Sponsor

Novartis

Generic Drug Name

Siponimod (BAF312)

Trial Indication(s)

Subjects with and without Renal Impairment were enrolled in the study, but the drug was not intended to treat the Renal Impairment condition.

Protocol Number

BAF312A2129

Protocol Title

A single-dose, open-label, parallel-group study to assess the pharmacokinetics of BAF312 in subjects with renal impairment compared to subjects with normal renal function

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

17-Jul-2013 (first subject first visit) - 03-Nov-2014 (last subject last visit)

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This was an open-label, non-randomized, parallel-group, non-confirmatory study in subjects with severe (Group 1), moderate (Group 2) and mild (Group 3) RI and healthy control subjects matched for age, sex and body mass index (BMI) (Group 4). A total of approximately 48 male and female subjects were planned to be enrolled in the study.

The study employed a “top down” study design, starting in severe renal impairment subjects with an interim PK/safety analysis after completion of eight severe renal impairment and eight matched healthy subjects. Enrollment of mild and moderate renal impairment groups was only planned, when interim PK review would have revealed ≥ 50% increase of total or free siponimod Cmax or AUC in subjects with severe renal impairment compared to matched healthy subjects. Here the Cmax stands for maximum concentration following drug administration [mass/volume] and AUC stands for area under concentration-time curve [mass x time/volume]. The results of the interim analysis of safety/PK data, did not fulfill the PK criteria of ≥ 50% increase of total or free siponimod Cmax or AUC in subjects with severe renal impairment compared to matched healthy subjects and no clinically significant safety or tolerability findings were detected. The study was hence completed with severe renal impairment subjects and matched healthy subjects only and enrollment of moderate and mild renal impairment subjects and their healthy matched subjects was not warranted.

Centers

2 centers in 2 countries: Romania (1), United States (1)

Publication

None

Objectives

Primary objective

To investigate the pharmacokinetics of siponimod and selected metabolites after administration of a single oral dose of 0.25 mg of siponimod in subjects with different degrees of renal impairment in comparison to healthy control subjects.

Secondary objective

To investigate the safety and tolerability of siponimod after a single oral dose of 0.25 mg of siponimod in subjects with different degrees of renal impairment in comparison to healthy control subjects.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral film-coated tablet of Siponimod 0.25 mg, single dose

Statistical Methods

Pharmacokinetics parameters (Cmax, AUClast and AUCinf) of siponimod and metabolites were compared between renal impaired group (Severe) vs. matched healthy subjects group. Log-transformed PK parameters were analyzed separately using a linear mixed effect model with subject group as fixed factor and matching

pair as random factor. Least square means for each group as well as estimated difference between renal impaired subjects and respective matched healthy subjects with corresponding 90% confidence intervals on the log-scale was calculated. These estimates were backtransformed to obtain geometric means, ratio of geometric means, and the associated 90% CI for the comparison of renal impaired group vs. matched healthy subjects.

Similar analysis as mentioned above was also performed to compare fu (fraction unbound) of siponimod between renal impaired group (severe renal impairment) vs. matched healthy subjects group. If there was a statistically significant difference in fu between renal impaired group (severe renal impairment) vs. matched healthy subjects group, the same analysis was also performed to compare siponimod [(AUClast)u, (AUCinf)u, and (Cmax)u] between the renal impaired group (severe renal impairment) vs. matched healthy subjects group.

Descriptive statistics of safety data were provided.

Study Population: Key Inclusion/Exclusion Criteria

The planned study population comprised of male and female subjects at the age of 18 to 70 years, with severe (Group 1, N=8), moderate (Group 2, N=8) and mild (Group 3, N=8) RI and equal number of matched healthy subjects. Subjects were only enrolled if they were able to give written informed consent. All subjects were CYP2C9 wild-type (CYP2C9*1 homozygous carriers) as determined during screening. Subjects with RI (Group 1-3) were required to satisfy the different criteria for the severity of disease (in order to define them as severe, mild and moderate RI patients) using Modification of Diet in Renal Disease (MDRD) formula for estimated glomerular filtration rate (eGFR) at the time of screening. Similarly, healthy subjects were screened for good health and also normal renal function.

