Poster P7.019

Development and validation of SCACOMS, a composite scale for assessing disease progression and treatment effects in spinocerebellar ataxia

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CONCLUSIONS

1. Using two natural history datasets, Spinocerebellar Ataxia Composite Scale (SCACOMS) was successfully developed and validated in subjects with spinocerebellar ataxia (SCA).
2. SCACOMS detects ataxia-related functional decline in patients with SCA, and can support development of clinical trials with increased power to detect small but meaningful clinical impacts of disease modifying treatments.
3. Analysis of troriluzole's treatment effect (BHV4157-206) using SCACOMS demonstrates a significant and meaningful reduction in disease progression, favoring troriluzole

References:
1. Klockgether T, Mariotti C and Paulson HL. Spinocerebellar ataxia. Nat Rev Dis Primers 2019: 5:24. doi 10.1038/s41572-019-0074-3. 2. Sullivan R, Yau WY, O'Connor E and Houlden H. Spinocerebellar ataxia: an update. J Neurol 2019: 266:533-44. doi 10.1007/s00415-019-9076-4. 3. Klockgether T, Lüdtke R, Kramer B, Abele M, Bürk K, Schöls L, Riess O, Laccone F, Boesch S and Lopes-Cendes I. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain: a journal of neurology 1998: 121:589-600.

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Data Acknowledgment:
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

- SCA is a rare inherited disorder characterized by progressive ataxia affecting limb coordination, balance, and speech.[1,2]
- While there have been recent developments of disease modifying treatments (DMTs) targeting SCA pathology[1], many have yet to be tested in SCA patients and none have been approved for this population.
- Due to heterogeneity of symptoms in SCA, clinical trial development can be challenging. Existing scales may not capture changes in response to DMTs with sufficient sensitivity over 1-year (a typical timeframe for interventional studies).[3]
- A more sensitive measure of clinical decline derived from existing scales would allow for more robust study design and would enable DMTs to reach SCA patients more efficiently.

OBJECTIVE To **develop a composite scale using natural history datasets to assess disease progression and treatment effects more accurately in patients with SCA.**

METHODS

Study Participants and Data

- The primary analysis was conducted using natural history data from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA; NCT01060371) and from the European Integrated Project on Spinocerebellar Ataxias (EUROSCA; NCT02440763), using patients with SCA3 genotype. Secondary analysis (not reported) repeated the analysis in all SCA genotype.
- Candidate items for SCACOMS included: the Clinical Global Impression of change [CGI], 4 items from the Modified-functional Scale for the Assessment and Rating of Ataxia [f-SARA]) and Friedreich's ataxia rating scale – functional stage (FARS-FUNC) [CRC-SCA only].

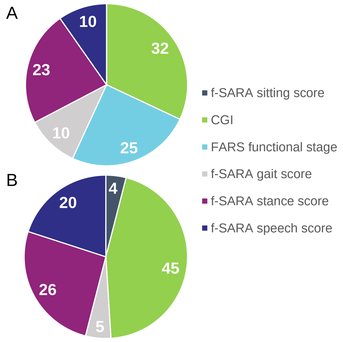
Statistical Analysis

- Sensitivity of individual items to progression in the natural history datasets was assessed using partial least squares (PLS) regression, with responsive items objectively selected and summed to create SCACOMS; item weights reflected sensitivity to decline.
- Scales were assessed for ability to detect disease progression using mean-to-standard deviation ratios (MSDR).
- SCACOMS were applied to data from BHV4157-206, a 48-week study evaluating troriluzole in SCA subjects (NCT03701399) to measure treatment effects (between group differences in mean change from baseline, least squared mean [LSM]).

RESULTS

- Baseline demographics of the natural history datasets are provided in **Table 1.**
- Using PLS regression, the CGI, FARS-FUNC, and f-SARA gait, speech, and stance items were selected for inclusion **(Table 2)**. Relative weightings of scale items are visualized in **Figure 1**.
- Improved sensitivity (e.g., increased MSDR) was observed for SCACOMS scales as compared to the original scale(s).
- Consistent results were found in the analysis of EUROSCA. With the absence of FARS-FUNC, the other items were distributed similarly, with CGI accounting for ~1/2 of the total score.
- Cross-validation between the natural. history sets yielded similar MSDRs, further supporting their validity.

Figure 1 Relative weightings (%) of scale items in SCACOMS for SCA3 patients, (A) CRC-SCA and (B) EUROSCA models



RESULTS

Table 1 Descriptive data for the CRC-SCA analytic dataset and EUROSCA analytic dataset used to derive SCACOMS

Baseline characteristic	CRC-SCA		EUROSCA	
	ALL SCA (n = 214)*	SCA3 (n = 77)*	ALL SCA (n = 423)*	SCA3 (n = 106)*
Age, mean (SD) years	52.3 (13.4)	51.3 (12.5)	47.3 (12.7)	50.3 (11.5)
Sex, % female	54.2	57.1	53.9	52.8
Genotype, %				
SCA1	18.2	0.0	23.9	0.0
SCA2	20.1	0.0	31.9	0.0
SCA3	35.5	98.7	25.1	100.0
SCA6	22.4	0.0	19.1	0.0
SCA8	2.3	0.0	0.0	0.0
SCA10	0.9	0.0	0.0	0.0
SCA3 and SCA8	0.5	1.3	0.0	0.0
f-SARA gait score, mean (SD)	1.5 (1.1)	1.4 (1.1)	1.6 (1.2)	1.9 (1.4)
f-SARA stance score, mean (SD)	1.3 (1.1)	1.3 (1.1)	1.5 (1.3)	1.4 (1.3)
f-SARA speech score, mean (SD)	0.7 (0.9)	0.4 (0.7)	1.1 (1.0)	0.9 (1.1)
f-SARA sitting score, mean (SD)	0.5 (0.8)	0.5 (0.7)	0.8 (1.0)	0.9 (1.1)
FARS functional stage, mean (SD)	2.8 (1.0)	2.9 (0.9)	NA	NA
CGI, mean (SD)	NA	NA	NA	NA

