

Success in Rare Disease Drug Development – Friedreich's Ataxia

Barbara Tate, PhD

Chief Scientific Officer

Friedreich's Ataxia Research Alliance (FARA)

FARA

Friedreich's
Ataxia
Research
Alliance

Disclosures

Nothing to Disclose



What is Friedreich ataxia?

Rare, Progressive, Neurodegenerative Disease



Rare genetic disease

- 1 in 50,000 people
- About 15,000 people worldwide



GAA repeat expansion

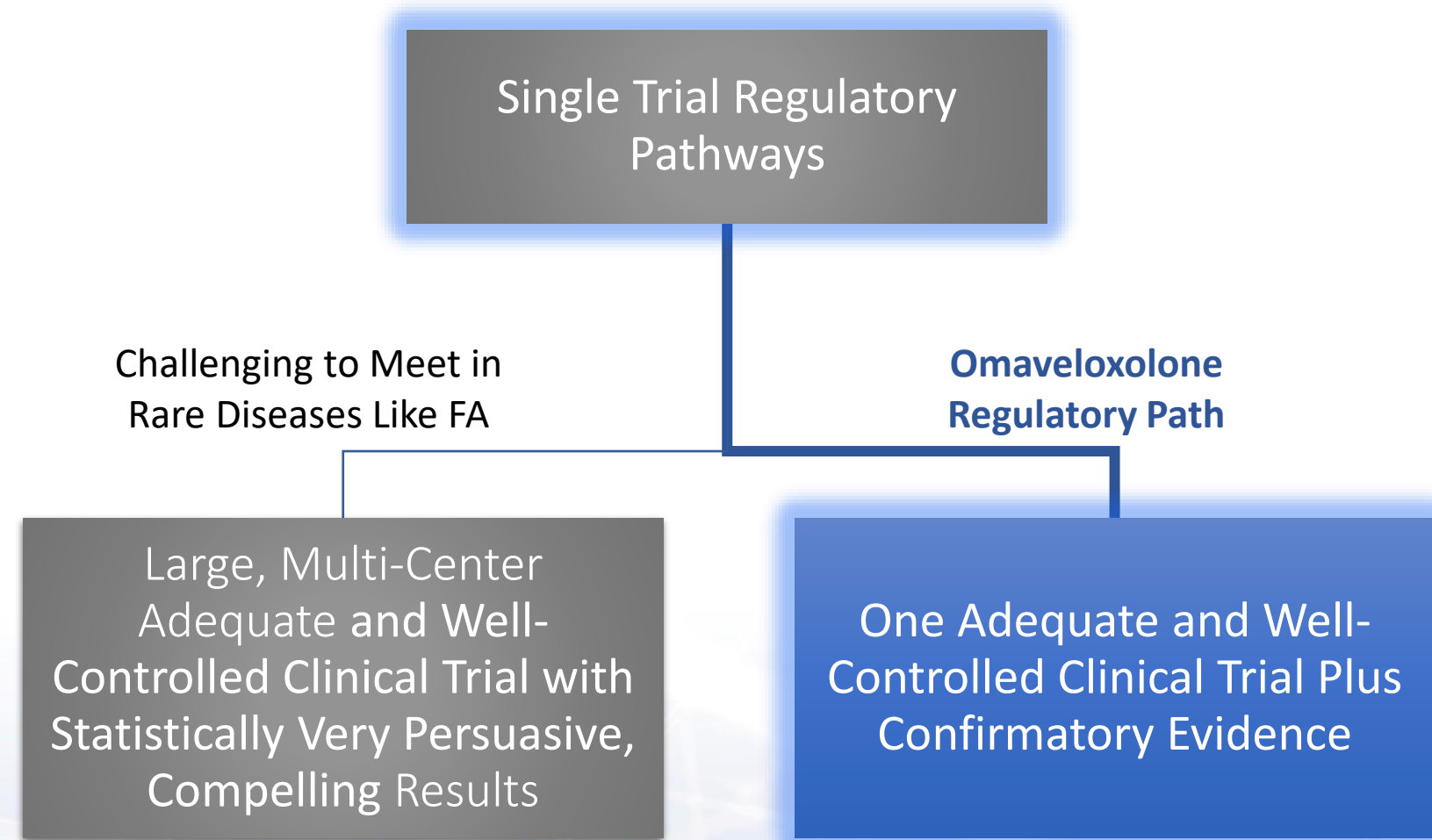
- ~95% mutation homogeneity
- Silences frataxin
- Impairs mitochondrial function



