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Research Article

An Open Label, Balanced, Randomized, Two Treatments, Three Sequences, Three Periods, Single Dose, Semi-Replicate, Crossover, Oral Bioequivalence: Study of Palbociclib 125 mg Capsules of Abbott Laboratories de Colombia vs. Ibrance (Palbociclib) 125 mg Capsules of Pfizer in Healthy, Adult, Human Subjects Under Fed Conditions

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ABSTRACT

Palbociclib is a kinase inhibitor that inhibits Cyclin-Dependent Kinases (CDK) 4 and 6 that is indicated for the treatment of Hormone Receptor (HR)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. The purpose of this study was to evaluate the bioequivalence between Palbociclib 125 mg Capsules of Abbott Laboratories de Colombia vs. Ibrance (Palbociclib) 125 mg Capsules of Pfizer in healthy subjects. An open label, balanced, randomized, two treatments, three sequences, three periods, single dose, semi replicate, cross over with washout period of 10 days under fed condition was carried out in 48 male subjects in the age group of 23 to 45 years who met the study eligibility criteria, participated in the study and 44 subjects completed both periods of the study. The pharmacokinetic samples collected from subjects who completed the study were analyzed to determine the plasma concentration of Palbociclib using bio-analytical method.

The ISCV of reference product for C_{max} is 11.21% and the 90% confidence interval of the relative mean C_{max} of the test to reference drug product for Ln-transformed data is within 80.00%-125.00% 90% confidence interval of the relative mean AUC_{0-72} of the test to reference drug product for Ln-transformed data were within 80.00%-125.00%, thus establishing bioequivalence.

Keywords: Palbociclib; Bioavailability; Bioequivalence; Pharmacokinetic

ABBREVIATIONS

AEs: Adverse Events; AUC: Area Under the Concentration versus Time Curve; AUC_{0-72}: Area Under the Plasma Concentration vs. Time Curve Truncated to 72 Hours; BMI: Body Mass Index; ECG: Electrocardiogram; FDA: United States Food and Drug Administration; C_{max}: Concentration Maximum; CV: Coefficient of Variation; IEC: Independent Ethics Committee; mg: milligram; mL: milliLitre; mM: milli Molar; ng/mL: nano gram per milliLiter; PK: Pharmacokinetic; T_{max}: Time Taken to Reach Maximum Concentration.

INTRODUCTION

The health authorities like United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), ANVISA, INVIMA, ISP, Chile and few other countries mandate the submission of bioequivalence studies, where the test product manufactured by the applicant is compared with that of the innovator product and proven to be bioequivalent [1-6].

If a product is bioequivalent, it is expected to have same efficacy as the innovator. As the generic product being efficacious as

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marketed product and cost effective, the patients will have access to the medicines for their treatment. Hence, the health authorities have been approving the drugs with same efficacy as that of the innovator. These generic drugs will be accessible and cost effective than the innovator products.

Ibrance (Palbociclib) is kinase inhibitors. The active ingredient of Ibrance is Palbociclib. Palbociclib inhibits the Cyclin-Dependent Kinases (CDK) 4 and 6. Cyclin Dl and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation. Each IBRANCE capsules contains 125 mg of Palbociclib. Palbociclib is designated chemically as 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin2yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-on [1,3,7-10].

This study was designed to evaluate the relative bioequivalence of the test Palbociclib 125 mg Capsules of Abbott Laboratories de Colombia versus reference Ibrance (Palbociclib) 125 mg Capsules of Pfizer in healthy, adult, human subjects [2,4].

MATERIALS AND METHODS

Materials

Test product, dose and mode of administration, lot: Palbociclib 125 mg capsules, 01 × 125 mg, Oral with 200 mL of water in sitting posture under fed conditions, E-0318.

Reference product, dose and mode of administration, batch: Ibrance (Palbociclib) 125 mg capsules, 01 × 125 mg, Oral with 200 mL of water in sitting posture under fed conditions, X28186.

Methodology

The study protocol with annexes was prepared and IEC approval was obtained before initiation of the study. Study subjects were screened and enrolled in the study as per the IEC approved protocol. Written informed consent was obtained from each volunteer in screening visit to initiation of screening procedure and for the study prior to enrolment. Individual counselling was then given to the willing volunteers by the Investigator in private and any questions and concerns were addressed prior to obtaining consent. The Principal investigator/sub-investigator/physician reviewed all the screening results to assess eligibility of each volunteer. Subjects were enrolled in the study based on the inclusion and exclusion criteria [1,2,4].

