SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Imbruvica®
Name of Active Ingredient(s)	JNJ-54179060 (PCI-32765) (ibrutinib)

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Status: Approved

Date: 15 September 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: PCI-32765CLL1006

Title of Study: An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects With Varying Degrees of Hepatic Impairment

NCT No.: NCT01767948

Clinical Registry No.: CR100944

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Publication (Reference): None

Study Period: 03 January 2013 to 15 November 2013. Database lock: 27 March 2014.

Phase of Development: 1

Objectives: The primary objective of this study was to characterize the pharmacokinetics (PK) of PCI-32765 in subjects with mild, moderate, or severe hepatic impairment. Secondary objectives of this study were to assess safety of PCI-32765 when administered to subjects with hepatic impairment.

Methodology: This was an open-label, single-dose, multi-center, non-randomized study to evaluate ibrutinib exposure in subjects who had hepatic impairment at baseline compared with a control group. Thirty subjects (24 subjects with renal impairment: 6 subjects with mild impairment [Grade A]; 9 subjects with moderate impairment [Grade B]; 9 subjects with severe impairment [Grade C] according to Child-Pugh criteria; and 6 subjects with normal liver function [control]) were to be enrolled. Subjects who received a liver transplant were excluded from the study. Subjects in the control group were enrolled after the subjects with mild or moderate hepatic impairment completed the study and were matched by sex, age (±10 years), and body mass index (BMI) to within 20% of the means of the mild and moderate hepatic

impairment groups. No other clinical criteria were matched. Subjects with severe liver impairment were enrolled after 6 subjects in both previous groups completed all assessments without significant toxicities.

Subjects were assessed for study eligibility during the Screening phase (Days -21 to Day -2). Eligible subjects were admitted to the study unit on Day -2. Subjects received a single oral dose of ibrutinib 140 mg on Day 1 with 240 mL of noncarbonated water following an overnight fast of at least 10 hours.

For each hepatic impairment group, after the first 3 subjects completed the study through the follow-up telephone call, the PK, safety, and clinical laboratory data were reviewed by a Study Evaluation Team (SET) consisting of the investigators, the medical monitor, and the sponsor's clinical pharmacologist(s). Decisions on possible dose adjustments or group expansion were made by the SET.

Blood samples for PK analysis of ibrutinib and the metabolite PCI-45227 were collected before dosing and over 96 hours after dosing. Urine was collected before dosing and at specified intervals in the 24 hours after dosing. Safety was assessed from the time of consent until the end of the study and included physical examinations, monitoring of adverse events (AEs), vital signs, electrocardiograms (ECGs), and clinical laboratory results (hematology, serum chemistry, urinalysis). Subjects were discharged from the study center after the 96-hour PK sample on Day 5 and safety procedures were performed. End-of-study assessments were performed on Day 5 or before discharge from the clinical site for subjects who withdrew from the study before completion. A follow-up telephone call approximately 10 (±2) days after dosing was made to capture any additional adverse events.

Number of Subjects (planned and analyzed): Planned: Approximately 30 subjects were planned to be enrolled (24 subjects with hepatic impairment at baseline and 6 subjects in the control group according to Child-Pugh criteria). Analyzed: 30 subjects with hepatic impairment levels defined in the protocol and who received study medication were included in the safety analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects were to be cancer-free, between 18 and 75 years of age, inclusive; BMI between 18 and 40 kg/m², inclusive and a body weight of not less than 50 kg. Control subjects were to be in good health, with no clinically significant findings from medical history, physical examination, laboratory evaluations, 12-lead ECGs and vital signs. Subjects in the control group who tested positive for Hepatitis B surface antigen or Hepatitis C antibodies were excluded from the study.

Subjects were to have stable hepatic function as measured during screening and within 48 hours prior to ibrutinib administration. Hepatic impairment subjects who tested positive for hepatitis surface antigen or hepatitis C antibodies at screening were permitted in the study. Subjects with hepatic impairment who had acute or exacerbating hepatitis, fluctuating or rapidly deteriorating hepatic function, were taking anticoagulant therapy, were receiving antiviral therapy for treatment of active hepatitis infection at the time of screening, had been previously diagnosed with hepatocellular carcinoma, or who had a history of cholestatic liver disease or biliary sepsis within the past 2 years or had hepatic encephalopathy >Grade 2 were excluded from participating in the study.

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib, size 0 hard gelatin capsule given orally as a single dose of 140 mg administered on Day 1. Batch No. L0308792/Expiration date: June 2014.

Based on results from the mild and moderate cohorts if dose reduction was warranted for subjects in the severe cohort, 1 to 2 size 2 hard gelatin capsules containing ibrutinib 40 mg were to be administered on Day 1. Batch No. 10-0040/Expiration date: June 2014.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: The planned duration of subject participation (assuming a screening period of 21 days) was 29 to 33 days.

