Novartis Clinical Trial Results

Name of finished product: N/A

Name of active ingredient: BAF312

Study number: CBAF312A2119

Title of study: A randomized, double blind, parallel group study to assess the tolerability, pharmacodynamics and pharmacokinetics of two modified-release BAF312 tablets compared to the immediate-release tablet and placebo in healthy volunteers.

Investigator: Dr. Stephen Youngberg

Study center: Celerion, 621 Rose Street, Lincoln, NE – 68502, USA.

Publication (reference): None

Study period

First subject enrolled: 29-Dec-2010

Last subject completed: 11-Feb-2011

Phase of development: I

Objectives: The primary objective of the study was to quantify the maximum change (Emax) in the time-matched, baseline-corrected negative chronotropic effect of two BAF312 modified release (MR) tablets (F10 and F16) compared to the immediate release (IR) BAF312 tablet over 24 hours.

The secondary objective of the study was to quantify the time to the maximum change (TEmax) in the time-matched, baseline corrected negative chronotropic effect of the two BAF312 MR tablets, compared to the IR tablet and placebo over 24 hours. The secondary objectives also included assessing the safety and tolerability of the two BAF312 MR tablets, compared to placebo; and measuring the pharmacokinetics (PK) of the two BAF312 MR tablets.

Methodology: This study was a single center, double-blind, randomized, placebo-controlled parallel group study in healthy subjects using single 4-mg dose of IR, F10, F16 or placebo.

Number of subjects (planned and analyzed): A total of 60 subjects were enrolled, randomized and completed the study; fifteen (15) each to BAF312 F16, F10 and IR formulations, and Placebo.

All 60 subjects were included in PK; pharmacodynamics (PD) and safety analysis set.

Diagnosis and main criteria for inclusion

Healthy male and non-childbearing female subjects, aged 18 to 55 years with a body mass index (BMI) between 18 - 32 kg/m^2, weighing at least 50 kg and in good health as determined by past medical history, physical examination, vital

signs, electrocardiogram and clinical laboratory evaluations at Screening were eligible for enrollment in this study after signing a written informed consent and meeting all other protocol specified inclusion and exclusion criteria.

Duration of treatment: There was a single treatment period in the study which lasted for 14 days. The study had four treatment arms in which subjects were randomized to receive either one of the treatment viz. BAF312 F16, BAF312 F10, BAF312 IR or Placebo.

Criteria for evaluation

Pharmacodynamics: Pharmacodynamics assessments consisted of holter cardiac monitoring for heart rate and cardiac rhythm; and absolute lymphocyte count (ALC).

Safety: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine and regular assessments of vital signs, physical condition and body weight.

Pharmacokinetics: All samples were processed as described in the protocol of the study. Analysis was performed by a validated LC-MS/MS method. The parameters measured were AUCinf, AUC0-t (t being 10, 16, and 24 hr), AUClast, Cmax, Tmax, Tlag and T1/2.

Statistical methods:

Pharmacodynamics

All 60 subjects were included in PD analysis set. The primary PD variable was:

- The daily maximum effect on heart rate (Emax). The primary aim was to compare the Emax of BAF312 F10 with BAF312 IR and Emax of BAF312 F16 with BAF312 IR

The secondary PD variables were:

- The time to the maximum change (TEmax) in the time-matched, baseline-corrected negative chronotropic effect of two BAF312 MR tablets compared to the IR tablet and placebo over 24 hours.
- The standardized heart rate (HR) area under the effect curve (AUEC calculated using the trapezoidal rule and standardized for time, AUEC/time) of two BAF312 MR tablets compared to the IR tablet over 24 hours.

Both hypotheses were tested with an analysis of covariance (ANCOVA) model. The corresponding statistical model did include baseline (over 24 hours) as covariate, the factor treatment and the residual error term. To preserve the overall significance level of 5% (one-sided) across the two primary hypotheses related to the F10 and F16 arm the Hochberg (Simes) procedure was applied.

In the analysis of the time to the maximum change (TEmax) the median and the 5th to 95^{th} percentile interval were computed. The point estimate as well as the

95% confidence interval for the difference between the BAF312 F10 tablet vs. BAF312 IR tablet and the BAF312 F16 tablet vs. BAF312 IR tablet was calculated by the nonparametric Hodges-Lehmann method. With regard to the heart rate AUEC the same analysis of covariance used for the primary endpoint was applied.

All PD date were also presented descriptively.

Safety

All 60 subjects were included in safety analysis set. Descriptive statistics of AEs, vital signs, ECG and laboratory evaluations were provided.

Pharmacokinetics

All 45 subjects treated with BAF312 were included in the PK analysis set.

The following pharmacokinetic parameters were determined for BAF312 F16, F10 and IR formulations, using non-compartmental methods by WinNonlin Pro (Version 5.2): AUCinf, AUC0-t (t being 10, 16, and 24 hr), AUClast, Cmax, Tmax, Tlag, T1/2, and other parameters as appropriate from plasma concentration-time data.

