P745

Estimating Long-Term Effect of Siponimod on Disability Progression versus Virtual Placebo in SPMS Using RPSFT Model: EXPAND Data Up to 7 Years

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Introduction

- In the core part of the Phase 3 EXPAND study, siponimod significantly reduced the risk of 6-month confirmed disability progression (6mCDP) versus placebo by 26% in patients with secondary progressive multiple sclerosis (SPMS)[1]
- In the long-term analysis (up to 5 years: data cut-off of April 2019) including data from the core and ongoing EXPAND-extension, the risk of 6mCDP was reduced by 22% and the time to 6mCDP was prolonged by 49% in the continuous siponimod group versus placebo-siponimod group[2]
- Long-term comparison of siponimod with placebo was not possible since placebo patients transitioned to open-label siponimod at the end of EXPAND core study (median duration of core part 21 months)
- Modelling of the long-term trajectory of patients initially randomised to placebo (virtual placebo) using Rank Preserving Structural Failure Time (RPSFT) was undertaken and then compared with long-term continuous siponimod group
  - In a previous analysis modelling a placebo treatment arm corrected for switch by RPSFT analysis in the overall SPMS population, the risk of 6mCDP in the continuous siponimod group was reduced by 31% (hazard ratio [HR]: 0.69, cut-off of April 2019) versus modelled placebo group and the time to 6mCDP was prolonged by ~50%–60%[3]
  - Different models were tested but only the RPSFT model produced predictions in a range consistent with the HR reported in the core part of the study. The accuracy and applicability of the RPSFT model to model a virtual placebo arm in the long term was further supported by simulations (for placebo patients after switching to siponimod) conducted under conditions similar to the EXPAND study, which included waning and increasing treatment effects[3]

Objective

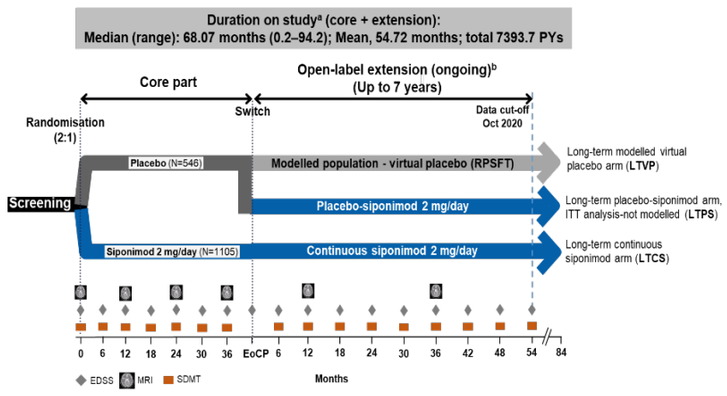
- To present the long-term efficacy of continuous siponimod versus virtual placebo using the RPSFT model and uncorrected placebo-siponimod switch intent-to-treat (ITT) analysis in the overall SPMS population as well as in the active and non-active subgroups from the core and extension parts of the EXPAND study with up to 7 years of follow-up

Methods

- The analysis included overall EXPAND SPMS population who received ≥1 dose of siponimod in the core study (ITT population)[1] and offered a switch to open-label siponimod in the ongoing extension (data cut-off: October 2020) for up to 7 years
- The long-term trajectory of placebo was estimated using the RPSFT model, a method that adjusts for treatment switch in trials with survival outcomes[4-6]
- In the present analysis, patients were grouped into the following (Figure 1):
  - Long-term continuous siponimod (LTCS) arm who received siponimod during the core and extension parts
  - Long-term placebo-siponimod arm (LTPS) who received placebo in the core and siponimod in the extension (ITT analysis, not modelled – 'uncorrected')
  - Long-term virtual placebo (LTVP) arm modelled ('corrected') by RPSFT method[3]
- Data were analysed in the overall population (siponimod [N=1105], placebo [N=546]) and in the subgroups of patients with active[a] (siponimod [N=400], placebo-siponimod [N=182]) and non-active[b] (siponimod [N=405], placebo-siponimod [N=207]) subgroups

[a]Defined as the presence of at least one relapse in the 2 years before screening and/or ≥1 gadolinium-enhancing (Gd+) T1 lesion at baseline; [b]Defined as no relapse in the 2 years prior to screening and no Gd+ T1 lesion at baseline.

Figure 1 Study design



[a]Extension data cut-off: Oct 2020 (Month 54 visit of extension]; total study duration (core+extension): up to 7 years; [b]Open-label starts when patient has an "event".
EDSS, Expanded Disability Status Scale; EoCP, end of core part; PYs, patient years; MRI, magnetic resonance imaging; N, total number of patients (safety set); RPSFT, Rank Preserving Structural Failure Time; SDMT, Symbol Digit Modalities Test

Outcomes

- Time to 6mCDP based on the Expanded Disability Status Scale (EDSS) score in the continuous siponimod (LTCS) versus placebo-siponimod arm modelled (LTVP) and ITT analysis-not modelled (LTPS) arms

Statistical analysis

- For both ITT and RPSFT analysis, the time to 6mCDP was analysed using a Cox proportional hazards model with treatment, country/region, baseline EDSS score and SPMS group (with-/without superimposed relapses, baseline definition) as covariates using combined EDSS data from the core and extension parts
- In the RPSFT analysis, patients randomized to placebo and crossing over to open-label siponimod were replaced by their counterfactual time to CDP without cross over based RPSFT model, e.g. modelling ('correcting') as if they had never switched to siponimod

