NOVARTIS

Novartis Clinical Trial Results

Name of finished product: N/A

Name of active ingredient: Siponimod/BAF312

Study number: CBAF312A2125

Title of study: An open-label, multiple dose, 2-period, single-sequence study in healthy subjects with the CYP2C9*1*1 (wild type) genotype to evaluate the effect of the CYP2C9/3A4 inducer rifampin on siponimod pharmacokinetics.

Investigator(s): Antonia M. Davidson, MD

Study center(s): PPD, 7551 Metro Center Drive, Austin, Texas 78744, USA

Study period

First subject enrolled: 19-Sep-2016 (first subject first visit)

Last subject completed: 01-Dec-2016 (last subject last visit)

Phase of development: I

Objectives:

The primary objective of this study was to assess the multiple-dose pharmacokinetics (PK) of siponimod in healthy subjects when given alone or in combination with the cytochrome P450 (CYP) 2C9/3A4 inducer rifampin.

The secondary objectives of this study were:

- To assess the safety and tolerability of siponimod at 2 mg once daily (q.d.) in healthy subjects when given alone or in combination with the CYP2C9/3A4 inducer rifampin.
- To assess the multiple-dose PK of metabolites, M3 and M5, when siponimod is given alone or in combination with the CYP2C9/3A4 inducer rifampin.

Methodology: This was a confirmatory, open-label, multiple-dose, 2-period, single-sequence study in healthy subjects to evaluate the PK of siponimod when given alone and in combination with the strong CYP2C9/3A4 inducer, rifampin. In Treatment Period 1 (siponimod alone), subjects received multiple oral doses of siponimod, up to a dose of 2 mg q.d. Steady state, achieved at 2 mg q.d., was reached on Day 12 using a 5-day up-titration scheme. In Treatment Period 2 (siponimod + rifampin), subjects received 600 mg q.d. rifampin in a fasted state (1 hour prior to meals) for 12 days (Days 13 through 24). Siponimod 2 mg q.d. administration was maintained from Days 13 through 24.

Number of subjects (planned and analyzed): Sixteen subjects were planned for the study, and a total of 16 subjects were enrolled. Fifteen subjects (93.8%) completed the study. All 16 subjects (100%) were included in the safety and PK analysis sets.

Diagnosis and main criteria for inclusion: Healthy male and female subjects (non-childbearing potential), non-smoking, with the CYP2C9*1*1 genotype, between 18 and 45 years of age, inclusive, body weight between 50 to 100 kg, inclusive, and a body mass index (BMI) between 18 to 30 kg/m^2, inclusive.

Test product, dose and mode of administration

- BAF312 (siponimod) 0.25 mg film-coated tablet, administered orally q.d.
- BAF312 (siponimod) 0.5 mg film-coated tablet, administered orally q.d.
- BAF312 (siponimod) 2 mg film-coated tablet, administered orally q.d.
- Rifampin 600 mg, administered orally q.d. as 2 × 300 mg capsule

Duration of treatment: Siponimod was administered q.d. on Days 1 through 12 (Treatment Period 1) according to a 5-day up-titration scheme. On Days 13 through 24 (Treatment Period 2), siponimod 2 mg q.d. was co-administered with rifampin 600 mg q.d.

Reference therapy, dose and mode of administration, batch number: Not applicable.

Criteria for evaluation

Pharmacokinetics: The PK analysis set included all subjects with at least 1 available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug, and who experienced no protocol deviations with relevant impact on PK data. Plasma concentrations of siponimod and metabolites, M3 and M5, were determined in plasma by validated liquid chromatography with tandem mass spectrometry methods. The PK parameters of primary interest were determined using non-compartmental methods and included Cmax,ss; AUClast,ss; and AUCtau,ss for total siponimod and metabolites, M3 and M5.

Safety: The safety analysis set included all subjects that received any study drug. Safety assessments consisted of physical examinations, vital signs (body temperature, blood pressure, and pulse rate), height and weight, clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiogram (ECG), 24-hour Holter ECG examinations, and adverse event (AE) and serious AE (SAE) monitoring (including renal and liver events, prospective suicidality assessment using the Columbia-Suicide Severity Rating Scale (C-SSRS), and pregnancy).

Statistical methods

Pharmacokinetics: Individual plasma concentration versus actual time data were used to calculate the PK parameters of siponimod and metabolites, M3 and M5, by standard single-dose and steady-state, non-compartmental methods.

Siponimod and metabolite (M3 and M5) plasma concentration data were listed by visit/sampling time point.

Descriptive summary statistics of siponimod and metabolite (M3 and M5) concentrations were provided by visit/sampling time point. Summary statistics included mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (arithmetic and geometric), median, minimum, and maximum. Concentrations below the limit of quantification (BLQ) were treated as zero in summary statistics. A geometric mean was not reported if the dataset included zero values.

Individual plasma concentration versus actual time plots of siponimod and metabolites (M3 and M5) were presented. However, for ease of presentation, nominal sampling time was used for presentation of mean (arithmetic) concentration versus time plot. Individual and mean plots were presented on linear scales. Concentration

SD was presented with mean concentrations on the linear scale only..