Relentlessly progressive

- Typically diagnosed between 7-15 yrs
- Requires mobility aids in teens / twenties
- Life expectancy - early adulthood

Regulatory Guidance for *Establishing Substantial Evidence for Efficacy*



Regulatory Guidance for *Confirmatory Evidence* (Sept 2023)

Single Trial Regulatory Pathways

Challenging to Meet in
Rare Diseases Like FA

Largely, Multi-Center
Adequate and Well-
Controlled Clinical Trial with
Statistically Very Persuasive,
Compelling Results

Omaveloxolone
Regulatory Path

One Adequate and Well-
Controlled Clinical Trial Plus
**Confirmatory
Evidence**

Characteristics of the FA Natural History Dataset:

- ✓ Study Duration
- ✓ Contemporary Enrollment
- ✓ Assessments
- ✓ Investigators
- ✓ Data Reliability and Provenance

FA-COMS Study Design

Inclusion

Genetically confirmed FA
All ages and stages
Representative population



Prospective, Longitudinal

Intentionally forward-looking
Long-term commitment
commensurate with the rate of
disease progression



Annual Visits

Nearly all in-person visits (except
some from 2020-2022 due to
COVID)



Consistency

Treated it as a non-interventional trial
– same protocol, visit schedules,
sops/standardized procedures, data
collection across all sites



