NOVARTIS

Novartis Clinical Trial Results

Name of finished product: BAF312

Name of active ingredient: Siponimod

Study number: CBAF312A2116

Title of study: A randomized, double-blind, placebo-controlled study to evaluate pharmacodynamic and/or pharmacokinetic interaction of BAF312 (siponimod) and propranolol when co-administered in healthy subjects.

Investigators: Thomas Marbury MD and Robert G. Perry MD

Study centers: This study was conducted at two centers in US: 1. Orlando Clinical Research Center, Orlando Florida, USA; 2. Elite Research Institute, Miami, Florida, USA

Study period
First subject enrolled: 07-Aug-2012

Last subject completed: 25-Oct-2012

Phase of development: I

Objectives:

Primary objective: To measure the negative chronotropic effect of siponimod and propranolol co- administration after 10 days of combined treatment in healthy subjects.

Secondary objectives:

- To measure the negative chronotropic effect of propranolol and siponimod co-administration on Day 20 when propranolol treatment is initiated after 10 days of siponimod treatment in healthy subjects.
- To measure the negative chronotropic effect of siponimod and propranolol co-administration at start and at the highest dose of siponimod titration regimen when siponimod is initiated after 10 days of propranolol treatment, as well as at start and Day 16 when propranolol is initiated after 10 days of siponimod treatment.
- To assess the cardiac and pulmonary effects of siponimod and propranolol co-administration on Day 11, 16 and 20 (Day 12 and 19 for pulmonary effects) when the combination treatment is initiated after 10 days of siponimod or propranolol treatment.
- To investigate whether the co-administration of siponimod and propranolol leads to a pharmacokinetic (PK) drug-drug interaction (effect of siponimod on the PK of propranolol and/or effect of propranolol on the PK of siponimod) at steady state in healthy subjects.

Methodology: This was a double-blind, randomized, placebo-controlled study in healthy subjects to evaluate any pharmacodynamic and/or pharmacokinetic drug-drug interaction when siponimod and the beta blocker propranolol are co-administered in healthy subjects. Furthermore, this study wanted to assess if siponimod can be safely co-administered with propranolol and provide guidance for use in the patient population. Each subject was randomly assigned to undergo one of the four following treatment arms.

Group A: Siponimod dose titration regimen (Day 1-6) + siponimod 2 mg (Day 7-20) and propranolol- placebo (Day 1-10) + propranolol 80 mg LA (Day 11-20)

Group B: Siponimod-placebo (Day 1-10) + siponimod dose titration regimen (Day 11-16) + siponimod 2mg (Day 17-20) and propranolol 80 mg LA (Day 1-20)

Group C: Siponimod-placebo (Day 1-20) and propranolol-placebo (Day 1-20) Group D: Siponimod-placebo (Day 1-20) and propranolol 80 mg LA (Day 1-20)

Number of subjects (planned and analyzed): A total of 76 subjects were randomized to participate in the study, of whom 73 completed the study as per protocol and 3 were discontinued (One subject from Group A was discontinued due to an AE of abnormal liver function test on Day 20, One subject from Group B discontinued due to administrative problems on Day 15 and one subject from Group C withdrew from the study for personal reasons on Day 16).

Diagnosis and main criteria for inclusion Key inclusion criteria:

- Healthy male and female subjects of 18 to 55 years of age included, and in good health as determined by past medical history, physical examination, vital signs, ECG, 24 h Holter evaluation (screening) and laboratory tests. Subjects were to have a predicted $FEV_1 \geq 90\%$ predicted normal at screening.
- At screening, and baseline, vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate) were assessed in the sitting position after the subject had rested for at least three minutes and again (when required) after three minutes in the standing position. Sitting vital signs were to be within the following ranges:
  - oral body temperature between 35.0-37.5 °C
  - SBP, 90-140 mm Hg
  - DBP, 50-90 mm Hg
  - pulse rate, 50 - 90 bpm

Key exclusion criteria:

- Women of child-bearing potential or pregnant/nursing (lactating) women
- Homozygous carrier for CYP2C9*3 genotype.
- Current (via 24 h Holter or ECG at screening /baseline) or medical history (as far as known by the subject) of any of the following cardiovascular findings as noted

by the 24 h Holter evaluations done at screening:

- 2nd and 3rd degree AV-block
- Average hourly heart rate < 50 beats/minute during waking hours in the 24 h Holter evaluation at screening
- clinically significant ECG findings (at screening or baseline)
- PR > 200 msec
- QRS complex > 120 msec
- QTcF > 450 msec (females) or > 430 msec (males) for subjects ≤ 30 years of age
- QTcF > 470 msec (females) or > 450 msec (males) for subjects > 30 years of age
- Prominent U waves or any significant morphological changes other than non-specific T-wave changes
- Presence or history of clinically significant ventricular arrhythmias
- Presence or history of clinically significant supraventricular arrhythmias (e.g. atrial fibrillation, atrial flutter, supraventricular tachycardia)
- Arrhythmias such as Brugada syndrome, Long QT syndrome, Wolff–Parkinson–White syndrome (WPW), Lown-Ganong-Levine syndrome (LGL), Arrhythmogenic right ventricular dysplasia (ARVD), etc.,
- Heart failure or known left ventricular dysfunction.