Descriptive statistics of pharmacokinetic parameters included mean, geometric mean, median, SD, CV, min and max.

Summary - Conclusions

Demographic and background characteristics: A total of 60 subjects were enrolled in the study. The overall median age of subjects in the safety analysis set was 27.5 years with a range of 19 - 55 years. With respect to race, 50 subjects (83.3%) were Caucasian, 9 subjects (15.0%) were black and 1 subject (1.7%) was of other race. With respect to ethnicity, 2 subjects (3.3%) were Hispanic/Latino and 58 (96.7%) were classified as other ethnicities. There were 56 male subjects (93.3%) and 4 female subjects (6.7%). With respect to the three formulations of BAF312 (F16, F10 and IR) and placebo cohorts the mean and median age, weight and BMI were comparable.

Pharmacodynamics results: The mean maximum effect on hourly HR (Emax) for the 4 mg F16 formulation was -4.3 bpm compared to the IR treatment; however, loss in bioavailability with the F16 formulation does not allow for comparison. The mean HR Emax from 24-hr Holter monitoring following a 4 mg F10 dose was numerically higher (2.9 bpm) compared to the IR. Findings on the mean hourly AUEC and Emax are consistent with those at the level of per 1-min assessment intervals with a slightly higher variability. Absolute lymphocyte count nadir is similar for the F16 and F10 formulation and ~10% less compared to IR treated subjects. Lymphocyte recovery is similar across all groups and consistent with PK; complete recovery at 144 hours post-dose.

Safety results: There were no clinically significant changes in clinical chemistry, hematology or urinalysis apart from the expected PD effects of BAF312, specifically a reduction in absolute peripheral lymphocyte counts. Similarly, AEs

which occurred during this study were consistent with those expected and reported in other studies with BAF312. Incidence of ECG related morphology, conduction and rate changes were as expected for the immediate release formulation and similar for the other two BAF312 formulations as compared to placebo. There was no difference between treatment groups, in number of subjects with ventricular or supraventricular ectopic events and there were no pauses of >2 seconds reported. All formulations were well tolerated with no SAEs. All reported AEs were transient and other than one case of hypotension which was treated with IV saline resolved without pharmacologic intervention.

Pharmacokinetics results: Delayed median Tmax of 8 hr and 6.98 hr were observed following administration of the modified release F16 (8 hr) and F10 (6.98 hr) tablets as compared with the immediate release tablet (3.98 hr). Relative to the IR formulation, the rate and extent of absorption were decreased with the two MR formulations. Mean Cmax was reduced by 16% and 55% for the F10 and F16 MR formulations, respectively, in comparison with the IR formulation. Mean AUCinf and AUClast were 51% and 16% lower for the F16 and F10 MR formulations, respectively, compared to the IR tablet.

Conclusion:

- All formulations were well tolerated by healthy volunteers, there were no SAEs and reported AEs were transient.
- Consistent with the MR formulation release profiles, Tmax was delayed 3-4 hours with F16 and F10 compared to IR.
- The Cmax with F16 was 55% and F10 was 16% lower than IR with an increase in CV% of 1.7 and 1.9-fold as compared to IR. AUCinf with F10 was 16% and F16 was 51% lower than IR with similar CV% (0.85 and 1.2- fold, respectively).
- The mean maximum effect (two-sided 95% confidence interval) on HR rate (Emax) for the 4 mg F16 formulation was -4.3 (-9.8 , 1.2) bpm (p=0.122) compared to the IR treatment; however, the loss in bioavailability with the F16 formulation does not allow for direct comparison. The mean (two-sided 95% confidence interval) HR Emax from 24-hr Holter monitoring following a 4 mg F10 dose was numerically higher (2.9 (-2.7 , 8.4) bpm ; p=0.845) compared to the IR. Findings on the mean hourly AUEC and Emax are consistent with those at the level of per 1-min assessment intervals with a slightly higher variability.
- There is no difference between treatment groups in number of subjects with SVEs, VEs and no pauses of >2 seconds were reported.
- Absolute lymphocyte count nadir is similar for the F10 and F16 formulation and ~10% less compared to IR treated subjects. Lymphocyte recovery is similar across all groups and consistent with PK; complete recovery at 144 hours post-dose.

Date of report: 12-Jan-2012 (content final)

Swiss Authorization date and authorization number
Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2119

EudraCT Number

Not applicable

Planned and Actual Number of Patients

Planned: 60 subjects

Enrolled: 60 subjects

Batch Numbers

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

Study drug and strength	Batch number	Basis/Variant
BAF312 4mg (F10 tablet)	X309 1010	6003197.002
BAF312 4mg (F16 tablet)	X308 1010	6003197.001

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

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

Study drug and strength	Batch number	Basis/Variant
BAF312 4mg (IR tablet)	X188 0909	6002702.001
Placebo	X221 0909	6002679.003

Publication(s)

None published.

Investigators & Information on Study Centers

Investigator	**Facility Name Address Country**
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