Comparison of Two Matching Methods to Assess Effectiveness of Troriluzole versus Untreated Natural History Cohort in Spinocerebellar Ataxia

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Disclosures

- **Michele Potashman is an employee of and owns stocks/options in Biohaven Pharmaceuticals**
- Melissa Beiner, Victoria Wirtz, Gil L'Italien, and Vlad Coric are employees and stockholders of Biohaven Pharmaceuticals, Inc.
- Basia Rogula and Lauren Powell are employees of Broadstreet Health Economics and Outcomes Research, which received funding from Biohaven for conduct of this work.
- Suzan Perlman has nothing to disclose.
- Jeremy Schmahmann has served on the editorial board for *The Cerebellum*, Editorial Board, 1999. Consultancy: Biohaven Pharmaceuticals, Inc. Site Principal Investigator: Biohaven Pharmaceuticals, Inc. clinical trials in ataxia and multiple system atrophy. Research support, commercial entities: Biohaven Pharmaceuticals, Inc. support of clinical trials. Research support, academic entities: National Ataxia Foundation. Research support, foundations, and societies: National Ataxia Foundation, 2019, Principal Investigator license fee payments. Technology or inventions: Brief Ataxia Rating Scale (BARS) and Brief Ataxia Rating Scale revised (BARS2). Copyright held by The General Hospital Corporation. Cerebellar Cognitive Affective/Schmahmann syndrome Scale. Copyright held by The General Hospital Corporation. Patient-Reported Outcome Measure of Ataxia. Copyright held by The General Hospital Corporation. Cerebellar Neuropsychiatric Rating Scale. Copyright held by The General Hospital Corporation.
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Overview

- Background/objectives
- Methods
- Results
- Conclusions

Background/Objectives

BHV4157-206 (NCT03701399) is a pivotal efficacy trial examining troriluzole in patients with spinocerebellar ataxia (SCA), consisting of a randomization period followed by open-label extension

The objective of this analysis was to estimate the effectiveness of troriluzole vs an external natural history (NH) control group over 3-years, comparing results obtained using two methodologies:

1) matching-adjusted indirect comparison (MAIC)

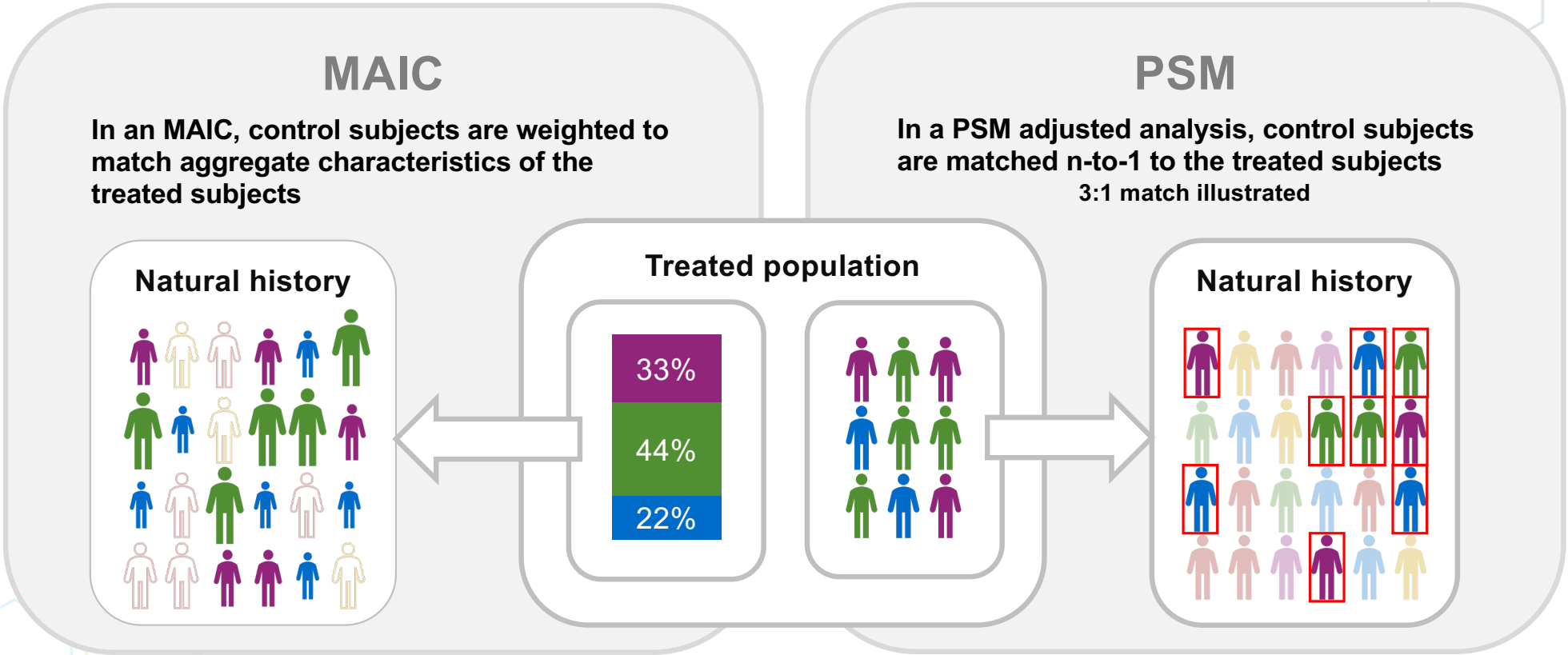
2) propensity score matching (PSM)

Methods

- When randomization did not occur and an indirect comparison is of interest, balance between "Treated" and "External Control" groups *must* first be achieved (e.g., adjusted comparison)
- Methods for population-adjusted indirect comparisons can use individual patient data (IPD) from the External data sources to achieve balance among variables that influence the outcome.*
  - In a MAIC, IPD from the External data source can be weighted to generate a cohort that achieves balance on each individual baseline variable (Treated summary statistics).†
    - Subjects (IPD) from the external control contribute varying weights to enable the creation of the matched cohort to mean values from Treated. "Closer" patients contribute higher weights.
  - PSM is based on the concept of 'propensities', the conditional probability of an individual being sampled into a group, given their covariate values.* PSM is based on logistic propensity score models of the IPD for Treated, which then takes the IPD from External to construct the cohort with the optimized match.
    - PSM requires IPD from both data sources, and matches patients based on these propensity scores.