- Recent (within the last three 3 years) and/or recurrent history of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).

Test product, dose and mode of administration, batch number: The investigational drug siponimod (0.25 mg and 1 mg) film-coated tablets, siponimod-placebo (exact match) film-coated tablets, and a non-exact matching placebo to propranolol were provided by Novartis and supplied to the investigator as open labeled bulk medication. These drugs were administered orally.

Reference therapy, dose and mode of administration, batch number: Propranolol (80 mg long acting preparation) is available as a prescription drug and was sourced locally by the sites. This drug was administered orally.

Duration of treatment: This study consisted of up to 28-day screening period, one baseline evaluation period of two days, and a treatment period of 20 days followed by a study completion evaluation approximately 10 days after the last drug administration. There were four parallel treatment arms for evaluation in the study.

Criteria for evaluation

Pharmacodynamics: The pharmacodynamics assessments performed in this study included: 12 Lead Holter recording and monitoring (HR, PR, bradyarrythmias), triplicate blood pressure measurement and pulmonary function test (spirometry).

Safety: Safety assessments consisted of collecting all AEs, SAEs, with their severity

and relationship to study drug, concomitant medications/therapies, and pregnancies. They included the regular monitoring of ECG, continuous cardiac monitoring (telemetry), Columbia-suicide severity rating scale (C-SSRS), hematology including absolute lymphocyte counts (ALC) and lymphocyte subsets (Flow Cytometry), blood chemistry, liver function tests, and urinalysis performed at the local laboratory, and regular assessments of vital signs, physical condition, body weight, height, and meal records.

Pharmacokineics: The PK parameters determined in this study included: Cmax,ss, Tmax,ss, Cmin,ss, Cav,ss, AUCtau,ss and Fluc,ss.

Bioanalytics: Plasma concentrations of siponimod were determined by a validated LC-MS/MS method. Plasma concentrations of propranolol were determined by a validated LC-MS/MS method.

Statistical methods: All data for vital signs, ECG evaluations, hematology, blood chemistry and urinalysis were listed for each subject and summarized by treatment group and visit/time. The pharmacokinetic concentration data was listed by treatment group, subject and sampling time. Summary statistics were provided by treatment group, profile day and time point.

The pharmacokinetic parameter data was listed by treatment group, subject and profile day. Summary statistics were provided by treatment group and profile day.

Log-transformed PK parameters (Cmax,ss and AUCtau,ss) were analyzed using linear model with treatment and subject as fixed factors. Point estimates and 90% CI for the ratio of treatment means of siponimod or propranolol and siponimod + propranolol combination were provided. Supportive analysis was performed using same model with treatment as fixed factor and subject as random factor.

Emax, the daily maximum effect on heart rate was analyzed by using mixed effects analysis of covariance (ANCOVA) model with treatment, day and interaction of treatment and day as fixed factors, average 24 h baseline value as covariate and subject as random factor. An appropriate contrast was used to estimate the difference of treatment Group A and B combined vs. treatment Group D on Day
20. The 95% confidence interval (CI) and the p-value for equality of the effects of siponimod + propranolol and propranolol were presented.

The secondary endpoints [Emax(0-12), Emax(0-24), AUEC and minimum hourly average heart rate for heart rate; Emax(0-12), Emax(0-24), AUEC and minimum MABP for blood pressure; time-matched change from baseline and raw values for PR interval and for pulmonary function test parameters (FEV1, FVC, FEF25-75% and FEV1/FVC) were also analyzed as above for the evaluation of different contrast of interest.

Summary - Conclusions

Demographic and background characteristics: A total of 76 subjects were randomized in the study. Of the 76 subjects participating in the study, 61 (80.3%) were males and 15 (19.7%) were females; 45 (59.2 %) subjects were Caucasians, 29 (38.2

%) were Black and two (2.6 %) were captured as “other”. The mean (SD) age for all subjects was 37.1 (10.27) years (range 19 - 55 years), the mean weight was 77.9 (11.39) kg (range 53.1 - 104.7kg), and the mean BMI was 26.16 (2.57) kg/m^2 (range 20.23 -
30.48 kg/m^2).

Pharmacodynamic results: The combination treatment at steady state (Group A and B combined on Day 20) showed an additional decrease of mean Emax HR by 6.21 bpm (95% CI: 2.32, 10.11; p=0.002) when compared to propranolol alone over 24 hours of evaluation.

