NOVARTIS

Novartis Clinical Trial Results

Name of finished product: Not applicable

Name of active ingredient: BAF312

Study number: CBAF312A2111

Title of study: A randomized, open-label, three-period crossover study to assess both the bioequivalence of the BAF312 final market image (FMI) tablet formulation as compared to the BAF312 market formulation (MF) and the effect of food on the relative bioavailability of the FMI after single 0.25 mg and 4 mg doses in healthy volunteers

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Study center(s): 2 in Australia and 1 in USA

Study period

First patient enrolled: 17-Oct-2011

Last patient completed: 14-May-2012

Phase of development: I

Objectives:

Primary:

- To investigate whether 0.25 mg and 4 mg of BAF312 FMI are bioequivalent to the same dose strengths of BAF312 MF tablet.
- To investigate the effect of food on the pharmacokinetics of the 0.25 mg and 4 mg BAF312 FMI tablet.

Secondary:

- To investigate the safety and tolerability of the two BAF312 formulations following a single oral dose strength of 0.25 and 4 mg.

Methodology:

This was an open-label, randomized, study in healthy volunteers who were homozygous for the CYP2C9*1 (wild type) allele, using a three-period, three-treatment, six-sequence, single dose, crossover design at each of two dose levels. The study consisted of a 28-day screening period, three baseline periods (one before each treatment period), and three treatment periods, each separated by at least 14 days washout and a Study Completion evaluation approximately 14 days after the last drug administration.

Number of subjects (planned and analyzed): Initially a total of 48 healthy volunteers were planned to be randomized, however, since the non-completion rate

was unexpectedly higher, the number of planned subjects was increased to up to approximately 60.

A total of 62 subjects were enrolled in this study out of which 47 (75.8%) subjects completed the study. All 62 subjects were analyzed for safety and pharmacokinetics. Three subjects were discontinued due to AEs, out of which one event was reported as serious. One subject was discontinued due to abnormal laboratory values. Eleven subjects (17.7%) were discontinued as these subjects withdrew their consent. The most common reasons for withdrawing consent were non-availability during the Christmas-New Year holiday period and long duration of the three periods.

Diagnosis and main criteria for inclusion

The study population comprised of non-smoking, healthy male and female subjects aged between 18 to 50 years (inclusive), who passed screening assessments, compliant with inclusion/exclusion criteria and provided written consent. Subjects were required to be CYP2C9 wild type (CYP2C9*1 homozygous carriers) as determined during screening.

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

The BAF312 tablets were provided as 0.25 mg and 4 mg tablets for oral administration.

Duration of treatment: The total study duration (from screening to end of study evaluations) was approximately 11 weeks.

Criteria for evaluation

Pharmacokinetics: The pharmacokinetic blood samples were collected at the following time points for all 3 periods: pre-dose, then 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 144, 216, and 312 hours after BAF312 intake.

Plasma concentrations of BAF312 were determined using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method.

Primary variables (also referred to as primary PK parameters) were AUCinf, AUClast, and Cmax. These were used in the statistical analysis of the bioequivalence and food effect. Secondary PK parameters were T1/2, Tmax, Tlag, CL/F and Vz/F.

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

Statistical methods

Descriptive statistics of PK parameters:

Descriptive statistics of PK parameters were calculated by treatment within dose, condition, and period. These included mean, geometric mean, standard deviation (SD), and coefficient variance (CV), minimum, median, and maximum. When a geometric mean and a geometric CV are presented, they were stated as such. Because Tmax and Tlag

are generally evaluated by a nonparametric method, median values and ranges were given for these parameters.

Statistical analysis of the bioequivalence and food effect assessments:

This study was aimed at estimating two true mean treatment ratios (test/reference) where reference for both ratios is FMI BAF312 fasted, and test is MF BAF312 fasted or FMI BAF312 fed. Along with the estimation, bioequivalence of test and reference was investigated. The 2-sided 90% confidence intervals around the observed geometric mean ratio were reviewed against the bioequivalence region of (0.80 – 1.25).

Natural log transformed PK parameters Cmax, AUClast, and AUCinf were subjected to a statistical analysis in order to determine bioequivalence.

For each dose, the primary analysis of each PK parameter were analyzed using a fixed effects model with subject, period and treatment (MF fasted, FMI fasted and FMI fed) as fixed effects.

A secondary mixed effects analysis, with subject as a random effect was also conducted for each dose. Additionally, this mixed model was also applied to the combined data, with dose as a further fixed effect. Each analysis assumed subjects were uniquely identified.

All analysis included all available and valid PK parameter data from the subjects included in the analysis set. In particular, a subject with available PK parameter data at one or two periods only was still included in the analysis because the mixed model analysis makes use of all available data. They were also included in the fixed effect models so subjects with two periods only still provide within subject treatment information.

Geometric mean treatment ratios (test/reference) were reported along with their 90% confidence intervals, where reference for both ratios was FMI BAF312 fasted, and test was MF BAF312 fasted or FMI BAF312 fed.

Summary - Conclusions

Demographic and background characteristics: Out of all 62 subjects that were dosed in the study, 61 (98.4%) subjects were male and 1 (1.6%) subject was female. Out of the 62 subjects, 42 (67.7%)
were Caucasian, 8 (12.9%) were Black, 8 (12.9%) were Asian, 1(1.6%) was a Pacific Islander and 3 (4.8%) were classified as Others..

Pharmacokinetic results:

The bioequivalence and the food effect analyze are (0.25 mg dose) and 4 mg dose). Geometric mean MF/FMI and Fed/Fasted ratios and 90% confidence intervals (CI) for geometric ratio of primary PK parameters are summarized.