Women of child bearing potential, pregnant or nursing (lactating) were not enrolled in the study. Also, ECG abnormalities, especially with regards to any type of atrioventricular (AV blocks), family history or presence of long QT syndrome, history of cardiac rhythm abnormalities or cardiac rhythm, total WBC or lymphocyte counts outside the 1.5-fold local laboratory normal range or platelet count < 30,000/µL at screening or baseline were excluded from the study.
Few important exclusion criteria specific to RI subjects were:

- Any surgical or medical condition other than RI which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study
- Requirement for hemodialysis
- Renal impairment (RI) due to hepatic disease (e.g., due to hepatorenal syndrome)
- History or presence of coronary heart disease (stable or unstable), myocardial infarction, myocarditis, cardiomyopathy, heart failure-New York Heart Association II – IV (NYHA II – IV)

Participant Flow Table

-- Treatment 0.25 mg BAF312 --

Disposition Reason	Severe RI patient N=8 n (%)	HS* N=8 n (%)	Total subjects N=16 n (%)
Completed	8 (100)	8 (100)	16 (100)

*HS: Matched healthy subjects.

Baseline Characteristics

		Treatment 0.25 mg BAF312	
		Severe RI patient N=8	Matched healthy subjects N=8
Age (years) +	Mean (SD)	57.9 (6.22)	54.9 (5.28)
	Median	56.5	53.0
	Range	51 - 68	49 - 66
Height (cm) ++	Mean (SD)	166.1 (12.36)	168.4 (7.45)
	Median	168.3	169.3
	Range	148 - 179	156 - 179
Weight (kg) ++	Mean (SD)	80.68 (13.987)	83.84 (13.727)
	Median	84.45	82.70
	Range	56.4 - 103.0	69.3 - 99.0
BMI (kg/m2) ++	Mean (SD)	29.13 (3.276)	29.50 (3.762)
	Median	28.46	30.09
	Range	24.5 - 33.0	24.0 - 34.9
Sex - n(%)	Male	4 (50%)	4 (50%)
	Female	4 (50%)	4 (50%)
Predominant race - n(%)	Caucasian	6 (75%)	6 (75%)
	Black	2 (25%)	2 (25%)
Ethnicity - n(%)	Hispanic/Latino	1 (12.5%)	3 (37.5%)
	Other	7 (87.5%)	5 (62.5%)

Note: + Age is calculated from date of screening and date of birth.
++ Weight, height and BMI are taken from screening vital signs evaluation

Summary of Efficacy

Not applicable. Efficacy was not measured.

Primary Outcome Result(s)

Summary statistics for Siponimod and metabolites plasma PK parameters of primary interest following single dose of 0.25 mg BAF312. PK analysis set.

Group	Statistics	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)
0.25 mg BAF312 (Patients with severe renal impairment)	n	8	8	8
	Mean (SD)	2.07 (0.360)	99.0 (45.9)	102 (46.6)
	CV% mean	17.4	46.4	45.8
	Geo-mean	2.04	91.0	93.7
	CV(%) geo-mean	18.2	45.1	44.4
	Median	2.12	87.2	88.4
	[Min; Max]	[1.56;2.53]	[52.0;193]	[53.7;197]
0.25 mg BAF312 (Healthy subjects matched to severe RI patients)	n	8	8	8
	Mean (SD)	2.27 (0.544)	76.4 (21.5)	78.2 (22.0)
	CV% mean	24.0	28.1	28.1
	Geo-mean	2.21	73.8	75.4
	CV(%) geo-mean	23.8	29.4	29.5
	Median	2.14	77.4	78.9
	[Min; Max]	[1.66;3.16]	[52.2;109]	[52.9;110]

Summary of Safety

Safety Results

No adverse events or deaths were reported in this study.

Other Relevant Findings

None.

Conclusion

The results of this study showed that Total and unbound siponimod pharmacokinetics were only marginally affected in subjects with severe renal impaired functions, with comparable Cmax and only slightly increased AUCs compared to healthy matched subject group. Mean fraction unbound (fu) at 4 hours post-dose was not significantly different between severe renal impaired and healthy matched subjects.

M3 exposure was similar and M5 exposure was slightly lower in subjects with severe renal impairment compared with matched healthy subjects.

Single oral doses of 0.25 mg of siponimod were safe and well tolerated in subjects with severe renal impairment and demographically matched healthy subjects.

The observations from this study underline the safety and tolerability of the starting dose of the established dose-titration regimen (0.25 mg) in subjects with renal impairment.

Date of Clinical Trial Report

29 Apr 2015