SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient(s)	PCI-32765 (ibrutinib)

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Status: Approved

Date: 3 October 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: PCI-32765CLL1001

Title of Study: Open-Label, Randomized, 4-Way Crossover Study to Determine the Effect of Food on the Pharmacokinetics of PCI-32765

NCT No.: NCT01820936

Clinical Registry No.: CR101204

Principal Investigator(s): Sandra M. Connolly, MD, CPI

Study Center(s): Celerion 1930 Heck Avenue, Building # 2, Neptune, NJ 07753 USA

Publication (Reference): None

Study Period: 03 January 2013 to 14 June 2013; Database lock date: 28 June 2013

Phase of Development: 1

Objectives:

Primary Objective
The primary objective was to evaluate the exposure of ibrutinib in healthy subjects when ibrutinib is administered with or without food.

Secondary Objectives
- The pharmacokinetics (PK) of metabolite PCI-45227 was evaluated.
- The safety and tolerability of ibrutinib was assessed.

Methodology:

This was a randomized, open-label, single-center, single-dose, 4-way crossover study. Following written informed consent, subjects were screened within 21 days (Day -21 to -1). During the Screening Phase, subjects were evaluated for inclusion and exclusion criteria. Women who were postmenopausal or surgically sterile were enrolled in addition to men. Subjects who successfully met all inclusion and none of the exclusion criteria were eligible for admission to the study center on Day –1. Subjects were randomized to 1 of 4 treatment sequences as described below. All subjects received a single oral dose of 420 mg ibrutinib with 240 mL of noncarbonated water on Day 1 of each treatment period. All subjects fasted for at least 10 hours before dosing or breakfast, whichever was scheduled to occur first. During

each of the treatments with controlled food intake, the entire breakfast was to be consumed within 30 minutes. For each treatment, lunch was provided approximately 4 hours after dosing. Water was allowed ad libitum 2 hours after each dose.

Blood samples for PK analysis of ibrutinib and metabolite PCI-45227 were collected before dosing and over 72 hours after dosing in each treatment period.

Subject's safety was assessed from the time of consent until the end of the study and included physical examination, adverse events (AE), electrocardiograms (ECGs), vital signs, and clinical laboratory results. Subjects were discharged from the study center after the final 72-hour PK sample in Period 4 and safety procedures. A follow-up visit approximately 10 (±2) days after the last dose was made to measure lymphocyte count and to capture any additional AEs.

After completion of the 4-way crossover, an additional separate cohort of 8 subjects were enrolled. These subjects participated in 1 treatment period and received a dose of 840 mg in combination with a high fat breakfast to document safety and PK.

Number of Subjects (planned and analyzed): 52 subjects were planned and analyzed (at least 25% women); 44 subjects in the 4-way crossover and 8 subjects in the optional cohort 840 mg + high fat breakfast.

Diagnosis and Main Criteria for Inclusion:

- Healthy men and women between 18 and 55 years of age, inclusive.
- Body mass index (BMI) between 18 and 30 kg/m², inclusive and a body weight of not less than 50 kg.
- Subjects must have normal coagulation tests and Platelet Function Assay (PFA-100).

Test Product, Dose and Mode of Administration, Batch/Lot No.:

Ibrutinib, 140 mg capsules, administered orally with 240 mL noncarbonated water. Lot No. L0309801.

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

Duration of Treatment: A screening phase (within 21 days before the first study drug administration of the first period) was followed by an open-label treatment phase consisting of 4 single-dose treatment periods. Doses in successive open-label treatment periods were separated by a washout period of 7 (±2) days. Subjects were confined to the study center from Day –1 of each treatment period, at least 10 hours before each study drug administration, until completion of the 72-hour PK blood sample collection. Subjects were discharged from the study following evaluations on Day 4 of Period 4. The total study length was from 65 days to a maximum of 85 days. In the cohort 840 mg + high fat breakfast, the total study length was 31 days.

Criteria for Evaluation:

Pharmacokinetics

Serial PK blood samples were collected for over 72 hours in each treatment period. The following key PK parameters were calculated for ibrutinib and PCI-45227: C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2}$, λ_z, F_{rel} (%). Additional PK parameters were determined as appropriate.

Safety

Safety and tolerability were evaluated throughout the study. The total amount of blood drawn for clinical laboratory tests and PK evaluations was approximately 360 mL for subjects in the 4-way crossover and approximately 110 mL for subjects in the 840 mg + high fat breakfast cohort.

Statistical Methods:

At least 36 subjects were to complete all study procedures of all 4 crossover treatment periods, including the 72-hour PK blood sample collections, and the end-of-study evaluations. Eight subjects were enrolled in the 840 mg + high fat breakfast cohort.

Sample Size Determination

Preliminary data (PCYC-1102-CA, PCYC-1104-CA, PCYC-1106-CA, and PCYC-1109-CA) indicated the intra-subject coefficients of variation were approximately 61% for C_{max} and 47% for AUCs of ibrutinib.

Assuming an intra-subject coefficient of variation of 61% for C_{max}, a sample size of 36 subjects was sufficient for the point estimates of the geometric mean ratios of C_{max} between Test and Reference to fall within 80% to 125% of the true value, with 90% confidence.

Assuming an intra-subject coefficient of variation of 47% for AUC, a sample size of 36 subjects was sufficient for the point estimates of the geometric mean ratios of AUC between Test and Reference to fall within 84% to 120% of the true value, with 90% confidence.