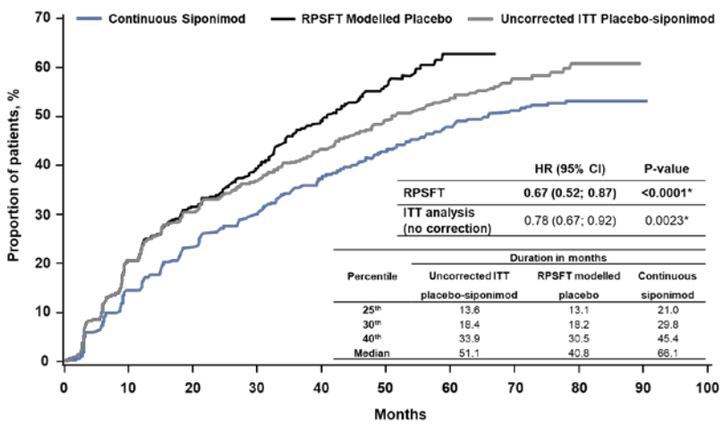
Result

Time to 6mCDP in the LTCS versus LTVP arms:

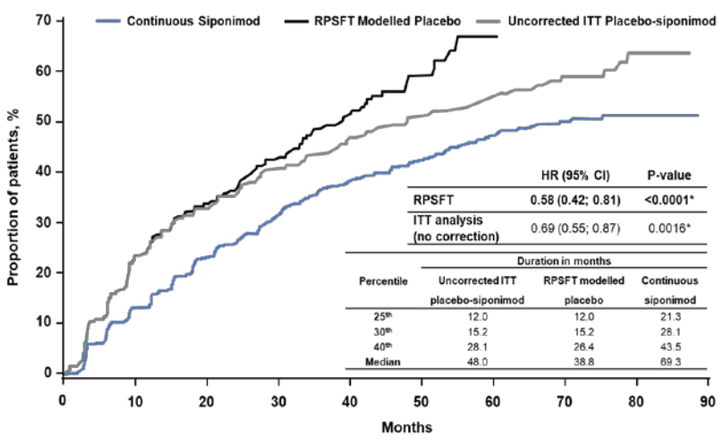
- **Overall population:** The risk of 6mCDP was reduced by 33% (p<0.0001) and the median time to 6mCDP was prolonged by 62% (**Figure 2a**)
- **Active SPMS population:** The risk of 6mCDP was reduced by 42% (p<0.0001) and the median time to 6mCDP was prolonged by 79% (**Figure 2b**)
- **Non-active SPMS population:** The risk of 6mCDP was reduced by 20% (p=0.0534) and the median time to 6mCDP was prolonged by 44% (**Figure 2c**)

Figure 2 Time to 6mCDP in LTCS versus LTVP and LTPS in (a) overall SPMS population, (b) active SPMS and (c) non-active SPMS subgroups

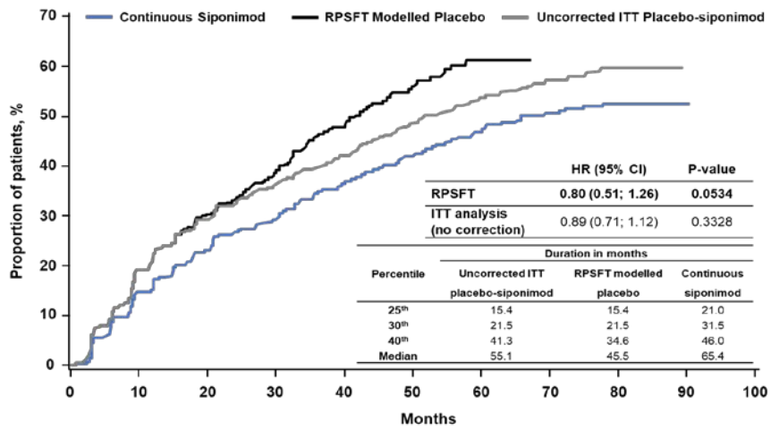
a) Overall SPMS population



b) Active SPMS subgroup



c) Non-active SPMS subgroup



*Indicates statistical significance (2-sided) at the 0.05 level.
6mCDP, 6-month confirmed disability progression; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LTCS, long-term continuous siponimod; LTPS, long-term placebo-siponimod (IIT analysis-not modelled); LTVP, long-term modelled virtual placebo; RPSFT, Rank Preserving Structural Failure Time; SPMS, secondary progressive multiple sclerosis

Conclusions

- This analysis confirmed the sustained efficacy of continuous siponimod up to 7 years in significantly reducing the risk of progression and prolonging the time to 6mCDP versus both modelled virtual placebo and placebo-siponimod switch ITT analysis (not modelled placebo-siponimod arm) in the overall SPMS patients
- In the active SPMS subgroup, the effect of siponimod on disability progression was more pronounced and sustained for up to 7 years
- In the non-active SPMS subgroup, a sustained strong trend favouring continuous siponimod was observed; longer time to 6mCDP in the placebo arm compared with the placebo arm in the active SPMS subgroup suggests longer observation periods are required to uncover the full impact of treatment in non-active SPMS subgroup
- RPSFT virtual placebo arm can be used to estimate the long-term treatment benefits of siponimod in reducing disability progression
- One limitation of this analysis is that it assumes an attrition (before observing the 6mCDP) which is balanced between treatment arms. Given that all patients are currently receiving open-label siponimod, this assumption is reasonable

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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 Synthon 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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