Novartis Clinical Trial Results

Name of finished product: N/A

Name of active ingredient: Siponimod/BAF312

Study number: CBAF312A2126

Title of study: A randomized, open-label, 2-part study to measure the absolute bioavailability, safety, tolerability, and pharmacodynamics of oral and intravenous siponimod in healthy subjects.

Investigator: Thomas L. Hunt, MD, PhD

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

Study period:

First subject enrolled: 05-Aug-2015 (first subject first visit)

Last subject completed: 05-Jan-2016 (last subject last visit)

Phase of development: I

Objectives:

The primary objective of this study was to determine the absolute bioavailability of a single oral dose of 0.25 mg of siponimod in healthy subjects.

The secondary objectives of this study were:

- To determine the pharmacokinetic (PK) profile of siponimod and metabolites (M16 and M17) following a single oral dose of 0.25 mg and single intravenous (i.v.) doses of 0.25 and 1 mg of siponimod in healthy subjects
- To determine the safety and tolerability of a single oral dose of 0.25 mg and single i.v. doses of 0.25 and 1 mg of siponimod in healthy subjects
- To evaluate the cardiac effects (including bradyarrhythmia) of single i.v. doses of 0.25 and 1 mg of siponimod in healthy subjects
- To determine the pharmacodynamic (PD) effect (heart rate (HR) and absolute lymphocyte count (ALC)) of a single oral dose of 0.25 mg and single i.v. doses of 0.25 mg and 4 consecutive doses of 0.25 mg over 6 hours (1 mg over 24 hours) of siponimod

Methodology:

This was a randomized, open-label, 2-part study in healthy subjects.

Part 1

Part 1 of this study consisted of a maximum 42-day screening period, 2 baseline periods (1 before each treatment period), and 2 treatment periods followed by an end-of-study (EOS) evaluation approximately 14 days after the last study drug administration.

Subjects who met the eligibility criteria at Screening were admitted to the study site approximately 24 hours before dosing in each treatment period for Baseline evaluations. All Baseline safety evaluation results were to be available before dosing in both

treatment periods. At first Baseline, all Baseline results were evaluated for final eligibility assessment before randomization.

Following a single oral or i.v. dose (3-hour infusion) of 0.25 mg siponimod, PK, PD, and safety assessments were made for up to 336 hours in each treatment period. Subjects underwent EOS evaluations and were discharged from the study at the end of Treatment Period 2.

Subjects were domiciled for 3 days in each treatment period from approximately 24 hours before dosing until 48 hours thereafter. Subjects could have been domiciled for a longer duration at the discretion of the Investigator for safety reasons or for subject convenience. Subjects returned to the site for ambulatory PK and PD blood collection and safety assessments.

Subjects were randomly assigned to 1 of the 2 different sequences:

- Sequence 1: Treatment A (siponimod 0.25 mg, single oral dose) followed by Treatment B (siponimod 0.25 mg single i.v. infusion over 3 hours)
- Sequence 2: Treatment B (siponimod 0.25 mg single i.v. infusion over 3 hours) followed by Treatment A (siponimod 0.25 mg, single oral dose)

As a precautionary measure for the first 2 subjects who received the i.v. formulation in the initial phase of recruitment (Treatment Period 1), only 1 subject per sequence per day was randomly assigned with a second subject for each sequence being randomly assigned 24 hours later. This allowed for sufficient time to review the online electrocardiogram (ECG) monitoring (if required) and 12-lead ECG data to ensure that the subsequent subject was randomly assigned only if no significant bradyarrhythmia of concern was noted in the initial 24 hours after study drug administration in the preceding subject. Once a total of 4 subjects received the study drug (2 subjects who received the i.v. formulation and 2 subjects who received the oral formulation), and the study drug was confirmed to be sufficiently safe and tolerated in these 4 subjects, all subsequent subjects were dosed in groups, and no precautionary time separation was required.

An interim analysis of the safety and PK data from Part 1 of the study was performed before initiating Part 2 of this study.

