Safety and Efficiency of Siponimod (BAF312) in patients with Relapsing-remitting Multiple Sclerosis: Results from Dose-blinded Extension Phase of BOLD study

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INTRODUCTION

Siponimod (BAF312) Novartis Pharma AG, Basel, Switzerland is a once-a-day orally administered sphingosine 1 phosphate (S1P) receptor modulator, being developed for the treatment of secondary progressive multiple sclerosis (SPMS).

In the adaptive dose-ranging, 12-week dose-ranging study, treatment-related adverse events (AEs) occurred at low frequencies and were generally reversible. The most frequent treatment-related AEs were dyspnea (10 mg doses) and heart rate decrease (≥1.25 mg doses).

A dose titration schedule was used to mitigate bradyarrhythmic effects of siponimod on treatment initiation. Accordingly, patients were started on siponimod 0.25 mg and titrated up to 10 mg as needed.

In the adaptive dose-ranging, 12-week (Dose-Blinded Extension Set) extension study, treatment-related adverse events (AEs) were reported at a low frequency and were generally reversible.

METHODS

Study Design and Subjects
- In the dose-blinded, phase 3 study, patients were randomized to one of six groups: ≤0.5 mg, 0.5 mg, 1.25 mg, 2 mg, 5 mg, or 10 mg siponimod.
- In the extension study, patients on ≥1.25 mg siponimod were re-randomized to 0.5 mg or 1.25 mg siponimod; patients on ≤1.25 mg siponimod were continued on their assigned dose.
- The safety population consisted of all patients who received at least one dose of extension study drug.

RESULTS

Subject disposition and demographics
- Of the 152 patients who completed the core study and were eligible to enter the extension, a total of 184 patients (73%) entered the 12-month extension without discontinuation; the core extension curve included 124 patients at 0.25 mg (n=40), 9 (12%), follow by 2.1 (17.2%) and 17 (21%) at 1.25 mg (n=25) and 2 mg (n=30) respectively.
- The most frequent treatment-related AEs were dyspnea (10 mg) and heart rate decrease (≥1.25 mg doses) (the majority of these cases occurred in the 0.25 mg group [n=4] followed by withdrawal of consent [n=4] and [n=6]).

Safety profile was manageable:
- Elevations in the liver enzymes were more frequent with siponimod versus placebo and were dose-dependent.
- Dose-dependent decrease in heart rate at treatment initiation was observed and was associated with dose titration.

Efficacy results

Gd-enhanced T1 lesions
- At extension Month 12, the effect on mean number of Gd-enhancing T1 lesions was comparable between the treatment groups and the placebo group (n=3, p=0.6).
- At core baseline, the mean number of Gd-enhancing T1 lesions was highest in the siponimod 10 mg group (3.5) compared to the other dose groups (Table 1).
- At extension month 24, close reductions in mean number of Gd-enhancing T1 lesions were observed at the higher dose groups (2 mg and 10 mg):
  - Mean number of Gd-enhancing T1 lesions at the extension months 24 were: siponimod 0.25 mg (2.0, 0.5 mg) 0.6 mg (0.3, 0.1 mg) and 2 mg (0.1, 0.1 mg).

New or newly enlarged T2 lesions
- At extension Month 12 compared to extension month 6, the number of new or newly enlarged T2 lesions was lower at higher doses (1.25 mg) compared to lower doses: siponimod 0.25 mg (1.4, 0.4), 0.5 mg (0.1, 0.0) and 1.25 mg (0.0, 0.0) (Table 1).
- A similar pattern was observed at extension Month 24 (compared to extension month 18): siponimod 0.25 mg (0.1, 0.0), 0.5 mg (0.0, 0.0), 1.25 mg (0.0, 0.0) and 2 mg (0.0, 0.0) (Table 2).

Table 2. Adverse events reported (≥2% patients in any group) and serious adverse events during the extension study

Conclusions

- Siponimod showed sustained efficacy on MRI and clinical measures in the higher dose groups (2 and 10 mg) in line with dose-finding results in the core study.
- Consistent with the core study, siponimod was well-tolerated during the 24 months extension phase of the BOLD study.
- No new safety signals were observed.