BHV4157-206-RWE Pivotal Study Results

Melissa Wolfe Beiner, M.D.
SCA Clinical Lead and Senior Medical Director, Biohaven

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BHV4157-206-RWE: Study Designed In Discussion with FDA

FDA Feedback	BHV4157-206-RWE Protocol
Follow Industry Guidance for RWE*	Regulatory precedent for NDA approval based on RWE
Submit Protocol and Analysis Plan for FDA review prior to database lock	Prespecified endpoints and analysis plan based on FDA input to both Protocol and SAP ahead of database lock
Use US SCA Natural History cohort as external control for primary analysis	Minimizes potential for bias: Biohaven trial & US SCA Natural History study conducted by same sites/investigators, evaluating similar scales, over similar time period, with same population, on same standard of care treatment
Use Propensity Score Matching (PSM) methodology	Minimizes potential for bias by balancing baseline characteristics between treatment group and external control; Used in other NDAs leveraging RWE**
Match populations based on trinucleotide repeat length	Minimizes potential for bias by matching treatment group and external control based on an additional genetic factor associated with disease burden
Match populations on year 1 placebo progression rates	Minimizes potential for bias by addressing non-linear patterns of disease progression and inherent heterogeneity of SCA genotypes

*Guidance for Industry Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision Making for Drug and Biological Products (https://www.fda.gov/media/171667/download
**Lynch DR, et. al. Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. Ann Clin Transl Neurol. 2024 Jan;11(1):4-16. doi: 10.1002/acn3.51897. Epub 2023 Sep 10. PMID: 37691319; PMCID: PMC10791025.

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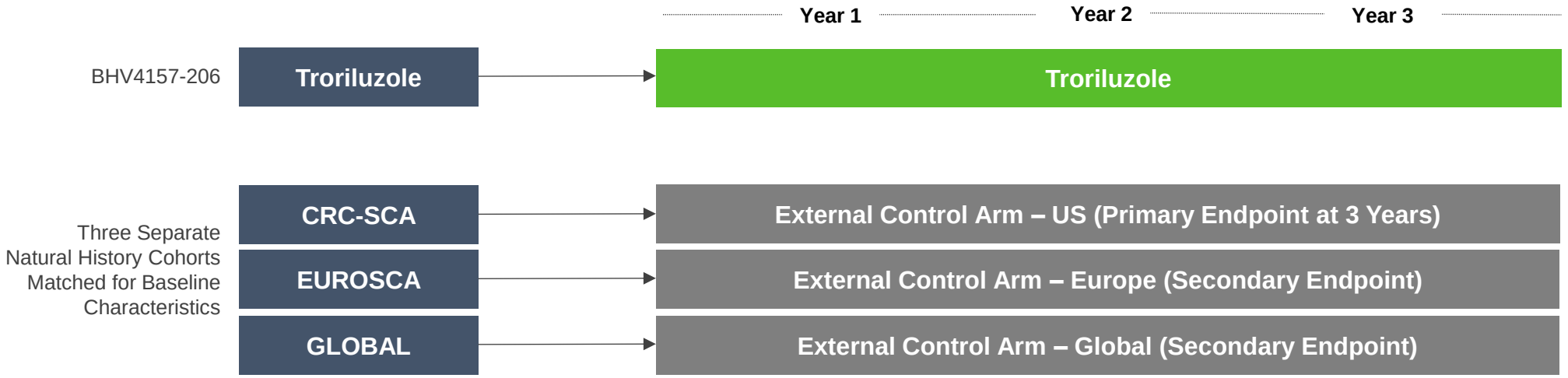
Study BHV4157-206-RWE



DESIGN	3 Year Real World Evidence Protocol with external control using Propensity Score Matching
PRIMARY ENDPOINT	**Total f-SARA Scale** Change from baseline at 3 years in troriluzole-treated subjects vs untreated subjects from US Natural History control (CRC-SCA)
SECONDARY ENDPOINTS INCLUDE	• f-SARA change from baseline at 1 and 2 years vs US Natural History external control (CRC-SCA) • f-SARA change from baseline at 1, 2, and 3 years vs EU Natural History external control (EUROSCA) • f-SARA change from baseline at 1, 2, and 3 years vs global US and EU Natural History external control (CRC-SCA and EUROSCA)

