Sponsor

Novartis

Generic Drug Name

Siponimod (BAF312)

Trial Indication(s)

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

Protocol Number

CBAF312A2122

Protocol Title

A single-dose, open-label, parallel-group study to assess the pharmacokinetics of BAF312 in subjects with mild, moderate and severe hepatic impairment compared to healthy control subjects

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

08-Oct-2012 (first subject first visit) to 04-Mar-2014 (last subject last visit)

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This was a multi-center, open-label, parallel-group, non-confirmatory study to assess the PK of siponimod in subjects with mild (Group 1), moderate (Group 2) and severe hepatic impairment (Group 3) compared to demographically matched healthy subjects (Group 4). The study consisted of a 21-day screening period, a baseline period (Day -1), a treatment period (Day 1) followed by a 21-day follow-up period. Approximately 3 weeks after drug administration the End of Study (EOS) evaluation was done.

Centers

3 centers in 2 countries: Hungary (2) and Russia (1)

Publication

Publication is in preparation. No published manuscripts at the time of results disclosure.

Objectives:

Primary objective:

To investigate the PK of BAF312 and selected metabolites after administration of a single dose of 0.25 mg of BAF312 in subjects with mild, moderate and severe hepatic impairment in comparison to healthy control subjects.

Secondary objective:

To investigate the safety and tolerability of BAF312 after a single dose of 0.25 mg of BAF312 in subjects with mild, moderate and severe hepatic impairment in comparison to healthy control subjects.

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

Siponimod 0.25 mg was administered orally.

Statistical Methods

Analysis of variance (ANOVA) was performed to compare the PK parameter of the hepatic impaired subjects in each severity category with the PK parameters of healthy control subjects matched by age, gender and BMI. Pharmacokinetic parameters Cmax, AUClast and AUCinf of siponimod were compared between each hepatically impaired group (mild, moderate and severe) vs. the matched control group. Log-transformed PK parameters were analyzed separately using a linear mixed effects model with group as fixed effect and matched pair as random effect (matched subject number was used as the matched pair variable). To avoid the duplication of subject data, separate analyses were performed for each comparison of PK parameters for hepatic impaired group versus the matched healthy group. Geometric means for each group with corresponding 90% confidence intervals were calculated. Back-transformed ratios and 90% confidence interval were provided. Though in this study a healthy subject was a match to maximum three different subjects with hepatic impairment from 3 severity groups, while performing statistical analysis of each group, the healthy subjects were distinct and hence it had no impact on the results of the statistical analysis.

Study Population: Key Inclusion/Exclusion Criteria

The study population comprised of healthy subjects and subjects with mild, moderate, and severe hepatic impairment, who passed screening assessments, complied with inclusion/exclusion criteria and provided written consent. Male and female subjects (females of non-childbearing potential, post-menopausal or surgically sterilized) aged between 18 to 70 years (inclusive); and who had body mass index (BMI) within the range of 18-35 kg/m2. Each healthy subject was matched in gender, age (±5 years), and BMI (±10%) to an individual subject with hepatic impairment.
Only CYP2C9*1 homozygous carriers were eligible to be enrolled in this study.

Participant Flow Table

	Child-Pugh classification n (%)				Matched healthy subjects n(%)					
	Mild N=8 n (%)	Moderate N=8 n (%)	Severe N=8 n (%)	Total N=24 n (%)	Mild N=8 n (%)	Moderate N=8 n (%)	Severe N=8 n (%)	Total N=14 n (%)	All healthy subjects N=16 n (%)	All subjects N=40 n (%)

	Child-Pugh classification n (%)				Matched healthy subjects n(%)					
	Mild N=8 n (%)	**Moderate N=8 n (%)**	**Severe N=8 n (%)**	**Total N=24 n (%)**	**Mild N=8 n (%)**	**Moderate N=8 n (%)**	**Severe N=8 n (%)**	**Total N=14 n (%)**	**All healthy subjects N=16 n (%)**	**All subjects N=40 n (%)**
Subjects										
Completed	8 (100.0)	8 (100.0)	8 (100.0)	24 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	14 (100.0)	16 (100.0)	40 (100.0)

The 'All healthy subjects' column includes all matched and unmatched healthy volunteers.