FA Natural History: Initiated in 2003 and still ongoing



COAs for FA



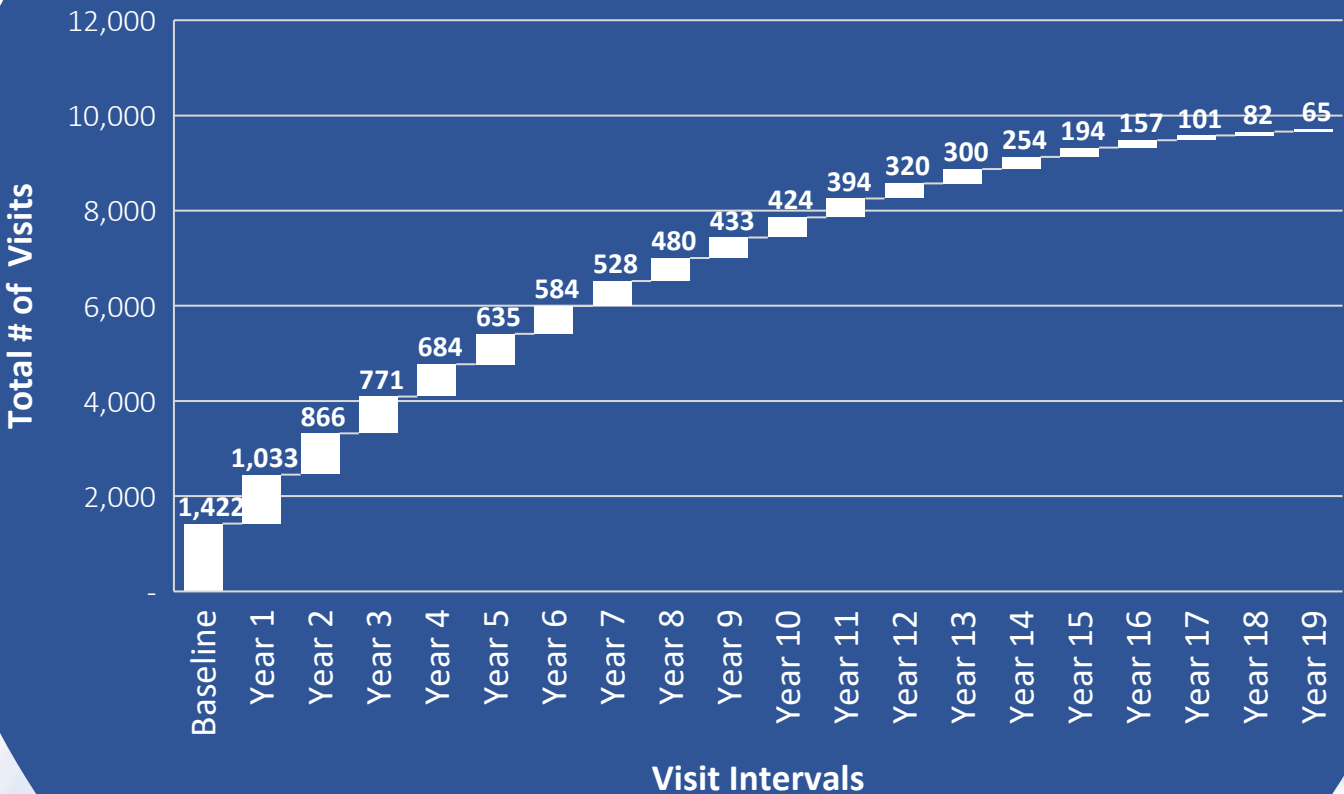
2003: Co-funded grant



Natural History Visits Begin

2006 : FARA commits to funding the natural history study and network

Strong FA-COMS Natural History Study Participation and Retention



Consistency and Comparability



Assessments

The natural history study uses the same assessments as clinical trials



Investigators

Same sites/investigators are conducting both the history study and clinical trials

Data Quality, Reliability, and Provenance



C-Path Partnership

Began in 2017

FA-ICD (Integrated Collaborative Database)

Includes FA-COMS & trial data

Available to industry sponsors, FDA, and RDCA-DAP

Data in CDISC STDM standard

PEER-REVIEWED PUBLICATIONS: >30 articles published based on the study's data

Multicenter Study > Diabetes Res Clin Pract. 2022 Apr;186:109828. doi: 10.1016/j.diabres.2022.109828. Epub 2022 Mar 14.

Friedreich's Ataxia related Diabetes: Epidemiology and management practices

Jaclyn Tamaroff¹, Anna DeDionisi-Vici², Karla Leavens⁴, Christian Rummey¹

Observational Study > Ann Clin Transl Neurol. 2021 Jun;9(6):1002/acn3.51352. Epub 2021 May 5. doi: 10.1002/acn3.51352.

Scoliosis in Friedreich's ataxia: characterization in a large heterozygous cohort

Christian Rummey¹, John M Flynn², George Wilmot⁵, Sub H Subramony⁶

> EClinicalMedicine. 2020 Jan 8;18:100213. doi: 10.1016/j.eclinm.2019.100213. eCollection 2020 Jan.

Predictors of loss of ambulation in Friedreich's ataxia

Christian Rummey¹, Jennifer M Farmer², David R Lynch³

> J Neuroophthalmol. 2020 Jun;40(2):213-217. doi: 10.1097/WNO.0000000000000878.

Correlation of Visual Quality of Life With Clinical and Visual Status in Friedreich Ataxia

Parisa Afsharian¹, Rachel Nolan-Kenney, Abigail E Lynch, Laura J Balcer, David R Lynch

> Ann Clin Transl Neurol. 2020 Sep;7(9):1708-1712. doi: 10.1002/acn3.51118. Epub 2020 Aug 11.

Test-retest reliability of the Friedreich's ataxia rating scale

> Neurol Genet. 2019 Oct 29;5(6):371. doi: 10.1212/NXG.0000000000000371. eCollection 2019 Dec.

