Bioequivalence Study of Test Formulation Fibroneurina and Reference Formulation Fingolimod 0.5 mg hard capsules under fasting conditions

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Clinical report

Accutest Study Code: ARL/15/727
Sponsor Study Code: BA 03/16

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of test formulation Fibroneurina and reference formulation Fingolimod 0.5 mg hard capsules in healthy, adult, male and female volunteers under fasting conditions.

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1 Title page

Study Code: ARL/15/727
Sponsor Study Code: BA 03/16
Study Title:

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of test formulation Fibroneurina and reference formulation Fingolimod 0.5 mg hard capsules in healthy, adult, male and female volunteers under fasting conditions. Study Design:

A randomized, single dose, two treatment, two period, two sequence, crossover, open label, laboratory blinded, bioequivalence (BE) study under fasting conditions.

Formulations	***Dose***
Test Product (T): Fibroneurina	
Manufactured by: Laboratorios Bagó, Argentina.	
1 x 0.5 mg	
Reference Product (R): Fingolimod 0.5 mg hard capsules	
Manufactured by: Novartis Pharma GmbH, Germany	
1 x 0.5 mg	
Development Phase:	Phase I, BE
Clinical Conduction:	
Period I Period II	06 August 2016 to 10 August 2016
14 October 2016 to 18 October 2016	
Subject Screening:	
Start Date: End Date:	03 August 2016
06August 2016	
Report Compilation	
Report Status:	Draft Report
Version:	D04
Dated:	03 February 2017
Supersedes Version:	D03
Dated:	21 January 2017

This study was conducted in compliance with the EMA guidelines, ICH GCP guideline and the current version of the Declaration of Helsinki (Brazil, October 2013) including the archiving of essential documents.

Principal Investigator (PI). Sponsor's Representative. Eduardo de la Puente. Designation: Medical Director

2 SYNOPSIS OF THE REPORT

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of test formulation Fibroneurina and reference formulation Fingolimod 0.5 mg hard capsules in healthy, adult, male and female volunteers under fasting conditions.

Investigators and other important participants in the study:

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Dr. Rakhi Sahane, Sub-Investigator
Dr. Suhas Khandave, Clinical Pharmacologist Vladimír Kube (Quinta), Analytical Investigator
Dr. Prashant Basapure, M.D. (Pathology) Mr. Deepak Mahajan, Bio-statistician Mr. Atul Solankar, Quality Assurance Head

Study Centre:
Clinical, Clinical Laboratory and:
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Development Phase: Phase I, Bioequivalence study
Study period:
Activity:
Period I
Period II
Clinical Conduction:
06 August 2016 to 10 August 2016
14 October 2016 to 18 October 2016
Dosing Date:
07 August 2016
15 October 2016
Date of Post-study evaluation:
20 October 2016
Date of Completion of
last follow up:
11 November 2016
Date of Completion of Clinical Phase of the study:
11 November 2016
Date of Completion of Analysis:
05 December 2016
Date of Completion of Report:
06 January 2017

Primary Objective: To assess the BE between test (T) and reference (R) products after a single dose of Fingolimod in healthy, adult, male and female volunteers under fasting conditions. Secondary Objective: To evaluate adverse events (AEs) and tolerability of Fingolimod after administration in healthy, adult, male and female volunteers under fasting conditions.

METHODOLOGY:

To ensure dosing of 40 subjects in the first period, 40 + 02 stand-by subjects were checked in. The subjects were confined within the facility from 10.50 hours

(hrs) before dosing until at least 72.00 hrs post-dose in each study period. After an overnight fast of 10.00 hrs a single oral dose (1 capsule) of test or reference product was administered as per randomization schedule in each study period with 240 ± 2 mL of water at ambient temperature in sitting position. A total of 23 blood samples (6 mL each) were collected from the subjects in pre-cooled K2-EDTA vacutainers during each study period at pre-dose (collected within 01.00 hr prior to dosing), 2.00, 4.00, 6.00, 8.00, 9.00, 10.00, 11.00, 12.00, 13.00, 14.00, 15.00, 16.00, 17.00, 18.00, 19.00, 20.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00 hrs in each study period.

Whole blood concentrations of fingolimod were measured using a validated High-Performance Liquid Chromatography–Mass Spectrometer/Mass Spectrometer (HPLC/MS/MS) bio-analytical method.

Number of Subjects (planned and analysed):

A total of eighty-nine (89) volunteers were screened in order to check in forty (40) subjects and two (2) stand-by subjects in the first period. In accordance with the study protocol, a total of forty (40) subjects were dosed in period I and 39 subjects in period II. Thirty-nine (39) subjects completed the clinical phase of the study. The whole blood samples of forty (40) subjects were analysed (subject no 04 didn't show up for second period) and data of thirty-nine (39) subjects was considered for pharmacokinetic and statistical analysis.

Diagnosis and main criteria for inclusion:

It was decided to include, healthy, non smoking adult, male and female subjects aged between 18 to 45 years (inclusive) with a body mass index (BMI) in a range of 18.5 kg/m2 to 30.0 kg/m2, who provided their written informed consent and who were willing to follow the protocol requirements. The subjects were enrolled in the study when the following inclusion screening test were determined and accepted by the Principal Investigator: breath alcohol test, demographic examination, BMI, medicalhistory, physical examination (including vital signs assessment), 12-lead electrocardiogram (ECG), and clinical laboratory tests [haemogram, biochemistry, infectious disease screening (human immuno deficiency virus (HIV), Hepatitis B and Hepatitis C, urinalysis]. Urine screen for drug abuse was done before check-in for each study period. Breath alcohol test was done for each visit. All enrolled subjects met the inclusion criteria and none of the exclusion criteria.

