Dynamics of progression to wheelchair in SPMS and impact of siponimod: Subgroup analyses from the EXPAND study

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- RG has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He, or the institution he works for, has received research support from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He has also received honoraria as a Journal Editor from SAGE and Thieme Verlag
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- SAr, SAn, DPM, GK and NR are employees of Novartis

Introduction

- Worsening of ambulation is a hallmark of SPMS, eventually leading to wheelchair dependence (EDSS score ≥7.0)
- Ambulation was impaired in the EXPAND population, with 56% of patients requiring the use of walking aids at baseline (EDSS score 6.0 or 6.5)
- In the Phase 3 EXPAND core study, siponimod significantly reduced the risk of 3mCDP and 6mCDP, and showed clinically meaningful benefits in cognitive processing speed on the SDMT as well as improvements in MRI measures related to neurodegeneration (grey matter atrophy and magnetisation transfer ratio) versus placebo

Objective

To evaluate the effect of siponimod on time to wheelchair versus placebo in patients with SPMS, including subgroups of active and non-active SPMS*

*Active SPMS was defined as the presence of one or more relapses in the 2 years before screening and/or at least one T1 Gd+ lesion at baseline

3mCDP, 3-month confirmed disability progression; 6mCDP, 3-month confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium; MRI, magnetic resonance imaging; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis;

