Leveraging Natural History Data to Support Approval of Skyclarys for the Treatment of Friedreich's Ataxia

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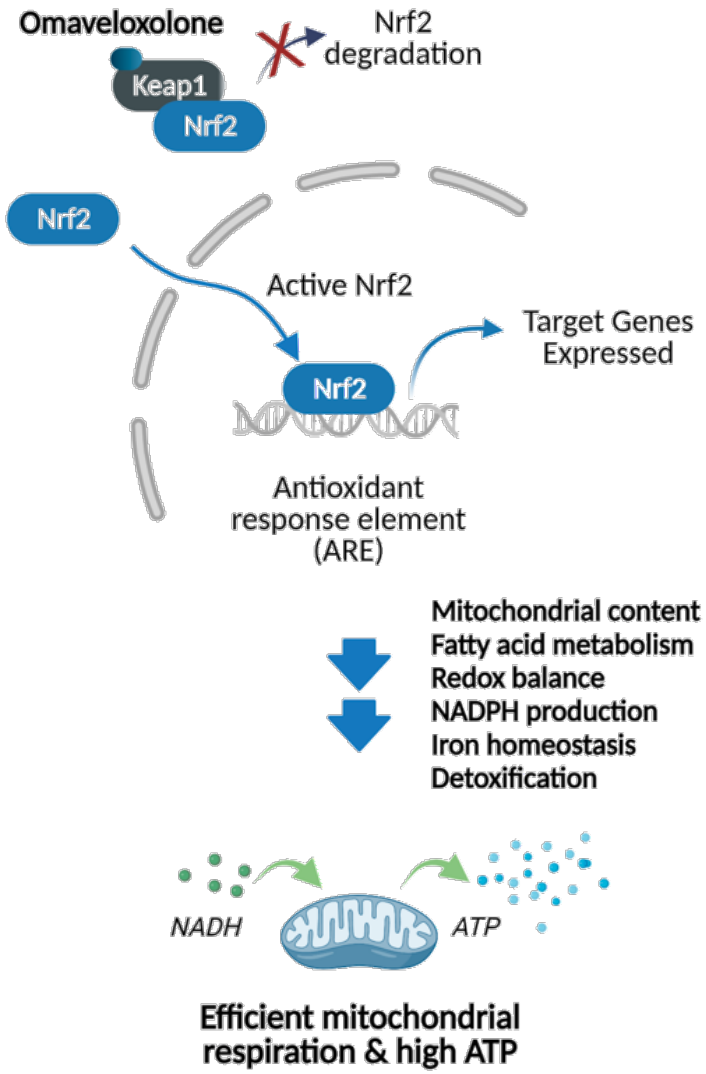
Outline

- Overview of Friedreich's ataxia (FA) pathology and omaveloxolone (Skyclarys©)
- FA-COMS natural history study and FA disease progression
- Omaveloxolone pivotal study results and regulatory guidance
- Regulatory criteria for demonstrating clinical effectiveness from single pivotal study
- Propensity matched analysis of omaveloxolone extension data to natural history data

FA Pathology and Omaveloxolone Mechanism Summary

- Nrf2 regulates genes that promote mitochondrial function
- FA is caused by mutations in *FXN* gene
  - Reduces frataxin protein levels
  - Results in Nrf2 suppression
- Nrf2 suppression leads to mitochondrial dysfunction
- Omaveloxolone restores Nrf2 activity and improves mitochondrial function