In the matched healthy group, some of the subjects were matched more than once.

Baseline Characteristics

		Child-Pugh classification				Matched healthy subjects					
		Mild N=8	**Moderate N=8**	**Severe N=8**	**Total N=24**	**Mild N=8**	**Moderate N=8**	**Severe N=8**	**Total N=14**	**All healthy subjects N=16**	**All subjects N=40**
Age (years)	Mean (SD)	53.9 (6.20)	47.8 (6.30)	51.8 (3.41)	51.1 (5.83)	52.4 (4.57)	49.1 (5.84)	50.6 (4.34)	50.1 (5.01)	50.1 (5.50)	50.7 (5.65)
	Median	52.5	46.5	51.5	50.5	53.5	48.5	50.0	50.0	50.0	50.0
	Range	47 - 63	40 - 56	47 - 57	40 - 63	44 - 58	41 - 58	45 - 58	41 - 58	41 - 58	40 - 63
Height (cm)	Mean (SD)	170.0 (10.81)	174.5 (8.28)	167.7 (10.00)	170.7 (9.76)	172.8 (8.78)	169.0 (10.85)	168.9 (7.22)	169.9 (9.53)	170.0 (9.47)	170.4 (9.53)
	Median	168.5	173.5	172.5	172.5	175.0	172.5	170.0	171.0	171.0	171.5
	Range	154 - 184	163 - 190	153 - 179	153 - 190	159 - 184	147 - 180	159 - 180	147 - 184	147 - 184	147 - 190
Weight (kg)	Mean (SD)	77.63 (17.402)	84.91 (11.645)	78.28 (20.156)	80.27 (16.383)	80.78 (13.001)	78.16 (8.716)	77.59 (12.327)	78.04 (12.424)	79.00 (12.554)	79.76 (14.809)
	Median	72.50	85.90	76.25	77.70	78.50	79.20	78.50	75.70	75.70	76.35
	Range	58.0 - 112.0	69.5 - 98.0	50.2 - 106.4	50.2 - 112.0	66.0 - 103.0	66.0 - 91.0	62.8 - 95.3	62.8 - 103.0	62.8 - 103.0	50.2 - 112.0
BMI (kg/m2)	Mean (SD)	26.738 (4.5390)	28.172 (5.3943)	27.561 (5.3942)	27.490 (4.9337)	27.098 (4.0963)	27.554 (3.8183)	27.229 (4.2345)	27.071 (3.8320)	27.332 (3.6493)	27.427 (4.4140)
	Median	24.533	27.724	26.035	25.995	25.617	27.420	25.617	25.617	27.080	25.995
	Range	22.16 - 33.08	21.14 - 34.89	21.44 - 34.75	21.14 - 34.89	22.46 - 32.59	22.46 - 32.44	22.53 - 32.59	22.46 - 32.59	22.46 - 32.59	21.14 - 34.89
Sex - n(%)	Male	6(75.0)	6(75.0)	4(50.0)	16(66.7)	6(75.0)	6(75.0)	4(50.0)	9(64.3)	10(62.5)	26(65.0)
	Female	2(25.0)	2(25.0)	4(50.0)	8(33.3)	2(25.0)	2(25.0)	4(50.0)	5(35.7)	6(37.5)	14(35.0)
Race - n(%)	Caucasian	8(100.0)	8(100.0)	8(100.0)	24(100.0)	8(100.0)	8(100.0)	8(100.0)	14(100.0)	16(100.0)	40(100.0)
Ethnicity - n(%)	Other	8(100.0)	8(100.0)	8(100.0)	24(100.0)	8(100.0)	8(100.0)	8(100.0)	14(100.0)	16(100.0)	40(100.0)

The 'All healthy subjects' column includes all matched and unmatched healthy volunteers.