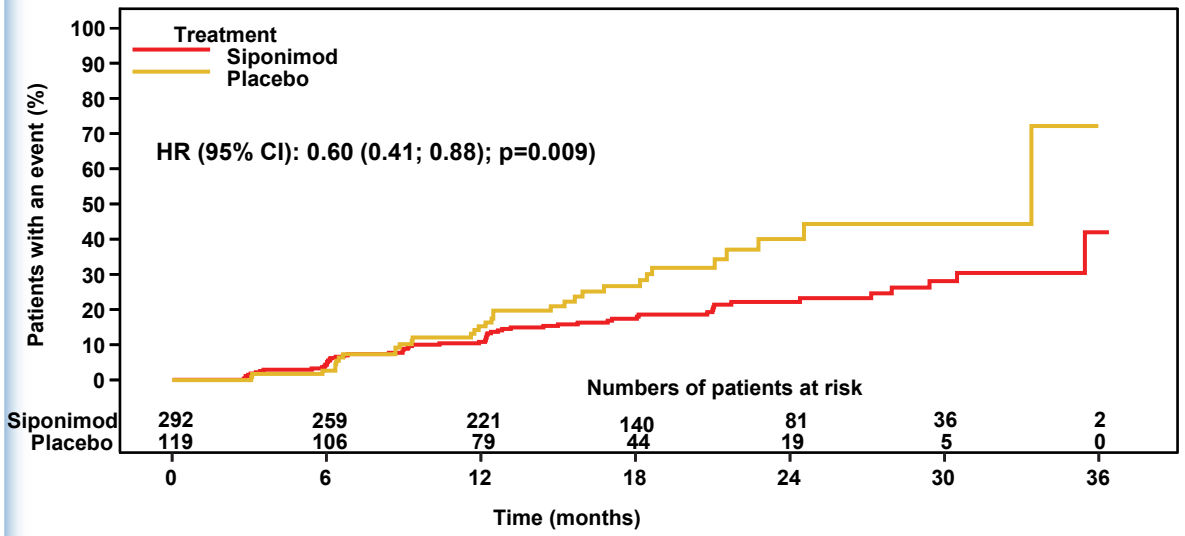
Methods

- The EXPAND CP was an event- and exposure-driven, double-blind, placebo-controlled study assessing the safety and efficacy of siponimod in patients with SPMS
  - Patients with 6mCDP during the CP were offered a switch in treatment to open-label siponimod
- Post hoc analyses assessed the time to sustained (until the end of the CP) progression to EDSS score ≥7.0 using Cox proportional hazards models and KM estimates in an mFAS
  - The mFAS excluded EDSS data following any switch to open-label siponimod in the CP
  - Analyses were performed on all patients (N=1642), and the active (n=778) and non-active (n=825) subgroups
- A multistate Markov model was used to extrapolate observed data beyond the follow-up time of the EXPAND CP in the overall mFAS population and in the active/non-active SPMS subgroups
  - To compare across study arms, a bootstrap method designed for hypothesis testing was used
  - Extrapolated data were compared against observed (KM) data of time to EDSS score ≥7.0 sustained until the end of the follow-up in the EP (data up to 6 years). These observed (KM) data were obtained for the subset of patients who received at least one dose of siponimod in the CP or EP

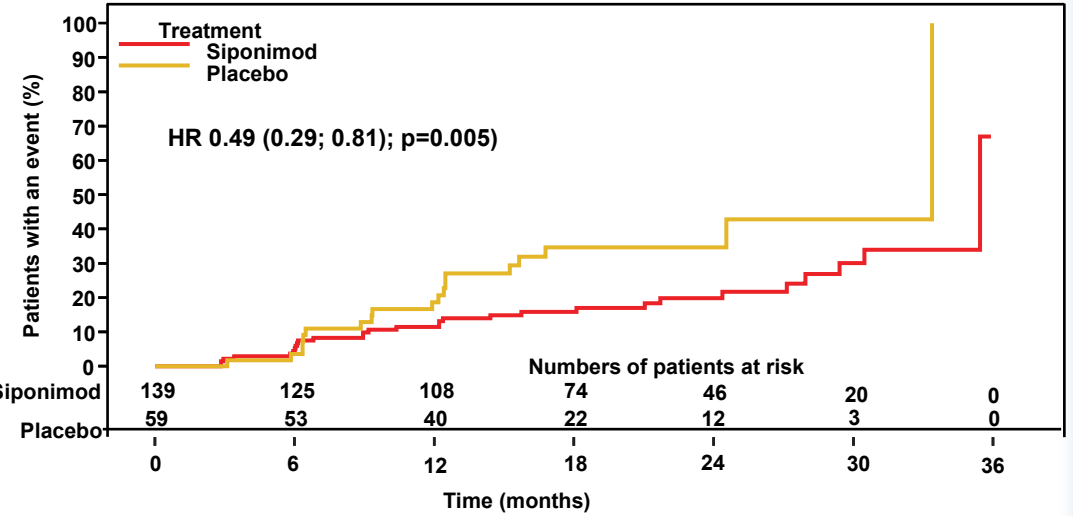
3-month confirmed disability progression, 6mCDP, 6-month confirmed disability progression; CP, core part; EDSS, Expanded Disability Status Scale; EP, extension part; KM, Kaplan-Meier; mFAS, modified full analysis set; SPMS, secondary progressive multiple sclerosis

Results: Effect of siponimod on the risk of reaching sustained EDSS score ≥7.0 in patients with SPMS

