Name of finished product: not applicable

Name of active ingredient: BAF312

Protocol Number: CBAF312A2102

Title of study: A randomized, parallel, double-blind, placebo-controlled, time-lagged, ascending multiple-dose, pharmacokinetic, pharmacodynamic, safety and tolerability study of BAF312 in healthy volunteers

Investigator(s): Dr. Bruce Rankin, DO (PI)

Study center(s): University Clinical Research, DeLand, FL USA

Publication (reference): None

Study period:

First subject dosed: 15-Oct-2007

Last subject completed: 27-Apr-2008

Phase of development: Phase 1

Objectives: The primary objective of the study was to evaluate the safety and tolerability of once daily, oral doses of BAF312 administered for 28 days in healthy volunteers. Secondary objectives included characterization of the once daily oral dose pharmacokinetics (PK) of BAF312 and to measure the effect on lymphocyte counts, leukocyte subsets, and the lymphocyte recovery period.

Methodology: This study was a randomized, double-blind, single center, placebo-controlled, time- lagged design with multiple ascending doses (0.3 mg, 1 mg, 2.5 mg, 10 mg and 20 mg) of BAF312 and matching placebo in healthy subjects under fasting conditions.

Number of patients (planned and analyzed): Sixty healthy subjects were enrolled into this study. A total of seven subjects were discontinued from the study. Only one subject was discontinued due to severe AEs thought to be study drug related by the investigator. The remaining six discontinued subjects were discontinued due to either insufficient study drug availability (n=5) or inability to complete the study due to personal reasons (n=1).

All 60 subjects were included in the safety population and PK analysis. However, in Cohort 5, five subjects (BAF312 20 mg, n=4 and placebo, n=1) did not complete the full 28 day treatment period, instead they had a truncated 11 day treatment period due to insufficient drug supply. All Day 28 PK assessments were performed on Day 11 and were all included in the Day 28 PK data analysis.

Diagnosis and main criteria for inclusion

The study was conducted in healthy male and non-childbearing potential female subjects between the ages of 18 to 55 years of age inclusive.

Test product, dose and mode of administration, batch number: Cohort 1 (0.3 mg

BAF312) and Cohort 2 (1 mg BAF312) were a liquid prepared from a 25 mg capsule of BAF312. Cohorts 3 (2.5 mg BAF312), Cohorts 4 (10 mg BAF312), and Cohorts 5 (20 mg BAF312 mg) were prepared from the appropriate number of 2.5 mg of BAF312 capsules. All doses of administration were oral.

Duration of treatment: Duration of treatment with BAF312 or matching placebo was 28 days.

Reference therapy, dose and mode of administration, batch number: Matching placebo preparations (liquid and solid) were prepared. All doses of administration were oral.

Criteria for evaluation

Efficacy: No efficacy evaluations were performed in this report.

Safety: Criteria for the evaluation of safety included adverse events, standard clinical assessments including laboratory evaluations, vital signs, ECG evaluations, special laboratory assessments including cystatin C and alpha-GST, additional blood pressure assessments (24 hour ABPM), additional data for cardiac function including 24 hour Holter and telemetry monitoring, pulmonary function tests, ophthalmologic and neurological exams.

Bioanalytics:

Plasma and urine levels of BAF312 were measured using a validated specific LC-MS/MS bioanalytical method for pharmacokinetic assessments. Absolute lymphocyte counts (ALC) and leukocyte subsets were evaluated for pharmacodynamic assessments.

Pharmacokinetic assessment:

The following plasma BAF312 PK parameters were determined for each individual using non- compartmental method(s):

- AUClast, AUC0-24h, AUC_T, Cmax, Cmax,ss, Cmin,ss, Cav,ss, Tmax, Tmax,ss , Tlag, T1/2, Racc, Fluc and any other PK parameter deemed appropriate.

The following PK parameters were calculated from urine data for BAF312:

- Ae0-t, CLR and any other PK parameters deemed appropriate.

Pharmacodynamic assessment:
Leukocyte subset percentages were summarized by visit and treatment. The changes for subset percentages were calculated from baseline and were also summarized by visit and treatment.

For ALC, time-matched change from baseline (placebo run-in Day -1) was calculated and the following summary endpoints determined:

- AUEC0-12h, Emax0-12h, and %Emax0-12h

Statistical methods:

Pharmacokinetics: Summary statistics were provided for PK parameters in steady-

state by dosing level including summary stats for single dose data.

Dose proportionality, following single dose on Day 1 and after multiple doses on Day 28, was assessed using a power model.

Pharmacodynamics: For lymphocyte count, the absolute values and their changes from time- matched baseline were summarized by cohort and timepoints, and graphic presentations were provided. In addition, summary endpoints AUEC0-12h and nadir at run-in Day-1, Day 1 and Day 28; maximum time-matched percentage change and maximum pre-dose percentage change were derived and summary statistics were given by cohort. ANCOVA model was applied to both AUEC0-12h and nadir with run-in value as covariate and treatment (dose level) as factor. Estimations on treatment effects and 90% confidence levels were provided.