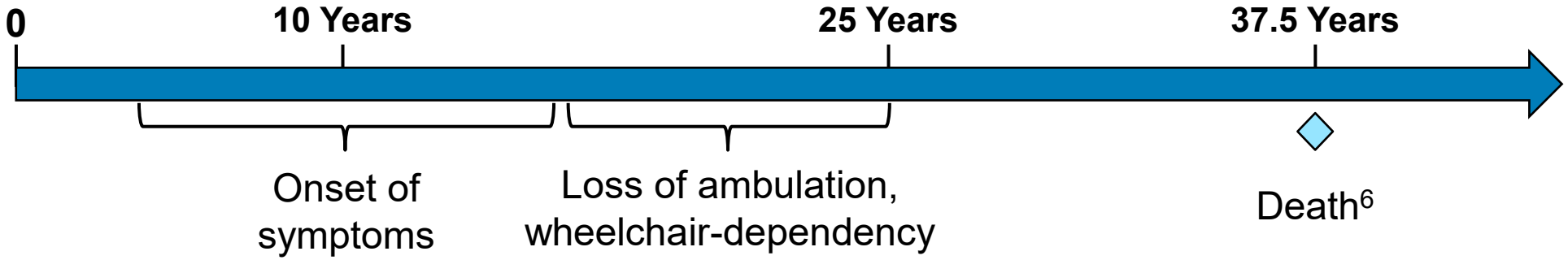


FA-COMS – Ongoing, Prospective Natural History Study[1]

- Largest global network of clinical research centers specializing in FA and funded by Friedreich's Ataxia Research Alliance (FARA)
- Ongoing, prospective collection of many clinical endpoints, including modified Friedreich's ataxia rating scale (mFARS)
  - All sites and investigators receive standardized training
  - Collect baseline demographics and disease characteristics prognostic for mFARS progression
  - mFARS contains 4 sections and assessed by trained neurologists
  - mFARS developed in collaboration with FDA
- Study has resulted in over 25 publications characterizing the course of FA, prognostic factors, and results of clinical endpoints over time

1. FA-COMS: Clinical Outcome Measures in Friedreich's Ataxia; ClinicalTrials.gov Identifier: NCT03090789

FA Disease Progression Is Inevitable, Well-Characterized, and Predictable[1,2,3,4,5]

