Longer-term Safety With Siponimod Treatment in Multiple Sclerosis: Pooled Analysis of Data From the BOLD and EXPAND Trials and Their Extensions

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Introduction

- More than half of patients with relapsing-remitting multiple sclerosis (RRMS) progress to secondary progressive MS (SPMS), with or without relapses, within 25 years of disease onset[1-3]
- To date, no disease-modifying therapy approved for relapsing MS has consistently been shown to slow disability progression in typical patients with SPMS[4-7]
- Siponimod is an oral, selective sphingosine1-phosphate ($S1P_{1,5}$) receptor modulator that:
  - Reduced clinical and MRI disease activity in patients with RRMS in the Phase 2 dose-finding BOLD study[8]
  - Reduced the risk of disability progression in a representative SPMS population (with and without relapses) in the Phase 3 EXPAND study[9]
- Here, we report the long-term safety data pooled from the BOLD and EXPAND studies as through December 2017

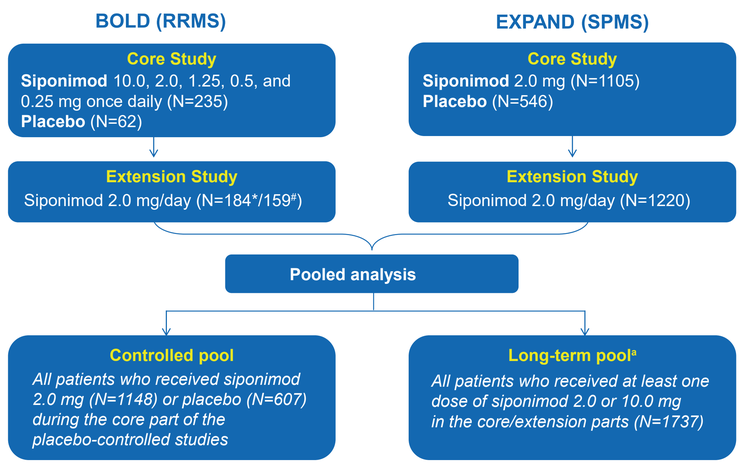
Objective

- To assess the longer-term safety of siponimod treatment for up to 6 years in MS patients using pooled data from the BOLD and EXPAND core and extension trials

Methods

- Pooled safety data from the BOLD and EXPAND core and extension parts were evaluated as shown in **Figure 1**

Figure 1. Analysis population



[a]in the BOLD study, data were collected while the patient was on any dose of siponimod (0.25, 0.5, 1.25, 2.0, or 10.0 mg) in the core part and switched to 2 mg during the extension part
*patients entered the dose-blinded part of the extension study
#patients entered open-label part of the extension study

- The safety analysis included incidence or incidence rates (IR)/100 patient-years (PYs) of adverse events (AEs), serious AEs (SAEs) and AEs of special interest with S1P modulators
- In addition, the relation of infections and lymphocyte counts was analysed in the EXPAND trial data

Results

Demographics

- The mean age of patients in the controlled pool was 47.5 years in the siponimod 2 mg group and 46.8 years in the placebo group; the mean age was 46.6 years in the long-term pool

Exposure to siponimod

- In the controlled pool, the median exposure to siponimod 2 mg was 17.4 months (1696.1 PYs), and 16.1 months (835.3 PYs) for placebo
- As of the latest cut-off of 31 December 2017, the median exposure in the long-term pool was 32.4 months (4619.8 PYs). A total of 44.7% (n=776) of patients were exposed for ≥36 months, and 7.3% (n=127) were exposed for ≥5 years

Note: Numbers per recent cut-off of December 2017 may slightly deviate from that of abstract, which is based on May 2017 cut-off

Safety profile

Controlled pool

- AEs were reported in 89.6% (IR, 258.1) of patients in the siponimod 2 mg group and 81.5% (IR,183.7) of patients in the placebo group
- SAEs were reported in 16.8% of patients in the siponimod 2 mg group and 12.2% of patients in the placebo group
  - The most common SAEs (by preferred term, ≥1% in the siponimod 2 mg group) in the siponimod 2 mg group were urinary tract infection (1.1%) and basal cell carcinoma (1.0%). These were reported in a similar proportion of patients (1.0% each) in the placebo group
  - The difference in SAE reporting between the two groups is not related to one specific category of AE but to the differences in individual AEs with <1.0% of occurrence
- AEs leading to discontinuation were reported in 8.0% and 4.9% of patients in the siponimod 2 mg and placebo groups, respectively