Duration of treatment:

A single oral dose of Fibroneurina or reference formulation Fingolimod 0.5 mg hard capsules was administered as per randomization under fasting conditions in each study period.

Period I: 07 August 2016
Period II: 15 October 2016
Subsequent periods were separated by a washout period of 69 calendar days.

Criteria for evaluation: Bioequivalence:

Assessment of bioequivalence was done by comparing pharmacokinetic parameters of the test product (T): Fibroneurina 0.5 mg capsule Manufactured by Laboratorios Bagó, Argentina with the reference product: Fingolimod 0.5 mg hard capsules Manufactured by Novartis Pharma GmbH, Germany.

The test product was to be concluded bioequivalent to the reference product if the 90% confidence interval of the Geometric mean (GMEAN) ratio of the maximum observed drug concentration in blood (Cmax) and the area under the concentration versus time curve from time 0 to 120 hrs (AUC0-120) between test and reference pro-

ducts fall within the range of 80.00% to 125.00% for Fingolimod.

Safety:

Safety measurements included monitoring of AEs, physical examination, well being assessment, vital signs assessment, 12-lead ECG and clinical laboratory tests.

Statistical methods:

For the primary end points Analysis of variance (ANOVA) was performed on ln-transformed pharmacokinetic parameters Cmax and AUC0-120 for Fingolimod.

The 90% Confidence Interval (CI) was calculated for the ratio of geometric least squares mean of the test (T) and reference product (R), obtained from the ln-transformed PK parameters Cmax and AUC0-120. All pharmacokinetics and statistical analyses have been performed using SAS® statistical software version 9.2.

SUMMARY

Conclusion Bioequivalence Results:

A total of 40 subjects were planned and enrolled in the study. Thirty-nine (39) subjects completed the clinical phase of the study and data of thirty-nine (39) subjects were considered for pharmacokinetic and statistical analysis.

The 90 % CI's of Ln-transformed parameters for Fingolimod are summarized below:

SAFETY RESULTS:

Two (02) AEs were reported during the clinical phase of the study which were unexpected and not related to study drug, mild in severity and were considered for lost to follow up.

No serious AEs (SAEs) were observed during the clinical phase.

CONCLUSION:

Based on the statistical analysis of Fingolimod on 39 subjects, it is concluded that the Test Product (T): Fibroneurina manufactured by Laboratorios Bagó, Argentina shows bioequivalence with the Reference Product Fingolimod 0.5 mg hard capsules Manufactured by Novartis Pharma GmbH, Germany. Date of the report: 04 February 2017.

Table 1: Geometric Means and 90% Confidence Interval for Fingolimod For Test Product T Versus (Vs) Reference Product R (N=39)

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC_{0-120}	42787.32	38460.73	111.25	108.05	114.54
C_{max}	493.71	441.92	111.72	108.07	115.50

* *Geometric mean has been taken as the antilog (exponential) of the Least square mean of the log transformed data.*

Figure 1: Fingolimod Mean Concentration Time Profile-Untransformed

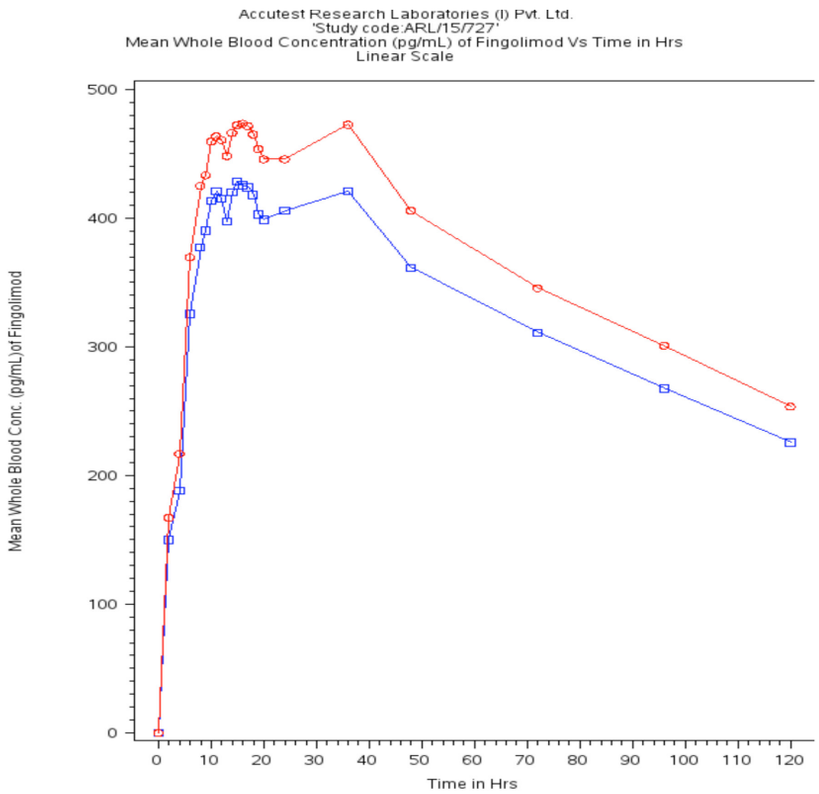

Figure 2: Fingolimod Mean Concentration Time Profile-Ln transformed