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

Bruce A.C. Cree1, Nicolas Rouyrre2, Robert J. Fox3, Patrick Vermeesch4, Gavin Giovannini5, Amit Bar-Or6, Ralf Gold7, Jeff Maca8, Daniela Piani-Meier9, Goeril Karlsson2, Ludwig Kappos9

1UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, CA, USA; 2Novartis Pharma AG, Basel, Switzerland; 3Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland, OH, USA; 4Univ. Lille, Inserm U1172, LIICog, CHU Lille, FUH Preque, Lille, France; 5Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; 6Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, PA, USA; 7Department of Neurology, St. Joseph-Hospital/Ruhr-University Bochum, Bochum, Germany; 8Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 9Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NBD), Departments of Medicine, Clinical Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland

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 compared to placebo group2

• 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 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, data cut-off of April 2019) versus modelled placebo group and the time to 6mCDP was prolonged by ~50%–60%2

• 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 effects3

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 populations and non-active subgroups from the core and extension parts of the EXPAND study 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 and survival outcomes4

• In the previous analysis, patients were grouped into the following (Figure 1):
  - Long-term continuous siponimod (LTCS) arm who received siponimod during the core and extension part
  - 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 (LTPV) arm modelled (‘corrected’) by RPSFT method

• Data were analysed in the overall population (siponimod [N=1105], placebo [N=546]) and in the subgroups of patients with a confirmed relapse (i.e., siponimod [N=400], placebo-siponimod [N=182] and non-active [i.e., siponimod [N=405], placebo-siponimod [N=207])

Figure 1 Study design

- 'Uncorrected data cut-off: Oct 2020 (Morris et al of evidence; trial study duration [extension-0] up to 7 years; 'censored data when patients switch to placebo' =EDSS, Expanded Disability Status Scale, EXC22, end of core part: 21 yrs, patient-years; 94% clinical time was modeled using RPSFT, hence RPSFT was not validated for CDP without superimposed relapses, baseline definition as covariates using EDSS data from the core and extension parts

- In the RPSFT analysis, patients who switched to placebo and crossing over to open-label siponimod were replaced by their counterfactual time to CDP if data cut-off was the same as observed for RPSFT model, e.g. modelling (‘correcting’) as if they had never switched to siponimod

Result

Time to 6mCDP in the LTCS versus LTPV 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 69% (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)

Outcomes

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

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

a) Overall SPMS population

- Continuous Siponimod (LTCS) arm modelled (‘corrected’) by RPSFT method

b) Active SPMS subgroup

- Active SPMS population

- Non-active SPMS subgroup

- Non-active SPMS subgroup

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 compared to 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

On 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

References


Disclosures

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Patrick Vermersch is an employee of Novartis and may hold stocks of Novartis.

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