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

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Background

Siponimod significantly reduced the risk of 3-/6-month confirmed disability progression (3m/6mCDP) vs placebo by 21% and 26%, respectively in patients with secondary progressive multiple sclerosis (SPMS), during the core part of the EXPAND study. 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; therefore, a long-term comparison between siponimod and placebo was not possible and a modeling for the placebo long-term trajectory was proposed using different statistical methodology.

Objectives

To estimate the long-term effect of siponimod versus placebo by modeling placebo treatment corrected for switch at the end of EXPAND-Core.

Methods

In the EXPAND-Extension part, 6mCDP was analyzed to assess disability. Time to 6mCDP to account for the switch to siponimod in placebo-treated patients was modeled by 3 methods: 1) Rank Preserving Structural Failure Time (RPSFT) model that uses the actual time to 6mCDP for switchers to compute a hypothetical time to 6mCDP as if they had never switched; 2) simulating the hypothetical time from the switch to 6mCDP based on core part data as if patients had never switched (Two-stage method); and 3) a parametrical model (Weibull distribution) to extrapolate a placebo survival curve.

Results

As of 6 April 2019, 878 patients (siponimod, n=593; placebo-siponimod switch, n=285) were still ongoing in the EXPAND-Extension. All 3 methods confirmed the long-term effect of siponimod vs placebo in the EXPAND population. The RPSFT model seems to provide the more accurate estimate for time to 6mCDP (hazard ratio [95% confidence interval]: 0.69 [0.53; 0.90]) vs the Two-stage (0.76 [0.64; 0.92]) and Weibull modeling methods (0.58 [0.49; 0.67]). The RPSFT results were indicative of a persistent treatment effect over 5 years with a ~50–60% increase in the time to 6mCDP in siponimod vs placebo-corrected switch (median time to 6mCDP: 42.5 months for placebo-corrected switch as opposed to 51.7 months for uncorrected placebo; median not reached with siponimod). Accuracy of RPSFT is supported by simulations conducted under conditions similar to the EXPAND study, which included waning and increasing treatment effects, that found very low difference between the true hazard ratio and the hazard ratio obtained with RPSFT.

Conclusions

The results support the reliability of RPSFT to model a virtual placebo arm in the long-term in a SPMS population. RPSFT results confirmed a long-term benefit of siponimod over placebo with a preserved hazard ratio on 6mCDP and ~50–60% prolongation of time to 6mCDP.

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