Long-term pool

- AEs were reported in 91.7% (IR, 207.9) of patients; IRs of the most common AEs reported in the long-term pool were consistent with the most common AEs observed in the controlled pool (**Figure 2**)
- SAEs were reported in 23.3% of patients; the most common SAEs (by preferred term, >1% in the siponimod 2 mg group) were urinary tract infection (1.8%) and basal cell carcinoma (1.5%)
- AEs leading to discontinuation were reported in 10.4% of patients

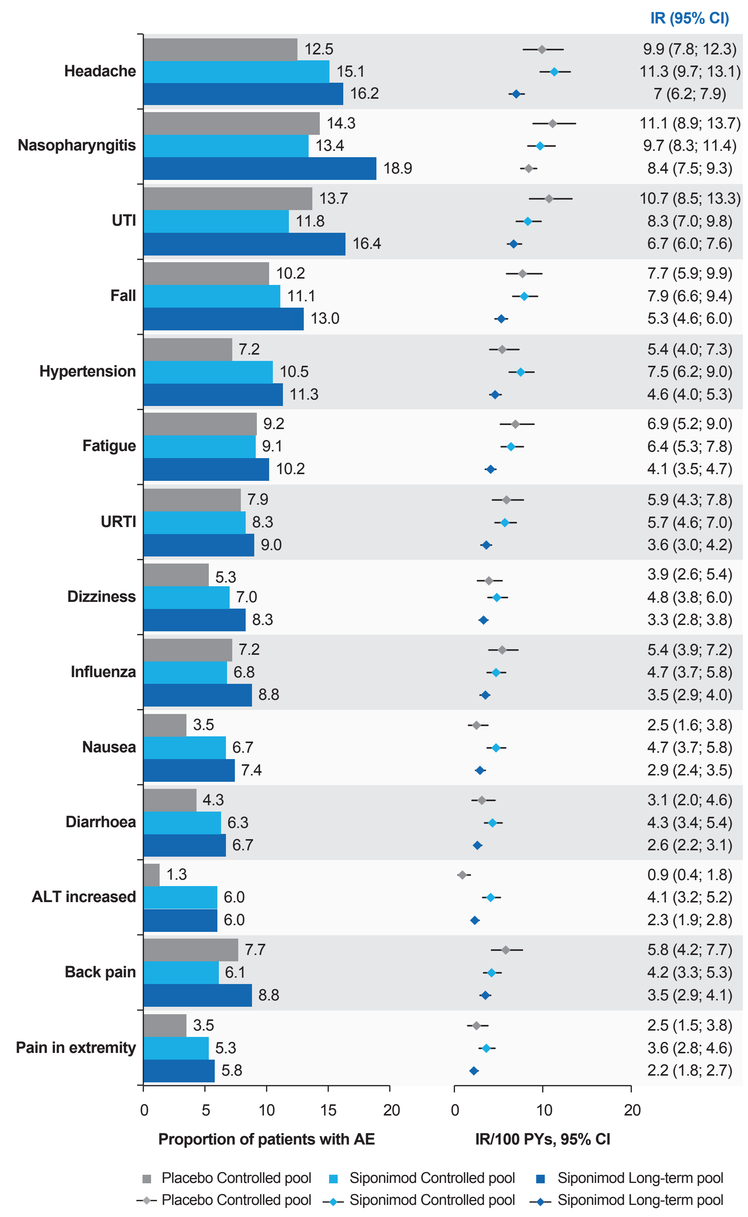
Infections

- In the controlled pool, the incidence of infections was similar between the siponimod 2 mg and placebo groups (48.9% [IR, 49.4] vs. 49.8% [IR, 54.1])
- In the long-term pool, infections were reported in 58.2% (IR, 41.4) of patients. The IRs of most common infections reported were comparable to those reported in the controlled pool (**Figure 3**)
- In the controlled pool, increase in the incidence of varicella zoster virus (VZV) infection was observed in the siponimod 2 mg group versus placebo (3.0% vs. 0.7%; **Figure 4**)
- There was no increase in IR of VZV infection in the long-term pool compared with siponimod 2 mg of controlled pool (IR, 1.7 vs. 2.0)
- There were no cases of progressive multifocal leukoencephalopathy and cryptococcal meningitis during the study