In the matched healthy group, some of the subjects were matched more than once.

Summaryof Efficacy

Not applicable. Efficacy was not measured.

Primary Outcome Results

Summary statistics for plasma PK parameters of primary interest for siponimod by group and subgroup (PK analysis set)

Group	Statistics	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)
Child-Pugh severity - Mild	n	8	8	8
	Mean ± SD (CV%)	68.3 ± 24.5 (36.0)	66.8 ± 24.4 (36.5)	2.03 ± 0.532 (26.2)
	Geo-mean	64.3	62.8	1.96
	CV(%) geo-mean	39.4	39.9	28.6
Matched healthy subjects - Mild	n	8	8	8
	Mean ± SD (CV%)	64.2 ± 20.8 (32.3)	62.5 ± 20.9 (33.5)	1.74 ± 0.439 (25.2)
	Geo-mean	61.4	59.6	1.69
	CV(%) geo-mean	32.9	34.4	25.0
Child-Pugh severity - Moderate	n	7	7	7
	Mean ± SD (CV%)	53.9 ± 7.57 (14.1)	52.3 ± 7.51 (14.4)	1.54 ± 0.191 (12.4)
	Geo-mean	53.4	51.9	1.53
	CV(%) geo-mean	13.2	13.5	13.0
Matched healthy subjects - Moderate	n	8	8	8
	Mean ± SD (CV%)	63.2 ± 18.6 (29.4)	61.7 ± 18.7 (30.2)	1.80 ± 0.417 (23.1)
	Geo-mean	61.1	59.6	1.76
	CV(%) geo-mean	27.4	28.3	21.9
Child-Pugh severity - Severe	n	8	8	8
	Mean ± SD (CV%)	73.7 ± 25.4 (34.5)	71.6 ± 24.5 (34.3)	1.58 ± 0.304 (19.3)
	Geo-mean	70.2	68.2	1.55
	CV(%) geo-mean	33.7	33.7	19.4
Matched healthy subjects - Severe	n	8	8	8
	Mean ± SD (CV%)	64.9 ± 23.6 (36.4)	63.4 ± 23.6 (37.3)	1.94 ± 0.603 (31.2)
	Geo-mean	60.8	59.1	1.86

Group	Statistics	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)
	CV(%) geo-mean	41.8	43.1	31.8

Statistical assessment (geometric mean ratio and 90% confidence intervals) of total siponimod PK parameters for subjects with hepatic impairment vs. matched healthy subjects (PK analysis set)

				Ratio of geometric means (Test/Reference)	
PK Parameter (unit)	Comparison	n	Geometric mean (90% CI)	Ratio	90% CI
AUCinf (h*ng/mL)	Child-Pugh classification: Mild (test)	8	64.3 (51.7-80.0)	1.05	(0.768, 1.43)
	Matched healthy subjects: Mild (ref)	8	61.4 (49.3-76.4)		
	Child-Pugh classification: Moderate (test)	7	54.7 (47.3-63.4)	0.895	(0.781, 1.03)
	Matched healthy subjects: Moderate (ref)	8	61.1 (53.1-70.4)		
	Child-Pugh classification: Severe (test)	8	70.2 (55.8-88.2)	1.15	(0.836, 1.59)
	Matched healthy subjects: Severe (ref)	8	60.8 (48.4-76.4)		
AUClast (h*ng/mL)	Child-Pugh classification: Mild (test)	8	62.8 (50.2-78.6)	1.05	(0.768, 1.45)
	Matched healthy subjects: Mild (ref)	8	59.6 (47.6-74.5)		
	Child-Pugh classification: Moderate (test)	7	53.2 (45.7-61.8)	0.893	(0.773, 1.03)
	Matched healthy subjects: Moderate (ref)	8	59.6 (51.5-68.9)		
	Child-Pugh classification: Severe (test)	8	68.2 (54.1-86.0)	1.15	(0.831, 1.60)
	Matched healthy subjects: Severe (ref)	8	59.1 (46.9-74.6)		
Cmax (ng/mL)	Child-Pugh classification: Mild (test)	8	1.96 (1.66-2.32)	1.16	(0.942, 1.42)
	Matched healthy subjects: Mild (ref)	8	1.69 (1.44-2.00)		
	Child-Pugh classification: Moderate (test)	7	1.53 (1.35-1.74)	0.868	(0.720, 1.05)
	Matched healthy subjects: Moderate (ref)	8	1.76 (1.57-1.98)		
	Child-Pugh classification: Severe (test)	8	1.55 (1.32-1.82)	0.837	(0.666, 1.05)
	Matched healthy subjects: Severe (ref)	8	1.86 (1.58-2.18)		