Part 2

Part 2 of this study consisted of a maximum 42-day screening period, a baseline period, and a treatment period followed by an EOS evaluation approximately 14 days after the completion of study drug administration.

Subjects who met the eligibility criteria at Screening were admitted to the study site approximately 24 hours before dosing for Baseline evaluations. All Baseline safety evaluation results were to be available for final eligibility assessment before randomization and dosing.

Following an i.v. dose of 1 mg siponimod (administered as 4 consecutive 6-hour i.v. infusions of 0.25 mg of siponimod; 24-hour infusion), PK, PD, and safety assessments were made for up to 336 hours. Subjects underwent EOS evaluations and were discharged from the study at the end of the treatment period.

Subjects were domiciled for 3 days in the treatment period approximately 24 hours before dosing until 48 hours thereafter. Subjects could have been domiciled for a longer duration at the discretion of the Investigator for safety reasons or for subject

convenience. Subjects returned to the study site for ambulatory PK and PD blood collection and safety assessments.

For the first 2 subjects, only 1 subject per day was dosed with i.v. 1 mg formulation. After dosing the first subject, a second subject was dosed at least 24 hours later. This allowed for sufficient time to review the online ECG monitoring and 12-lead ECG data to ensure that the subsequent subject was dosed only if no significant bradyarrhythmia of concern was noted in the initial 24 hours after study drug administration in the preceding subject. Once a total of 2 subjects received the study drug (both with i.v. 1 mg formulation), and the study drug was confirmed to be sufficiently safe and tolerated in these 2 subjects, all subsequent subjects were dosed and no precautionary time separation was required.

Number of subjects (planned and analyzed): Thirty-two subjects were planned for the study (16 subjects per part in Parts 1 and 2). A total of 16 subjects were enrolled and 14 subjects (87.5%) completed Part 1 of the study. All 16 subjects (100%) in Part 1 were included in the safety, PK, and PD analysis sets.

A total of 17 subjects were enrolled and completed Part 2 of the study. All 17 subjects (100%) in Part 2 were included in the safety and PD analysis sets. Fifteen subjects (88.2%) were included in the PK analysis set. Two subjects were excluded from the PK analysis set for Part 2.

Diagnosis and main criteria for inclusion:

Healthy male and female subjects (non-childbearing potential), non-smoking, between 18 and 50 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 final market image (FMI) tablet, administered as a single oral dose
- BAF312 (siponimod), 0.25 mg lyophilisate in vial, administered as a single 3 hour i.v. infusion (Part 1; 0.25 mg) or as 4 consecutive 6-hour infusions (Part 2; 1 mg)

Duration of treatment:

Subjects received a single dose of siponimod 0.25 mg film-coated tablet and 0.25 mg single i.v. infusion over 3 hours on Day 1 or Day 15 of Part 1, depending on the treatment sequence. Subjects received a 1 mg single i.v. infusion of siponimod (as 4 consecutive 6-hour infusions; 24-hour infusion) on Day 1 of Part 2.

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 experienced no protocol deviations with relevant impact on PK data. Plasma concentrations of siponimod and its metabolites, M16 and M17, were determined in plasma by validated liquid chromatography with tandem mass spectrometry methods. Pharmacokinetic parameters were determined using non-compartmental methods:

- After oral administration (Part 1 only): Cmax, Tmax, AUClast, AUCinf, Lambda_z, T1/2, Vz/F (siponimod only), CL/F (siponimod only), adjusted R^2,

%AUCextrap, and MR Cmax (M16 and M17 only), MR AUClast (M16 and M17 only), and MR AUCinf (M16 and M17 only) from the plasma concentration-time data.

- After i.v. administration (Parts 1 and 2): Cmax, Tmax, AUClast, AUCinf, Lambda_z, T1/2, Vz (siponimod only), CL (siponimod only), adjusted R^2, %AUCextrap, MR Cmax (M16 and M17 only), MR AUClast (M16 and M17 only), and MR AUCinf (M16 and M17 only) from the plasma concentration time data.
- The absolute bioavailability (F) was defined as the oral to i.v. ratio of AUCinf values (Part 1 only).

