NOVARTIS

Novartis Clinical Trial Results

Name of finished product: N/A

Name of active ingredient: BAF312 hemifumarate or BAF312-AEA

Study number: CBAF312A2101

Title of study: A first-in-human study for BAF312: A two parts, single center, randomized, double- blind, placebo controlled ascending single dose study to explore the safety, tolerability, pharmacokinetics and pharmacodynamics of oral BAF312 in healthy volunteers

Investigator: Bruce Rankin, DO

Study center(s): University Clinical Research-Deland, Florida USA

Study period

First patient enrolled: 28-Oct-2006, Last patient completed: 05-Aug-2007

Phase of development: Phase I

Objectives:

The primary objective for Part I was:

- To evaluate the safety, tolerability, pharmacokinetic (PK) profile, and maximal tolerated dose (MTD) of single, ascending oral doses of BAF312 in healthy volunteers.

The secondary objectives for Part I were:

- To determine the pharmacodynamic (PD) effect of single, ascending oral doses of BAF312 on lymphocyte counts and the lymphocyte recovery period and determine the PK/PD relationship of BAF312.
- To explore the dose responses of single ascending oral doses of BAF312 on cardiac rate and rhythm in healthy volunteers.
- To figuree the pharmacodynamic (PD) effect of single, ascending oral dose of BAF312 on pulmonary function.

The primary objective for Part II was:

- To compare the PK, safety, and tolerability of oral BAF312 under fed and fasted conditions.

Methodology: This was a two-part, single center, randomized, double-blind, placebo controlled ascending single dose study. The administered dose levels of BAF312 ranged from 0.1 mg to 75 mg.

Number of patients (planned and analyzed): Ninety-seven subjects were planned; 98 subjects were recruited and analyzed. Four subjects were part of an unblinded, tolerability run-in group (the very first subject received 2.5 mg, after adjustment of the starting dose level another 3 subjects received 0.1 mg). Eight out of the 9 blinded cohorts (Cohort 1-3 administering a liquid formulation, Cohort 5-9 administering a solid formulation) had 10 subjects in an 8:2 study drug:placebo ratio. One cohort (Cohort 4) had 14 subjects in order to compare the bioavailability of liquid and solid formulations (1:1 ratio) of BAF312.

Diagnosis and main criteria for inclusion: The study enrolled healthy male and non-child-bearing- potential females, age 18 to 55 years included, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening. Vital signs were within the following ranges at screening and baseline: oral body temperature between 35.0-37.5°C, systolic blood pressure, 90-150 mm Hg, diastolic blood pressure, 50-95 mm Hg, pulse rate, 55 - 100 bpm, and with no indication of postural hypotension. In addition, subjects had a body mass index within the range of 18 to 30 and were able to communicate with the

investigator and provide written informed consent.
A subject was excluded if he/she was a smoker, had a history of drug or alcohol abuse, had taken any prescription drugs within 4 weeks prior dosing, or over-the-counter medication within 2 weeks prior to dosing. Pregnant or lactating females were also excluded as were any subject that had participated in any clinical investigation within 4 weeks prior to dosing or donated/lost ≥ 400 ml of blood within 8 weeks prior to dosing. Finally, a subject was excluded if he/she had any of the following:

- A significant illness, including acute or chronic infectious diseases, within 2 weeks prior to dosing or received live vaccine 4 weeks prior to dosing.
- A past medical history or family history of clinically significant ECG findings (including prolonged QT-interval syndrome), atrial or ventricular arrhythmias or atherosclerotic cardiovascular disease; hypokalemia or hypomagnesemia, or history of heart failure or known left ventricular dysfunction (EF <45%).
- A history of autonomic dysfunction, acute or chronic bronchospastic disease, clinically significant drug allergy or history of atopic allergy, or any surgical or medical condition which significantly altered the absorption, distribution, metabolism or excretion of drugs.
- A history of immunodeficiency diseases and/or a positive test result for HIV, Hepatitis B surface antigen, or Hepatitis C test.

Test product, dose and mode of administration, batch number:

All doses were administered p.o. BAF312: 2.5 mg, BAF312; 25 mg BAF312.
Placebo: matching 2.5 mg and 25 mg.