*Subjects in the analytic dataset were required to have baseline and either 12- or 24-months values on the measures of interest
CGI, Clinical Global Impression - Global Improvement Scale; CRC-SCA, Clinical Research Consortium for the Study of Cerebellar Ataxia; EUROSCA, European Integrated Project on Spinocerebellar Ataxias; FARS, Friedreich ataxia rating scale; f-SARA, Modified functional Scale for the Assessment and Rating of Ataxia; NA, not available; SCA, spinocerebellar ataxia; SD, standard deviation

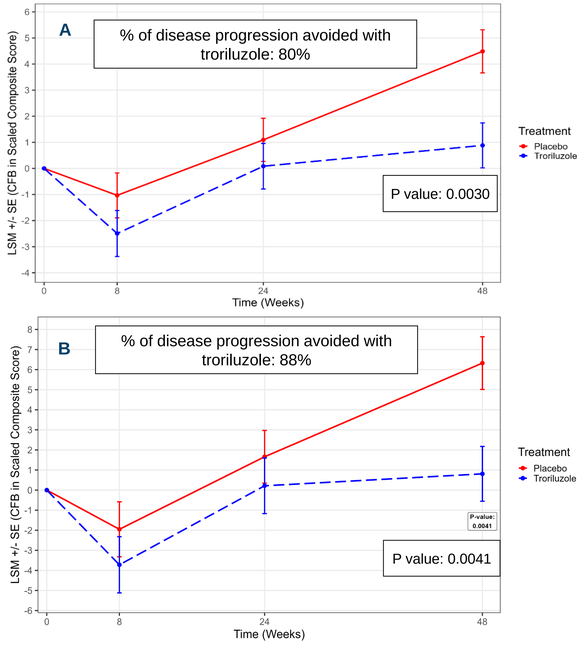
Table 2 VIP scores and PLS coefficients for SCA3 patients, CRC-SCA and EUROSCA models

Item	Item MSDR*	VIP	PLS weight	% contribution
SCA3 patients, CRC-SCA dataset (N=77)				
f-SARA gait score	0.4604	0.6417	4.5390	10.45
FARS functional stage	0.1688	0.4741	10.8056	24.87
f-SARA stance score	0.2683	1.0522	9.9743	22.95
f-SARA speech score	0.2614	0.4952	4.2284	9.73
f-SARA sitting score	0.2538	Removed	0.0000	--
CGI	0.9125	1.7353	13.9060	32.00
SCACOMS MSDR	**0.9171**			
SCA3 patients, EUROSCA dataset (N=106)				
f-SARA gait score	0.2952	0.6718	2.5315	4.83
FARS functional stage	--	--	--	--
f-SARA stance score	0.5629	1.0763	13.5141	25.76
f-SARA speech score	0.2320	0.6486	10.7757	20.54
f-SARA sitting score	0.3056	0.5132	2.0793	3.96
CGI	1.0742	1.645	23.562	44.91
SCACOMS MSDR	**1.1157**			

CGI, Clinical Global Impression - Global Improvement Scale; CRC-SCA, Clinical Research Consortium for the Study of Cerebellar Ataxia; EUROSCA, European Integrated Project on Spinocerebellar Ataxias; FARS, Friedreich ataxia rating scale; f-SARA, Modified functional Scale for the Assessment and Rating of Ataxia; MSDR, mean to standard deviation ratio; PLS, partial least squares; SCA, spinocerebellar ataxia; VIP, Variable Importance of Projection
*The MSDR of changes in total f-SARA score was 0.4826.

- Examination of SCACOMS treatment effects at 48-weeks in BHV4157-206 SCA3 subjects (n=85) showed a statistically significant treatment effect in subjects, favoring troriluzole **(Figure 2)**.
- The percentage of progression avoided was 80% for the CRC-SCA derived model, Cohen's d of 0.56; and 88% for the model derived from EUROSCA subjects, Cohen's d of 0.59 **(Figure 2)**.

Figure 2 SCACOMS outcomes in BHV4157-206 SCA3 subjects using the (A) CRC-SCA model and (B) EUROSCA model



DISCUSSION

- The overall MSDRs indicated that SCACOMS endpoints were highly sensitive to detecting progression and showed an improvement in responsiveness when compared to the original component scales.
- Application of SCACOMS to analysis of data from the BHV4157-206 study, SCA3 genotype subpopulation, yielded compelling and consistent treatment effects across CRC-SCA and EUROSCA composite score models at 48-weeks.
- This study highlights the potential usefulness of SCACOMS for clinical and research purposes. The availability of a scale that detects small but meaningful changes in disease progression and treatment effects will lead to more efficient trial design and support the development of novel DMTs for patients with SCA.