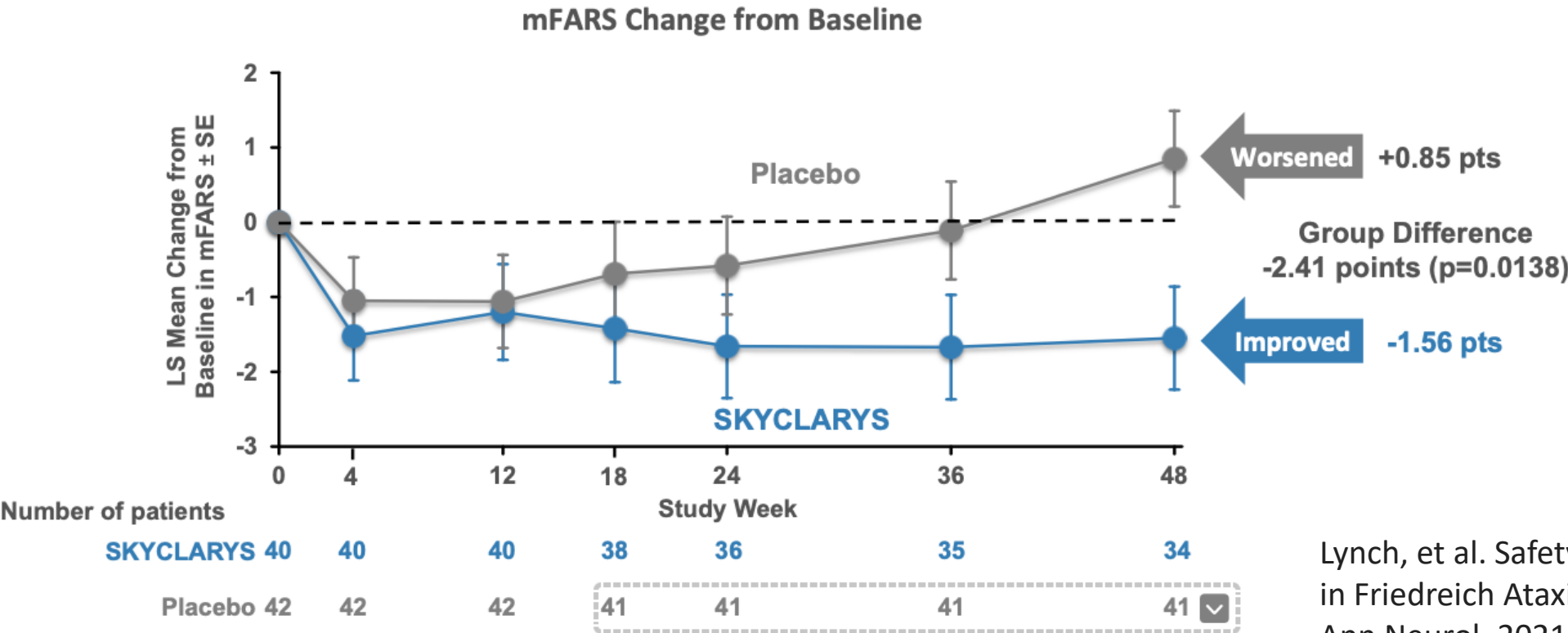
Psychometric properties of the Friedreich Ataxia Rating Scale

Christian Rummey¹, Louise A Corben¹, Martin B Delatycki¹, S H Subramony¹, Khalaf Bushara¹, Christopher M Gomez¹, Joseph Chad Hoyle¹, Grace Yoon¹, Bernard Ravina¹, Katherine D Mathews¹, George Wilmot¹, Theresa Zesiewicz¹, Susan Perlman¹, Jennifer M Farmer¹, David R Lynch¹

First NDA in FA: Omaveloxone (now Skyclarys)

MOXIe Part 2 met its primary endpoints

Treatment with SKYCLARYS™ resulted in statistically significant lower (improved) mFARS scores relative to placebo at Week 48



Lynch, et al. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). Ann Neurol. 2021 Feb.

FA Natural History dataset was used to conduct a propensity-matched analysis

Table 3. Demographics and baseline characteristics used as covariates for propensity score calculation (primary pooled population).

Characteristic	Statistic	Matched FACOMS	MOXle extension
Age (years)	<i>n</i>	136	136
	Mean (SD)	26.2 (13.7)	26.6 (7.3)
	Min, max	6, 64	16, 41
	<i>p</i> value	–	0.76
Age at FRDA onset	<i>n</i>	136	136
	Mean (SD)	15.2 (10.5)	15.5 (5.3)
	<i>p</i> value	–	0.81
Sex (<i>n</i> [%])	<i>n</i>	136	136
	Female	70 (51.5%)	70 (51.5%)
	Male	66 (48.5%)	66 (48.5%)
	<i>p</i> value	–	1
mFARS	<i>n</i>	136	136
	Mean (SD)	41.0 (16.1)	42.2 (12.6)
	Min, max	5.3, 77.0	8.2, 73.5
	<i>p</i> value	–	0.50
Gait (assessment #7 in FARS section E [upright stability])	<i>n</i>	136	136
	Mean (SD)	2.7 (1.69)	2.8 (1.36)
	<i>p</i> value	–	0.58

p value for the difference between MOXle extension and matched FACOMS was obtained by two-sample *t* test for age, age at FRDA onset, mFARS and gait and by chi-square test for sex.
FRDA, Friedreich ataxia; FARS, Friedreich ataxia rating scale; Max, maximum; mFARS, modified Friedreich ataxia rating scale; Min, minimum; SD, standard deviation.