*Phillippo DMA, A.E.; Dias, S.; Palmer, S.; Abrams, K.R.; Welton, N.J. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. http://www.nicedsu.org.uk/.
†Signorovitch 2012, doi: https://doi.org/10.1016/j.jval.2012.05.004

Methods


MAIC
In an MAIC, control subjects are weighted to match aggregate characteristics of the treated subjects
PSM
In a PSM adjusted analysis, control subjects are matched n-to-1 to the treated subjects
3:1 match illustrated
Natural history
Treated population
33%
44%
22%
Natural history

Methods - Analysis

An MAIC was conducted by selecting and weighting individual patient-level NH data to create a cohort matched to troriluzole-treated subjects based on several key baseline characteristics.

For PSM, the same characteristics were analyzed via logistic regression to estimate a propensity score for each patient that was then used to match NH to troriluzole treated patients and at a ratio of 3 to 1.

The between-group least squares (LS) mean change from baseline (CFB) differences on f-SARA were derived at years 1, 2, and 3 to estimate troriluzole effectiveness.

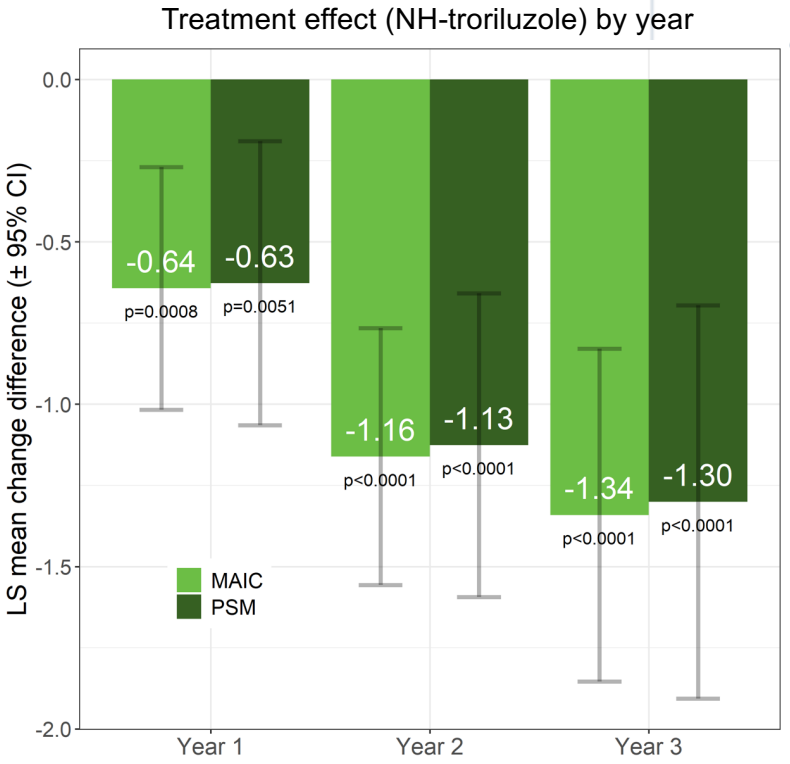
Results

Baseline characteristics of the troriluzole-treated and natural history subjects before and after matching

	Troriluzole-treated subjects (n=96)	Natural history		
		Before matching (n=611)	MAIC (n=611) ESS = 323.8	PSM (n=288)
Female %	55.2	52.5	55.2	58.7
Mean age	48.1	49.4	48.1	49.0
Age at symptom onset, mean (SD)	38.5	39.1	38.5	40.0
Genotype, n (%)				
SCA1	14.6	23.7	14.6	16.3
SCA2	31.2	31.6	31.2	27.1
SCA3	39.6	33.6	39.6	44.8
SCA6	4.2	9.5	4.2	8.3
SCA7	4.2	0.3	4.2	0.7
SCA8	3.1	1.0	3.1	2.1
SCA10	3.1	0.3	3.1	0.7
Mean baseline f-SARA, total score	4.9	4.7	4.9	5.2

Results

- A total of 96 troriluzole-treated subjects and 611 untreated NH subjects were the basis for the analysis.
- LS mean change differences in f-SARA were favoring troriluzole at all years and statistically significant (all p<0.01):
  - At Year 1: -0.64 (MAIC) and -0.63 (PSM)
  - At Year 2: -1.16 (MAIC) and -1.13 (PSM)
  - At Year 3: -1.34 (MAIC) and -1.30 (PSM)
- Comparison with MAIC or PSM both demonstrated greater ataxia-related impairment and clinical decline amongst the NH cohort when compared to troriluzole-treated subjects.



	Baseline	Year 1	Year 2	Year 3
Natural History (MAIC/PSM)	611/288	568/264	384/180	273/111
Troriluzole	96	94	79	35

Conclusions

- Compelling and sustained treatment effects over 3 years were observed when troriluzole-treated subjects were compared to an untreated matched NH cohort
- Results were consistent across MAIC and PSM methodologies