similarly, patients receiving omaveloxolone take 6.5 years longer to reach an mFARS score of 60 compared to those on SoC (21.7 years vs. 15.2 years).
- The times for the predicted average mFARS score to reach a certain threshold are shown in **Table 1** and **Figure 1**.

Table 1. Time (Years) to mFARS* from Treatment Initiation

Time to Reach	Omaveloxolone	SoC	Difference
mFARS 50	11.3	8.1	3.2
mFARS 60	21.7	15.2	6.5
mFARS 70	31.0	22.8	8.2

Abbreviations: mFARS = modified Friedreich Ataxia Rating Scale; SoC = standard of care
* The mean time in years for the predicted average mFARS score to reach a certain mFARS threshold for all age-at-onset subgroups (population-weighted mean based on the number patients alive in the subgroup at that timepoint).

Figure 1. mFARS Progression (Mean mFARS*) Over Time in Model



Abbreviations: mFARS = modified Friedreich Ataxia Rating Scale; SoC = standard of care
* This graph shows the trajectory of the mean mFARS over the full population at each timepoint.

mFARS Progression and Functional Burden

- FACOMS and MOXIe2 show concordance in patient burden by mFARS score—thus demonstrating that both the registry and trial patients experience similar burden trajectories.
- In MOXIe2, severe gait challenges were observed in 75% of patients with an mFARS score of 50 to 59 vs. only 36% of patients with a score of 40 to 49. FACOMS data showed a similar pattern, with 64% and 18% for 50 to 59 and 40 to 49 mFARS scores, respectively (**Table 2**).
  - Gait, stance, dysmetria and speech are commonly affected even at low- to mid-range mFARS scores. However, FA appears to most severely impact gait and stance, which show the most pronounced increase during the disease course.
- Omaveloxolone is predicted to delay time to certain mFARS ranges, where both MOXIe2 and FACOMS suggest notably increased patient burden. **Figure 2** visually demonstrates the increased functional burden measure on the mFARS' upright stability items.

Table 2. Functional Burden by mFARS Range

Functional Burden	Source	mFARS Range		
		40 to 49	50 to 59	60 to 69
Patient counts (n)	MOXIe2	47	28	6
	FACOMS	310	276	231
Severe gait issues* (%)	MOXIe2	36	75	100
	FACOMS	18	64	95
Severely impacted wide stance^ (%)	MOXIe2	11	46	100
	FACOMS	6	50	93
Severely impacted closed stance¥ (%)	MOXIe2	47	86	100
	FACOMS	50	90	>99
Impacted speech† (%)	MOXIe2	43	46	83
	FACOMS	42	51	63
Moderate dysmetria‡ (%)	MOXIe2	83	89	100
	FACOMS	88	95	99

In reference to both **Table 2** and **Figure 2**

Abbreviations: FACOMS = Friedreich's Ataxia Clinical Outcome Measures Study; mFARS = modified Friedreich Ataxia Rating Scale; MOXIe2 = MOXIe part 2. Patients can be included more than once.

* Defined as gait score (E7) of 4 (severe ataxia/veering; walker or two helping hands needed) or 5 (wheelchair-bound) at first visit of mFARS in specified range.

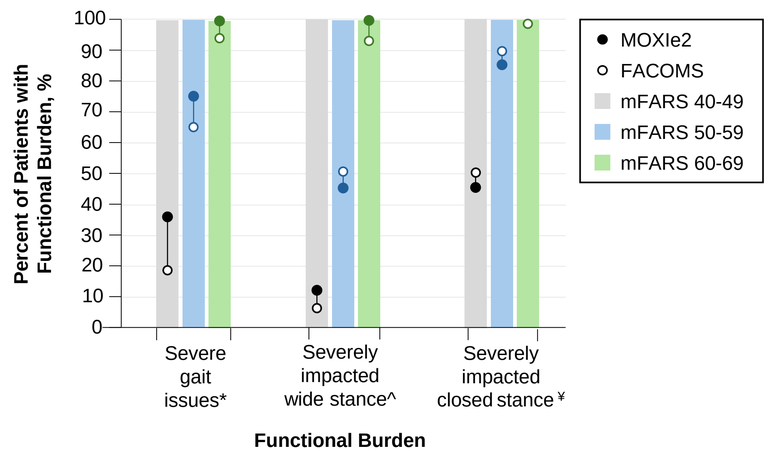
^ Defined as feet apart with eyes open score (E2a) of 4 (less than 15 seconds or needs hands held by assistant/device or cannot assume start position) at first visit of mFARS in specified range.

¥ Defined as feet together with eyes open score (E3a) of 4 (less than 15 seconds or needs hands held by assistant/ device or cannot assume start position) at first visit of mFARS in specified range.

† Defined as speech score (A4) of ≥1 (anything other than normal) at first visit of mFARS in specified range.

‡ Defined as dysmetria score (B3) of ≥2 (mild dysmetria or worse on both hands or moderate dysmetria or worse in at least one hand) at first visit of mFARS in specified range.

Figure 2. Upright Stability Functional Burden by mFARS Range



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