Success in Rare Disease Drug Development – Friedreich’s Ataxia

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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

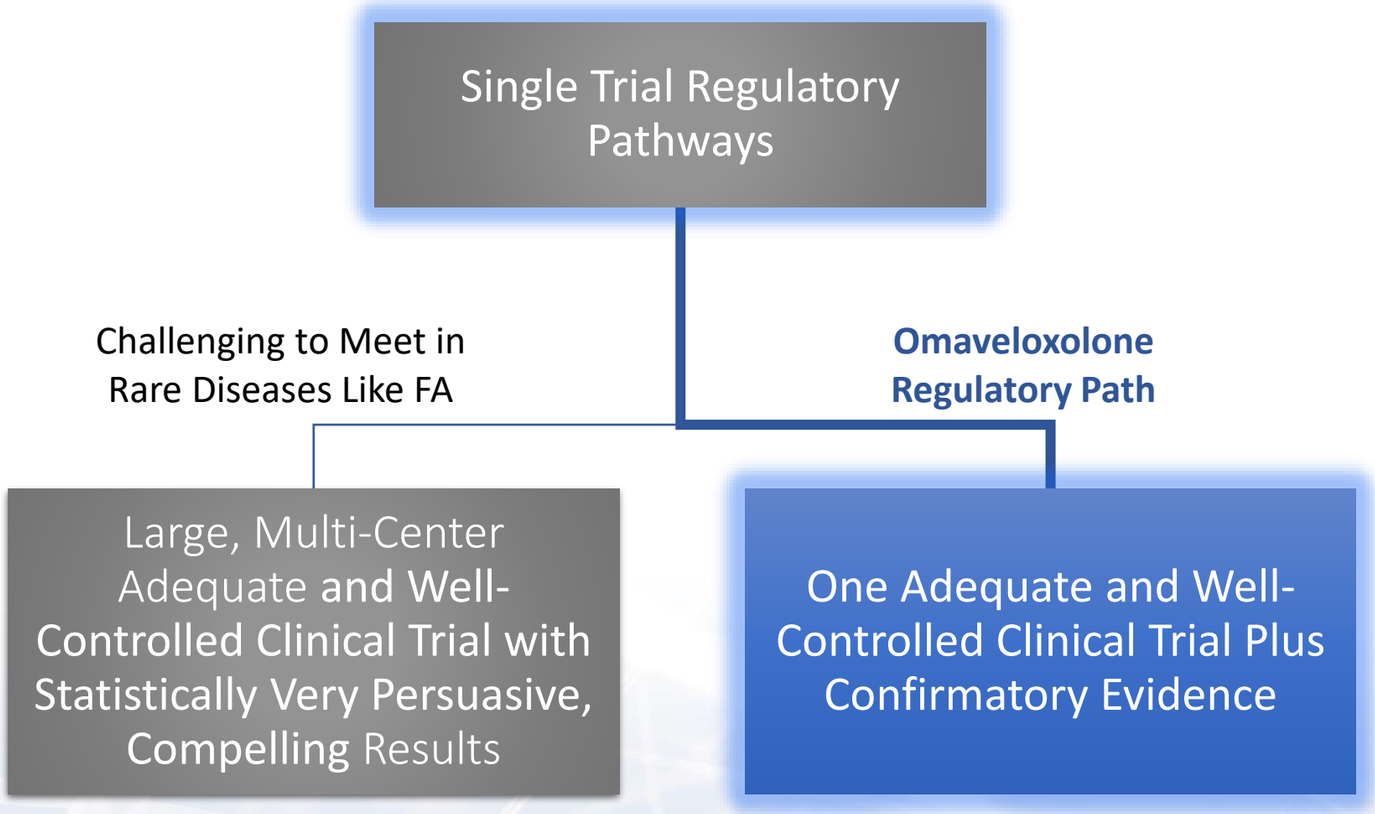
GAA repeat expansion

