Matching-Adjusted Indirect Comparison of Troriluzole versus Untreated Natural History Cohort in Spinocerebellar Ataxia

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Introduction

- Spinocerebellar ataxias (SCAs) are rare, neurodegenerative, debilitating diseases with no effective treatments available to slow disease progression.

- Troriluzole is a glutamate modulator targeting glutamate dysfunction, a hallmark of neurodegeneration in patients with SCA
  - Troriluzole is a prodrug of riluzole designed to improve bioavailability, pharmacokinetics, safety and dosing

- BHV4157-206 (NCT03701399) was a pivotal efficacy trial examining troriluzole vs placebo, consisting of a 48-week double blinded period followed by a 3-year open-label extension.

SCA, spinocerebellar ataxia.

Objective

To understand the treatment effect of troriluzole over 3 years in patients with SCA by conducting a matching-adjusted indirect comparison (MAIC) of troriluzole-treated subjects vs subjects in a pooled natural history cohort

In rare diseases, natural history cohorts can serve as an appropriate external control group to assess treatment effects.

MAIC, match-adjusted indirect comparison; **SCA**, spinocerebellar ataxia.

Methods: Data Sources

Treated subjects

- Troriluzole clinical trial (BHV4157-206; NCT03701399)
  - Subjects eligible for this analysis were between the ages of 18 to 75 years, with genetic confirmation of SCA1, 2, 3, 6, 7, 8, or 10, a screening f-SARA total score of ≥3 and f-SARA gait score of ≥1 (able to ambulate at baseline)
  - Included subjects originally randomized to troriluzole
  - All subjects had opportunity to complete 2-years of treatment

Combined natural history, untreated comparison

- Clinical Research Consortium for the Study of Cerebellar Ataxia (CRC-SCA; NCT01060371)
- European Integrated Project on Spinocerebellar Ataxias (EUROSCA; NCT02440763)
  - Due to the small number of subjects with 3-years longitudinal data, pooling was key to achieving sufficient sample size and statistical power

Clinical care and treatments for SCA are comparable in the US and Europe; thus, pooling of SCA cohorts was feasible and did not result in significant heterogeneity

f-SARA, Modified functional Scale for the Assessment and Rating of Ataxia; **SCA**, spinocerebellar ataxia.

Methods: MAIC

- A matching-adjusted indirect comparison (MAIC) was used to compare the change in ataxia symptoms, as measured by the modified functional Scale for the Assessment and Rating of Ataxia (f-SARA).

MAIC

- Patient-level natural history data were weighted to match baseline characteristics of BHV4157-206 (f-SARA score, genotype, sex, age and age of symptom onset).
- Achieving equipoise ~ analogous to randomization
- MAIC balances covariates in the study populations without sacrificing sample size of the troriluzole-treated patients.

- Analyses were conducted for subjects with any SCA genotype and for the SCA3 genotype.
- Matched data were used to perform the indirect treatment comparison via a mixed models for repeated measures (MMRM).
- The linear regression models included fixed effect covariates for cohort (troriluzole treated vs NatHx), year (1, 2, or 3), cohort by year interaction and baseline f-SARA scores.

f-SARA, Modified functional Scale for the Assessment and Rating of Ataxia; **MAIC**, match-adjusted indirect comparison; **MMRM**, mixed models for repeated measures; **SCA**, spinocerebellar ataxia.

Results: Baseline Demographics

	All SCA genotypes			SCA3 genotype		
	BHV4157-206 (n=96)	Combined natural history (n=611)	p-value	BHV4157-206 (n=38)	Combined natural history (n=205)	p-value
Female, n(%)	53 (55)	321 (53)	0.7058	20 (53)	104 (51)	0.9693
Age, mean (SD)	48.1 (12.9)	49.4 (13.3)	0.3670	47.6 (11.2)	50.3 (11.9)	0.1734
Age at symptom onset, mean (SD)	38.5 (12.5)	39.1 (12.7)	0.6993	40.0 (11.2)	39.3 (11.6)	0.7282
Genotype, n (%)						
SCA1	14 (15)	145 (24)	0.0005	0 (0)	0 (0)	--
SCA2	30 (31)	193 (32)		0 (0)	0 (0)	
SCA3	38 (40)	205 (34)		38 (100)	205 (100)	
SCA6	4 (4)	58 (9)		0 (0)	0 (0)	
SCA7	4 (4)	2 (0)		0 (0)	0 (0)	
SCA8	3 (3)	6 (1)		0 (0)	0 (0)	
SCA10	3 (3)	2 (0)		0 (0)	0 (0)	
Baseline f-SARA, total score, mean (SD)	4.9 (1.6)	4.7 (4.0)	0.3476	4.9 (1.6)	4.8 (4.2)	0.8571
Baseline f-SARA gait score, mean (SD)	1.5 (0.8)	1.6 (1.2)	0.2118	1.6 (0.8)	1.8 (1.4)	0.1916