The effect of rifampin on the PK of siponimod and metabolites (M3 and M5) in healthy subjects was analyzed by using a mixed-effects model. Log-transformed PK parameters Cmax,ss and AUCs (AUClast,ss and AUCtau,ss) of siponimod and metabolites (M3 and M5) were analyzed using a mixed-effects model including study treatment (siponimod alone, siponimod + rifampin) as a fixed effect and subject as a random effect. The point estimate of the difference in adjusted means, along with 90% confidence intervals (CIs) on the log scale, were calculated for the contrast siponimod + rifampin (Test) versus siponimod alone (Reference). The results were back-transformed to the original scale to obtain adjusted geometric mean ratios and the corresponding 90% CIs.

Individual subject treatment ratios were plotted along with the geometric mean ratios (90% CI) for Cmax,ss; AUClast,ss; and AUCtau,ss of siponimod and metabolites (M3 and M5).

Safety: All treatment-emergent AEs (TEAEs)leading to study drug discontinuation and AEs requiring dose interruption were listed by subject for the safety analysis set. Adverse events leading to death and SAEs were to be listed for all subjects. All AEs recorded during the study were presented for all subjects. All C-SSRS findings data were listed by subject and visit/time. Laboratory test results, vital sign measurements, and ECGs were summarized by presenting descriptive statistics of raw data (Baseline and post-Baseline) and changes from Baseline by treatment and visit/time. Concomitant medications and significant non-drug therapies prior to and after the start of the study drug were listed.

Boxplots to visualize trends in longitudinal vital sign, ECG, and laboratory data (including absolute lymphocyte count (ALC)) were created and summarized raw data (Baseline and post-Baseline) by treatment for all subjects in the safety analysis set. Spaghetti plots to visualize trends in individual ALC data were created and displayed raw data by study day and by visit for all subjects in the safety analysis set.

Summary - Conclusions

Demographic and background characteristics: A total of 16 subjects were enrolled with an overall mean age of 31.1 years (range 18 to 43 years), a mean weight of 79.2 kg (range 62.9 to 93.1 kg), and a mean BMI of 25.8 kg/m^2 (range 20.0 to 29.4 kg/m^2). More males were enrolled (15 subjects, 94%) than females (1 subject, 6%). The majority of subjects were black (8 subjects, 50.0%), and 10 subjects (62.5%) were of ethnicity other than Hispanic/Latino or mixed ethnicity.

Pharmacokinetic results: The ratio of geometric means for Test (Period 2 Day 24, siponimod with rifampin) to Reference (Period 1 Day 12, siponimod alone) for siponimod Cmax,ss was 0.55, while the ratio for AUCtau,ss and AUClast,ss was 0.43. The 90% CI for the Test-Reference ratio for all exposure parameters fell below the default no-effect 90% CI of 0.80 to 1.25. Co-administration of rifampin with siponimod did not alter the median Tmax (4 hours) of siponimod between Periods 1 and 2. The results indicate that rifampin significantly decreased the exposure parameters of siponimod.

The ratio of geometric means for Test (Period 2 Day 24, siponimod with rifampin) to Reference (Period 1 Day 12, siponimod alone) for M3 Cmax,ss was 1.53. The 90% CI for the Test-Reference ratio for Cmax,ss was (1.30 – 1.81), above the default no-effect limits of 0.80 to 1.25. The geometric mean ratios (90% CI) for AUCtau,ss and

AUClast,ss were both 0.90 (0.78, 1.03), indicating little to no effect of rifampin on total exposure of M3. Co-administration of rifampin with siponimod did not alter the median Tmax (6 hours) of M3 between Periods 1 and 2. The results indicate that rifampin significantly increased the Cmax,ss of M3 but did not significantly change total exposure of M3.

The ratio of geometric means for Test (Period 2 Day 24, siponimod with rifampin) to Reference (Period 1 Day 12, siponimod alone) for M5 Cmax,ss was 0.96, while the ratio for AUCtau,ss and AUClast,ss was 0.63. The 90% CI for the Test-Reference ratio for Cmax,ss (0.86 – 1.07) was within the default no-effect limits of 0.80 to 1.25 while those for the AUCs (0.58 – 0.68) were entirely below the (0.80, 1.25) interval. Co-administration of rifampin with siponimod displayed a shorter median Tmax for Period 2 (3 hours) than for Period 1 (6 hours). The results indicate that rifampin did not change Cmax,ss of M5, but significantly decreased the AUCs of M5.

Safety results: Overall, multiple oral doses of siponimod (up-titrated from 0.25 to 2 mg on Days 1 through 12) alone and in combination with multiple oral doses of rifampin (600 mg q.d. on Days 13 through 24) were safe and well tolerated by the healthy subjects in this study. No deaths or SAEs were reported during the study. One subject discontinued due to a TEAE of viral infection that was suspected to be related to siponimod. One subject had a tooth extraction related to a TEAE of tooth fracture.