Safety: The safety analysis set included all subjects that received any study drug. Safety assessments included physical examinations, 12-lead safety ECGs, vital signs (body temperature, blood pressure, and pulse rate), standard clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), adverse event (AE) and serious AE (SAE) monitoring (including renal and liver events, and pregnancy), 25-hour Holter ECG evaluation (for retrospective cardiac safety evaluation and PD analysis (HR analysis)), and cardiac telemetry (24 hours or longer at the discretion of the Investigator).

Pharmacodynamics: The PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. The PD effects of siponimod were determined through HR analysis (25-hour Holter ECGs) and ALC evaluation. Pharmacodynamic parameters of ALC included: area under the effect curve (AUEC), maximum effect (Emax), and time to maximum effect (TEmax). Heart rate analyses included 5-minute and hourly average data from 25-hour Holter ECGs in i.v.-treated subjects only. The 1-minute average HR data were stored in the database for potential retrospective analysis, if deemed necessary.

Statistical methods:

Pharmacokinetics:

Siponimod and metabolites (M16 and M17) plasma concentration data were listed by part, treatment, subject, and visit/sampling time point.

Descriptive summary statistics of siponimod and metabolites (M16 and M17) plasma concentration data were provided by treatment and visit/sampling time point. Summary statistics included mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV; 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 for siponimod and metabolites were presented. For ease of presentation, nominal sampling time was used for presentation of mean (arithmetic and geometric) concentration versus time plot by treatment. Plots were presented on both linear and semi-logarithmic scales. All BLQ and missing values were indicated in the data listings.

Siponimod and metabolites (M16 and M17) PK parameters were listed by part, treatment, and subject. Summary statistics of PK parameters of siponimod and metabolites included mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this was Tmax where median, minimum, and

maximum were presented.

For Part 1, siponimod PK parameters AUClast, AUCinf and Cmax were compared between the 2 formulations, siponimod oral FMI tablet (test) and i.v. formulation (reference). For each of those PK parameters, the log-transformed data were analyzed using a linear model including treatment, period, sequence, and subject within sequence as fixed factors. Only subjects with evaluable data in both treatment periods were used for this analysis. A point estimate and a 90% confidence interval (CI) for the ratio of treatment geometric means on the original scale were provided for each comparison. Note that the ratio of AUCinf oral/i.v. gave the estimate of absolute bioavailability (F).

Subjects with missing PK parameters (e.g., Cmax, AUClast, AUCinf) in some but not all treatment periods were included in a mixed model analysis assuming missing at random.

The analysis was conducted by use of PROC MIXED procedure in SAS® software.

For Part 2, no inferential statistical analysis was performed. Pharmacokinetic results were summarized descriptively.

Safety:

Summary tables for AEs included only treatment-emergent AEs (TEAEs). All TEAEs leading to study drug discontinuation, AEs requiring dose adjustment or interruption, AEs leading to death, and SAEs were listed. All AEs recorded during the study were presented in listings. Laboratory test results and vital sign measurements, and ECGs were summarized by presenting descriptive statistics of raw data (Baseline and post-Baseline) and changes from Baseline by part and treatment and visit/time. Concomitant medications and significant non-drug therapies, prior to and after the start of the study drug were listed.

Pharmacodynamics:

Absolute lymphocyte counts were analyzed and summarized by treatment. Summary statistics for ALC included mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Summary statistics for ALC change from Baseline (predose) and ALC percentage change from Baseline (predose) included mean (arithmetic), SD, CV (arithmetic), median, minimum, and maximum.

Absolute lymphocyte counts were analyzed graphically by presenting individual and mean (arithmetic and geometric) ALC, and arithmetic mean change from Baseline, and percent change from Baseline ALC for all subjects by treatment and time point. Individual ALC versus actual time was presented graphically.