Safety: For pulmonary function parameters, heart rate from Holter monitor, cardiac intervals (ECG), systolic blood pressure and diastolic blood pressure, absolute values and changes from baseline were summarized by cohort and timepoints, and graphic presentations were provided. For pulmonary function, a mixed effect model was applied with baseline value as covariate, treatment, time and treatment time interaction as fixed effects and subject (nested in treatment) as random effect. For heart rate and blood pressure, AUEC0-24h at run-in Day -1 and corresponding post-dose dates (Days 1, 2, 13, and 27 for HR, and Days 8, 14, 28, and 35 for BP) were derived from continuous monitor data and summary statistics were given for these summary endpoints. Mixed effect modeling was applied to AUEC0-24h with baseline value as covariate, treatment, day and their interaction as fixed effect and subject (nested in treatment) as random effect.

Summary - Conclusions:

Efficacy results: There were no efficacy evaluations performed in this study.

Safety results:

Adverse events

During the study there were 50 AEs reported for 24 subjects (about 40% of the safety population). The AEs were about evenly distributed across the active dose groups, but less for the placebo group. The adverse events seen in the study were mostly transient and graded by the Investigator as mild or moderate. Headache comprised about 25% of the AEs, and acetaminophen was used to relieve the symptoms. There was 1 subject that was discontinued due to AEs, but there were no deaths or SAEs reported for this study.

Clinical laboratory results

There were elevations in LFTs in three subjects reported as AEs. Elevated LFTs were generally observed in subjects in the BAF312 20 mg dose group suggesting a dose-effect relationship. Other laboratory variables had sporadic out-of-range values but did not show an overall trend. Although levels of cystatin C and α-GST levels were elevated in subjects across all doses, the test results were not predictive of renal or hepatic dysfunction. The reductions in ALC reflected the pharmacodynamic effect of

BAF312 and were not associated with any infections occurring in the trial.

Cardiac effects

Cardiovascular safety evaluations were compromised by malfunctioning ambulatory blood pressure monitoring and telemetric monitoring of heart rate. 12-Lead ECG recording during the study were generally unremarkable, except for occasional T wave changes or depressed ST segments. There were no clear trends of drug exposure on PR, QRS, and QT intervals. From Holter assessments, a transient dose-dependent decrease in mean ventricular HR was observed on Day 1 which was maximal for the BAF312 10 mg and 20 mg dose groups. A first degree AV block was observed and recorded as an AE in one subject on Day 1 in the 1 mg dose group. Second degree AV blocks (Mobitz Type I) were observed during Day 1 in 5 subjects at BAF312 doses between 0.3 mg and 2.5 mg. None of the AV blocks were symptomatic. All 2nd degree AV blocks were considered by the Investigator to be benign and clinically insignificant as the duration of the events was short and the conduction disturbance was not continuous. The observed negative chronotropic effects of BAF312 were characteristic of an S1P receptor modulator and were all benign, transient and did not require intervention.

Pulmonary effects

Statistically significant decreases in pulmonary function test (PFT) variables were noted in the trial suggesting a consistent effect of BAF312 on pulmonary function. These changes in pulmonary function test variables (treatment differences in all BAF312 groups compared to time-matched placebo) ranged for FVC from -1.12 to +0.45 L, i.e. between 26 % decrease and 11 % increase, respectively, and for FEV1 from -0.78 to 0.25 L, i.e. between 23 % decrease and 7.8 % decrease, respectively. These changes were considered mild to moderate and their magnitude seemed to be unrelated to dose and day in any treatment groups. Of note, the higher than expected exposure to BAF312, in the 10 mg and 20 mg dose groups was not associated with exceptional pulmonary effects. Importantly, there were no AEs or clinical symptoms related to bronchoconstriction or dyspnea.

CNS and visual effects

There were no notable changes noted in the Snellen scores over the course of the study, regardless of the dose of BAF312 administered. In the BAF312 1 mg dose group there were large changes in foveal and retinal thicknesses observed for a few subjects.

Neurological exams including Mini Mental State Examination and trailmaking tests for attention/vigilance, executive function and visuomotor speed were normal regardless of dose. All variations in MMSE and trailmaking test were comparable to those observed in the placebo group.

Bioanalytical results:

Pharmacokinetic assessment:

Due to indications of inappropriate dosing in Cohorts 4 and 5, data from these two cohorts were not included in the summary tables.

- On Day 28, the profiles for all but two subjects in Cohort 4 were 5-11 fold higher than the day 1 profile, while only two-fold accumulation was expected.
- Five subjects in Cohort 5 demonstrated 7-10 fold higher than expected plasma concentrations on Day 1. Several fold higher than expected BAF312 plasma levels were also observed on day 5 for all but one subject in Cohort 5, while trough concentrations suggested that the dosing was stopped or decreased after day 5 for all subjects.

