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

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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 (NH) 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) 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 are associated with severe disability and premature death.
- 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.

OBJECTIVE To use propensity score matching to estimate the **effectiveness of troriluzole over 3-years vs an untreated external control group** in patients with SCA.

METHODS

Study Participants and Data

- Data on troriluzole were obtained from BHV4157-206 (NCT03701399), a 48-week double blinded study with 3-year open-label extension.
- Three NH cohorts were leveraged as untreated external controls:
  - **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 NH 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 NH dataset.
- The modified functional Scale for the Assessment and Rating of Ataxia (f-SARA) was mapped from SARA in the NH datasets to ensure comparability with BHV4157-206.
- f-SARA scores were compared after 3-years of treatment between troriluzole-treated subjects and subjects in the NH datasets.

Statistical Analysis

- The analysis included subjects randomized to troriluzole in BHV4157-206 with any genotype, who took at least one dose in the double-blind phase, and contributed to one post-baseline f-SARA score.
- Patient-level NH data were matched to troriluzole-treated subjects using PSM (2:1 for CRC-SCA and EUROSCA, and 3:1 for the Global dataset) based on baseline f-SARA, genotype, CAG length, sex, age, and age of symptom onset.
- Treatment effects at years 1, 2, and 3 were estimated using mixed models for repeated measures (MMRM).
- The least squares mean (LSM) change from baseline (CFB) in f-SARA was assessed at years 1, 2, and 3.
- The percent disease progression delay at 3-years was derived from the LSM difference in CFB on f-SARA (NH – troriluzole), divided by the NH LSM, multiplied by 100%.
- To assess the impact of unmeasured confounders on the estimated treatment effect, the E-value approach was utilized.[1]
- The E-value quantifies the minimum strength of association (with both treatment and outcome) required for unmeasured confounders to nullify an observed treatment effect.

RESULTS

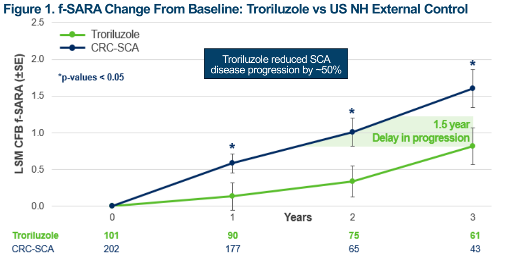
- PSM successfully achieved balance on baseline characteristics across troriluzole and the CRC-SCA and EUROSCA external controls (**Table 1**).
- Comparison of 101 troriluzole-treated subjects and 202 CRC-SCA subjects showed LSM differences in f-SARA CFB of -0.45, -0.67, and -0.79 at years 1, 2, and 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 NH 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 NH external control arms

Matching variables	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)	-	-

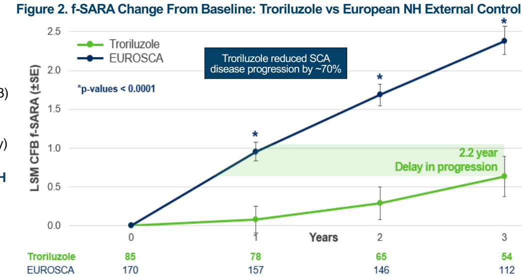
Abbreviations: CRC-SCA, Clinical Research Consortium for SCA; EUROSCA, European Integrated Project on SCAs; f-SARA, Functional Scale for the Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia; SD, standard deviation.

Figure 1. f-SARA Change From Baseline: Troriluzole vs US NH 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; NH, natural history; SE, Standard error; US, United States.

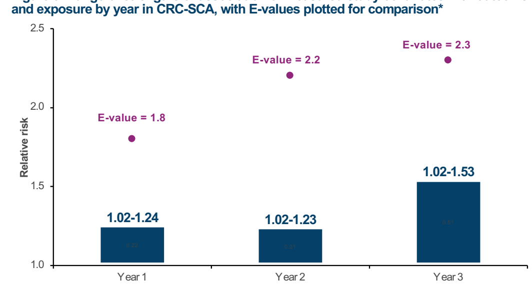
Figure 2. f-SARA Change From Baseline: Troriluzole vs European NH External Control



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

- At year 3, the E-value for a postulated unmeasured confounder was 2.3, suggesting a confounder would need to have a relative risk higher than 2.3 on both treatment and outcome to nullify the treatment effect (**Figure 3**).
  - However, the association of each covariate (sex, SCA 1, 2, 3, age at symptom onset, CAG repeat length) with the outcome and treatment group ranged from 1.02 to 1.53 in magnitude. Thus, an unmeasured confounder is unlikely to explain away the treatment effect.

Figure 3. Range of strengths of association of measured study covariates with outcome and exposure by year in CRC-SCA, with E-values plotted for comparison*



*All relative risk estimates were flipped to be above 1 - directionality to be ignored

DISCUSSION

- Troriluzole demonstrated a clinically meaningful treatment benefit out to 3-years across analyses utilizing 2 large independent NH 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 demonstrates the utility of PSM in cases where clinical trials lack long term comparison to placebo by matching treatment groups to external NH cohorts.
- This methodology accelerates the development of novel disease modifying therapies for SCA by increasing the robustness of clinical trial open label extension data.