PSM Successfully Achieved Balance on Baseline Characteristics Across Troriluzole and External Control Arms

	Troriluzole	CRC-SCA	p-value
n	101	202	
Age (years)			0.5068
mean (SD)	47.9 (12.92)	48.8 (11.29)	
median (range)	49 (18, 73)	52 (18,73)	
Sex			1.0000
Male (%)	44 (43.6)	88 (43.6)	
Female (%)	57 (56.4)	114 (56.4)	
Age at symptom onset (years)			0.6183
mean (SD)	37.9 (12.39)	38.6 (12.37)	
median (range)	38 (10, 71)	40 (1, 69)	
f-SARA			0.2827
mean (SD)	5.0 (1.61)	4.6 (3.27)	
median (range)	4 (2,10)	4 (1,15)	

	Troriluzole	CRC-SCA	p-value
n	101	202	
Genotype (%)			0.5778
SCA1	15 (14.9)	33 (16.3)	
SCA2	30 (29.7)	57 (28.2)	
SCA3	40 (39.6)	85 (42.1)	
SCA6	5 (5.0)	10 (5.0)	
SCA7	5 (5.0)	4 (2.0)	
SCA8	3 (3.0)	11 (5.4)	
SCA10	3 (3.0)	2 (1.0)	
CAG trinucleotide by genotype, mean (SD)			0.2580
SCA1	47.4 (5.23)	46.5 (3.67)	
SCA2	39.8 (3.21)	40.4 (3.11)	
SCA3	72.3 (4.56)	71.4 (6.84)	
SCA6	22.6 (1.52)	23.0 (1.89)	
SCA7	44.4 (4.10)	47.8 (12.55)	
SCA8	139.7 (42.16)	125.7 (49.75)	
SCA10	1744.3 (251.66)	1320.5 (1683.62)	

PSM achieved balance for all 3 external control arms (US, EU, and Global)

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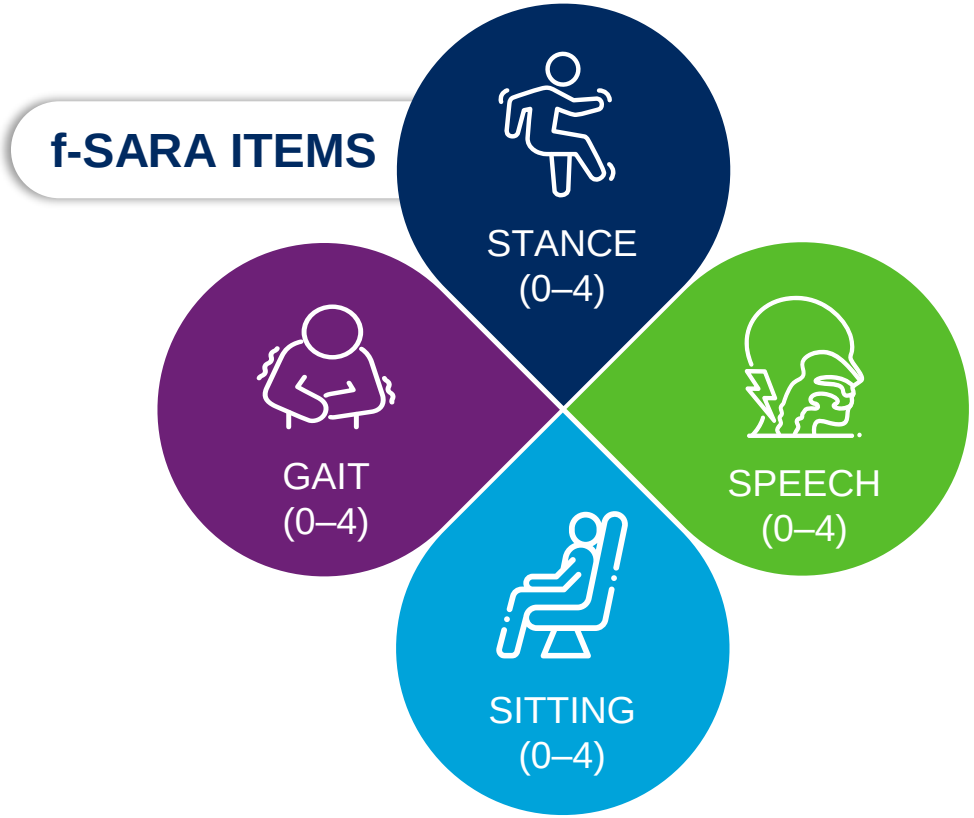
f-SARA Primary Outcome Measure: Reliable and Validated Scale That Objectively Measures Cerebellar Function