Overall, 15 subjects (93.8%) experienced at least 1 TEAE during the study. With the exception of 1 moderate TEAE of presyncope in Treatment Period 1, all TEAEs were mild in severity. All TEAEs resolved by the end of the study.

Overall, 7 subjects (43.8%) reported TEAEs that were suspected to be related to siponimod. Four subjects (25.0%) reported TEAEs (dizziness, muscle tightness, nausea, headache, fatigue, oral herpes, viral infection, and nasal congestion) that were suspected to be related to siponimod after receiving siponimod alone (Treatment Period 1), and 5 subjects (33.3%) reported TEAEs (headache, nausea, myalgia, dizziness, oral herpes, and blurred vision) that were suspected to be related to siponimod after receiving siponimod co-administered with rifampin (Treatment Period 2).

Ten subjects reported TEAEs (chromaturia, nausea, diarrhea, headache, abnormal urine odor, and blurred vision) that were suspected to be related to rifampin.

A treatment-emergent decrease in ALC was observed in all subjects. Mean ALC at Baseline was 1.83 × 10^9/L (normal range: 1 to 3.2 × 10^9/L) and decreased to a minimum value of 0.69 × 10^9/L at Period 2 Day 17 (mean change from Baseline −1.14 × 10^9/L). Mean ALC returned to within the normal range at Period 2 Day 31/end of study (EOS) (1.73 × 10^9/L). With the exception of 1 subject, all subjects had ALC values below the normal range; however, none were reported as TEAEs by the Investigator.

Mean ALC increased slightly during the combination treatment with rifampin in Treatment Period 2. However, mean ALC remained at low levels below 1.0 × 10^9/L until the completion of Treatment Period 2 and the discontinuation of the study drug, consistent with the magnitude of steady-state ALC reduction in previous studies at the 1-mg dose level.

Mean ALC recovered to near baseline levels by the EOS visit (approximately 7 days after the last dose), consistent with the ALC recovery pattern in previous studies at the same dose level.

No clinically relevant changes in clinical laboratory results, vital sign measurements, 12-lead ECG results, and C-SSRS findings were noted during the study, and no individual value was reported as a TEAE by the Investigator.

Conclusion:

- Siponimod AUCtau,ss and Cmax,ss were decreased by 57% and 45%, respectively, in the presence of rifampin.
- M3 AUCtau,ss was decreased by 10% while Cmax,ss was increased by 53% in the presence of rifampin. M5 AUCtau,ss was decreased by 37% while Cmax,ss was comparable in the presence of rifampin.
- Siponimod mean trough levels in Period 2 suggest that the maximum induction conditions were achieved by Day 24.
- Final recommendations on the concomitant use of siponimod and strong CYP3A4/moderate CYP2C9 inducers will be made upon availability and review of all pertinent preclinical and clinical data.
- Multiple oral doses of siponimod (up-titrated from 0.25 to 2 mg on Days 1 through 12) alone and in combination with multiple oral doses of rifampin (600 mg q.d. on Days 13 through 24) were safe and well tolerated by the healthy subjects in this study.
- Magnitude and time course of the mean ALC reduction in Treatment Period 1 (siponimod alone) were similar to observations in previous studies during dose titration and at the 2-mg dose level on Day 8.
- Mean ALC increased slightly during the combination treatment with rifampin in Treatment Period 2. However, mean ALC remained at low levels below 1.0×10^9/L until the completion of Treatment Period 2 and the discontinuation of the study drug, consistent with the magnitude of steady-state ALC reduction in previous studies at the 1-mg dose level.
- Mean ALC recovered to near baseline levels by the EOS visit (approximately 7 days after the last dose), consistent with the ALC recovery pattern in previous studies at the same dose level.

Date of report: 27-Apr-2017

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2125

EudraCT Number

Not applicable.

Planned and Actual Number of Patients
Planned: 16 subjects

Enrolled: 16 subjects

Batch Numbers

- BAF312 (siponimod) 0.25 mg film-coated tablet, administered orally q.d. (Batch number 1010004141)
- BAF312 (siponimod) 0.5 mg film-coated tablet, administered orally q.d. (Batch number 1010004142)
- BAF312 (siponimod) 2 mg film-coated tablet, administered orally q.d. (Batch number 1010004145)
- Rifampin 600 mg, administered orally q.d. as 2 × 300 mg capsule (Lot number: 3145675)

Information on comparators drug dosage, route of administration, batch numbers

Not applicable.

Publication(s)

Gardin A, Gray C, Neelakantham S, Huth F, Davidson AM, Dumitras S, Legangneux E, Shakeri-Nejad K. Siponimod Pharmacokinetics, Safety and Tolerability in Combination with Rifampin, a CYP2C9/3A4 Inducer, in Healthy Subjects. European Journal of Clinical Pharmacology. 2018 Dec; 74(12):1593-1604. doi: 10.1007/s00228-018-2533-2. Epub 2018 Aug 13.

Investigators & Information on Study Centers

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