SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-54179060 (ibrutinib)

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Status: Approved

Date: 1 December 2016

Prepared by: Janssen Research & Development, LLC

Protocol No.: PCI-32765FLR2002

Title of Study: An Open-label, Multicenter, Single-arm, Phase 2 Study of PCI-32765 (ibrutinib) in Subjects with Refractory Follicular Lymphoma

EudraCT Number: 2012-004097-26

NCT No.: NCT01779791

Clinical Registry No.: CR100956

Coordinating Investigator(s): Nathan H. Fowler, MD University of Texas MD Anderson Cancer Center; Department of Lymphoma/Myeloma; [redacted], United States

Study Center(s): Study centers in the following countries enrolled subjects into this study: Australia (3 sites), Belgium (3 sites), France (3 sites), Germany (3 sites), Italy (4 sites), Poland (3 sites), Russia (5 sites), Spain (3 sites), United Kingdom (2 sites), United States (16 sites).

Publication (Reference): None

Study Period: Study initiated 21 March 2013; Clinical cutoff 18 May 2016; Database lock 5 July 2016.

Phase of Development: Phase 2

Objectives: The primary objective of the study was to evaluate the overall response rate (ORR) of ibrutinib, as assessed by the Independent Review Committee (IRC), in subjects with chemoimmunotherapy (CIT)-resistant follicular lymphoma (FL). The secondary objectives were to evaluate duration of response (DOR) and safety. Other secondary objectives included progression-free survival (PFS), overall survival (OS), time to response, incidence of subjects who experienced resolution of lymphoma-related B-symptoms, pharmacokinetics of ibrutinib, exploring potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information, and identifying biomarkers that alter B cell receptor signaling or activate alternative signaling pathways and exploring their association with response to ibrutinib.

Methodology: This was an open-label, multicenter, single-arm, Phase 2 study of ibrutinib in approximately 110 subjects with CIT-resistant FL. The efficacy evaluations were performed by an IRC according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma. The study included a Screening Phase (up to 30 days prior to the first dose of study drug), a Treatment Phase (until disease progression or unacceptable toxicity), and a Posttreatment Follow-up Phase (until death, lost to follow-up, withdrawal of consent, or study end [defined as 2 years after the last subject is enrolled]).

Number of Subjects (planned and analyzed): The planned total sample size was approximately 110 subjects, and a total of 110 subjects were enrolled. All enrolled subjects received treatment with at least one dose of ibrutinib and thus were analyzed.

Diagnosis and Main Criteria for Inclusion: Key inclusion criteria: 18 years of age or older with histologically-confirmed Grade 1, 2, or 3a FL at initial diagnosis without clinical or pathological evidence of transformation; treated with at least 2 prior lines of therapy (received at least 1 prior rituximab-containing combination chemotherapy regimen; last prior line included an anti-CD20 monoclonal antibody-containing regimen); resistant disease to the last prior therapy, defined as progression of disease during or within 12 months of the last dose of a CD20 antibody combination chemotherapy regimen; at least 1 measurable site of disease based on IWG Revised Response Criteria for Malignant Lymphoma; Eastern Cooperative Oncology Group performance status Grade 0 or 1; hematology and biochemical values within limits within 7 days prior to treatment.

Key exclusion criteria: Prior nitrosoureas within 6 weeks, chemotherapy within 3 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy or other investigational agents within 3 weeks, or major surgery within 4 weeks of first dose of study drug; prior treatment with ibrutinib or other Bruton's tyrosine kinase inhibitors; subjects who progressed or became refractory while on treatment with phosphoinositide 3 kinase inhibitors; known central nervous system lymphoma; prior allogeneic hematopoietic stem cell transplant; history of prior malignancy; history of stroke or intracranial hemorrhage with 6 months prior to enrollment; required treatment with strong cytochrome P450 3A subtype inhibitors, or anticoagulation treatment with warfarin or equivalent vitamin K antagonists; known history of human immunodeficiency virus or active infection with hepatitis C or active infection with hepatitis B or any uncontrolled active systemic infection requiring intravenous antibiotics.

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib capsules were provided as a hard gelatin capsule containing 140 mg of ibrutinib. The subject was assigned by an interactive web response system to receive study drug. Subjects received 560 mg oral ibrutinib once daily administered as 4 capsules containing 140 mg each. The capsules were taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). Each dose of study drug was taken at least 30 minutes before eating or at least 2 hours after a meal. If a dose was missed, it could be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it had been more than 6 hours since the missed dose, the dose was skipped and the subject continued treatment at the scheduled time the next day. Ibrutinib drug product was supplied for this study from 9 batches (L0400218, L0404313, L0404955, L0407872A, L0402420, L0400218, L0409196A, L0409672B, and L0409672B).

Duration of Treatment: Subjects were to receive continuous daily treatment until disease progression or unacceptable toxicity, whichever occurred earlier.

Criteria for Evaluation: The primary endpoint of the study was ORR according to the IWG Revised Response Criteria for Malignant Lymphoma as assessed by IRC. Response assessments were done by the investigators at the site to assess continuation of treatment. Disease assessments were performed as scheduled, according to the Time and Events Schedule and were conducted until disease progression, withdrawal of consent from study participation, death, or the end of study. For subjects who discontinued study drug before disease progression was documented, disease assessments were continued in the Posttreatment Follow-up Phase until progressive disease (PD), death, lost to follow-up, withdrawal of consent, or study end; whichever came earlier.