Bioequivalence between MF and FMI was demonstrated for Cmax, AUClast, and AUCinf after the administration of 0.25 mg and 4 mg BAF312 in fasted subjects.

Similarly, bioequivalence criteria were met for all three primary PK parameters between fasted and fed states when the FMI formulation was administered at both doses. There was no effect of food on the PK of BAF312 as per the bioequivalence criteria. Even though median Tmax was slightly delayed in the fed group for both

doses, ranges of values overlapped between fed and fasted states, . and this mild effect on Tmax is not expected to be clinically relevant.

Geometric mean, estimated geometric mean ratio and 90% confidence intervals for PK variables for formulation and fasting status for the 0.25 mg dose

			Geometric mean ratio*		
Treatment	PK parameter (unit)	Adjusted geometric means*	Estimate (Test/Reference)	Lower 90% CI	Upper 90% CI
0.25 mg BAF312 MF Fasted (Test)	Cmax [ng/mL]	1.95	1.01	0.97	1.06
	AUClast [hr*ng/mL]	69.42	1.02	1.00	1.05
	AUCinf [hr*ng/mL]	71.48	1.02	0.99	1.05
0.25 mg BAF312 FMI Fed (Test)	Cmax [ng/mL]	1.92	1.00	0.95	1.04
	AUClast [hr*ng/mL]	67.31	0.99	0.97	1.02
	AUCinf [hr*ng/mL]	69.73	1.00	0.97	1.02
0.25 mg BAF312 FMI Fasted (Reference)	Cmax [ng/mL]	1.92			
	AUClast [hr*ng/mL]	67.74			
	AUCinf [hr*ng/mL]	70.03			

* Back-transformed from log scale

Model: The log transformed PK parameter data were analyzed using a fixed effect model with treatment, period and subject as fixed effects.

Geometric mean, estimated geometric mean ratio and 90% confidence intervals for PK variables for formulation and fasting status for the 4 mg dose

			Geometric mean ratio*		
Treatment	PK parameter (unit)	Adjusted geometric means*	Estimate (Test/Reference)	Lower 90% CI	Upper 90% CI
4 mg BAF312 MF Fasted (Test)	Cmax [ng/mL]	29.53	1.00	0.94	1.06
	AUClast [hr*ng/mL]	1045.99	0.98	0.94	1.02
	AUCinf [hr*ng/mL]	1052.84	0.98	0.94	1.02
4 mg BAF312 FMI Fed (Test)	Cmax [ng/mL]	27.02	0.91	0.86	0.97
	AUClast [hr*ng/mL]	1022.33	0.96	0.92	1.00
	AUCinf [hr*ng/mL]	1029.41	0.96	0.92	1.00
4 mg BAF312 FMI Fasted (Reference)	Cmax [ng/mL]	29.57			
	AUClast [hr*ng/mL]	1067.16			
	AUCinf [hr*ng/mL]	1074.10			

* Back-transformed from log scale

Model: The log transformed PK parameter data were analyzed using a fixed effect model with treatment, period and subject as fixed effects.

Safety results: There were no deaths in the study. There was one SAE (presyncope and bradycardia during blood collection nearly 8 hours after 4 mg dose) suspected to be related to the study drug. The subject recovered spontaneously. The most frequent AEs were headache, bradycardia, dizziness, fatigue, nausea and infections of mild to moderate in severity. The infections were not related to the study drug. Three subjects discontinued due to AEs (bradycardia and presyncope which was a SAE; bradycardia; bradycardia and irregular heart rate 14 days post dose and not related to study drug) in the 4 mg group. One subject was discontinued due to abnormal laboratory value (elevated QTcF nearly 13 days post 4 mg dose) which was not clinically significant or reported as an AE. Overall, BAF312 administered at dose levels of 0.25 and 4 mg under fasted and fed conditions was well tolerated and safe. Higher frequency and intensity of AEs were reported at 4 mg group compared to 0.25 mg. The AE profiles were similar across the formulations (FMI and MF) and fasted/fed conditions for the FMI formulation. There were no cardiovascular AEs in the 0.25 mg group except for one subject who had palpitations for one minute at the time of dose administration in Period 1.

Conclusion:

This study was designed to investigate the bioequivalence (BE) between the BAF312 FMI tablet and the BAF312 MF tablet after single dose administration of 0.25 and 4 mg in healthy volunteers.

Results of this study showed that the FMI and MF formulations of BAF312 were bioequivalent for both 0.25 mg and 4 mg doses. Similarly, FMI fasted and FMI fed fulfilled the bioequivalence criteria at both doses. The slightly increased Tmax in both dose groups and the 10% lower Cmax in the 4 mg FMI fed group were considered clinically non relevant.

The AE profiles were similar across the formulations (FMI and MF) and fasted/fed conditions for the FMI formulation. Higher frequency and intensity of AEs were reported at 4 mg group compared to 0.25 mg. In particular, no bradyarrhythmic event was noted in the 0.25 mg group. Overall, BAF312 administered at dose levels of 0.25 and 4 mg under fasted and fed conditions was well tolerated and safe.

Date of report: 22-Jun-2012 (content final)

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: October 22, 2020

Novartis Study Code

CBAF312A2111

EudraCT Number

Not applicable.

Planned and Actual Number of Patients
Planned: 48 subjects

Enrolled: 62 subjects

Batch Numbers

Study drug and strength	Batch number
BAF312 0.25 mg (MF)	X139 0411
BAF312MF 4 mg (MF)	X141 0411
BAF312 0.25 mg (FMI)	X198 0811
BAF312MF 4 mg (FMI)	X199 0811

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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