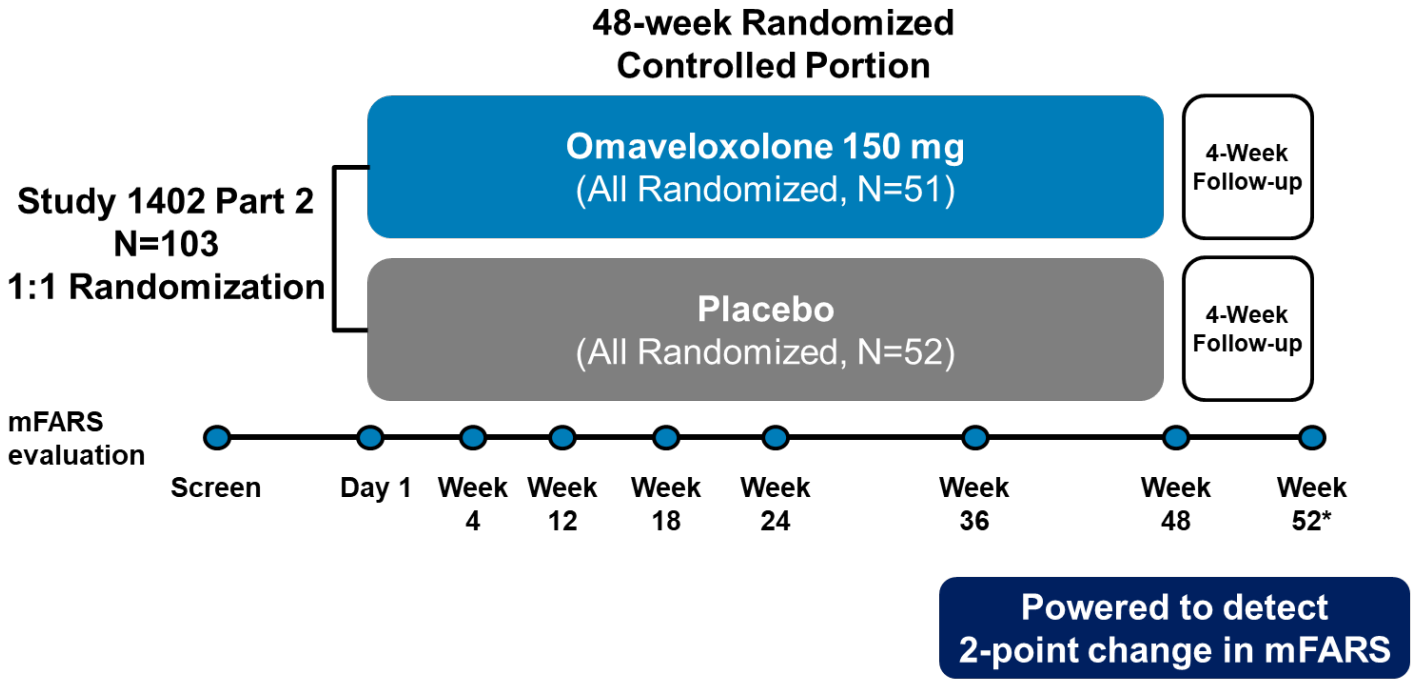


- Typical onset of symptoms occurs between ~ 5 and 15 years of age
  - Primary presenting symptoms are ataxia and fatigue
  - Most lose ability to ambulate and become wheelchair dependent by mid-20s
- Mean life expectancy of 37.5 years[6] generally due to cardiovascular complications[7]

1. Pandolfo, *Arch Neurol* 2008; 2. Patel et al, *Ann Clin Transl Neurol* 2016; 3. http://curefa.org; 4. Lynch et al, *Arch Neurol* 2002; 5. Rummey et