Overall SPMS patient population



Patients with active SPMS

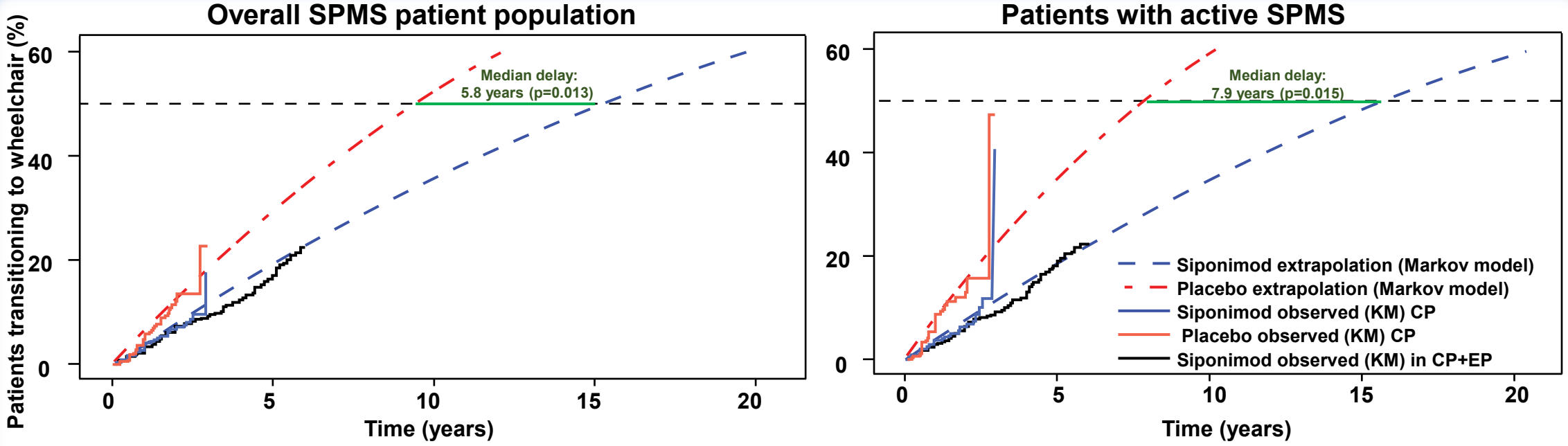


Number of sustained EDSS score ≥7.0 events by baseline EDSS categories (mFAS)		
Baseline EDSS category	Siponimod (N=1097, n/m)	Placebo (N=545, n/m)
<6.5	8/805	11/426
>6.5	57/292	33/119

- Siponimod significantly reduced the risk of reaching sustained EDSS score ≥7.0 by 40% (p=0.009) in the overall population and by 51% (p=0.005) in active SPMS versus placebo
- In non-active SPMS, the risk was numerically reduced by 22% (0.78 [0.42; 1.45]; p=0.437), versus placebo

CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; m, number of patients per category; mFAS, modified full analysis set; n, number of sustained EDSS >=7 events; SPMS, secondary progressive multiple sclerosis

Results: Extrapolation of percentage of patients with progression to sustained EDSS score ≥7.0 using a Markov model



- Extrapolation demonstrated that siponimod significantly delayed the median time to wheelchair by 5.8 years versus placebo (15.3 vs 9.4 years, p=0.0134) in the overall population, and by 7.9 years (15.5 vs 7.6 years, p=0.015) in active SPMS
- In non-active SPMS, in which patients seem to progress more slowly, a delay of 3.0 years (15.5 vs 12.6 years, p=0.398) was observed for siponimod versus placebo
- In the siponimod group, extrapolation beyond the follow-up time in the EXPAND CP was consistent with observed EP data

CP, core part; EDSS, Expanded Disability Status Scale; EP, extension part; KM, Kaplan-meier; SPMS, secondary progressive multiple sclerosis

Conclusions

- Reaching EDSS score ≥7.0 is an important milestone for patients with SPMS
- Siponimod reduced the risk of transition to wheelchair (EDSS score ≥7.0) versus placebo in the overall SPMS population by 40%
  - The effect was most prominent in patients with active disease, with a risk reduction of 51% versus placebo
- Extrapolation beyond the follow-up of the CP of the EXPAND study relies on the assumption that the treatment effect is sustained, and the limitations of such an analysis are acknowledged
- Extrapolation for the siponimod arm closely matched the observed siponimod data from the CP and EP, supporting the robustness of the extrapolation approach
  - Extrapolation demonstrated that siponimod delayed the median time to wheelchair by 5.8 years in the overall population and 7.9 years in patients with active SPMS
- The delay in time to wheelchair reported here further corroborates the clinical efficacy of siponimod in slowing down disability progression in patients with SPMS

CP, core part; EDSS, Expanded Disability Status Scale; EP, extension part; SPMS, secondary progressive multiple sclerosis