Pharmacodynamic parameters of ALC (AUEC, Emax, and TEmax) were calculated and summarized by treatment.

Descriptive statistics for HR averages, minimums, and maximums (5-minute and hourly) and change from Baseline HR were presented by part for the i.v. treatment. Averaged individual and mean, minimum, and maximum HR data were presented graphically. The plot of mean HR included a 95% CI for the mean. All hourly average HR data were listed by treatment sequence and subject for Part 1 and by subject for Part 2. Mean 1-minute average HR data were collected and captured in the clinical database for potential retrospective analysis, if deemed necessary.

A table of the occurrence of different types of atrioventricular (AV) blocks and sinus

pauses for all i.v.-treated subjects was provided. A figure of the diurnal pattern of occurrence of different types of AV blocks and sinus pauses for all i.v.-treated subjects was provided. All AV block and sinus pause data were listed by treatment sequence and subject for Part 1 and by subject for Part 2.

Summary - Conclusions

Demographic and background characteristics: A total of 16 subjects were enrolled in Part 1 with an overall mean age of 32.9 years (range 22 to 45 years), a mean weight of 80.08 kg (range 54.5 to 92.1 kg), and a mean BMI of 26.25 kg/m^2 (range 21.9 to 29.7 kg/m^2). More males were enrolled (93.8%) than females (6.3%). The majority of subjects were Caucasian (62.5%) and of ethnicity other than Hispanic/Latino or mixed ethnicity (56.3%). Demographic characteristics were generally similar for both treatment sequences.

A total of 17 subjects were enrolled in Part 2 with a mean age of 31.2 years (range 21 to 44 years), a mean weight of 73.08 kg (range 56.0 to 90.6 kg), and a mean BMI of 25.63 kg/m^2 (range 21.8 to 29.7 kg/m^2). More males were enrolled (70.6%) than females (29.4%). The majority of subjects were Caucasian (70.6%) and of ethnicity other than Hispanic/Latino or mixed ethnicity (47.1%).

Pharmacokinetic results: The total exposure (AUClast and AUCinf) of oral siponimod was approximately 84% of the values observed after i.v. dosing at the same dose level, displaying an absolute bioavailability of 84%. The route of administration did not alter the terminal half-life (27 to 28 hours) after a single 0.25-mg dose via either oral or i.v. route of administration. Following oral administration, siponimod concentrations showed a broad shoulder which peaked at 8 hours after dosing. After i.v. dosing, Cmax was reached at the end of the 3-hour infusion. The oral Cmax was approximately 52% of the i.v. Cmax.

Overall, these results indicate that the oral dosing of siponimod exhibited good exposure of siponimod compared with the i.v. dosing.

The metabolite M16 was BLQ at all time points for both routes of administration. The median oral and i.v. M17 Tmax was observed at 96 hours after dosing. The geometric mean M17-to-parent molecular ratios were also comparable between the 2 routes of administration, ranging from 0.81 to 0.97 based on AUCinf, suggesting that siponimod is extensively metabolized to M17. The metabolite, M17, represents about 81% to 97% of the parent exposure (based on AUCinf) and was identified in the current study as the most prominent systemic metabolite in human. It should be noted that the extrapolation of AUCinf was high (> 20%) in most subjects due to the long T1/2 of the M17 metabolite. However, the correlation coefficient for the slope of the terminal phase was noted to be strong.

Following a 1 mg i.v. siponimod infusion over 24 hours (4 consecutive 6-hour i.v. infusions of 0.25 mg of siponimod), mean plasma concentrations of siponimod peaked at the end of the infusion (median Tmax 23.9 hours) and then decreased with a geometric mean terminal half-life of 33.1 hours. Total systemic clearance and Vz were comparable to the values observed after a single 0.25 mg i.v. dose. The PK of M16 and M17 were also comparable after a 1 mg dose to what was observed after a single 0.25 mg i.v. dose (M16 was BLQ at all time points). It should be noted that the extrapolation of AUCinf was high (> 20%) in most subjects due to the long T1/2 of the M17 metabolite. However, the

correlation coefficient for the slope of the terminal phase was noted to be strong.