Criteria for Evaluation:

Pharmacokinetics: Serial PK blood and urine samples were collected before ibrutinib administration and after dosing according to the Time and Events Schedule. Plasma and urine concentrations of ibrutinib and its metabolite PCI-45227 were assayed using a validated liquid chromatography coupled to tandem mass spectrometry method. Pharmacokinetic parameters included C_{max}, t_{max}, AUC_{24}, AUC_{last}, AUC_{∞}, $\%AUC_{\infty,ex}$, $t_{1/2,\lambda}$, λ_z, CL/F, Vd/F, Ae, and Ae%dose. Plasma protein binding of ibrutinib was assessed. Additional PK parameters (ie, metabolite/parent ratio [M/P]) and unbound C_{max} [$C_{max,unb}$] and unbound AUC [AUC_{unb}]) were determined.

Safety: Safety was to be evaluated throughout the study, and included assessment of AEs, laboratory values, physical examinations, vital signs, and ECGs.

Statistical Methods:

Sample Size Determination: Based on clinical considerations, following the FDA Guidance for Industry regarding Pharmacokinetics in Patients with Impaired Hepatic Function, approximately 30 subjects were planned to be enrolled (24 subjects with hepatic impairment [6 mild, 9 moderate, and 9 severe] at baseline and 6 subjects in the control group according to Child-Pugh criteria). The proposed sample size was considered sufficient to compensate for a drop-out rate of approximately 20%. A subject could be replaced in each group if the number of completers was less than 6 subjects in a group. Any replacement subject during the active treatment phase was to be given a new identification number.

For all subjects who received study drug, descriptive statistics (mean, standard deviation, median, minimum, maximum) were provided for age, BMI, weight, height and renal function. Sex and race were listed and tabulated.

Pharmacokinetics: Data were listed for all subjects with available plasma and urine concentrations per treatment group. Subjects were excluded from the PK analysis if their data did not allow for accurate assessment of the PK parameter. The PK population included all subjects who had sufficient and interpretable PK assessments to calculate the noncompartmental PK parameters of ibrutinib and were included in the statistical comparison of subjects with hepatic impairment versus the control group.

The plasma concentrations of ibrutinib and PCI-45227 at each time point, PK parameters, and plasma protein binding were summarized by subject group with mean, median, standard deviation, minimum value, maximum value, and coefficient of variation (CV). For each subject group, individual and scatter plots of plasma concentration time profiles of ibrutinib and PCI-45227 were plotted on both original and log scales. Mean plasma concentration time profiles were graphically presented for each group.

The primary parameters of interest for the statistical analysis were AUC and C_{max}. The analysis was performed on log-transformed estimated PK parameters. An analysis of variance (ANOVA) model was applied on the log-transformed PK parameters. The geometric mean ratios and the associated 90% confidence intervals for AUCs and C_{max} were constructed for the following pairs: (1) mild hepatic impairment versus (vs) normal hepatic function; (2) moderate hepatic impairment vs normal hepatic function; (3) severe hepatic impairment vs normal hepatic function.

Safety: All subjects receiving study drug were to be included in the safety population. Safety and tolerability were evaluated throughout the study and consisted of assessment of AEs, 12-lead ECGs, physical examinations, vital signs, and laboratory safety (hematology, serum chemistry, urinalysis). Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 15.1. Adverse event severity was graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system Version 4.03. Laboratory data was to be descriptively summarized. All serious adverse events (SAEs), discontinuations due to AE, and deaths were to be listed. No formal statistical analyses were planned.

RESULTS:

STUDY POPULATION:

Thirty subjects between 35 years and 65 years of age, inclusive, were dosed in this 4-center study (Note: Site 1004 received study drug but did not enroll subjects). The median age was 53 years and the mean BMI was 30.0 kg/m^2. The demographic and baseline characteristics were consistent with those of the planned study population described in the study protocol.

Per protocol, approximately 30 subjects were to be enrolled (24 subjects with hepatic impairment [6 mild, 9 moderate, and 9 severe] at baseline and 6 subjects in the control group according to Child-Pugh criteria). One subject, assigned in error to the severe group, was reclassified prior to database lock to the moderate group and was analyzed for safety and PK with that group. All 30 subjects received a single 140 mg oral dose of ibrutinib on Day 1. All subjects, (6 mild, 10 moderate, and 8 severe liver impairment and 6 control subjects) completed the study.

PHARMACOKINETIC RESULTS:

Based on geometric mean ratios, a 5.2-, 8.8-, and 7.0-fold increase in ibrutinib plasma C_{max} was estimated for the mildly, moderately, and severely impaired subjects, respectively, when compared to healthy control subjects. A 2.7-, 8.0-, and 9.5-fold increase in plasma AUC_{∞} was estimated for the mildly, moderately, and severely impaired subjects, respectively. Intersubject variability was high ranging from 87.8% to 153.9% for C_{max} and 31.6% to 180.8% for AUC_{∞}. Unbound ibrutinib C_{max} increased 5.7-, 9.9-, and 9.7-fold and unbound AUC_{∞} increased 4.4-, 9.6-, and 13.1-fold with mild, moderate, and severe hepatic impairment, respectively.