This study was designed based on the known pharmacokinetic profile of the investigational product and general accepted standards for the conduct of bio-equivalence study [5,6,10].

Forty-eight male subjects were selected, enrolled and randomly assigned to one of the sequences of Test product (T) and Reference product (R) (TRR or RTR or RRT) for study drug administration. The study was conducted in two groups with 24 subjects (S01-S24) in group 01 and group 02 comprised of 24 subjects (S25-S48).

A washout period of 10 days was maintained between each treatment, in order to minimize any possibility of carryover effect from the preceding treatment. The blood samples were collected at pre-defined time intervals for the measurement of concentration and pharmacokinetic parameters of Palbociclib in each period.

All the protocol restrictions were respected by the subjects throughout the study. The pharmacokinetic samples collected from 44 study completers were analysed to determine Palbociclib concentrations using a validated bio-analytical method in LC-MS/MS.

The pharmacokinetic and statistical analysis of Palbociclib was performed using the concentration data obtained for 44 study completers.

Bioequivalence was determined by statistical comparison of Ln-transformed data of C_{max} and AUC_{0-72} of the test and reference formulations using SAS® version 9.4.

Criteria for inclusion/exclusion of subjects

Healthy volunteers, aged 20 to 45 years, and with BMI of 18.50-29.99 Kg/m^2 and weight>50 Kg were eligible to be enrolled in the study (Tables 1 and 2).

Table 1: Summarized demographic profile of all subjects enrolled for palbociclib (N=48).

Parameter	Mean	SD	Min	Max
Age (years)	33	6	23	45
Height (m)	1.673	0.055	1.531	1.776
Weight (Kg)	70.5	9.1	56.2	93.4
BMI (Kg/m^2) (Kg/m^2) (Kg/m^2) (Kg/m^2)	25.12	2.59	20.14	29.81

Table 2: Summarized demographic profile of study completers for palbociclib (N=44).

Parameter	Mean	SD	Min	Max
Age (years)	33	6	23	45
Height (m)	1.674	0.056	1.531	1.776
Weight (Kg)	70.8	9.2	57.0	93.4
BMI (Kg/m^2)	25.20	2.63	20.14	29.81

Inclusion criteria encompassed no evidence of cardiac, pulmonary, gastrointestinal, hepatic, renal, hematologic, or neurologic disorders, or any acute or chronic disease, no history of drug or alcohol addiction, normal laboratory tests (complete blood counts, urinalysis, liver and kidney function, and blood sugar); and serological negativity HIV, hepatitis B.

Subjects were informed by an investigator about the purposes and risks of the study. They were asked to abstain from using concomitant medications, including over-the-counter products, dietary supplements and natural products which potentially modify kinetics/dynamics of Palbociclib, 14 days prior to dosing and throughout the end of the study. Consumption of grapefruit and/or its products were not allowed within 10 days prior to the start of the study. Caffeine and/or xanthine-containing products or alcohol were not allowed 48 hours prior the first administration of the study medications and throughout the blood sampling periods.

Sample size and power

For the expected mean difference of 5% between the formulations, with an assumed intra-subject CV of 36% for C_{max}, about 72 subjects would be required to prove bioequivalence at 0.80 power in a two way crossover, considering partial replication of treatments and on the basis of crossover design and considering possible dropouts due to expected Adverse Drug Reaction (ADR), a sample size of 48 subjects in a semi-replicate design was considered for this pivotal

bioequivalence study.

Subjects drug administration and blood sampling

After an overnight fasting of 10 hours, subjects were provided with high fat high calorie breakfast 30 minutes prior to drug administration, following completion of high fat high calorie breakfast subjects were administered with a single oral dose of either test product or reference product with 240 mL of water as per the randomization schedule in sitting posture at ambient temperature in each period. Compliance to drug administration was assessed by examination of the oral cavity and hands of the subject immediately after dosing.

Subjects were in sitting posture for 04 hours after dosing. During this restriction period, the subjects were permitted to walk for reasons such as but not limited to the following: Natural exigencies. Subjects were restricted from consumption of water for 01 hour before and 01 hour after dosing in each period and were allowed to drink water ad libitum thereafter.

The pharmacokinetic profile (in terms of rate and extent of absorption) of both test and reference products was evaluated based on measured concentration of drug in the human plasma samples collected during the clinical phase. Blood samples for pharmacokinetic analysis were designed appropriately for characterizing the pharmacokinetic profile for the given treatments at the dose administered.

A total of 20 blood samples of 04 mL each at 00.00 hour (pre-dose), 01.00, 02.00, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 07.50, 08.00, 09.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hours post-dose were collected for measurement of pharmacokinetic parameters in all the periods.