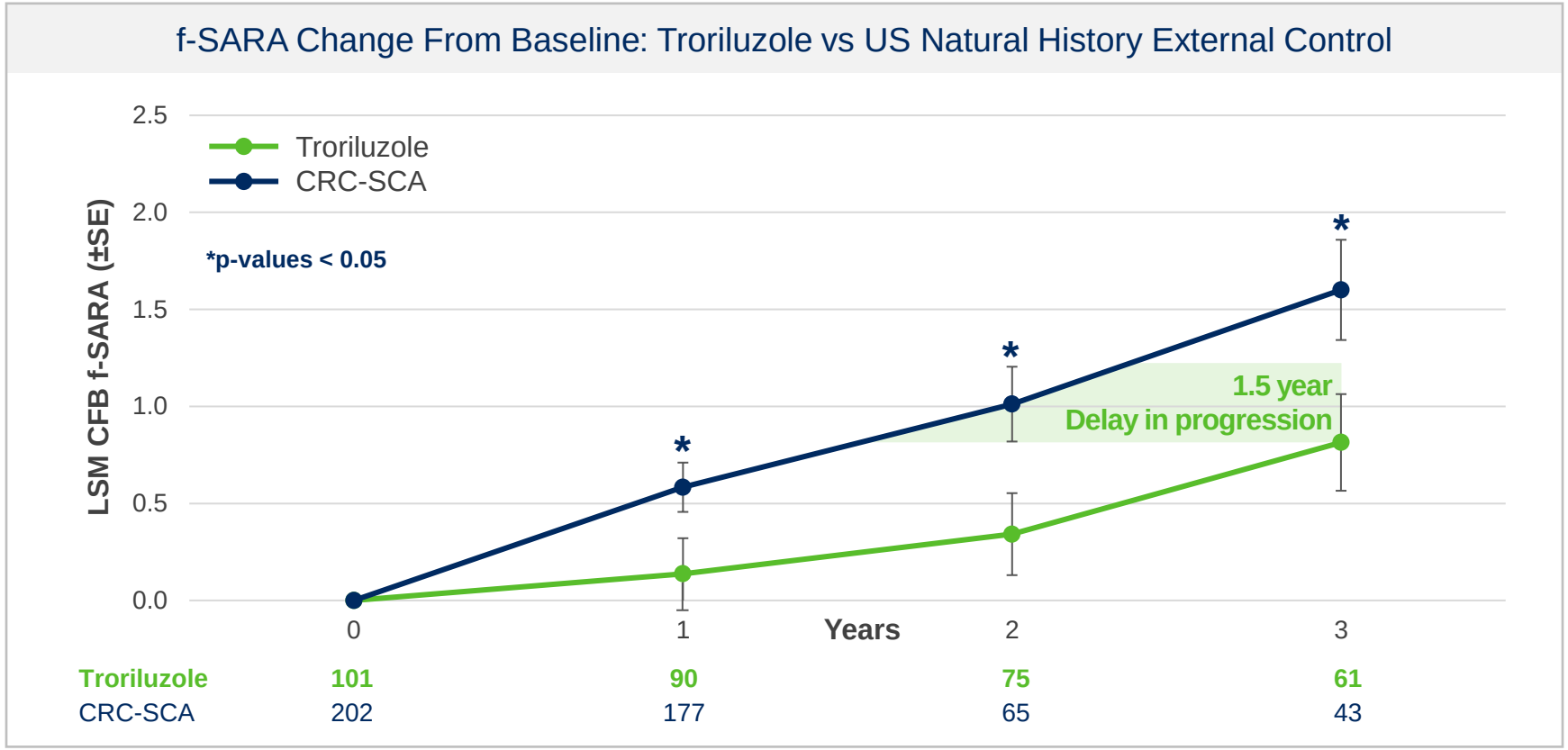
- Developed based on specific FDA input
- Neurologist-assessed objective scale for SCA
- Measures 4 core functional items with response categories reflecting clearly distinguishable and clinically meaningful changes in patient function
- Individual items rated 0–4 with total score 0–16
- Increases (worsens) approximately 0.5 points annually
- Psychometric and qualitative validation performed according to Regulatory guidance[1,2]