al, *EClinicalMedicine* 2020; 6. Giugliano & Sethi, *Tex Heart Inst J* 2007; 7. Tsou et al, *J Neurol Sci* 2011

Pivotal Study 1402 Part 2 Design

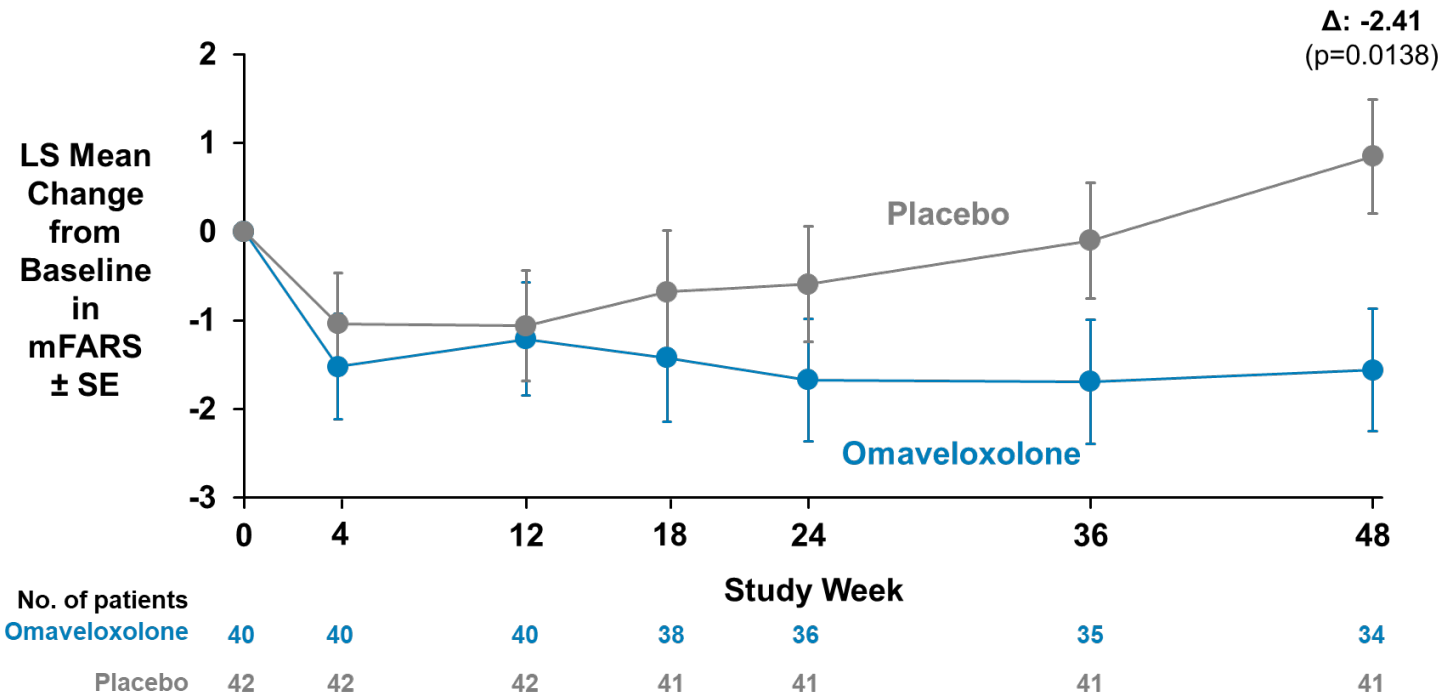
- Part 1 dose-ranging study identified dose
- Part 2 was a double-blind, placebo-controlled, randomized trial (n=103)
- Enrolled a wide range of patients with FA aged 16 to 40 years
- Primary endpoint: change from baseline in mFARS at Week 48
- Patients from Part 1 and 2 allowed to enroll in open-label extension



