Modeling a long-term virtual placebo arm for the SPMS population in the EXPAND study: Comparing different statistical methods

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Disclosures

Bruce A.C. Cree has received personal compensation for consulting from Abbvie, Akili, Alexion, Biogen, EMD Serono, Novartis, Sanofi Genzyme, and TG Therapeutics.

Robert J. Fox has received personal consulting fees from Actelion, Biogen, Celgene, EMD Serono, Genentech, Immunx, Novartis, Sanofi, Teva, and TG Therapeutics. He has served on advisory committees for Actelion, Biogen, Immunx, and Novartis, and received clinical trial contract and research grant funding from Biogen and Novartis.

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Gavin Giovannoni is a steering committee member on the daclizumab trials for Abbvie, the BG12 and daclizumab trials for Biogen, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva, and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck KGaA, Sanofi Genzyme, and in relation to DSMB activities for Synthorx BV, as well as honoraria for speaking at the Physicians’ summit and several medical education meetings. He is also the co-chief editor of Multiple Sclerosis and Related Disorders (Elsevier).

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Background and objective

- EXPAND is a randomized, double-blind, parallel-group, placebo-controlled, event-driven Phase 3 trial in a broad range of SPMS patients that evaluated the efficacy and safety of siponimod (EXPAND-Core).
- At the end of EXPAND-Core, patients were offered a switch to open-label siponimod in the ongoing EXPAND-Extension allowing follow-up for up to an additional 7 years.
- In the EXPAND-Core, siponimod significantly reduced the risk of disability progression versus placebo.
- Since at the end of the Core period, patients randomized to placebo switched to siponimod in the Extension, assessment of the long-term effect of siponimod versus placebo on confirmed disability progression was not possible.
- Modeling of the long-term trajectory of patients initially randomized to placebo as if they had never switched to siponimod was undertaken.

Objective

To explore 3 different statistical methods to estimate the long-term effect of siponimod versus placebo by modeling a placebo treatment arm corrected for switch at the end of EXPAND-Core.

SPMS, secondary progressive multiple sclerosis.

Methods: Modeling strategies

- **Rank Preserving Structural Failure Time (RPSFT) model**\(^1\-\(^3\)
  - Use of the actual time to 6mCDP in those who switched treatment to compute a hypothetical time to 6mCDP as if they had never switched
  - Most commonly used in oncology studies
- **Two-stage method**\(^1\,\(^2\)
  - Simulate the hypothetical time from the switch to 6mCDP based on data from the Core period data as if patients had never switched
- **Weibull distribution**\(^1\,\(^2\)
  - A parametrical model to extrapolate a placebo survival curve

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The RPSFT model seems to provide the most accurate estimate for time to 6mCDP while making use of the totality of the information, including time to 6mCDP collected after treatment switch.

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*Extension data cut-off: April 2019 (Month 36 visit of extension); total study duration (core + extension): ≤5 years
6mCDP, 6-month confirmed disability progression; EDSS, Expanded Disability Status Scale; EoCP, end of core part; N, total number of patients; MRI, magnetic resonance imaging; RPSFT, Rank Preserving Structural Failure Time; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis
Methods: RPSFT

Estimating time to 6mCDP after the switch by shrinking the observed time after the switch

- The RPSFT method represents a SNM approach designed specifically for an RCT context as it provides a randomization-based treatment effect estimator
  – Assumes that treatment effect is the same regardless of when the experimental treatment is initiated

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6mCDP, 6-month confirmed disability progression; RCT, randomized controlled trial; RPSFT, Rank Preserving Structural Failure Time; SNM, structural nested models

**Results**

*Simulated time to 6mCDP for the placebo-treated patients switching to siponimod*

The RPSFT model produces a reasonable shape of the curve with a HR consistent with effect reported in the Core part of the study.

<table>
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<tr>
<th>Time (Months)</th>
<th>Placebo-siponimod</th>
<th>Siponimod</th>
<th>RPSFT corrected placebo</th>
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**Proportion of patients with 6mCDP based on the EDSS score**

HR (95% CI)

- ITT analysis (no correction): 0.78 (0.66; 0.92)
- RPSFT: 0.69 (0.53; 0.90)

6mCDP, 6-month Confirmed Disability Progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan-Meier; RPSFT, Rank Preserving Structural Failure Time
Conclusions and limitations

**Conclusions**

- The results support the applicability of RPSFT to model a virtual placebo arm in the long-term in an SPMS population.
- Results from the RPSFT model suggest a long-term benefit of siponimod over placebo with a preserved hazard ratio on 6mCDP and ~50–60% prolongation of time to 6mCDP.
- Accuracy of RPSFT is supported by simulations conducted under conditions similar to the EXPAND study, which included waning and increasing treatment effects.

**Limitations**

- Although simulation work showed robustness of the RPSFT model, it is not possible to verify the accuracy of the prediction with the study data.
- Validation with external real world data may help to further confirm the utility of this model.
Thank you