f-SARA assesses objective cerebellar symptoms reflected in daily activites

1. Potashman M, Rudell K, Pavisic I, et al. Content Validity of the Modified Functional Scale for the Assessment and Rating of Ataxia (f-SARA) Instrument in Spinocerebellar Ataxia. Cerebellum 2024.
2. Potashman M, Popoff E, Powell L, et al. Psychometric Validation of the Modified Functional Scale for the Assessment and Rating of Ataxia (f-SARA) in Patients With Spinocerebellar Ataxia. Cerebellum 2024.

Positive Prespecified Primary and Secondary Endpoints: Troriluzole vs US Natural History External Control



KEY POINT

Troriluzole reduced SCA disease progression by ~50%

CRC-SCA, Clinical Research Consortium for SCA; **EUROSCA,** European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM,** least squares mean; **PSM**, Propensity Score Matching; **CFB**, Change from baseline

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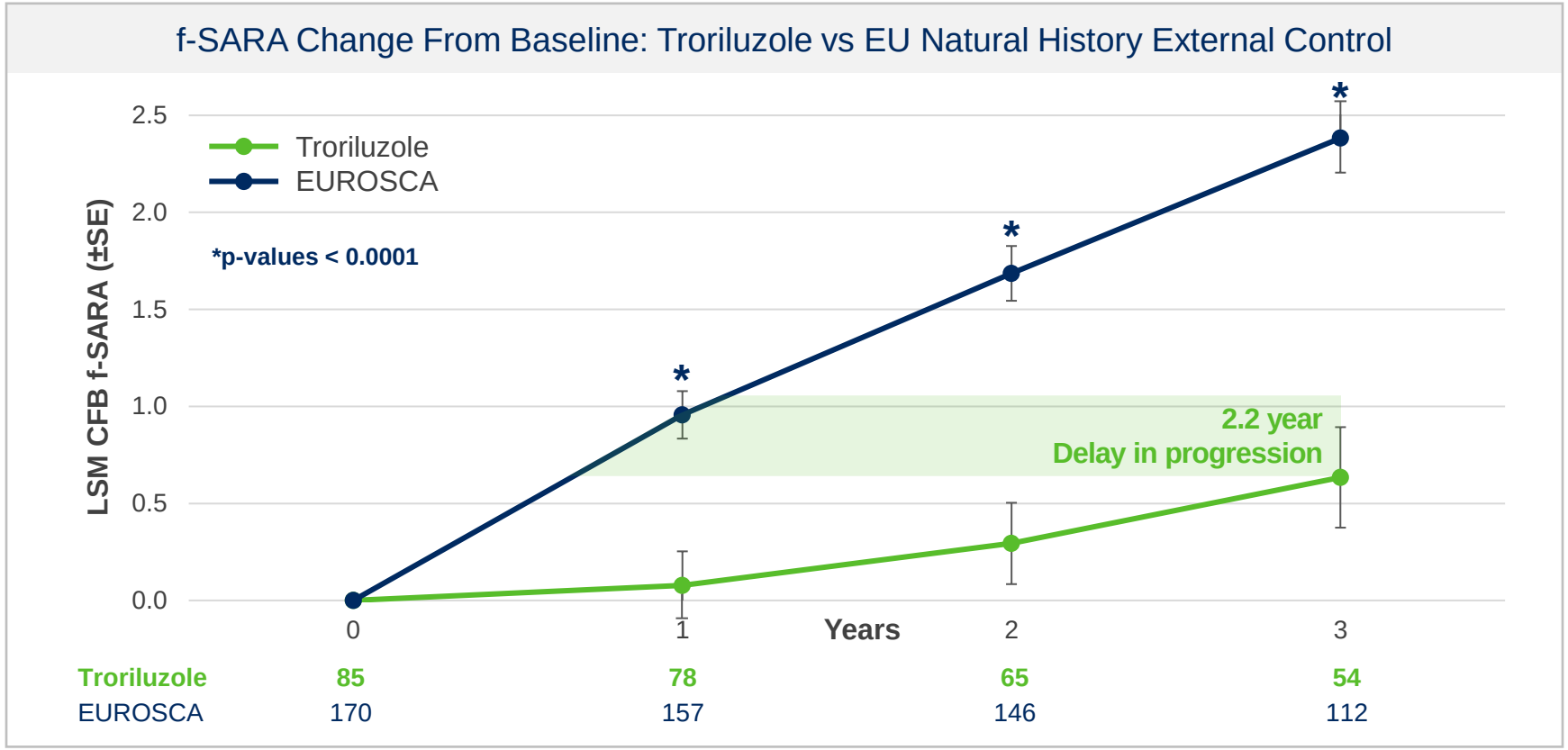
Positive Prespecified Secondary Endpoints: Troriluzole vs Independent EU Natural History External Control