mFARS=modified Friedreich's ataxia rating scale
Patients self-administered study treatment once daily for 48 weeks and were off treatment in the 4-week follow-up period.
***mFARS data at Week 52 collected at Extension Day 1.**

Pivotal Study 1402 Part 2 Met Primary Endpoint

- Pivotal study met traditional threshold for success with p-value <0.05
  - All populations favored Omav
  - All sections of mFARS favored Omav
  - Major subgroups favored Omav
- Did not meet traditional approval pathways:
  - Two adequate and well-controlled studies
  - Single, highly persuasive study
- FDA requested additional data or analyses to support approval



Δ = Difference between treatment groups (omaveloxolone – placebo); Lynch, Ann Neurol 2021

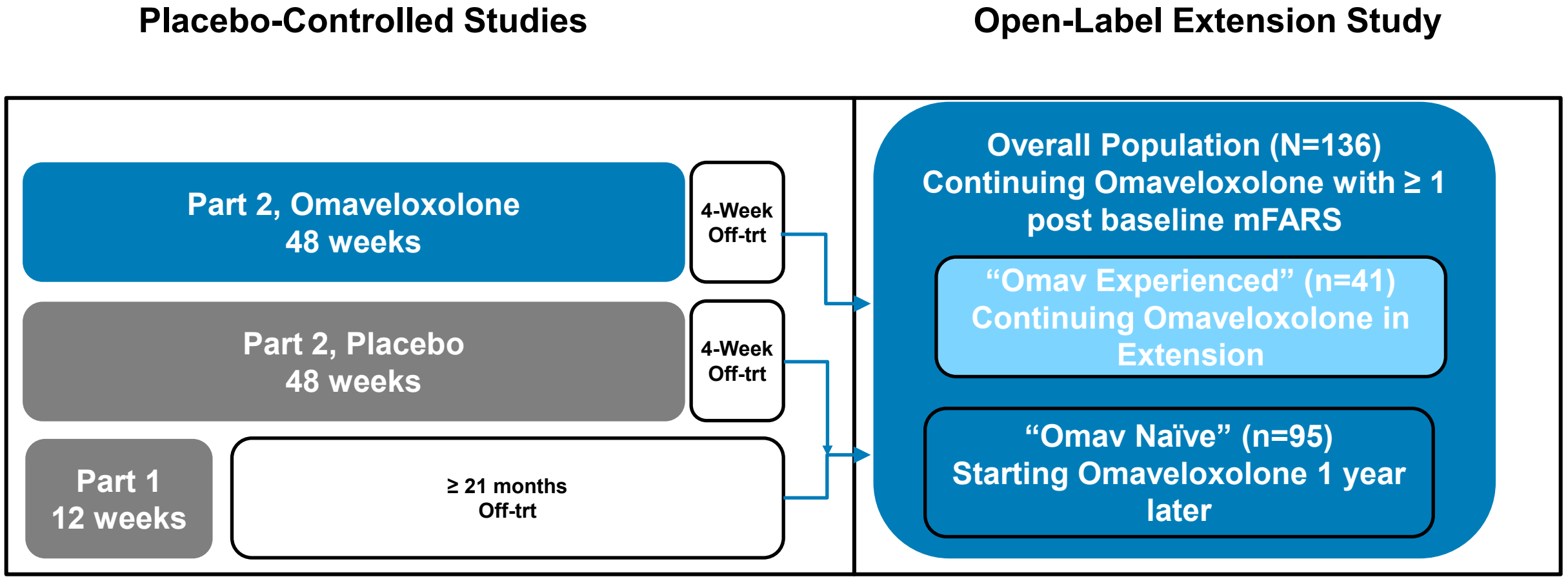
Regulatory Criteria for Demonstrating Clinical Effectiveness from Single Pivotal Study Met

Circumstances for Reliance on Single Study	
Adequate well-controlled study	✓
Confirmatory evidence	✓

Circumstances for Regulatory Flexibility	
Severely debilitating or life-threatening	✓
Rarity of disease	✓
Unmet medical need	✓