The combination treatment (Groups A and B combined on Day 20) at steady state showed an additional Emax MABP decrease of 2.93 mmHg (95% CI: -0.28, 6.14; p= 0.0734) in comparison to propranolol alone over 24 hours of evaluation.

The change from baseline in combination treatment at steady state (Groups A and B combined on Day 20) showed a mean increase of PR interval by 2.45 msec (95% CI: -5.32, 10.22; p=0.5341) at 2.5 hours post-dose and 7.06 msec (95% CI: 0.05, 14.07; p=0.0485) at 6.5 hours post-dose, in comparison to propranolol alone. In approximately, 76 x 6 days of 24 hour Holter recordings on study treatment days, only a few bradyarrythmias were reported. None of the events were associated with any clinical signs or symptoms.

The change from baseline in combination treatment at steady state (Day 19) showed an additional change of FEV1 by mean -0.07 L (95% CI: -0.17, 0.03; p=0.1804) when propranolol was administered on top of siponimod (after dose titration in Group A) and -0.05 L (95% CI: -0.15, 0.05; p=0.2957) when siponimod was administered on top of propranolol (Group B), in comparison to propranolol alone.

Safety results:

- Siponimod was generally well tolerated in this study.
- There were no deaths or SAEs or AE of severe grade reported in this study. All the AEs were of mild to moderate grade.
- One subject was discontinued in the study due to AE of elevated liver enzymes. Three subjects had elevated liver enzymes more than or nearly 5 times of normal in treatment arm A (siponimod from Day 1-10, siponimod + propranolol from Day 11-20), including one subject who was discontinued. These events were resolved during the follow up period.
- There was no cardiovascular AE noted in the study except for one AE of orthostatic lightheadedness in arm D (propranolol from Day 1-20) and it resolved spontaneously during treatment.

Pharmacokinetic results: The study results showed that co-administration of siponimod and propranolol decreased siponimod AUCtau,ss and Cmax,ss by approximately 7% and decreased the propronolol AUCtau,ss and Cmax,ss by approximately 18% and 15% respectively. The 90% CI of geometric mean ratio remained in the bioequivalence range for siponimod Cmax, ss and AUCtau,ss. However, the lower limits of 90% CI of geometric mean ratio are outside the

bioequivalence limit for propranolol Cmax,ss and AUCtau,ss.

Siponimod Cmax,ss and AUCtau,ss observed in this study were comparable to a historical study in which healthy subjects received siponimod 2mg q.d for 10 days without co- medications. The variability of siponimod Cmax,ss and AUCtau,ss were comparable between studies. Hence, the steady state PK of siponimod was consistent with the historical studies such as

Conclusion:

- The combination treatment led to a mean Emax HR decrease of 6.21 bpm compared to propranolol alone and the mean minimum hourly average HR remained above 50 bpm. Addition of propranolol on top of siponimod had lesser negative chronotropic effects in comparison to addition of siponimod on top of propranolol. There was slight decrease in BP in the combination treatment in comparison to propranolol alone.
- There was a trend for slight prolongation of PR interval with the combination treatment. There was no 2nd degree AV block or sinus pause of more than 3 sec duration noted in the study during the combination treatment.
- There were no clinically significant changes in the pulmonary function with either drug alone or combination treatment.
- Concomitant administration of siponimod and propranolol had only minor effect on siponimod Cmax,ss and AUCtau,ss (7% decrease), while the propranolol Cmax,ss and AUCtau decreased by 15 and 18% respectively.
- The combination treatment was well tolerated in a healthy subject population.

Date of report: 30-Jul-2013

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2116

EudraCT Number

Not applicable.

Planned and Actual Number of Patients

Planned: 76 subjects

Enrolled: 76 subjects

Batch Numbers

Study drug and strength	Formulation control number	Batch number
Siponimod 0.25 mg film-coated tablets	6002636.008	X0090112
Siponimod 1 mg film-coated tablets	6002630.009	X0120112
Siponimod-placebo film-coated tablets	6002679.003	X1380411
Generic placebo hard gelatin capsule	3755667.032	H503EE

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

Propranolol (80 mg long acting preparation) is available as a prescription drug and was sourced locally by the sites. This drug was administered orally.

Publication(s)

Biswal S, Polus F, Pal P, Veldandi UK, Marbury TC, Perry R, Legangneux E. Pharmacokinetic and pharmacodynamic interaction of siponimod (BAF312) and propranolol in healthy subjects. Int J Clin Pharmacol Ther. 2015 Oct;53(10):855-65. doi: 10.5414/CP202369.

NOVARTIS

Investigators & Information on Study Centers

Investigator	Facility Name Address Country
Thomas C. Marbury	Orlando Clinical Research Center 5055 S. Orange Ave, Orlando FL 32809, US
Robert Perry	Elite Research Institute 15705 NW 13th Avenue, Miami, FL 33169, US