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

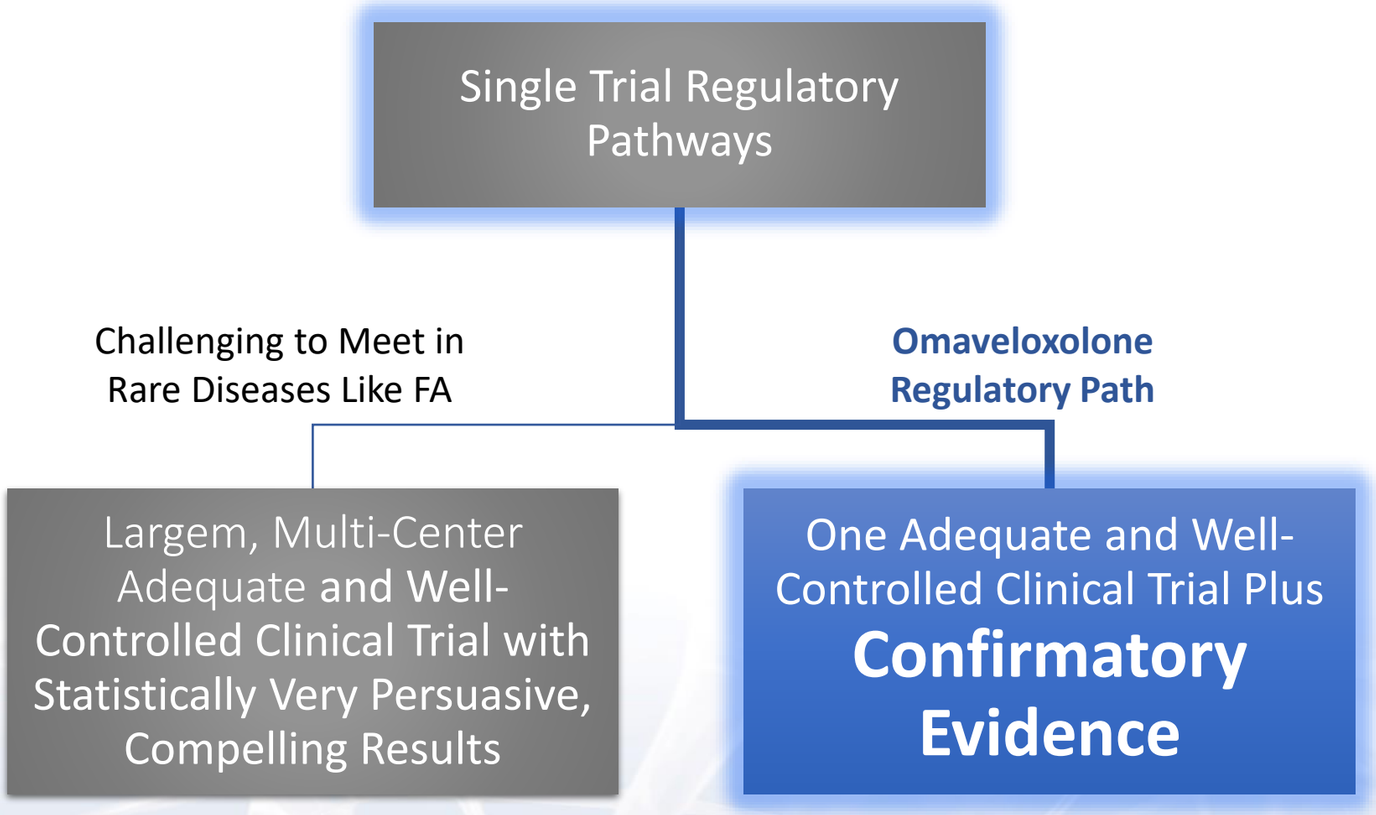
Relentlessly progressive

- 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)*



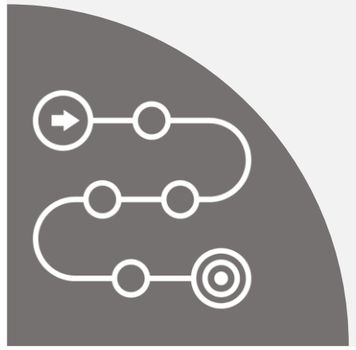
Characteristics of the FA Natural History Dataset:

- ☑ 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

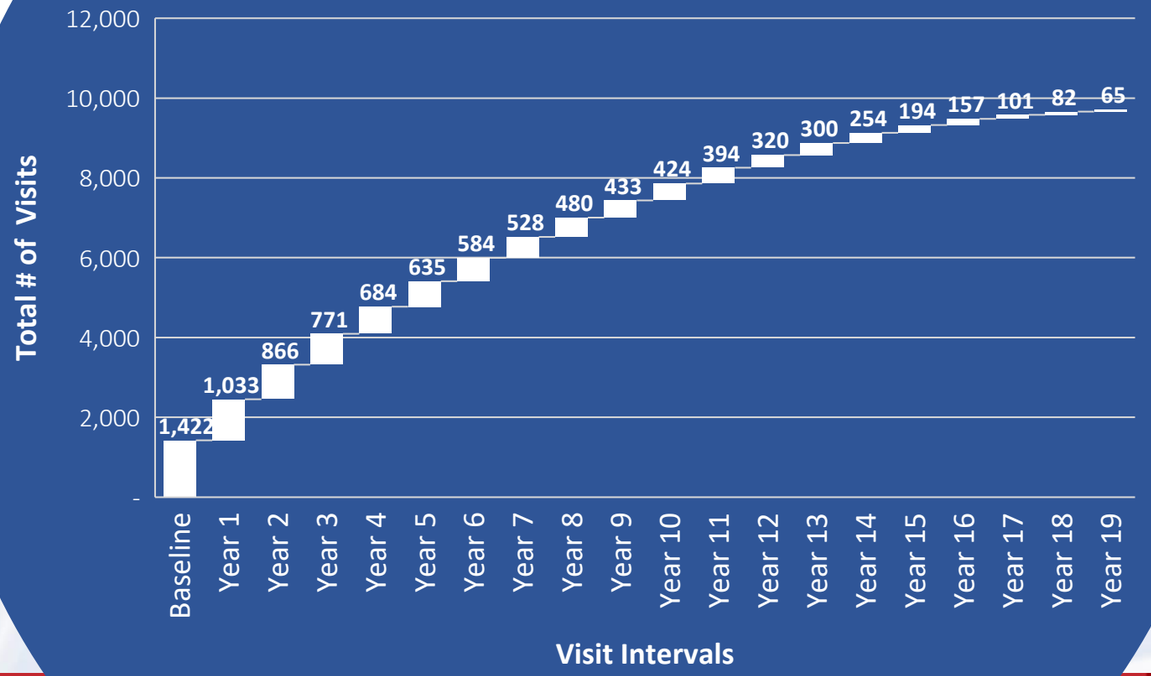
COAs for FA

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

PEER-REVIEWED PUBLICATIONS:

