Comparative Effectiveness of Troriluzole versus Untreated Natural History Cohorts in Spinocerebellar Ataxia (SCA) Leveraging Propensity Score Matching Methods

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CONCLUSIONS

1. Compelling and sustained treatment effects were observed out to 3 years when troriluzole-treated subjects were compared to 3 different matched untreated natural history cohorts.
2. This supports that long-term daily dosing of troriluzole attenuates the progression of disease among SCA subjects.
3. This study demonstrates the utility of propensity score matching (PSM) methodology to interpret clinical trial open label extension data, thereby accelerating the development of novel disease modifying therapies for SCA.

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Data Acknowledgment: To preserve participants privacy, raw data for the natural history and troriluzole datasets are not publicly available. Researchers can submit requests for the CRC-SCA data at https://www.ataxia.org/crc-sca/academic-research/ and EUROSCA data at https://www.eurosca.org.

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INTRODUCTION

- Spinocerebellar ataxias (SCAs) are rare, autosomal-dominant, neurodegenerative diseases predominantly characterized by atrophy of the cerebellum, and associated with severe disability and premature death.
- Currently, there are no treatments available for SCA to slow disease progression, and testing novel treatments in clinical trials can be challenging due to low prevalence and disease heterogeneity.
- There is interest in using different strategies to optimize the quality and robustness of clinical trial data to address the urgent need for novel treatments.
- Troriluzole is a third-generation tripeptide prodrug of riluzole that has been compared with placebo in SCA subjects in two studies.
- The pivotal efficacy study (BHV4157-206) included a 48-week placebo-controlled period, followed by a multi-year open-label extension (OLE).

OBJECTIVE To examine the treatment benefits of troriluzole over 3 years in patients with SCA by conducting a matched comparison of troriluzole-treated subjects vs untreated external controls.

METHODS

Study Participants and Data

- Data on troriluzole treatment was obtained from BHV4157-206 (NCT03701399), data from RCT (48-week) and OLE (2-years) periods.
- Study included patients originally randomized to troriluzole.
- Three natural history cohorts were leveraged as comparators:
  - **Clinical Research Consortium for SCA** (CRC-SCA [NCT01060371]): A prospective observational study of approximately 1,000 untreated patients from the US (Data collection from 2010 to the present).
  - **The EUROSCA Natural History Study** (EUROSCA [NCT02440763]): A European longitudinal cohort study (Data used for the current analysis from 2005 to 2009).
  - **CRC-SCA/EUROSCA ("Global") Cohort:** Both datasets were combined to create a Global natural history dataset.
- The modified functional Scale for the Assessment and Rating of Ataxia (f-SARA) was mapped from SARA in the natural history datasets to ensure comparability with BHV4157-206.
- f-SARA scores were compared between troriluzole-treated patients after 3 years of treatment and patients in the natural history datasets.

Statistical Analysis

- The analysis included subjects in study BHV4157-206 with any genotype, randomized to troriluzole, who took at least one dose in the double-blind phase, and contributed to one post-baseline f-SARA score.
- Patient-level natural history data were matched to troriluzole-treated subjects with PSM to create equipoise.
- The PSM used 2:1 matching with CRC-SCA and EUROSCA datasets and 3:1 matching with the Global dataset.
- Matching was done on baseline characteristics: f-SARA, genotype, CAG length, sex, age, and age of symptom onset.
- The between-group least squares mean (LSM) change from baseline (CFB) differences on f-SARA were derived at years 1, 2, and 3.
- Delay in disease progression at 3-years was calculated by dividing the LSM difference in CFB on f-SARA divided by the natural history LSM.

RESULTS

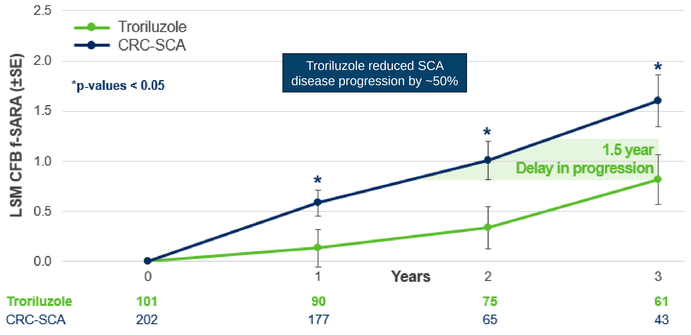
- PSM successfully achieved balance on baseline characteristics across troriluzole and the CRC-SCA and EUROSCA external cohort arm (**Table 1**). Similar results were achieved for the Global external control arms.
- Comparison of 101 troriluzole-treated subjects and 202 CRC-SCA subjects showed LSM differences in f-SARA CFB of -0.45, -0.67, and -0.79 at years 1, 2, and 3, favoring troriluzole (all p<0.005) (**Figure 1**).
- Comparison of 85 troriluzole-treated subjects and 170 EUROSCA subjects (SCA genotypes 1/2/3) showed LSM differences in f-SARA CFB of -0.88, -1.39, and -1.75 at Years 1, 2, and 3, favoring troriluzole (all p<0.0001) (**Figure 2**). Results with the Global natural history cohort were comparable.
- These results correspond to a 50-70% slowing of disease progression (i.e., 1.5 to 2.2 years delay) for troriluzole-treated subjects, compared to the untreated external controls (**Figures 1 & 2**).