Tolerability

Subjects were monitored for Adverse Events (AEs) during both periods of the study. Subjects were instructed to inform clinic personnel of any untoward medical symptoms and/or events that arose during the study. Prior to check in of each period, subjects were questioned concerning unusual symptoms that may have occurred after the previous administration of the study drug. The principal investigator/sub-investigator/study physician also evaluated the subjects for subsequent dosing. Each adverse event reported by the subjects during the study was assessed for its seriousness, severity, relationship with the study drug and outcome.

Subject's Safety was assessed *via* continuous monitoring and scheduled recording of safety measurements throughout the study through clinical examinations, vital assessment, 12-lead Electrocardiogram (ECG), clinical laboratory parameters (e.g., Hematology, Biochemistry, Urine analysis and Serology test) and monitoring subjects' well-being, symptoms and signs for adverse events.

No serious adverse events were reported during the conduct of this study. There was 01 non-serious adverse event reported by 01 subject following administration of test product.

All AEs reported in the study resolved without sequelae and were assessed to be moderate in intensity. The incidence of AEs in the study for test product was 02.22%.

Among the non-serious AE reported in the study AE was probably related to study medication and was expected following exposure to Palbociclib.

Pharmacokinetic and statistical analysis

Pharmacokinetic and statistical analysis of Palbociclib was performed using the concentration data obtained from 44 subjects who completed both periods of the study.

In order to test the two one-sided tests for bioequivalence, ratio analysis, 90% confidence intervals for the difference between treatments' least-square mean was calculated for Ln-transformed C_{max} and AUC_{0-72} of Palbociclib.

Pharmacokinetic parameters were calculated using non-compartmental model of Phoneix® WinNolin® version 8.1 (Tables 3 and 4) and statistical analysis was carried out using the SAS® statistical software, version 9.4 of SAS Institute Inc., USA (Tables 5-7).

Table 3: Summary of pharmacokinetic parameters for palbociclib of reference product-R.

Parameter	N	Reference (R) (Mean ± SD)
C_{max} (ng/mL)	88	60.111 ± 14.113
AUC_{0-72} (ng.hr/mL)	86	1766.312 ± 297.762
*T_{max} (hr)	88	8.00 (4.50-24.00)

Note: *Expressed in terms of median (range)

Table 4: Summary of pharmacokinetic parameters for palbociclib of test product-T

Parameter	N	Test (T) (Mean ± SD)
C_{max} (ng/mL)	44	67.606 ± 15.551
AUC_{0-72} (ng.hr/mL)	44	1893.981 ± 364.664
*T_{max} (hr)	44	6.75 (4.50-12.00)

Note: *Expressed in terms of median (range)

Table 5: Statistical results of test product-t versus reference product- R for palbociclib.

Parameters		Ln AUC_{0-72}	Ln C_{max}
Least square mean	Test product (T)	1859.9532	65.8619
	Reference product (R)	1741.4689	58.3854
T/R Ratio (%)		106.8	112.81
90% Confidence interval		104.08%-109.59%	108.46%-117.32%
Intra-subject CV (%)T vs. R		8.36	12.83
Intra-subject CV (%)R vs. R		7.16	11.21
Power		1.0000	1.0000

The mean, standard deviation, standard error, geometric mean, coefficient of variation, minimum, median, maximum and range were calculated for C_{max}, AUC_{0-72} and T_{max}.

RESULTS AND DISCUSSION

Forty-eight male subjects in the age group of 23 to 45 years, who met the study eligibility criteria, participated in the study and 44 subjects completed both periods of the study; four subjects were withdrawn from the study for the following reasons:

- Subject withdrew his consent due to personal reasons prior to dosing in period I.
- Two subjects did not report for period II, hence were withdrawn from the study.

- Subject was withdrawn from the study due to adverse event during check-in of period III.

The clinical phase of the study was conducted over a period of 26 days. Blood sampling was done at pre-defined intervals up to 72.00 hours in both periods. The plasma concentrations of Palbociclib were quantified in samples of 44 study completers using a validated bio-analytical method in LC-MS/MS.

The pharmacokinetic and statistical analysis of plabociclib was performed using the concentration data obtained following analysis of 44 study completers.

The ISCV of reference product for C_{max} is 11.21% and the 90% confidence interval of the relative mean C_{max} and AUC_{0-72} of the test to reference drug product for Ln-transformed data is 108.46%-117.32% and 104.09%-109.59% respectively, which are within 80.00%-125.00% (Figures 1 and 2 and Tables 6 and 7).

