Effects of Therapeutic and Supratherapeutic Doses of Siponimod (BAF312) on Cardiac Repolarization in Healthy Subjects

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ABSTRACT

Purpose: The International Conference on Harmonisation E14 guideline mandates an intensive cardiac safety evaluation in a clinical thorough QT study, typically in healthy subjects, for all new non-antiarrhythmic drugs with systemic bioavailability. This thorough QT study investigated the effects of therapeutic (2 mg) and supratherapeutic (10 mg) doses of siponimod (BAF312) on cardiac repolarization in healthy subjects.

Methods: The study was a randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled, multiple oral dose study. Eligible subjects were randomly assigned to 3 groups to receive siponimod (up-titration to 2 and 10 mg over 18 days), placebo (Days −1 to 18), or moxifloxacin 400 mg Days 10 and 18). Triplicate ECGs were extracted at prespecified time points from Holter ECGs recorded from 1 hour predose until 24 hours postdose at baseline and on-treatment assessment Days 10 and 18. The primary pharmacodynamic variable was the time-matched, placebo-corrected, baseline-adjusted mean QTcF (ΔΔQTcF) at steady-state conditions. In addition, the pharmacokinetic parameters of siponimod and its main circulating metabolite M3 and its metabolite M5 were evaluated.

Findings: Of the 304 enrolled subjects, 281 (92.4%) were included in the pharmacodynamic analysis and 270 (88.8%) completed the study. The upper bounds of the 2-sided 90% confidence intervals (CIs) for ΔΔQTcF at both siponimod doses were within the regulatory threshold of 10 milliseconds (ms) at all predefined on-treatment time points, with the absence of any dose-related effects. The highest observed upper limits of the 2-sided 90% CIs of 9.8 and 9.6 ms for therapeutic and supratherapeutic doses, respectively, were both observed at 3 hours postdose. No treatment-emergent QTc values >480 ms and no QTc increases of >60 ms from baseline were observed. Similar results were obtained with individualized heart rate correction of cardiac repolarization (QTcI). Assay validity was demonstrated by maximum ΔΔQTcF of >5 ms after 400 mg moxifloxacin on both on-treatment assessment days. The selected supratherapeutic dose produced approximately 5-fold higher exposures (C_{max} and AUC) than the therapeutic dose, and was considered appropriate to investigate the effects of siponimod on QT/QTc at substantial multiples of the anticipated maximum therapeutic exposure.

Implications: The findings provide evidence that siponimod is not associated with a significant arrhythmogenic potential related to QT prolongation. (*Clin Ther.* 2015;37:2489–2505)

Key words: BAF312, cardiac repolarization, healthy subjects, moxifloxacin, siponimod, thorough QT.

INTRODUCTION

Siponimod (BAF312) is a selective sphingosine 1-phosphate (S1P) receptor modulator that is currently being developed for the treatment of secondary

Accepted for publication September 13, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.09.006
0149-2918/$ - see front matter

progressive multiple sclerosis.[1] The therapeutic efficacy of S1P receptor modulation in multiple sclerosis has been reported using fingolimod.[2–5] Siponimod has shown nanomolar affinity for $S1P_{1/5}$ receptors, inducing a profound and long-lasting internalization of $S1P_1$ receptors.[1,6] The internalization of $S1P_1$ receptors renders lymphocytes unresponsive to S1P, depriving them of an obligatory signal to egress from the lymph nodes and recirculate into the central nervous system, which, in turn, reduces neuroinflammation.[7] Siponimod metabolism is well characterized. Siponimod is eliminated from the systemic circulation mainly due to metabolism and subsequent biliary and fecal excretion. The predominant hepatic enzymes responsible for siponimod metabolism are CYP2C9 (>70%) and, to a lesser extent, CYP3A4 (20%). After oral administration, siponimod is metabolized to M5 mainly by hydroxylation. M5 (hydroxylated metabolite) is converted to M3 by glucuronidation. These 2 metabolites have been tested for the agonistic activity on $S1P_1$ receptors in vitro and were found to have a weak agonistic activity (M5, EC_{50}: 470 [71] nmol/L and M3, EC_{50}: >10,000 nmol/L) as compared with the parent compound (siponimod, EC_{50}: 1.1 [0.41] nmol/L) (unpublished data on file, Novartis Pharma AG, Basel, Switzerland).

Expression of $S1P_1$ receptors in atrial, septal, and ventricular cardiomyocytes and in the endothelial cells of cardiac vessels in humans implicates their role in the regulation of heart rate (HR).[8,9] Transient, dose-dependent decreases in HR and occasional asymptomatic first- and second-degree atrioventricular blocks (AVB) have been reported with S1P receptor modulators.[4,5] Consistent with the effects of S1P receptor modulators on HR, previous studies with siponimod identified a transient, dose-dependent decrease in HR at treatment initiation.[1,6,10] However, the established dose-titration regimen of siponimod was able to attenuate the onset of bradyarrhythmic effects typically observed with other S1P receptor modulators.[11]

Drugs that prolong cardiac repolarization are associated with an increased risk of polymorphic ventricular tachycardia (Torsades de Pointes).[12–14] Hence, intensive cardiac safety evaluation is mandated by the International Conference on Harmonisation (ICH) E14 guideline in a clinical thorough QT (TQT) study, typically in healthy subjects, for all new non-antiarrhythmic drugs with systemic bioavailability.[15–17] In accordance with the regulatory guidelines, the present study assessed the effect of siponimod on cardiac repolarization, as evidenced by the QT and corrected QT interval (QTc) at steady state after administration of the therapeutic dose of 2 mg and a supratherapeutic dose of 10 mg in healthy subjects. The primary objective was to assess whether the effects of therapeutic and supratherapeutic doses of siponimod on the time-matched, placebo-corrected, baseline-adjusted mean QTcF (ΔΔQTcF) exceeded the 5-ms regulatory threshold level of concern, as evidenced by an upper bound of a 2-sided 90% CI or a 1-sided 95% CI for the largest mean QTc effect of 10 ms. Secondary objectives included the evaluation of the effects on other ECG variables, including QTcI, HR, PR, and QRS and of morphologic ECG changes related to cardiac repolarization (abnormal ST segment, T or U waves). The pharmacokinetic (PK) properties of siponimod; PK and pharmacodynamic (PD) relationship of plasma concentrations of siponimod (and its main circulating metabolite M3, as well as its active metabolite M5) and the ECG variables; and the overall safety profile and tolerability of siponimod were also assessed.

METHODS

Study Design

This was a randomized, double-blind, placebo-, and moxifloxacin-controlled, multiple oral dose study conducted in parallel groups of healthy adult male and female subjects. The study consisted of a screening period of up to 42 days, a 2-day baseline period, a treatment period of up to 18 days, and an end-of-study evaluation at approximately 14 to 21 days after the last administration of study drug (Figure 1). On baseline Day −1, all subjects underwent pre-dose safety assessments and received siponimod placebo. Eligible subjects were randomly assigned to 1 of 3 treatments groups and remained at the study site until Day 19. In treatment group A (n = 92), subjects underwent an up-titration regimen (Days 1−6), followed by 4 additional days of stable dosing (Days 7−10) to establish stepwise steady-state conditions for the clinical therapeutic dose of 2 mg. This was followed by further up titration (Days 11 to 14) and 4 additional days of stable dosing (Days 15−18) to establish steady-state conditions for a supratherapeutic dose of 10 mg. Siponimod placebo was given on Day −1 and moxifloxacin placebo on the 2