>30 articles published based on the study's data

Began in 2017

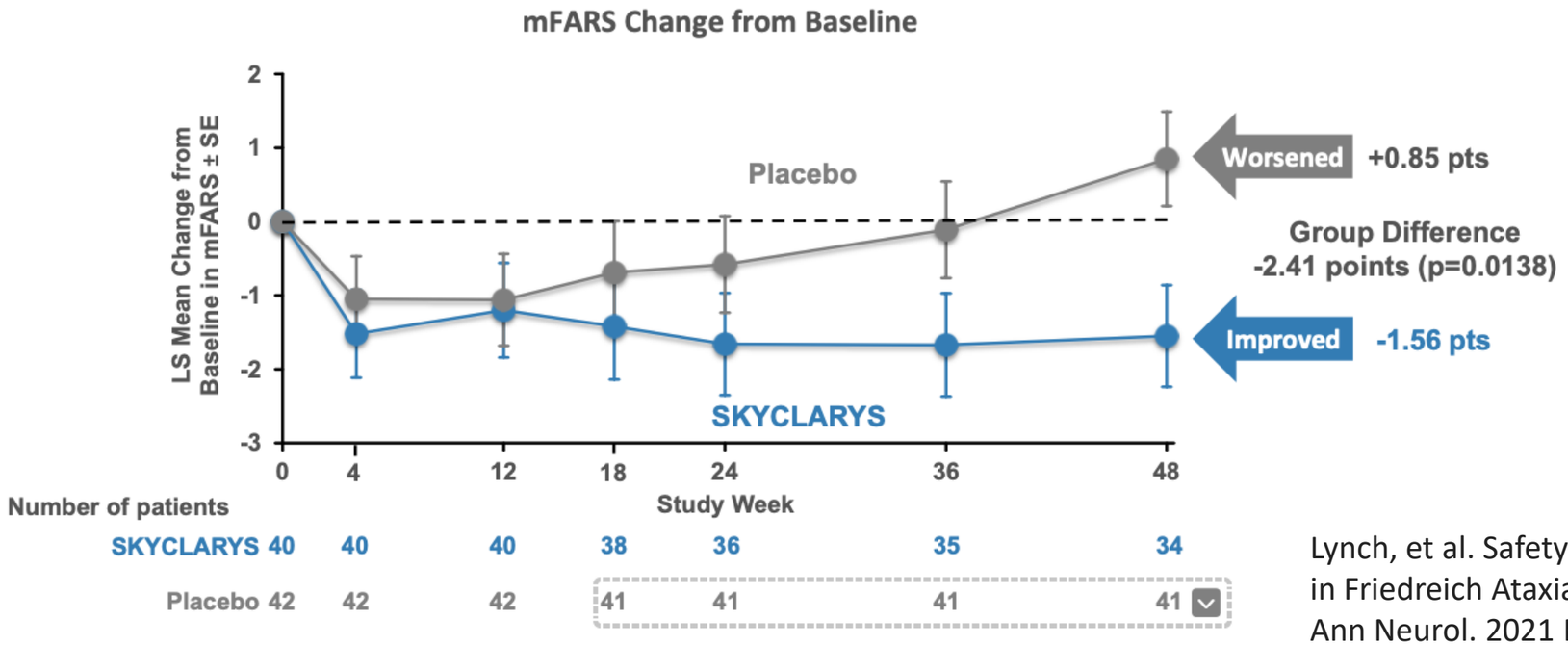
FA-ICD (Integrated Collaborative Database)

- Includes FA-COMS & trial data
- Available to industry sponsors, FDA, and RDCA-DAP
- Data in CDISC STDM standard

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).

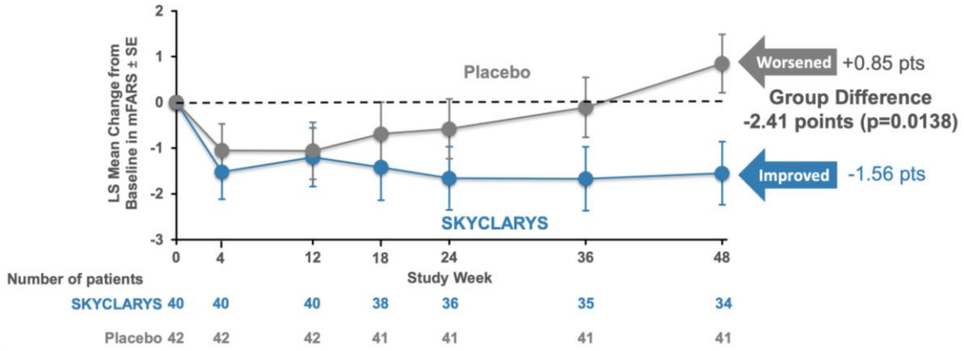
Characteristic	Statistic	Matched FACOMS	MOXIe extension
Age (years)	*n*	136	136
	Mean (SD)	26.2 (13.7)	26.6 (7.3)
	Min, max	6, 64	16, 41
	p value	–	0.76
Age at FRDA onset	*n*	136	136
	Mean (SD)	15.2 (10.5)	15.5 (5.3)
	p value	–	0.81
Sex (*n* [%])	*n*	136	136
	Female	70 (51.5%)	70 (51.5%)
	Male	66 (48.5%)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

p value for the difference between MOXIe 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