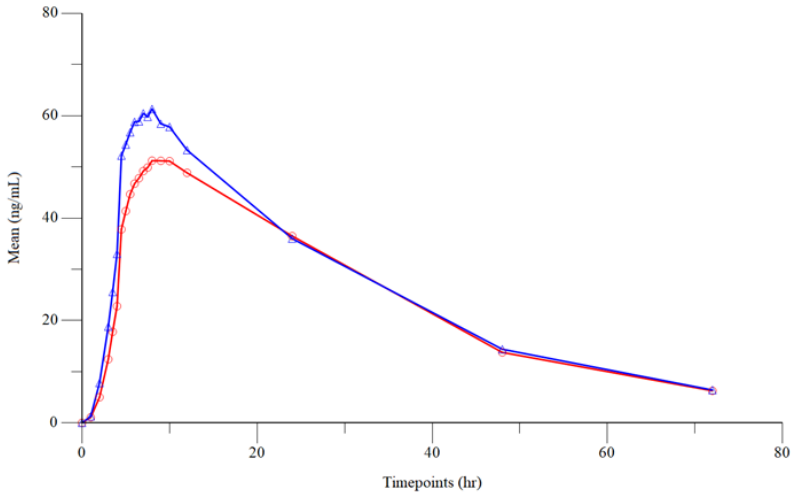

Figure 1: Linear plot of geometric mean plasmatic palbociclib concentration vs. time points (N=44). Note: (—) R, (—) T.

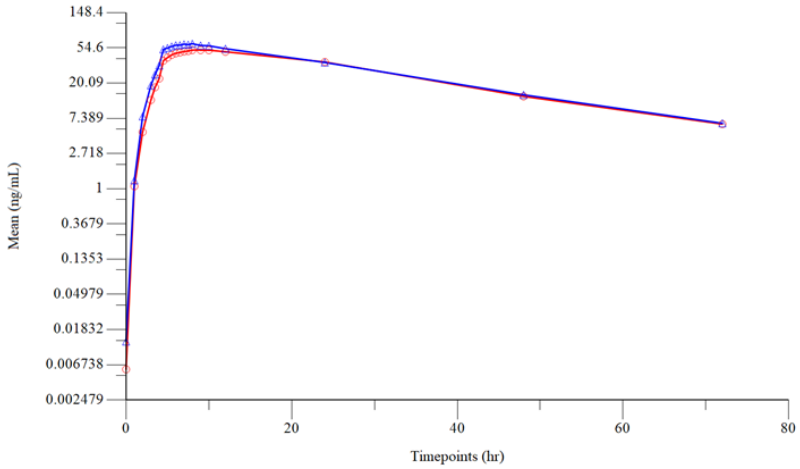

Figure 2: Semi log plot of mean plasmatic palbociclib concentration vs. time points (N=44). Note: (—) R, (—) T.

Table 6: Statistical results of test product-T versus reference product-R for palbociclib.

Parameters	Antilog least square mean		Point estimate (%)	90% Confidence interval	Intra subject CV (%) T vs. R	Intra subject	Power
	Test product (T)	Reference product (R)					
Ln (C_{max})	65.8619	58.3854	112.81	108.46%-117.32%	12.83	11.21	1.0000
Ln (AUC_{0-72})	1859.953	1741.4668	106.8	104.09%-109.59%	8.36	7.16	1.0000

Table 7: p -Value for C_{max} and AUC of palbociclib.

Parameters	C_{max}	AUC_{0-72}	Significance
Sequence effect	0.5872	0.7916	Insignificant for C_{max} and AUC_{0-72}
Period effect	0.8682	0.3247	Insignificant for C_{max} and AUC_{0-72}
Treatment (formulation) effect	<0.0001	<0.0001	Significant for C_{max} and AUC_{0-72}
Subjects nested within sequence	<0.0001	<0.0001	Significant for C_{max} and AUC_{0-72}

Note: P<0.10 for Sequence effect and P<0.05 for all other effects considered to be significant

CONCLUSION

Bioequivalence was demonstrated between palbociclib 125 mg Capsules of Abbott Laboratories de Colombia versus Ibrance (palbociclib) 125 mg Capsules of Pfizer in healthy, adult, human subjects. The 90% CI of C_{max} and AUC_{0-72} of the test to reference drug product for Ln-transformed data is 108.46%-117.32% and 104.09%-109.59% respectively, which are within 80.00%-125.00%. Based on the adverse events and proceeds of the study it can be concluded that the study medications were relatively well tolerated by the study subjects at selected dose level.

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