Duration of treatment: Subjects were monitored for 14 days after a blinded single dose drug administration.

Criteria for evaluation

Safety:

The standard safety variables were the collection of all AEs and SAEs, including their severity and relationship to study drug, regular monitoring of hematology, blood chemistry, and urinalysis. Vital signs were monitored and included body height, body weight, body temperature, pulse rate and measurement of both sitting and orthostatic blood pressure. Two special laboratory tests, cystatin C and alpha-glutathione S-transferase (α-GST), were evaluated for their use in future trials as safety measurements and evaluate liver and kidney damage.

The additional safety assessments were increased electrocardiography; 24 hr Holter ECG reading, pulmonary function with spirometry, and neurological and ophthalmological exams.

Bioanalytics:

Pharmacokinetic analysis
Blood and urine was collected for PK analysis. Quantitative analysis of plasma was performed using a validated liquid chromatography mass spectrometry/mass spectrometry bioanalytical method. The lower limit of quantification was 5 ng/mL for 0.1 mL of plasma.

Pharmacodynamic analysis
The change in peripheral absolute lymphocyte count served as the marker for pharmacodynamics. Blood samples were collected at the protocol-specified timepoints and analyzed at the local laboratory.

Pharmacogenetic analysis
Blood was collected from subjects who provided written consent for participation in PG

analysis.

Statistical methods:
For PK, power model was used to assess dose proportionality and Mixed effect model was used to assess food effect. For PD and key safety endpoints (cardiac, pulmonary, blood pressure) ANCOVA analysis was preformed to assess the treatment effects. Descriptive statistics was provided for all safety endpoints (or their change from baseline) by treatment group and visit.

Summary - Conclusions

Safety results:
The AEs seen in the study were as expected for this class of drug. They were mostly transient and either mild or moderate. The majority of subjects (61 subjects, 62.2%) did not have an AE under fasted conditions. There were no severe AEs, SAEs or deaths during the study. The AEs reported by ≥ 5% of subjects were headache (29 subjects, 29.6%), dizziness (11 subjects, 11.2%), and nausea (11 subjects, 11.2%). The incidence of AEs was similar regardless of dietary status. However, the frequency of AEs within the cardiac disorder system organ classification was higher in the cohort given 5.0 mg of BAF312 under fed conditions (4 of 6 subjects, 66.7%) than for the cohort given 5.0 mg of BAF312 under fasted conditions (1 of 8, 12.5%) and consisted of both 1st and 2nd degree atrioventricular blocks.

Transient, dose-dependent decreases in ventricular rate were observed and peaked between 4 to 8 hours post-dose. No events of bradycardia were reported at doses of 1.0 mg and below or in the fed cohort. At doses of 2.5 mg and higher, 18 subjects had ECG values indicative of bradycardia under fasted conditions. Three of these incidents (one incident under each, 2.5 mg, 10 mg, and 75 mg) were considered clinically significant and were reported as AE. In the fed cohort, 2 subjects had ECG values indicative of bradycardia; however, neither of these was clinically significant.

Junctional rhythm abnormalities were noted in one subject in both, the 25 mg and 75 mg cohorts, respectively, and were not seen at baseline or during the placebo run-in phase.

QTc interval assessments showed different results, depending upon the correction methodology used. When expressed as change from baseline, QTcF values ranged from approximately -10 msec to 10 msec over the first 4 hours after exposure. In contrast, QTcB intervals decreased from baseline at doses of 5.0 mg and above. At the highest doses, QTcB intervals fell by nearly 30 msec compared to 10 msec for placebo during the first 4 hours after dosing. Both QTcF and QTcB results need to be interpreted with caution as this SD study was not designed or powered as a QT study. The significant bradycardia made QT calculation and corrections inadequate. Significant variability was noted in QTc over 10 msec, and no dose-response relationship was observed.