Relationship between infections and lymphocyte counts

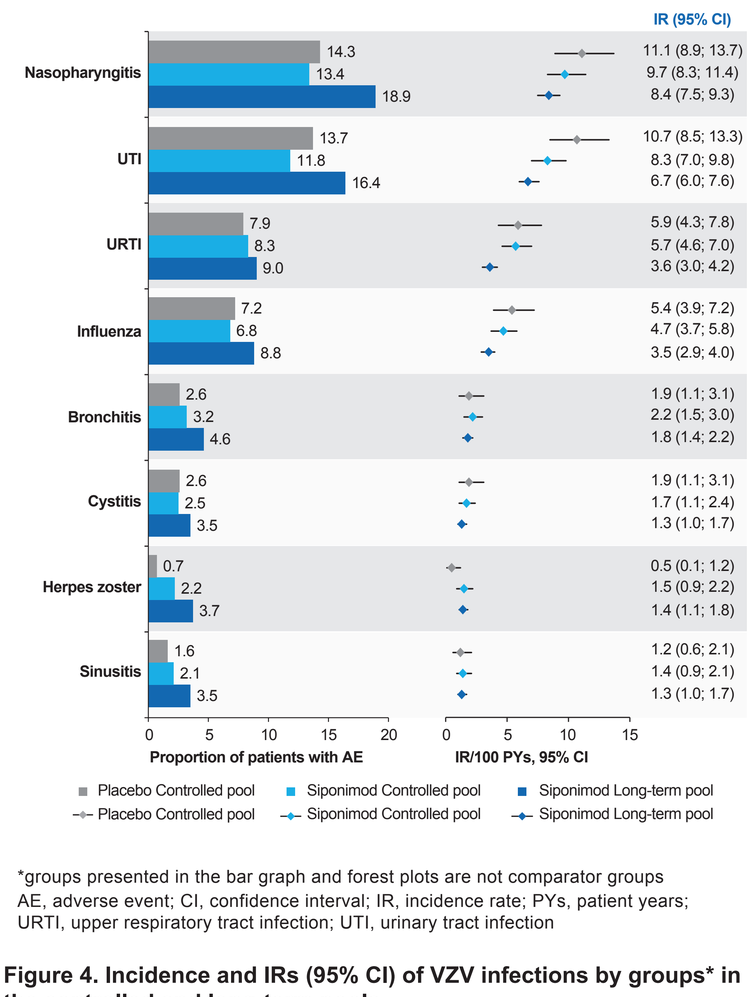
- Among patients with at least one measured lymphocyte count <0.4×10⁹/L at any time, 52.9% had experienced one or more infections
  - Similarly, 45.0% of patients in the 0.4–0.6×10⁹/L and 42.3% in the >0.6×10⁹/L categories experienced infections which were similar/lower to the rate in the placebo group (49.8%; **Figure 5**)

Figure 2. Incidence and IRs (95% CI) of the most frequent AEs by groups* (by preferred term; >5% in the siponimod 2 mg group of the controlled pool)



*groups presented in the bar graph and forest plots are not comparator groups
AE, adverse event; ALT, alanine aminotransferase; CI, confidence interval; IR, incidence rate; PYs, patient years; URTI, upper respiratory tract infection; UTI, urinary tract infection

Figure 3. Incidence and IRs (95% CI) of AEs of infections by groups* (≥2.0% in the siponimod 2 mg group of the controlled pool)