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* December 2019

Open-Label Extension Study Provided Additional Data to Interrogate



To interpret the long-term effect of omaveloxolone in extension study, a comparator was needed and for this we turned to FA-COMS

FA-COMS is an Optimal Source for External Control Comparators

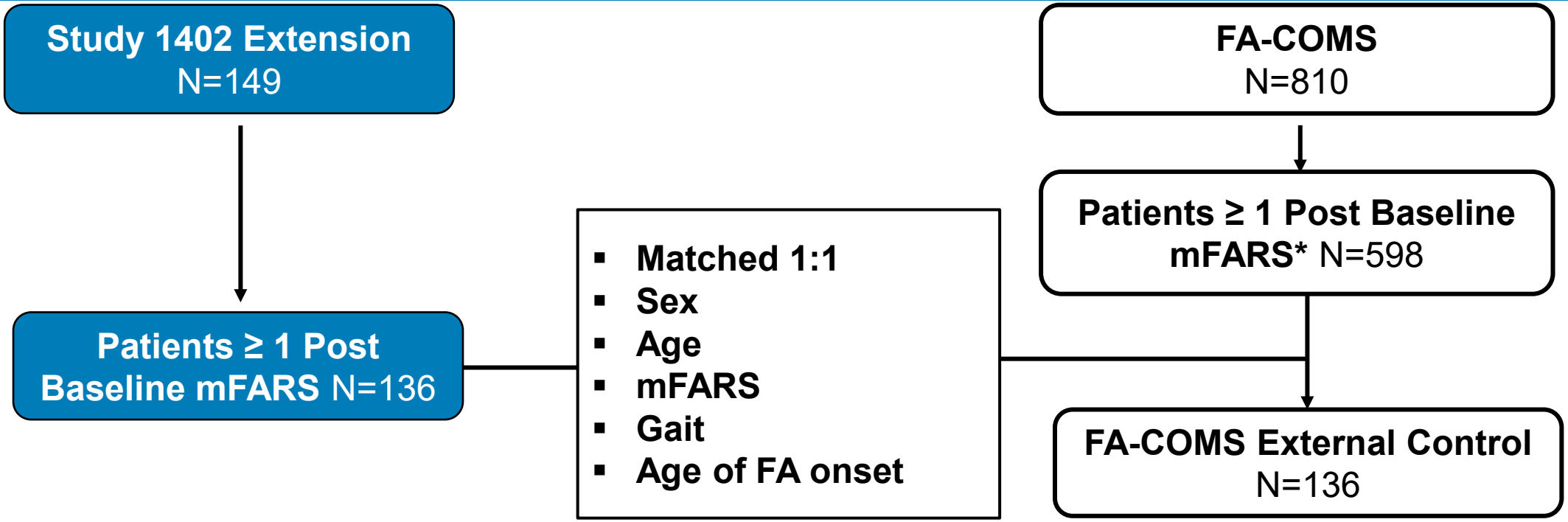
ICH E10 Points to Consider*	Characteristics of Study 1402 Extension and FA-COMS Natural History Study
Diagnostic criteria	Both studies enrolled patients with genetically confirmed FA
Institutions/Clinical settings	~20 centers globally are specialized in conducting the mFARS Substantial overlap of sites across both studies
Observational conditions for endpoints	mFARS was prospectively collected with standardized methodology including similar training of neurologists from both studies
Concomitant medications	Lack of potential confounding by concomitant medications since there were no effective agents for FA
Covariates influencing outcome of mFARS	FA has well-defined prognostic factors for mFARS progression, collected in both studies