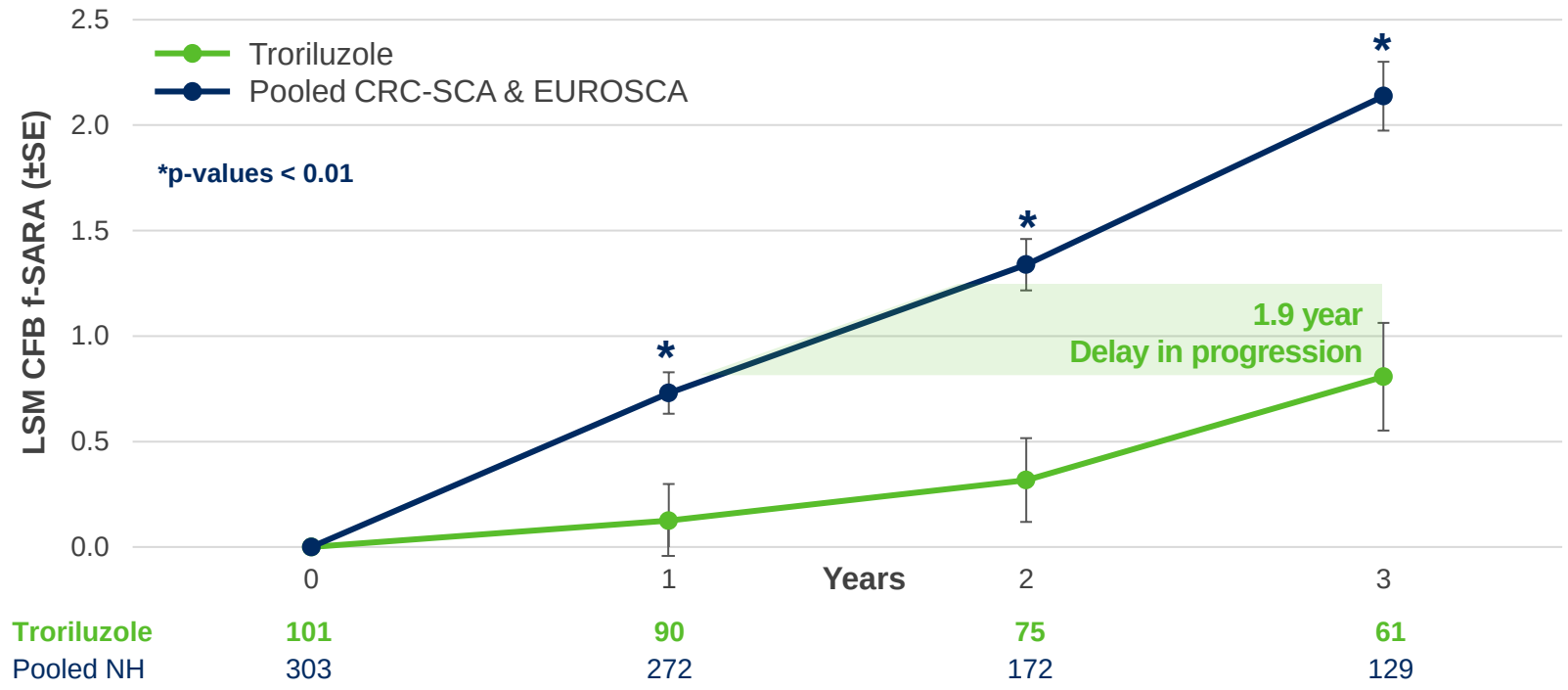
KEY POINT

Troriluzole reduced SCA disease progression by ~70%

CRC-SCA, Clinical Research Consortium for SCA; **EUROSCA,** European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM,** least squares mean; **PSM**, Propensity Score Matching; **CFB**, Change from baseline

Positive Prespecified Secondary Endpoints: Troriluzole vs Pooled US and EU Natural History External Control

f-SARA Change From Baseline: Troriluzole vs Pooled US and EU Natural History External Control



Troriluzole	**101**	**90**	**75**	**61**
Pooled NH	303	272	172	129

KEY POINT

Troriluzole reduced SCA disease progression by ~60%

CRC-SCA, Clinical Research Consortium for SCA; **EUROSCA,** European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM,** least squares mean; **PSM**, Propensity Score Matching; **CFB**, Change from baseline