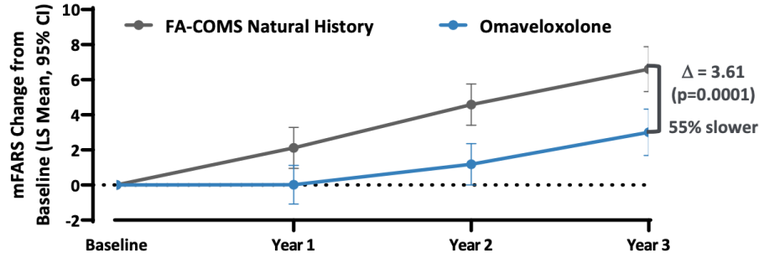
MOXIe Part 2 Trial: mFARS Change from Baseline



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



	Baseline	Year 1	Year 2	Year 3
MOXIe Extension (n)	136	133	102	77
FA-COMS Natural History (n)	136	108	103	83

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**

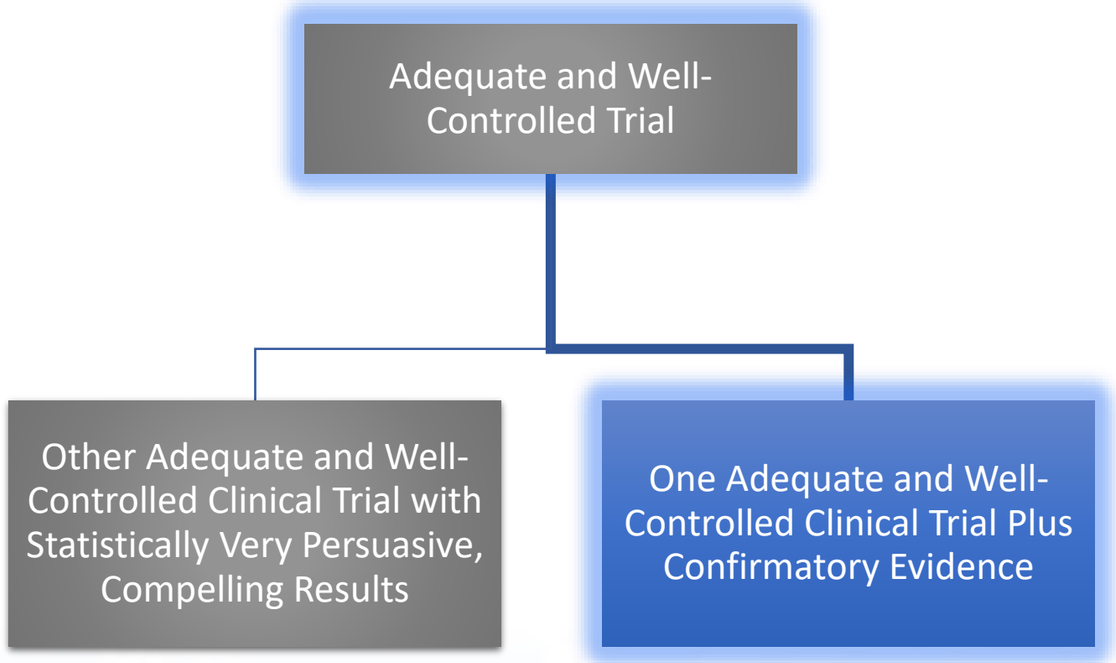
MOXIe a study in Friedreich's ataxia

REATA PHARMACEUTICALS

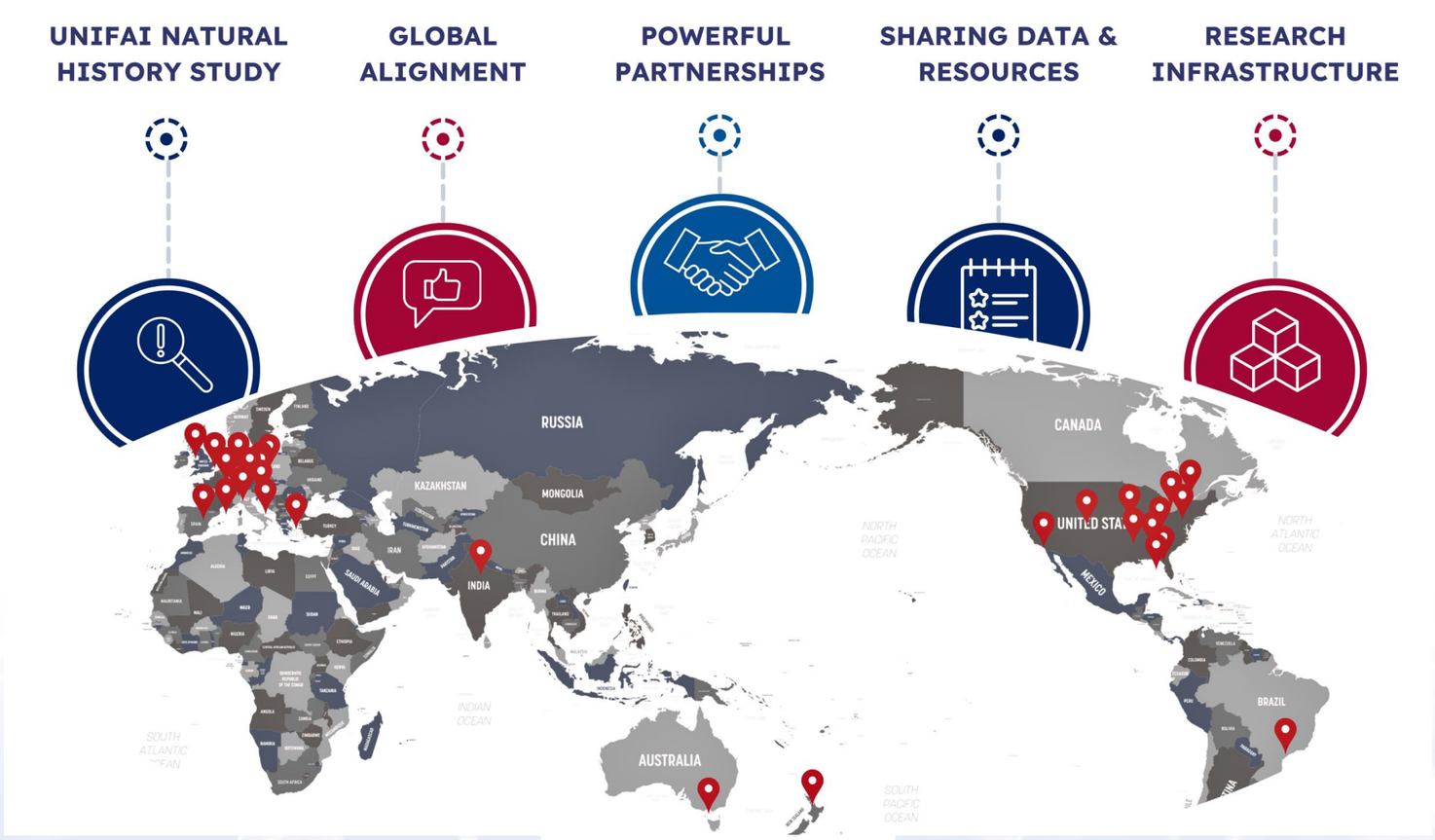
Reata Pharmaceuticals Announces FDA Approval of SKYCLARYS™ (omaveloxolone), the First and Only Drug Indicated for Patients with Friedreich's Ataxia

FARA Friedreich's Ataxia Research Alliance

Regulatory Pathways



THE FA GCC
GLOBAL CLINICAL CONSORTIUM



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)	
**visit since January 2022*	
< 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

Communcation & 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