*ICH E10: Choice of Control Group and Related Issues in Clinical Trials

Propensity-Matched Factors Identified Based on Medical Rationale in Collaboration with FARA

Covariate	Medical Rationale
Sex	▪ Sexual dimorphisms inconsistently observed in ataxia studies
Age	▪ Primary determinant of phenotypic severity
Age of FA onset	▪ Surrogate for relative rate of progression and GAA repeat length
mFARS score at baseline	▪ Allows matching of patients at the same level of function
Gait score at baseline	▪ Allows matching of patients at the same level of function

Propensity Matching Robust Method for Leveraging Similarities Between Studies

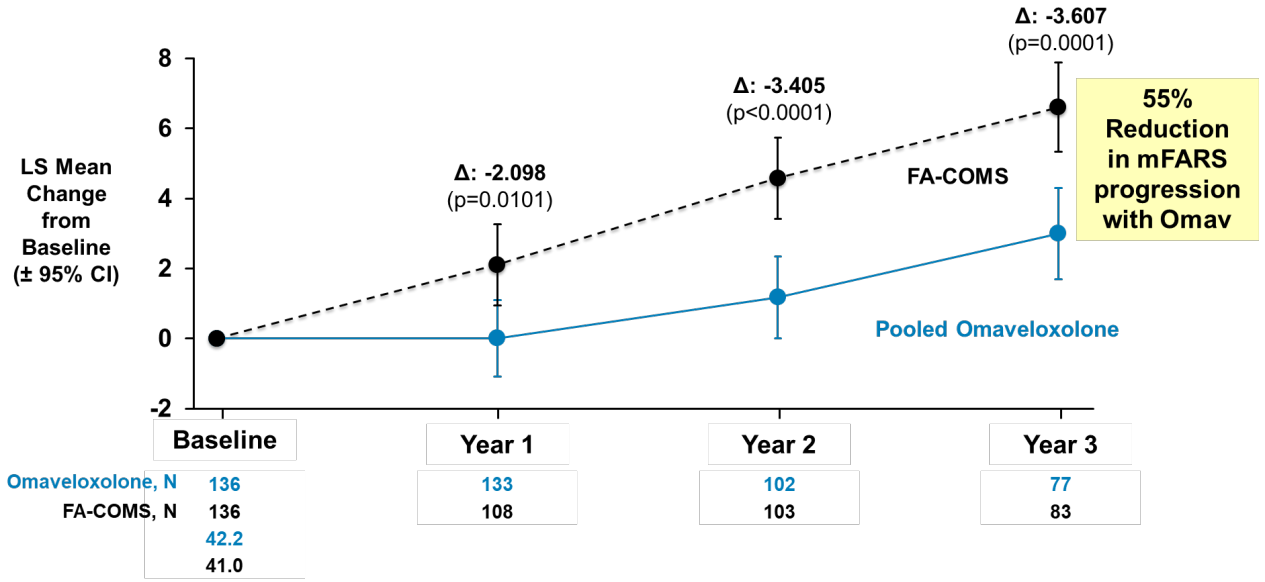


Process for propensity matching was repeated to identify FA-COMS external controls for "Omav-Naïve" (N=95) and "Omav-Experienced" (N=41)

*Having baseline, at least one post-baseline mFARS within 3 years, and all baseline characteristics used for propensity score calculation

Pooled Omaveloxolone Patients Progress Slower vs Matched FA-COMS External Control

- More than 50% slowing in mFARS at Year 3 across all populations
  - All sections of mFARS and all subgroups favored Omav
  - Effect in treatment-naïve patients at Year 1 is similar to effect in Study 1402 Part 2
  - Similar results in sensitivity populations (rematched with higher level of stringency)
- More than 3x the number of patients in the Propensity-Matched analysis vs Study 1402 Part 2 (272 vs 82) and 3x the follow-up time (3 years vs 1 year)



Baseline Characteristic	Omav	FA-COMS	Favors Omaveloxolone / Favors FA-COMS	Year 3 mFARS Treatment Difference (95% CI)
Age (years)				
< 18	9	44		**-3.05** (-9.03, 2.93)
≥ 18	127	92		**-2.86** (-4.88, -0.83)
Age (years)				
< 25	62	77		**-3.74** (-6.37, -1.11)
≥ 25	74	59		**-3.02** (-5.55, -0.49)
Sex				
Male	66	66		**-2.96** (-5.55, -0.37)
Female	70	70		**-4.25** (-6.82, -1.68)
GAA1 Repeat Length ≥ 675				
Yes	66	54		**-3.62** (-6.49, -0.76)
No	53	75		**-3.39** (-6.07, -0.71)
mFARS				
< 45	79	80		**-4.67** (-7.06, -2.29)
≥ 45	57	56		**-2.30** (-5.16, 0.57)
Severe Pes Cavus				
Yes	43	43		**-2.57** (-5.97, 0.83)
No	93	93		**-4.02** (-6.20, -1.85)
Age at FA Onset				
≤ 15	75	92		**-3.33** (-5.68, -0.97)
> 15	61	44		**-3.47** (-6.37, -0.57)

-10 -8 -6 -4 -2 0 2 4 6 8

Extension data as of March 2022; Δ = Difference between treatment groups (omaveloxolone – FA-COMS)

Regulatory Criteria for Demonstrating Clinical Effectiveness from Single Pivotal Study Met

Regulatory Pathway	Omaveloxolone Data
Adequate well-controlled study	▪ Well-designed, placebo-controlled study ▪ Primary endpoint showed clinically relevant benefit to omaveloxolone-treated patients of 2.41 points over course of year (p=0.0138) ▪ Sensitivity analyses support robustness of results
Confirmatory evidence	
Supportive natural history	▪ Patients on omaveloxolone progress slower than FA-COMS Difference: -3.607 (p=0.0001) [mentioned on label]
Delayed-start analysis	▪ Patients treated with omaveloxolone early did better vs those who started on placebo [not mentioned on label]
Mechanistic evidence	▪ Activation of Nrf2, which is suppressed in FA, associated with clinical benefit [not mentioned on label]
Regulatory flexibility depending on seriousness of disease and unmet need	▪ Rare, progressive, fatal disease

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* December 2019