Model: The log transformed PK parameter data are analyzed using a linear mixed effects model with severity group as a fixed effect and matched pair as a random effect. Estimates and confidences intervals were back-transformed.

PK Parameter (unit)	Comparison	n	Geometric mean (90% CI)	Ratio of geometric means (Test/Reference) Ratio	90% CI

Subjects that are not matched are excluded from this analysis. N=8 for all subgroups.

Secondary Outcome Results

See AE tables in “Safety Results” section below.

Safety Results

Incidence of AEs by primary system organ class - n(percent) of subjects by group and subgroup (Safety analysis set)

	Child-Pugh classification n (%)				Matched healthy subjects n (%)					
	Mild N=8 n(%)	Moderate N=8 n(%)	Severe N=8 n(%)	Total N=24 n(%)	Mild N=8 n(%)	Moderate N=8 n(%)	Severe N=8 n(%)	Total N=14 n(%)	All healthy subjects N=16 n(%)	All subjects N=40 n(%)
Subjects with AE(s)	0	1 (12.5)	1 (12.5)	2 (8.3)	0	0	0	0	1 (6.3)	3 (7.5)
System organ class										
Cardiac disorders	0	0	1 (12.5)	1 (4.2)	0	0	0	0	0	1 (2.5)
Infections and infestations	0	1 (12.5)	0	1 (4.2)	0	0	0	0	0	1 (2.5)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	0	0	1 (6.3)	1 (2.5)

The 'All healthy subjects' column includes all matched and unmatched healthy volunteers.

In the matched healthy group, some of the subjects were matched more than once.

Incidence of AEs by preferred term - n(percent) of subjects by group and subgroup (Safety analysis set)

	Child-Pugh classification n (%)	Matched healthy subjects n (%)

	Mild N=8 n(%)	Moderate N=8 n(%)	Severe N=8 n(%)	Total N=24 n(%)	Mild N=8 n(%)	Moderate N=8 n(%)	Severe N=8 n(%)	Total N=14 n(%)	All healthy subjects N=16 n(%)	All subjects N=40 n(%)
Subjects with AE(s)	0	1 (12.5)	1 (12.5)	2 (8.3)	0	0	0	0	1 (6.3)	3 (7.5)
Preferred term										
Atrioventricular block first degree	0	0	1 (12.5)	1 (4.2)	0	0	0	0	0	1 (2.5)
Pain in extremity	0	0	0	0	0	0	0	0	1 (6.3)	1 (2.5)
Tonsillitis	0	1 (12.5)	0	1 (4.2)	0	0	0	0	0	1 (2.5)

The 'All healthy subjects' column includes all matched and unmatched healthy volunteers.

In the matched healthy group, some of the subjects were matched more than once.

Serious Adverse Events and Deaths

None

OtherRelevantFindings

None

Conclusion

Single oral dose administration of 0.25 mg siponimod in mild, moderate and severe hepatic impairment subjects and matched healthy controls was safe and well tolerated. The plasma exposure (Cmax and AUCinf) of total siponimod was comparable between subjects with mild, moderate and severe hepatic impairment and their matched healthy subjects.

Date of Clinical Trial Report

18 Sep 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

12 Dec 2014

Date of Latest Update

Not applicable

Reasonfor Update

Not applicable