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Prespecified Sensitivity Analysis:

Untreated SCA Patients at Greater Risk of Significant Disease Worsening

	Odds Ratio of f-SARA ≥2-Point Worsening in Untreated	P-Value
US External Control vs. Troriluzole*	**2.4**	0.0359
EU External Control vs. Troriluzole	**6.1**	<0.0001
Global External Control vs. Troriluzole	**4.1**	<0.0001

*prespecified

f-SARA ≥2-point change: represents high, clearly clinically important threshold based on SCA disease progression expected over 3 years

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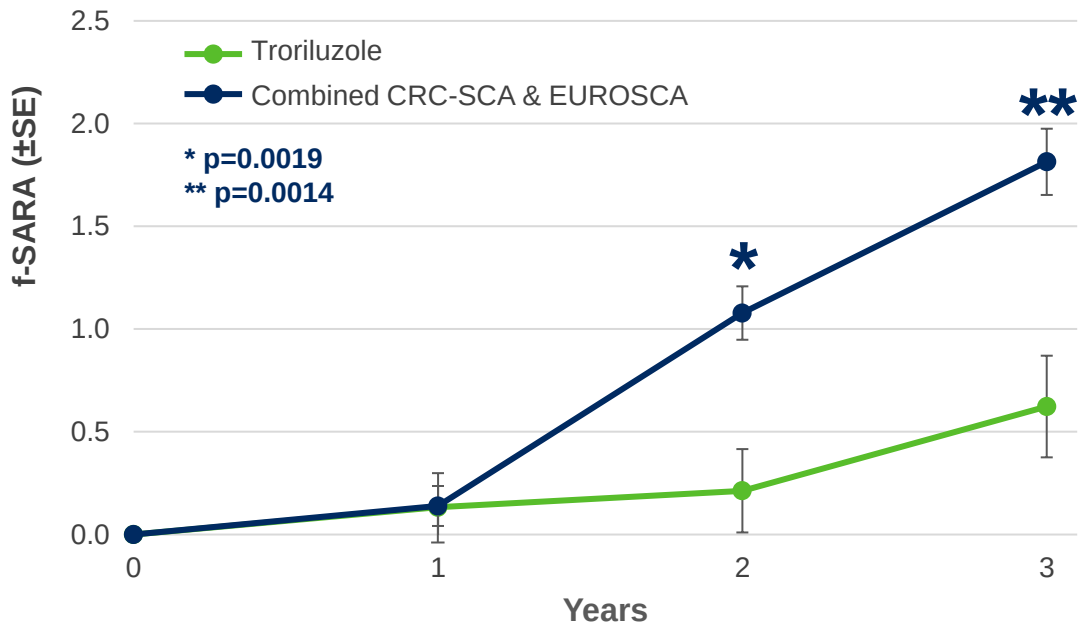
Prespecified Sensitivity Analysis:

External Control Anchored to Year 1 Progression Rate Observed in Study 206 PBO

Treatment Benefit Consistent with Primary Results



External control mimics original placebo arm of RCT with 3-year duration

Addresses non-linear patterns of disease progression and inherent heterogeneity of SCA genotypes

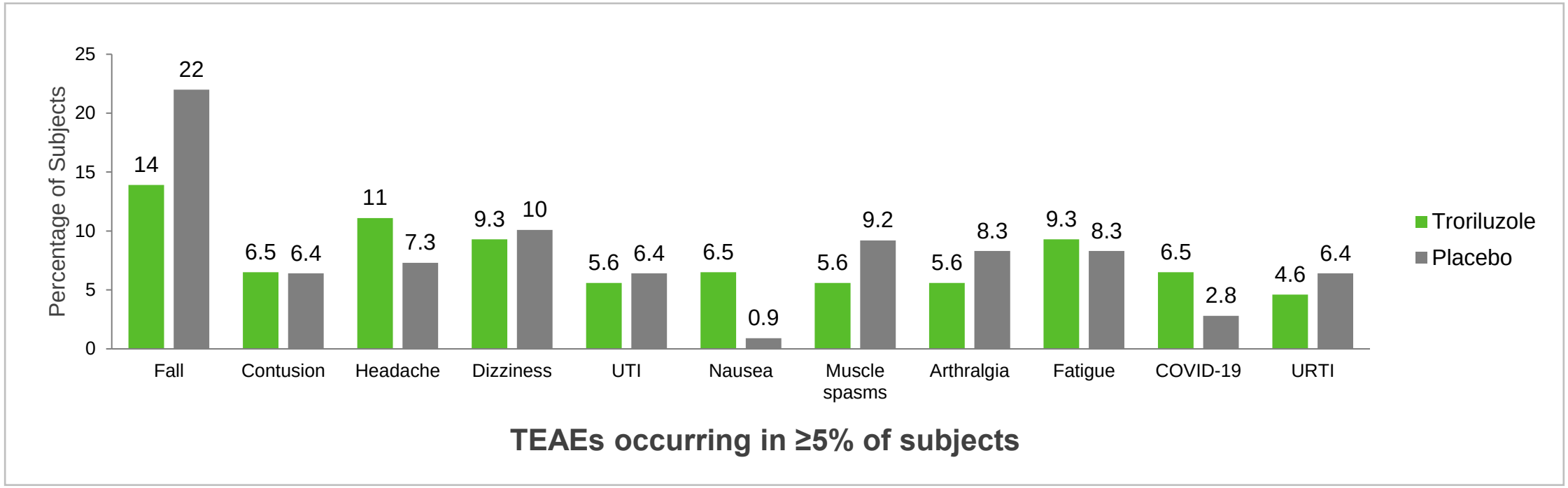
KEY POINT

Consistent Treatment Benefit at Year 2 and Year 3 in Anchored External Control

CRC-SCA, Clinical Research Consortium for SCA; **EUROSCA,** European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM,** least squares mean; **PSM**, Propensity Score Matching

Troriluzole was Well-Tolerated in Clinical Trials

	Troriluzole N=108	Placebo N=109
Serious TEAE	**6 (5.6)**	8 (7.3)
Severe TEAE	**3 (2.8)**	8 (7.3)
TEAE Leading to Discontinuation	**5 (4.6)**	5 (4.6)



Study BHV4157-206 double-blind phase results; falls were captured as adverse events if reported as “worsening falls” or if the fall resulted in an injury. July 2024 datalock.

Troriluzole 200 mg QD dosed orally in patients with SCA

MET THE STUDY'S PRIMARY ENDPOINT

on the change from baseline on the f-SARA at 3 years in all study population genotypes