Lynch, D. R., Goldsberry, A., Rummey, C., Farmer, J., Boesch, S., Delatycki, M. B., et al. (2024). Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. *Annals of Clinical and Translational Neurology*, 11(1), 4–16.

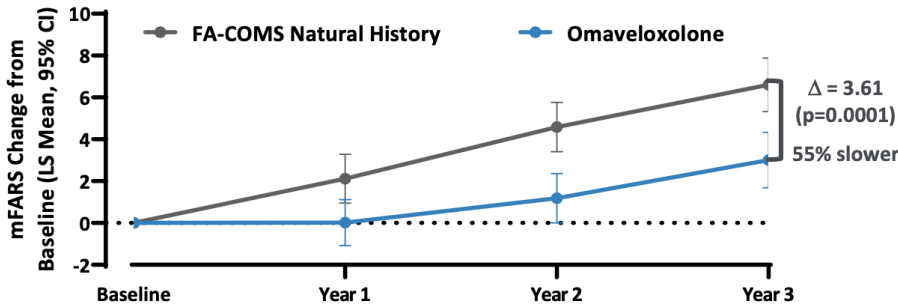
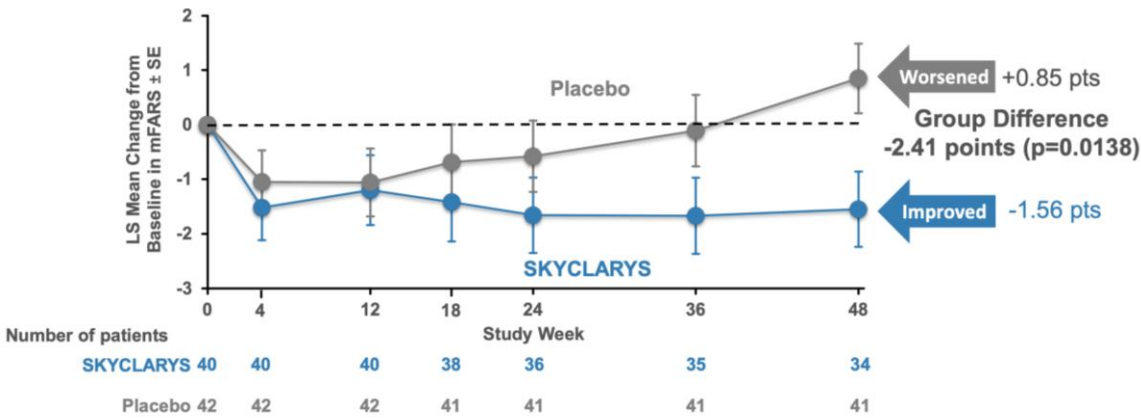
FA Natural History dataset was used to conduct a propensity-matched analysis

Propensity-Matched Analysis Primary Pooled Population

Patients in the matched FA-COMS group progressed 6.61 mFARS points at Year 3 vs. 3.00 mFARS points for patients treated with omaveloxolone in MOXIe Extension (nominal p=0.0001)

mFARS progression 55% slower in MOXIe Extension patients compared to matched FA-COMS patients at Year 3