Table 1. Demographic and baseline characteristics after PSM adjustment for troriluzole and natural history external control arms

Matching variables	Troriluzole matched to CRC-SCA		Troriluzole matched to EUROSCA	
	Troriluzole	CRC-SCA	Troriluzole	EUROSCA
n	101	202	85	170
Age in years, mean (SD)	48 (13)	49 (11)	48 (13)	48 (14)
Male sex, n (%)	44 (44)	88 (44)	35 (41)	80 (47)
Age in years at symptom onset, mean (SD)	38 (12)	39 (12)	38 (12)	38 (12)
f-SARA, mean (SD)	5 (2)	4.6 (3)	5 (2)	5 (4)
Genotype (%)				
SCA1	15 (15)	33 (16)	15 (18)	39 (23)
SCA2	30 (30)	57 (28)	30 (35)	62 (36)
SCA3	40 (40)	85 (42)	40 (47)	69 (41)
SCA6	5 (5)	10 (5)	-	-
SCA7	5 (5)	4 (2)	-	-
SCA8	3 (3)	11 (5)	-	-
SCA10	3 (3)	2 (1)	-	-
CAG trinucleotide by genotype, mean (SD)				
SCA1	47 (5)	47 (4)	47 (5)	50 (7)
SCA2	40 (3)	40 (3)	40 (3)	40 (4)
SCA3	72 (5)	71 (7)	72 (5)	70 (4)
SCA6	23 (2)	23 (2)	-	-
SCA7	44 (4)	48 (13)	-	-
SCA8	140 (42)	126 (50)	-	-
SCA10	1,744 (252)	1,321 (1684)	-	-

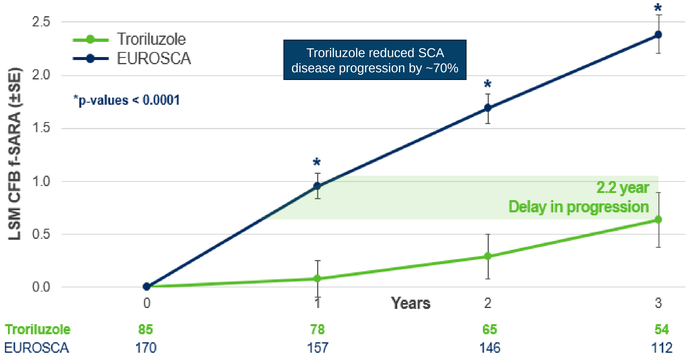
Abbreviations: CRC-SCA, Clinical Research Consortium for SCA; EUROSCA, European Integrated Project on SCAs; f-SARA, Functional Scale for the Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia; SD, standard deviation.

Figure 1. f-SARA Change From Baseline: Troriluzole vs US Natural History External Control



Abbreviations: CFB, Change from baseline; CRC-SCA, Clinical Research Consortium for SCA; f-SARA, Functional Scale for the Assessment and Rating of Ataxia; LSM, least squares mean; SE, Standard error; US, United States.

Figure 2. f-SARA Change From Baseline: Troriluzole vs EU Natural History External Control



Abbreviations: CFB, Change from baseline; EU, European; EUROSCA, European registry of SCA; f-SARA, Functional Scale for the Assessment and Rating of Ataxia; LSM, least squares mean; SE, Standard error.

DISCUSSION

- Troriluzole demonstrated a clinically meaningful treatment benefit out to 3 years across analyses utilizing 2 large independent natural history external controls from the US and Europe.
- Patients treated with troriluzole experienced a 50-70% slowing of disease progression when compared to the untreated external controls.
- This study demonstrated the utility of PSM methodology in cases where clinical trials lack long term comparison to placebo by matching treatment groups to external natural history cohorts.
- This methodology can be used to accelerate the development of novel disease modifying therapies for SCA by increasing the robustness of clinical trial OLE data.