The mean PK profile of BAF312 in plasma following a single oral dose administration on Day 1 is summarized in the table below:

Parameter	BAF312 0.3 mg (N=9)	BAF312 1 mg (N=9)	BAF312 2.5 mg (N=9)
Tlag (h)[1]	0.00 (0.00-0.25)	0.00 (0.00-0.25)	0.25 (0.00-0.73)
Tmax (h)[1]	6.00 (3.00-16.00)	6.00 (2.00-8.00	5.93 (2.95-7.97)
Cmax (ng/mL)[2]	2.15 [31]	7.40 [29]	21.5 [16]
AUClast (h.ng/mL)[2]	37.9 [31]	133 [27]	353 [13]
AUC0-24h (h.ng/mL)[2]	37.9 [31]	133 [27]	353 [13]

[1] Median (min-max); [2]Geometric mean [%CV geo mean]

The mean PK profile of BAF312 in plasma following 28 days of daily oral administration is summarized in the table below:

Parameters	BAF312 0.3 mg qd (n=8)	BAF312 1 mg qd (n=8)	BAF312 2.5 mg qd (n=9)
Tlag (h)[1]	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Tmax,ss (h)[1]	2.50 (1.50-8.00)	2.50 (1.00-8.00)	2.00 (0.00-6.00)
Cmax,ss (ng/mL)[2]	4.52 [33]	13.6 [41]	44.1 [30]
AUClast (h.ng/mL)[2]	250 [54]	609 [61]	1900 [35]
AUCτ (h.ng/mL)[2]	82.6 [36]	231 [49]	789 [33]
CLz/F (L/h)[2]	3.63 [36]	4.33 [49]	3.17 [33]
Vz/F (L)[2]	412 [30]	472 [57]	316 [37]
Cav,ss (ng/mL)[2]	3.44 [36]	9.63 [49]	32.9 [33]
Cmin,ss (ng/mL)[2]	2.21 [52]	4.87 [48]	22.2 [31]
T1/2 (h)[2*]	88.7 [24]	75.7 [11]	75.8 [26]
Fluc (%)[2]	39.75 [79]	45.05 [30]	50 (21)[3]
Racc[2]	2.20 [16]	1.77 [35]	2.24 [28]

[1] Median (min-max); [2]Geometric mean [%CV geo mean], [3]Arithmetic mean (%CV);
*Corresponds to T1/2,β. The effect half-life (based on drug accumulation at steady-state) is between 20-28 h.

Urine samples were collected but they were not analyzed for BAF312 concentrations in Cohorts 1 to 3 in this study due to observed analyte container surface adsorption in urine matrix, which was not anticipated during urine sample collection and transfer. This issue was resolved for Cohorts 4 and 5 and urine samples were analyzed for BAF312 concentrations. However, due to indications of inappropriate dosing in these 2 cohorts, PK analysis of urine data was not performed.

Pharmacodynamic assessment:

On Day 1 the absolute lymphocyte counts (ALC) declined in a dose-dependent manner with the maximal reduction observed at approximately 4 to 6 hours post-dose. Changes in ALC (over days) showed a dose-dependent decline between the BAF312 0.3 mg to 10 mg dose. Due to evidence of inappropriate dosing, conclusions on pharmacodynamics effects of BAF312 could not be accurately summarized for the higher dose groups.

The effect of BAF312 on the peripheral counts of different leukocyte subtypes could not be concluded. There were a number of subjects for whom samples for the leukocyte subset testing were clotted upon arrival at Covance and could not be analyzed, as well as many of the parameters were not quantitatively analyzed.

Therefore, the summary of the leukocyte subset data reflect those subjects for whom results were available. With the amount of missing data, the results were at best indicative of trends, and no quantitative conclusion could be made.

Conclusions:

This study, as conducted, did not meet the objectives as set forth for the study. Because of a number of problems with study conduct, evidence of inappropriate dosing, and malfunctioning equipment during the study, and the study results were considered unreliable.

Date of the report: 28-Oct-2009.

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2102

EudraCT Number

Not applicable

Planned and Actual Number of Patients

Planned: 60 subjects

Enrolled: 60 subjects

Batch Numbers

Product	Dose Level	Batch #/Product Code
BAF312 Hard Gelatin Capsules	2.5 mg	F001BD/#6002122.003
	25 mg	F024GC/#6002122.003
Placebo Hard Gelatin Capsules	0 mg	X004 1004/#3755667.016

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

Matching placebo preparations (liquid and solid) were prepared from Batch# X0040104. All doses of administration were oral.

Publication(s)

Not Published

Investigators & Information on Study Centers

Investigator	**Facility Name** **Address** **Country**
Bruce Rankin	University Clinical Research DeLand, FL 32720 USA