MOXIe Part 2 Trial:
mFARS Change from Baseline



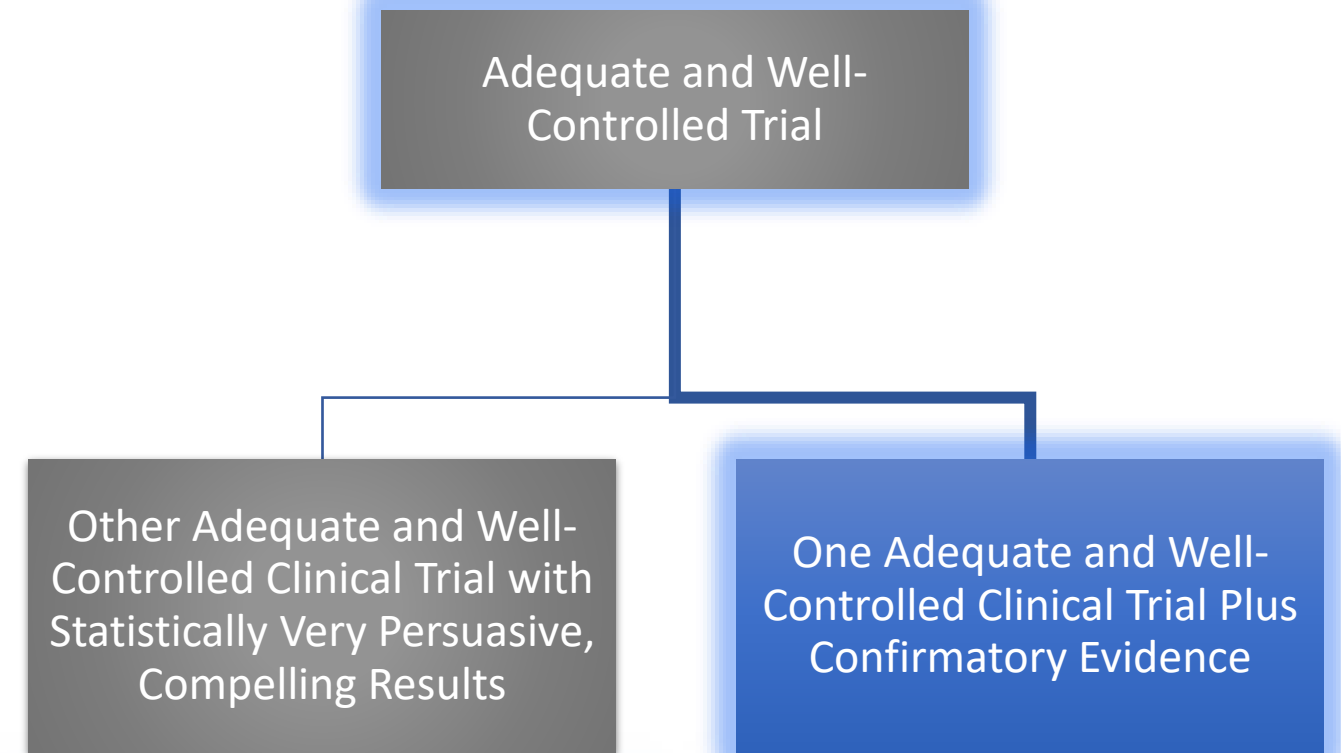
mFARS	Baseline	Year 1	Year 2	Year 3
	Mean (SD)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)
MOXIe Extension	42.2 (12.60)	0.015 (0.56)	1.18 (0.59)	3.00 (0.66)
Matched FA-COMS	41.0 (16.10)	2.11 (0.59)	4.58 (0.59)	6.61 (0.65)
Difference	-	-2.10 (0.81) p=0.0101	-3.41 (0.84) p< 0.0001	-3.61 (0.93) p=0.0001

**REATA PHARMACEUTICALS
ANNOUNCES FDA APPROVAL OF
SKYCLARYS™
(OMAVELOXOLONE),
THE FIRST AND ONLY DRUG
INDICATED FOR PATIENTS WITH
FRIEDREICH'S ATAXIA**

FARA

Friedrich's
Ataxia
Research
Alliance

Regulatory Pathways





THE FA GCC GLOBAL CLINICAL CONSORTIUM

UNIFAI NATURAL
HISTORY STUDY

GLOBAL
ALIGNMENT

POWERFUL
PARTNERSHIPS

SHARING DATA &
RESOURCES

RESEARCH
INFRASTRUCTURE



34 Global Sites

Characteristic	n (%)
Sex (N = 2605)	
Male	1306 (50.1%)
Female	1299 (49.9%)
Age of Onset (N = 2543)	
Early (0-7 years)	656 (25.8%)
Typical (8-14 years)	1006 (39.6%)
Intermediate (15-24 years)	575 (22.6%)
Late (> 24 years)	306 (12.0%)
Age at Baseline (N = 2605)	
< 12 years	296 (11.4%)
12-17 years	497 (18.1%)
>= 18 years	1812 (69.6%)
Age of Active* Participants (N=1494) <i>*visit since January 2022</i>	
< 12 years	56 (3.7%)
12-17 years	167 (11.2%)
>= 18 years	1271 (85.1%)

Data Quality and Process Considerations

Reliable, High-Quality Data

Essential datasets
included:

- Mechanistic data
- Established, trusted Natural History study
- **BLINDED** open-label extension study

Published data:

- Transparency
 - From Reata & site investigators led to scientific consensus

Communication & Collaboration

Both Reata and
the FDA committed to:

- Multiple meetings
- Working together to apply regulatory flexibility
- Determination of the data sets necessary for valid confirmatory evidence
- Focused on quality data AND meeting regulatory standards