The safety labs showed that median levels of C-reactive protein were above the upper limit of normal at Day 2 for all cohorts receiving ≥ 5 mg of BAF312. This spike in median CRP levels resolved at Day 3. Other laboratory variables had sporadic out-of-range values, but did not show an overall trend. Only 1 event of increased ALT and AST was considered clinically significant and was reported as an AE. Circulating cystatin C levels were elevated to ≥ 1.70 mg/L in 15 subjects, 6 of which were members of the 17.5 mg cohort, but none was member of the 25.0 mg or 75.0 mg cohorts or the 5 mg fed cohort. Transient increases of circulating alpha-GST levels were observed in 9 subjects given BAF312 and 4 subjects given placebo. These transient increases of alpha-GST peaked at either Day 1, 2 or 4 and showed no relation to dose level.
BAF312 did not show a substantial effect upon FEV1 or FEF25-75 pulmonary function. All neurological function results were normal regardless of dose.

Overall eight subjects experienced changes from screening in corrected Snellen scores for eye examination after receiving doses of either 17.5 mg or 25.0 mg. Three subjects had increased acuity while 5 subjects had decreased acuity. The changes failed to demonstrate a dose-response relationship, suggesting background variability.

Pharmacodynamic results:

The mean values for absolute lymphocyte count showed a dose-dependent decline between the 0.3 mg dose and the 10 mg dose of BAF312. The absolute lymphocyte count reduction of at least 80% was reached at the 10 mg dose or higher. For most cohorts, the maximum decline occurred between 3 and 7 hours. Dietary status of the subjects did not alter the trend.

Pharmacokinetic results:

For PK, dose proportionality was observed for each of the AUC values. The median plasma concentration of BAF312 peaked between 3 and 6 hr post-dose, and the decay was mono-exponential with a geometric mean apparent terminal $t_{1/2}$ of between 27.2 and 56.69 hrs. Maximum exposure (906 ng/mL and 16,800 ng*h/mL for Cmax and AUC0-24h, respectively) stayed well below the maximum systemic exposure recommended by the FDA (Cmax of 2,700 ng/mL or an AUC0 24h of 35,000 ng*h/mL). A delayed median tmax was observed after food intake; however, geometric mean AUCs and Cmax were similar under both fasted and fed conditions. Both tlag and tmax appeared to be slightly delayed for the capsule compared to the liquid solution. C_{max} and AUC_s were comparable between both formulations.

Conclusion:

- In healthy volunteers, BAF312 was shown to be safe and well tolerated, but it was still associated with acute, negative, chronotropic effects.
- The MTD was determined to be 25.0 mg.
- PK showed dose proportionality in the dose range of 0.1 - 75 mg, as analyzed by AUC. Median tmax was between 3 and 6 hr and an apparent terminal t1/2 of 27-57 hr was determined. A delayed median tmax was observed after food intake; however, mean AUC_s and C_{max} were similar under both fasted and fed conditions. Both tlag and tmax appeared to be slightly delayed for the capsule compared to the liquid solution. C_{max} and AUC_s were comparable between both formulations.
- BAF312 affected the peripheral lymphocyte count in a dose-dependent manner, with a plateau of effect starting at 5 mg. Recovery was not observed until the end-of-study visit for subjects receiving the highest dose (75 mg).
- Transient dose-dependant decreases in ventricular rate and corresponding increases in PR intervals were observed and mirrored the effects on the absolute lymphocyte count.
- BAF312 did not produce clinically significant effects upon pulmonary function or neurological assessments. Eye examination produced indifferent results, suggesting background variability.
- Administration of BAF312 under fed conditions did increase the proportion of AEs within the cardiac disorder SOC and consisted of both 1st and 2nd degree atrioventricular blocks.
- Analysis of PG relationships will be reported separately.

Date of the report: 11JUN2008

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: October 22, 2020

Novartis Study Code

CBAF312A2101

EudraCT Number

Not applicable.

Planned and Actual Number of Patients

Planned: 97 subjects

Enrolled: 98 subjects

Batch Numbers

BAF312: 2.5 mg, batch numbers F023GC BAF312 and F001BD BAF312; 25 mg, batch number F024GC BAF312.
Placebo: batch number X004 0104 (matching 2.5 mg and 25 mg).

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

Not applicable.

Publication(s)

None published.

Investigators & Information on Study Centers

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