Novartis Clinical Trial Results

Name of finished product: N/A

Name of active ingredient: siponimod 0.25 mg film coated tablets

Study number: CBAF312A2128

Title of study: Open-label study to assess the pharmacokinetics, safety and tolerability of siponimod in healthy subjects with CYP2C9 extensive (EM) and poor metabolizer (PM) phenotype

Investigator(s): Dr. Jason Lickliter, et al.

Study center(s): Australia (one center), France (one center), Jordan (one center) and United States (one center).

Study period:

- First subject enrolled: 23-May-2013 (first subject first visit)
- Last subject completed: 01-May-2015 (last subject last visit)

Phase of development: Phase I

Objectives:

Primary objective: To compare the PK of siponimod in healthy subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes with those of wild-type subjects (CYP2C9*1/*1) at a single, oral dose of 0.25mg.

Secondary objectives:

- To evaluate the PK profile of siponimod (and its metabolites M3 and M5) in healthy subjects with the CYP2C9 PM phenotype (=CYP2C9*2/*3 and CYP2C9*3/*3) after 0.5mg dose preceded by 0.25mg qd over two days.
- To compare the pharmacokinetics of siponimod metabolites M3 and M5 in healthy subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes with those of wild-type subjects (CYP2C9*1/*1) at a single oral dose of 0.25mg.
- To assess the safety and tolerability of siponimod in healthy subjects with the CYP2C9 EM and PM phenotype at a single oral dose of 0.25mg and at 0.5 mg dose preceded by 0.25 mg qd over two days for subjects with the CYP2C9 PM phenotype.

Methodology: This was a multicenter, open label study that had two parts.

Part 1 included CYP2C9 Extensive metabolizers (EM) and Poor metabolizers (PM) receiving a single, oral dose of 0.25mg siponimod.

Part 2 included PMs that had completed Part 1 receiving 0.25 mg (Day 1 and 2) and 0.5mg (Day 3) of siponimod.

Number of subjects (planned and analyzed): A total of 36 subjects were planned to be recruited in the study. However, only 24 subjects including 12 EMs and 12 PMs were actually enrolled. All subjects completed the study and were included in the PK and safety analysis set.

Diagnosis and main criteria for inclusion:

The study population comprised of healthy male and female subjects with the CYP2C9 extensive (i.e. CYP2C9*1/*1 genotype) or poor metabolizer phenotype (i.e. CYP2C9*2/*3 or CYP2C9*3/*3 genotype) who passed screening and baseline assessments, complied with inclusion/exclusion criteria and provided written informed consent.

Each subject carrying with a CYP2C9*1/*1 genotype was matched by body weight (± 10%) to a subject with a CYP2C9*2/*3 or *3/*3 genotype. Each female subject had to be of non-childbearing potential

Main inclusion criteria:

- Age: 18 to 70 years
- Body weight: ≥50kg
- BMI: 18-30 kg/m^2

Main exclusion criteria:

Clinically significant disease of any major system organ class not resolved within 2 weeks prior to initial dosing.

- History or presence of any clinically significant ECG abnormalities
- History or presence of any of relevant adverse cardiovascular findings
- Any surgical or medical condition other than hepatic impairment which could significantly alter the absorption, distribution, metabolism, or excretion of drugs
- Smokers as defined by use of tobacco products in the previous 3 months

Test product, dose and mode of administration:

The investigational drug, siponimod 0.25mg, was prepared by Novartis and supplied to the Investigator as open label bulk medication.

Study medication was administered orally with 180-240mL of water in the morning following an overnight fast of at least 10 h.

Duration of treatment:
Part 1: 0.25 mg single dose
Part 2: 0.25mg single dose was administered on Day 1 and Day 2 and 0.5mg on Day 3.

Reference therapy, dose and mode of administration, batch number:

Not applicable

Criteria for evaluation

PK:

Part 1:

The PK of siponimod was studied in plasma up to 984 h post-dose (Day 42) at the following time points pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 144, 216, 312 (Day 14), 408 (Day 18), 504 (Day 22), 600 (Day 26), 720 (Day 31), 840 (Day 36) and 984 h post-dose (Day 42).