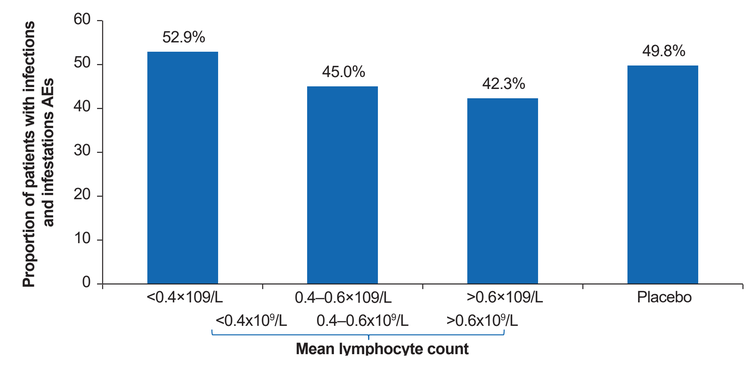


*groups presented in the bar graph and forest plots are not comparator groups
AE, adverse event; CI, confidence interval; IR, incidence rate; PYs, patient years; URTI, upper respiratory tract infection; UTI, urinary tract infection

Figure 4. Incidence and IRs (95% CI) of VZV infections by groups* in the controlled and long-term pools

*groups presented in the bar graph and forest plots are not comparator groups
CI, confidence interval; IR, incidence rate, VZV, varicella zoster virus

Figure 5. Incidence of infections and infestations and lymphocyte counts

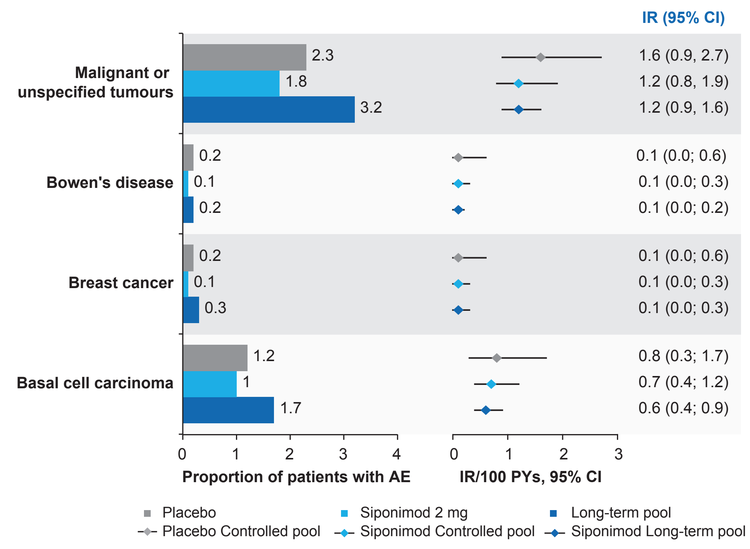


AEs, adverse events

Malignancies

- In the controlled pool, the incidence of malignancies was similar between the siponimod 2 mg and placebo groups (1.8% [IR, 1.2] vs. 2.3% [IR, 1.6])
- No increase in the IR of malignancy-related events was observed in the long-term safety pool (1.2 vs. the controlled pool (1.2; **Figure 6**)
  - Skin related malignancies followed a similar pattern in the long-term safety pool compared with the controlled pool (0.7 vs. 0.9])

Figure 6. Incidence and IRs (95% CI) of AEs of malignant or unspecified tumours by groups* (≥0.2% patients in the long-term pool)



*groups presented in the bar graph and forest plots are not comparator groups
AEs, adverse events; CI, confidence interval; IR, incidence rate; PYs, patient years

Conclusions

- Treatment over 2 years with siponimod 2 mg did not reveal an increase in the incidence of AEs with time and no new safety findings were observed in the long-term pool versus the controlled pool
  - The incidence/IR of the most common AEs was comparable between the siponimod 2 mg and placebo groups in the controlled pool
  - The incidence of VZV infections was higher in siponimod 2 mg versus placebo in the controlled pool with no further increase in the IR in the long-term pool
  - No increase in the overall IR of infections was observed in the long-term pool compared with siponimod 2 mg and placebo groups of the controlled pool
  - No increase in the overall IR of malignant or unspecified tumours including skin malignancies was observed in the long-term pool versus siponimod 2 mg and placebo groups of the controlled pool
- No relationship was observed between the peripheral lymphocyte count and infection rates

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