Approximately 44 subjects were needed to be enrolled to ensure at least 36 subjects complete all 4 crossover treatments. A sample size of 8 subjects was considered adequate to explore safety in the optional cohort 840 mg + high fat breakfast.

Randomization

Randomization is as described below. All subjects were to receive each of the 4 treatments (A to D).

Sequence	N	Period 1	Period 2	Period 3	Period 4
1	11	D	C	A	B
2	11	A	D	B	C
3	11	B	A	C	D
4	11	C	B	D	A

Treatment groups were as follows:

- Treatment A: Ibrutinib, 420 mg, administered with 240 mL noncarbonated water, 30 minutes after completing a high-fat breakfast (Fed)
- Treatment B: Ibrutinib, 420 mg, administered with 240 mL noncarbonated water after fasting for at least 10 hours and 30 minutes before starting a high-fat breakfast
- Treatment C: Ibrutinib, 420 mg, administered with 240 mL noncarbonated water 2 hours after completing a high-fat breakfast
- Treatment D (Reference): Ibrutinib, 420 mg, administered with 240 mL noncarbonated water Fasted)
- Treatment E: Ibrutinib, 840 mg, administered with 240 mL noncarbonated water, 30 minutes after completing a high-fat breakfast (Fed)

Pharmacokinetics

Individual and mean plasma ibrutinib and PCI-45227 concentration-time profiles were plotted for each treatment. Plasma concentration data at each timepoint were summarized with mean, median, minimum, maximum, standard deviation (SD) and coefficient of variation (%) for each treatment. All estimated PK parameters of ibrutinib and PCI-45227 were summarized for each treatment with mean, median, geometric mean, minimum value, maximum value, SD, and coefficient of variation (%). Relative bioavailability (F_{rel} [$AUC_{\infty Test}/AUC_{\infty Ref}$]) was calculated for each subject and summarized with mean, median, geometric mean, minimum value, maximum value, SD, and coefficient of variation (%).

Statistical analysis included all subjects who has completed at least 1 treatment period with PK evaluable data. The primary PK parameters of interest were AUC_{last}, AUC_{∞}, and C_{max} of ibrutinib. A mixed-effect model that included the treatment period, the treatment sequence as fixed effects, and subject as a random effect, were used to estimate the least squares means and intra-subject variance. Ninety percent confidence intervals for the ratio of mean AUC_{last}, AUC_{∞} and C_{max} were constructed for the following pairs of treatments, using the estimated least squares means and intra-subject variance from the mixed effects model of log-transformed PK parameters: (1) Treatment A versus Treatment D, (2) Treatment B versus Treatment D, and (3) Treatment C versus Treatment D.

Exploratory analysis on other treatment comparisons was performed.

No statistical comparisons were made for PCI-45227.

Safety

Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the Screening Phase through study completion, including the washout interval. Safety and tolerability analysis included: baseline for all laboratory evaluations, vital signs, and 12-lead ECG measurements were defined as the last evaluation done before the first study drug administration.

RESULTS:

STUDY POPULATION

All subjects who were randomly assigned to a treatment sequence and received at least 1 dose of the study:

- Fifty-two subjects were enrolled, treated with ibrutinib and 51 completed the study. All subjects met eligibility criteria. All 52 subjects were included in the safety analysis and the PK analysis sets for the inferential analysis included 44 subjects of the main cohorts. There was 1 premature discontinuation from the study due to withdrawal by the subject following completion of Period 1.
- A total of 45 men and 7 women were enrolled. The median age was 39 years (range 24 to 55 years of age, inclusive).
- There was 1 major protocol deviation of non-collection of the 72-hour sample for 1 subject (#10101) during Treatment A.
- There were no treatment-related deviations.
- All 44 subjects in the Treatment A to D cohorts received at least 1 single oral dose of 420 mg (3 x 140 mg) ibrutinib and 8 subjects in Treatment E received a single oral dose of 840 mg (6 x 140 mg) of ibrutinib.

PHARMACOKINETIC RESULTS

Compared with fasted condition, ibrutinib C_{max} was 2.6-, 3.2-, and 3.8-fold higher when dosed 30 minutes before, 30 minutes after, or 2 hours after a high-fat breakfast, respectively. AUC_{last} was 1.6-, 1.9-, or 1.8-fold higher.

SAFETY RESULTS

- Single oral doses of ibrutinib of 420 mg and single doses of 840 mg ibrutinib were well tolerated.
- All AEs reported were mild to moderate in severity (Grade 1 to 2) and resolved.
- There were no SAEs, deaths, or discontinuations due to an AE.
- There were no clinically significant changes in laboratory safety parameters, ECG, and vital signs during this study.

STUDY LIMITATIONS

No notable study limitations were identified by the Sponsor.

CONCLUSIONS

- Compared with fasted condition, ibrutinib C_{max} was 2.6-, 3.2-, and 3.9-fold higher when dosed 30 minutes before, 30 minutes after, or 2 hours after a high-fat breakfast, respectively. AUC_{last} was 1.6-, 1.9-, or 1.8-fold higher.
- Administration of ibrutinib in a fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to either 30 minutes before or 2 hours after a high fat breakfast. By contrast, when ibrutinib was taken 30 minutes after a meal (fed condition), the exposure (AUC_{last}) was comparable to the dosing conditions of either 30 minutes before or 2 hours after the meal.
- Oral doses of ibrutinib of 420 mg and 840 mg, resulting in average C_{max} and AUC values up to 190 ng/mL and 905 ng.h/mL, respectively, were well tolerated in healthy subjects.

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