The following PK parameters of siponimod were determined using the actual recorded sampling times and non-compartmental method(s) with WinNonlin Pro (Version 5.2 or higher):

- Cmax, Tmax, AUClast, AUCinf, T1/2, Vz/F and systemic clearance (CL/F) and other parameters as appropriate from the plasma concentration-time data.

Part 2:

- The PK of siponimod was studied in plasma at the following time points:
- Days 1 and 2: pre-dose
- Day 3: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 h post-dose
- Selected metabolites M3 and M5 were quantified in both Parts 1 and 2 using the same samples as described above.
- AUC0-24h, Cmax, Tmax and other parameters as appropriate from the plasma concentration- time data.

The same PK parameters were determined for selected metabolites M3 and M5.

Safety

Safety assessments included documentation of all adverse events (AEs). In addition, laboratory, vital sign, ECG and suicidality assessments were repeatedly conducted during the study. Holter ECG monitoring was applied over a 25h-period in part 1 (Day 1) and 73h-period in part 2 (Day 3).

Statistical methods: The primary endpoints were the PK parameters Cmax, AUClast and AUCinf from part 1 of the study. The log-transformed PK parameters were analyzed by a fixed effects model, with genotype as a fixed factor and baseline body weight as a covariate. The geometric mean ratios and 90% confidence intervals of the PM phenotypes vs the EM phenotype were obtained from the analysis.

In addition a supportive analysis on the log-transformed PK parameters was performed using a fixed effects model, with genotype as a fixed factor and subject pairing as a covariate.

Summary - Conclusions

Demographic and background characteristics:

- Mean age: 41.9 years (SD 16.4)
- Mean body weight: 70.83 (SD 9.873)
- Mean BMI:24.021 (SD 2.3232)
- Gender distribution: N=21/3 (male/female)

Demographic and other baseline characteristics were similar when comparing EM and PM phenotype groups.

PK results

Primary pharmacokinetic results

In Part 1, siponimod PK parameters of PMs after a single oral dose of 0.25mg were compared with reference data of EMs (CYP2C9*1/*1 genotype).

AUCinf and AUClast of siponimod were approx. 2- and 4-fold, while Cmax was only 21% and 16% greater in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotype respectively, compared to subjects with the CYP2C9*1/*1 genotype.

Median siponimod Tmax was comparable in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotype and EMs (4-5 h).

Siponimod T1/2 was prolonged in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes (51h and 126h, respectively) compared to EMs (28h).

Secondary pharmacokinetic results

In Part 1, Cmax and AUCs of the metabolites M3 and M5 were markedly lower in PM subjects especially in CYP2C9*3/*3 carriers, compared to CYP2C9*1/*1 subjects.

In Part 2, after an administration of a 0.5 mg dose preceded by 0.25 mg q.d. over two days, subjects with CYP2C9*2/*3 and CYP2C9*3/*3 genotypes were comparably exposed to siponimod, while a 4-5- fold lower M3 and M5 Cmax and AUC0-24h were observed in CYP2C9*3/*3 subjects compared to CYP2C9*2/*3 carriers.

Safety results

General safety & tolerability

Siponimod (0.25 and 0.5 mg) was safe and tolerated in subjects with EM and PM genotypes at single oral doses of 0.25 mg in Part 1, and after consecutive doses up to 0.5 mg in Part 2 (0.25 mg on Day 1 and Day 2 and 0.5 mg on Day 3).

There were no deaths or other SAEs. None of the AEs reported led to individual study discontinuation.

Overall, five of 24 subjects exposed to BAF312 presented with an AE during the study. Headache was the most commonly reported AE that occurred in two subjects, while all other AEs occurred in a reduced frequency were identified in single subjects only.

There was only a single AE that was suspected to be study drug-related (somnolence).

Most AEs were of mild intensity, while only two AEs were of moderate intensity (conjunctivitis, viral rash).

With the exception of 2 events all AEs resolved by the end of study visit. These

two AEs which were still ongoing at EOS visit include skin discoloration, temporomandibular joint syndrome.

No systematic, clinically relevant alterations of laboratory, vital sign or ECG data were identified.

Cardiovascular safety

Bradyarrhythmic events

Arrhythmia analysis revealed no major imbalance with regards to the incidence of relevant ECG findings between CYP2C9 genotype groups. There were no cases of supraventricular or ventricular arrhythmia.