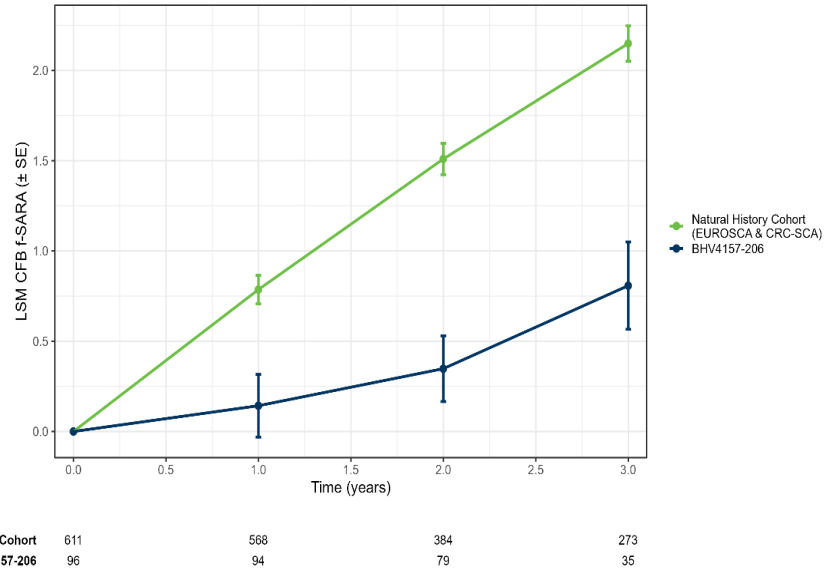
f-SARA, Modified functional Scale for the Assessment and Rating of Ataxia; **SCA**, spinocerebellar ataxia; **SD**, standard deviation.

Results: All SCA genotypes, differences in LS mean change from baseline on f-SARA at years 1, 2 and 3

Results showed treatment benefit for troriluzole subjects vs the natural history cohort for all SCA genotypes over 3 years

		BHV4157-206 (n = 96)	Combined natural history (n = 611)	Difference from combined natural history
Year-1	n	94	568	—
	LS Mean	0.14	0.79	-0.64
	SE	0.174	0.079	0.190
	95% CI	-0.20, 0.48	0.63, 0.94	-1.02, -0.27
	p-value	—	—	0.0008
Year-2	n	79	384	--
	LS Mean	0.35	1.51	-1.16
	SE	0.182	0.087	0.202
	95% CI	-0.01, 0.71	1.34, 1.68	-1.56, -0.77
	p-value	—	—	<0.0001
Year-3	n	35	273	—
	LS Mean	0.81	2.15	-1.34
	SE	0.242	0.099	0.261
	95% CI	0.33, 1.28	1.96, 2.34	-1.85, -0.83
	p-value	—	—	<0.0001

LSM CFB f-SARA score (BHV4157-206 vs Natural History Cohort)
ALL SCA GENOTYPES



At 3-years, the percentage of progression avoided with troriluzole treatment was 62%

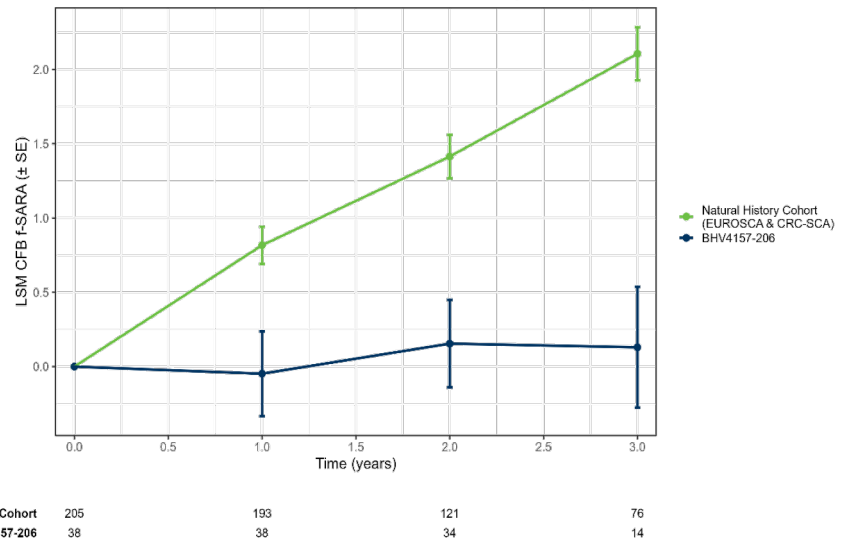
CI, confidence interval; **f-SARA**, Modified functional Scale for the Assessment and Rating of Ataxia; **LS**, least square; **SCA**, spinocerebellar ataxia; **SD**, standard deviation; **SE**, standard error.

Results: SCA3 genotype, difference in LS mean change from baseline on f-SARA at years 1, 2, and 3

Results showed treatment benefit for troriluzole subjects vs the natural history cohort for SCA3 genotype over 3 years

		BHV4157-206 (n = 38)	Combined natural history (n = 205)	Difference from combined natural history
Year-1	n	38	193	--
	LS Mean	-0.05	0.70	-0.75
	SE	0.282	0.137	0.314
	95% CI	-0.60, 0.51	0.43, 0.97	-1.36, -0.13
	p-value	--	--	0.0181
Year-2	n	34	121	--
	LS Mean	0.16	1.27	-1.11
	SE	0.290	0.157	0.330
	95% CI	-0.41, 0.73	0.96, 1.58	-1.76, -0.46
	p-value	--	--	0.0009
Year-3	n	14	76	--
	LS Mean	0.15	2.07	-1.92
	SE	0.386	0.192	0.431
	95% CI	-0.61, 0.91	1.70, 2.45	-2.77, -1.08
	p-value	--	--	<0.0001

LSM CFB f-SARA score (BHV4157-206 vs Natural History Cohort) SCA3



At 3-years, the percentage of progression avoided with troriluzole treatment was 93%

CI, confidence interval; **f-SARA**, Modified functional Scale for the Assessment and Rating of Ataxia; **LS**, least square; **SCA**, spinocerebellar ataxia; **SD**, standard deviation; **SE**, standard error.

Conclusions

- Compelling and sustained treatment effects were observed out to 3-years when troriluzole-treated subjects were compared to a matched untreated natural history cohort.

- These results suggest that long-term daily dosing of troriluzole attenuates the progression of disease among subjects with SCA3 and all SCA genotypes.

Thank you!