Pharmacodynamic results: Following the single i.v. or oral dose of 0.25 mg siponimod, the observed nadir ALC (Emax) was comparable between the 2 routes of administration. The median TEmax was 6.17 hours for both 0.25 mg i.v. and oral siponimod (Treatment A and B, respectively). Siponimod displayed a longer TEmax (approximately 24 hours) for Treatment C (1 mg i.v. dosing) compared with the TEmax of Treatment A and B (approximately 6 hours) due to continuous infusion over 24 hours. Siponimod displayed a dose-dependent effect with a greater decrease in ALC change from Baseline and a longer time in return to Baseline when the i.v. dose was increased from 0.25 mg to 1 mg. Absolute lymphocyte counts returned to Baseline approximately 48 hours after a single 0.25 mg dose (i.v. or oral) siponimod, while ALC returned to Baseline 144 hours after a 1 mg i.v. infusion. The nadir of the mean ALC change from Baseline occurred at 6 hours after dosing for Treatments A and C and at the end of infusion (24 hours) for Treatment C. The mean ALC change from Baseline was −0.333 10E9/L (−17.6%) for Treatment A, −0.440 10E9/L (−23.6%) for Treatment B, and −0.763 10E9/L (−41.7%) for Treatment C.

Heart rate analyses were based on averaged individual and mean, minimum, and maximum 1-minute, 5-minute, and hourly average HR data from 25-hour Holter ECG recordings in i.v.-treated subjects. No clinically relevant or symptomatic effect on mean hourly average HR was observed and mean hourly average HR remained above 50 bpm during the entire 25-hour Holter ECG recording period (from 1 hour before and until 24 hours after the start of infusion) period following i.v. administration of 0.25 mg siponimod over 3 hours (Treatment B) and 1.0 mg infusion over 24 hours (Treatment C). Bradyarrhythmic events such as AV blocks and sinus pauses detected in the online cardiac monitoring/25-hour Holter ECG recording were asymptomatic and their frequency, duration, and diurnal pattern of occurrence was consistent with observations from previous clinical studies and yielded no new safety signals.

Safety results: Overall, a single oral dose of 0.25 mg and single i.v. doses of 0.25 mg over 3 hours and 1 mg over 24 hours (4 consecutive 6-hour i.v. infusions of 0.25 mg) of siponimod were safe and well tolerated by the healthy subjects in this study. There were no deaths or SAEs reported during the study. Two subjects in Part 1 discontinued due to TEAEs (back pain and asymptomatic non-sustained ventricular tachycardia).

Overall, 7 subjects (43.8%) in Part 1 experienced at least 1 TEAE during the study and 4 subjects (25.0%) reported TEAEs (headache, fatigue, and feeling abnormal) that were suspected to be related to study treatment. All TEAEs in Part 1 were mild in severity and resolved by the end of the study.

Six subjects (35.3%) in Part 2 experienced at least 1 TEAE during the study and 2 subjects (11.8%) reported TEAEs (blurred vision, feeling hot, dizziness, and headache) that were suspected to be related to study treatment. All TEAEs Part 2 were mild in severity and resolved by the end of the study.

No clinically relevant changes in clinical laboratory results and vital sign parameters were noted during the study and no individual value was reported as a TEAE by the investigator.