One subject (CYP2C9*3/*3 genotype) presented with bradyarrhythmic events during the course of this study. Three asymptomatic episodes of 2nd degree AVBs and one episode of sinus pause of 2.25 s have been identified in a subject with the CYP2C9*3/*3 genotype. Two of the 3 observed episodes of 2nd degree AVBs Mobitz 1 were detected during resting/nocturnal hours. All events were asymptomatic and based on their nature and total number not considered to be of clinical relevance, which are associated with increased vagal tone leading to increases in PR interval as a result of negative dromotropic effects at the AV node and to a higher physiological incidence of brady arrhythmic events such as AVBs and SPs. All detected AVBs and sinus pauses were observed in one subject only, were entirely asymptomatic and based on their nature and total number not considered to be of clinical relevance.

Heart rate analysis

HR over time: In Part 1/Day 1 the mean hourly/5-min average HR did not show any clinically relevant difference between the different CYP2C9 genotype groups. The mean hourly/5-min average HR reached its daytime nadir during the 25 h Holter recording on Day 1 at around 11 or 12 AM in the whole subject population and in the different genotype groups (i.e. approximately 3-4 hours after dose administration, which is approximately consistent with the median siponimod plasma concentration Tmax) and remained above 50 bpm during the entire recording. The daytime nadir of the mean hourly/5-min average HR in subjects with CYP2C9 genotype *3/*3 was approximately 3 bpm lower compared to the daytime nadir of subjects with other genotypes and the lower bound of the 90% CI of the mean hourly HR around the daytime nadir and during the “nocturnal dip” was below 50 bpm. In Part 2 during the continuous Holter ECG assessments on Days 1-3 (including the morning of Day 4), the mean hourly/5-min average HR did not show any clinically relevant difference between the different CYP2C9 genotype groups. The mean hourly/5-min average HR reached its daytime nadir on each day of up-titration at around 11 or 12 AM in the whole subject population and in the different genotype groups (i.e. at the time of median Tmax) and the daytime nadir remained above 50 bpm during the entire recording period. In both study parts, the observed HR effects during the nocturnal hours and in the first hours after siponimod administration were asymptomatic in all subjects and were

considered to be of no clinical relevance.

Exposure response: In both study parts, concentration-response analysis for total siponimod plasma concentration and the actual HR in all subjects (all CYP2C9 genotypes) and in different CYP2C9 genotypes revealed negative correlations. The negative regression lines remained above 50 bpm in the investigated exposure range.

Conclusion

Siponimod was safe and tolerated in healthy subjects with different CYP2C9 genotypes including extensive (CYP2C9*1/*1) and poor metabolizers (CYP2C9*2/*3 or CYP2C9*3/*3) at single oral doses of 0.25 mg and during multiple dosing for 3 days (0.25 mg q.d. on Day 1 and 2 and 0.5 mg q.d. on Day 3).

After a single oral doses of 0.25 mg, the AUCinf and AUClast of BAF312 was approx. 2- and 4-fold higher in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotype, respectively, compared to extensive metabolizers (CYP2C9*1/*1). However, there was only a minor increase of Cmax determined by 16% and 21%, respectively.

At single oral doses of 0.25 mg and during multiple dosing for 3 days (0.25 mg q.d. on Day 1 and 2 and 0.5 mg q.d. on Day 3) average HR and arrhythmia analysis did not show any clinically relevant difference between CYP2C9 genotype groups. All detected AVBs and sinus pauses were observed in one subject only, were entirely asymptomatic and based on their nature and total number not considered to be of clinical relevance.

Along with the favorable exposure-response analyses of the HR effects in both study parts the results of this study indicate that the first part of the established dose titration regimen with siponimod efficiently attenuates bradyarrhythmic effects in CYP2C9 poor metabolizer subjects with *2/*3 and *3/*3 genotypes.

Date of report: 29-Sep-2015

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2128

EudraCT Number

2012-005445-20

Planned and Actual Number of Patients
Planned: 36 subjects

Enrolled: 24 subjects

Batch Numbers

The investigational drug, siponimod 0.25mg, was prepared by Novartis and supplied to the Investigator as open label bulk medication. The batch numbers of siponimod were X009 0112 & X238 0613.

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.

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