Geometric mean ratios for PCI-45227 C_{max} were 1.7, 1.1, and 0.9 for the mildly, moderately, and severely impaired subjects, respectively, compared to healthy control subjects. Intersubject variability ranged from 38.7% to 119.1% for C_{max}. Geometric mean ratios for AUC_{∞} were 1.6, 1.5, and 1.5, respectively. Intersubject variability ranged from 17.6% to 76.8% for AUC_{∞}.

Parameter[a]	Test/ Reference[c]	N	LS Mean[b]	Ratio: Test/Reference (%)[c]	90% Confidence Interval (%)[d]	CV (%)
Ibrutinib						
C_{max} (ng/mL)	Severe	8	43.30	695.75	(309.16, 1565.74)	106.6
	Moderate	10	54.51	875.89	(403.29, 1902.31)	87.8
	Mild	6	32.11	516.01	(216.81, 1228.14)	153.9
	Control	6	6.22			103.3
AUC_{∞} (ng.h/mL)	Severe	8	601.76	946.46	(529.69, 1691.15)	31.6
	Moderate	10	506.00	795.84	(456.87, 1386.31)	57.4
	Mild	5	168.62	265.20	(138.34, 508.41)	180.8
	Control	6	63.58			43.5
PCI-45227						
C_{max} (ng/mL)	Severe	8	19.01	89.83	(49.24, 163.90)	119.1
	Moderate	10	23.80	112.46	(63.29, 199.85)	61.8
	Mild	6	35.22	166.44	(87.52, 316.54)	54.3
	Control	6	21.16			38.7
AUC_{∞} (ng.h/mL)	Severe	8	429.03	153.52	(91.80, 256.76)	72.1
	Moderate	10	418.93	149.91	(91.68, 245.13)	60.8
	Mild	5	453.38	162.24	(91.14, 288.79)	76.8
	Control	6	279.45			17.6

[a]Parameter data were natural log (ln) transformed prior to analysis.
[b]Least square (LS) means from ANOVA, transformed back to the linear scale (ie, geometric means).
[c]Ratio of parameter means (expressed as a percent), transformed back to the linear scale. Normal Hepatic Function group was used as the reference group.
[d]90% confidence interval for ratio of parameter means (expressed as a percent), transformed back to the linear scale.
Note: AUC_{∞} was not calculated in 1 subject due to unacceptable high variability in the terminal phase (r^2adj <0.90).
C_{max}=maximum observed plasma concentration; AUC_{∞}=area under the plasma concentration-time curve from time 0 to infinity

A decrease was observed in both albumin and α1-acid glycoprotein concentration as a function of hepatic impairment; with a corresponding increase in the unbound fraction of ibrutinib.

SAFETY RESULTS

Among the six (20%) of 30 subjects with at least 1 observed adverse event, no discernable pattern of adverse events was seen among the different groups. No pattern of increased adverse events with increased severity of hepatic impairment was noted. Overall, the treatment emergent toxicities, categorized as per NCI-CTCAE criteria, were Grade 1 or 2 in severity across all groups. There was one observed Grade 1 adverse event in a subject in the severe group that was considered by the investigator to be probably related to ibrutinib (dry eyes); no serious adverse events, deaths, or discontinuations due to an adverse event were reported. The safety profile appeared consistent with the adverse event profile expected in subjects with varied levels of hepatic impairment.

Assessment of the administration of ibrutinib on laboratory parameters showed no clear pattern in the occurrence of hematology, serum chemistry, coagulation, PFA-100 assay, or urinalysis abnormalities in relation to the administration of ibrutinib; the observed abnormalities appeared to be consistent with the disease pathology associated with hepatic impairment or other concomitant disease and did not meaningful increase after single dose administration of ibrutinib. No clinically significant findings in temperature, systolic and diastolic blood pressure, respiratory rate or pulse rate following administration of ibrutinib across the identified groups was observed and physical examination abnormalities were consistent with the medical histories and the underlying disease pathologies of the study population. Although some ECGs were interpreted as “abnormal not clinically significant” by the investigator, in the

majority of cases, abnormalities were also present on the day of screening or predose. None of these ECG-related findings were determined to be clinically significant by the investigator.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

- The pharmacokinetic results from this study show that there was a 5.2-, 8.8-, and 7.0-fold increase in ibrutinib C_{max} and a 2.7-, 8.0-, and 9.5-fold increase in AUC_{∞} in subjects with mild, moderate and severe hepatic impairment, respectively. Unbound ibrutinib C_{max} increased 5.7-, 9.9-, and 9.7-fold and unbound AUC_{∞} increased 4.4-, 9.6-, and 13.1-fold with mild, moderate, and severe hepatic impairment, respectively. The highest observed C_{max} was 103 ng/mL and the highest AUC_{∞} was 971 ng.h/mL.
- Oral doses of ibrutinib 140 mg were tolerated in healthy subjects and subjects with noted hepatic impairment. Observed laboratory safety abnormalities appeared to be consistent with the disease pathology associated with hepatic impairment. No serious adverse events, deaths, or discontinuation due to an adverse event were observed.

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