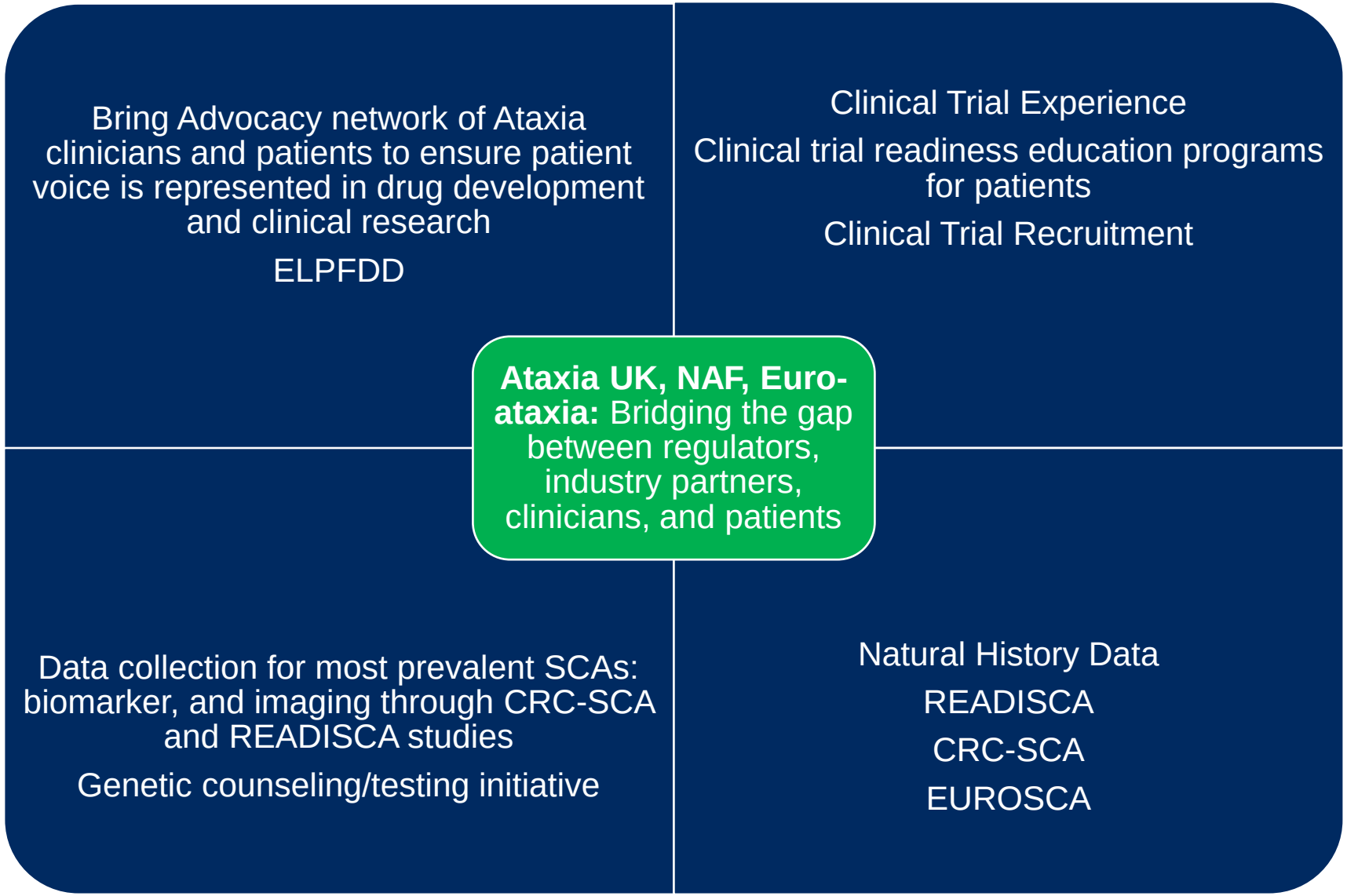
Sustained and clinically meaningful treatment benefit out to 3 years across analyses utilizing 2 large independent natural history external controls

- Troriluzole achieved statistically significant superiority on a total of **9 consecutive, prespecified primary and secondary endpoints**
- SCA patients treated with troriluzole showed a **50–70% slowing of disease progression**, representing 1.5–2.2 years delay in disease progression over the 3-year study period

Large safety database demonstrates troriluzole is well tolerated in SCA

Leveraged RWE from CRC-SCA and EUROSCA as Independent Cohorts

The Importance of Patient Advocacy Groups in Clinical Trial Readiness and Advancing Ataxia Clinical Trials



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Thank you, Euro-ataxia, Ataxia UK, and NAF!