Conclusion:

Pharmacokinetics

- The absolute bioavailability of siponimod as a single 0.25 mg dose administered orally was 84%, as compared with a single 0.25 mg siponimod i.v. dose administered over 3 hours in healthy subjects.
- Mean peak exposure of oral siponimod was approximately 48% lower than that of i.v. siponimod (both at 0.25 mg).
- Median oral siponimod Tmax was observed 8 hours after dosing, while median i.v. siponimod Tmax was observed at the end of the 3-hour infusion.
- After administration of a single i.v. or oral dose of siponimod 0.25 mg or as 4 consecutive 0.25-mg i.v. infusions over 24 hours (1 mg), concentrations of M16 were not detected.
- After administration of a single i.v. or oral dose of siponimod 0.25 mg or as 4 consecutive 0.25-mg i.v. infusions over 24 hours (1 mg), concentrations of LYS815 (M17) displayed a median Tmax of 96 hours. The geometric mean metabolite-to-parent molecular ratios for M17ranged from 0.687 to 0.974 for AUCinf. It was noted that extrapolation of AUCinf was high with a strong correlation coefficient in the terminal phase and should have limited interpretation.

Pharmacodynamics

- Mean ALC and mean ALC change from Baseline were comparable after a single 0.25 mg oral and i.v. dose of siponimod.
- Mean ALC returned to Baseline approximately 48 hours after dosing of 0.25 mg siponimod.
- When the dose increased from 0.25 mg to 1 mg i.v., the maximum mean ALC reduction from Baseline increased from 0.440 10E9/L to 0.763 10E9/L and the mean time to return to Baseline increased from 48 hours to 144 hours after dosing.
- Treatment C AUEC was higher (677 h*10E9/L) compared with AUEC of Treatment A (612 h*10E9/L) and Treatment B (618 h*10E9/L).
- Emax of Treatment C was lower (1.03 10E9/L) compared with Emax of Treatment A (1.39 10E9/L) and Treatment B (1.38 10E9/L).
- Median TEmax of Treatment C was longer (approximately 24 hours) compared with median TEmax of Treatment A and B (approximately 6 hours).
- Heart rate analyses were based on averaged individual and mean, minimum, and maximum 1-minute, 5-minute, and hourly average HR data from 25-hour Holter ECG recordings in i.v.-treated subjects. No clinically relevant or symptomatic effect on mean hourly average HR was observed and mean hourly average HR remained above 50 bpm during the entire 25-hour Holter ECG recording period (from 1 hour before and until 24 hours after the start of infusion) period following i.v. administration of 0.25 mg siponimod over 3 hours (Treatment B) and 1.0 mg infusion over 24 hours (Treatment C).
- Bradyarrhythmic events such as AV blocks and sinus pauses detected in the online cardiac monitoring/25-hour Holter ECG recording period were asymptomatic and their frequency, duration, and diurnal pattern of occurrence was consistent with observations from previous clinical studies and yielded no new safety signals.

Safety

- A single oral dose of siponimod 0.25 mg and a single i.v. infusion of siponimod 0.25 mg over 3 hours were safe and well tolerated by healthy subjects in this study.
- An i.v. infusion of siponimod 1 mg over 24 hours (4 consecutive 6-hour i.v. infusions of 0.25 mg siponimod) was safe and well tolerated by healthy subjects in this study.

Date of report: 12-Aug-2016

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2126

EudraCT Number

Not applicable.

Planned and Actual Number of Patients
Planned: 32 subjects

Enrolled: 33 subjects

Batch Numbers

- BAF312 (siponimod) 0.25 mg film-coated final market image (FMI) tablet, administered as a single oral dose (Batch number 1010004141)
- BAF312 (siponimod), 0.25 mg lyophilisate in vial, administered as a single 3 hour i.v. infusion (Part 1; 0.25 mg) or as 4 consecutive 6-hour infusions (Part 2; 1 mg) (Batch number 1010006310)

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

Not applicable.

Publication(s)

Shakeri-Nejad K, Gardin A, Gray C, Neelakantham S, Dumitras S, Legangneux E. Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of Intravenous Siponimod: A Randomized, Open-label Study in Healthy Subjects. Clinical Therapeutics 2020 Jan;42(1):175-195. doi: 10.1016/j.clinthera.2019.11.014. Epub 2020 Jan 8.

Investigators & Information on Study Centers

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