Statistical Methods: Approximately 110 subjects were planned to be enrolled, assuming an ORR of 30% in the study population, so that the study would have approximately 85% power to declare that the lower bound of the 95% confidence interval (CI) for ORR would exceed 18%. The primary efficacy endpoint, ORR, was defined as the proportion of subjects who achieved complete response (CR) or partial response (PR), as assessed by the IRC, according to the IWG Revised Response Criteria for Malignant Lymphoma. The ORR analysis was performed on the all-treated population as the primary analysis. The response rate

and its 95% exact (Clopper-Pearson) CI was calculated, and the null hypothesis was rejected if the lower bound of the CI exceeded 18%. Subgroup analysis was provided. The secondary endpoint DOR was defined as the interval between the date of initial documentation of a response (CR or PR) and the date of first documented evidence of PD (or relapse for subjects who experienced CR during the study) or death, whichever occurred first. The distribution of DOR was estimated using the Kaplan-Meier method. The primary analysis was based on response data by IRC assessment. Subgroup analysis was also provided. Sensitivity analysis was performed using the response data by investigator assessment. Other secondary endpoints summarized were time to response, PFS, OS, resolution of lymphoma-related symptoms, time to PD on prior last line of treatment, and time to next treatment (TTNT) on last prior line of therapy. Analysis of safety data was conducted on the safety population, which included subjects who received study drug. Safety variables were tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing was planned for safety.

RESULTS:

STUDY POPULATION: One hundred ten subjects were enrolled and all received at least 1 dose of study treatment. As of the clinical data cutoff of 18 May 2016 for the primary analysis, all 110 subjects (100%) discontinued the study, and the subjects who were continuing to benefit from treatment were rolled over into the extension Study PCI-32765CAN3001.

The median age of the all-treated population was 61.5 years (range: 28 to 87 years), with 39.1% of subjects ≥65 years of age. Most subjects had Stage IV FL at study entry (54.5%) and histology Grade 2 FL (55.5%, as per World Health Organization histological grading), 19.1% of subjects had tumor bulk >6 cm and 44.5% of subjects had lactic acid dehydrogenase (LDH) values above normal. More than half of subjects (55.5%) received 3 or more lines of prior systemic therapy, and 68.2% of the subjects received prior bendamustine therapy. Relapsed status (relapsed or disease progression after achieving at least a PR to the last regimen prior to study entry) was reported for 59.1% of subjects, while 40.9% of subjects had refractory status (defined as failure to achieve at least a PR to the last regimen prior to study entry) to the last line of prior therapy.

EFFICACY RESULTS: A final summary of efficacy results as of the clinical cutoff of 18 May 2016 is summarized below:

- The ORR by IRC assessment was 20.9% (95% CI: 13.7%, 29.7%). The lower bound of the CI did not exceed the pre-specified efficacy criteria of 18% (with p-value = 0.247); thus, the ORR did not meet the primary objective of the study.
  - The ORR determined by the investigator was consistent with the IRC assessment (23.6%; 95% CI: 1%, 32.7%).
  - In total, 51.8% of subjects had a response of stable disease (SD) or better (CR=10.9%, PR=10.0%, SD=30.9%).
  - Thirty-three percent (36/110) of subjects with SD or better as their best response had responses lasting ≥6 months (14 of the 36 subjects had SD as best response); 21.8% (24/110) had responses lasting ≥1 year (5 of the 24 subjects had SD as best response).
- The median time to initial response for responders as assessed by IRC was 5.7 months (range: 2.6 to 13.8 months). The median time to best response was 8.3 months (range: 2.7 to 19.3 months).
- The median DOR by IRC assessment was 19.4 months.
- The median PFS by IRC assessment was 4.6 months (95% CI: 2.8, 5.5 months).
  - The median PFS by investigator assessment was 5.5 months (95% CI: 4.3, 8.1 months).
- After a median follow-up of 27.7 months, the median OS could was not estimable for ibrutinib-treated subjects. An estimated 63% of subjects were alive at 2 years.

- Thirty-nine subjects had lymphoma symptoms at baseline, and 26 subjects had resolution of lymphoma symptoms at any visit during the course of the study.
- The estimated median TTNT was 16.03 months (95% CI; 10.71, 19.12 months), and even after 2 years of ibrutinib treatment, one third of the subjects did not require subsequent anticancer therapy, further suggestive of clinical benefit.

PHARMACOKINETIC RESULTS: The observed ibrutinib plasma concentrations were consistent with previous assessments. Average (standard deviation) area under the curve for the 24 hour dosing interval and plasma concentration at 24 hours after dosing at steady-state were 539 (360) ng.h/mL and 5.77 (3.56) ng/mL, respectively.

SAFETY RESULTS: Safety findings for the 110 subjects in the safety population were consistent with the overall ibrutinib safety profile and demonstrated that continuous treatment with ibrutinib 560 mg orally once per day is well tolerated by subjects with refractory FL who progress after an anti-CD20 or rituximab-containing chemotherapy regimen.

One hundred and seven (97.3%) subjects experienced treatment-emergent adverse events (TEAEs). The most common (≥20%) TEAEs (all grade) were diarrhea (50.9%), fatigue (40.0%), cough (35.5%), muscle spasms (31.8%), nausea (29.1%), oedema peripheral (28.2%), pyrexia (24.5%) and anemia (22.7%).

Grade 3 or 4 TEAEs were reported for 56.4% of subjects, with the most common (≥5%) being neutropenia (13.6%), anemia (9.1%), pneumonia (6.4%), and fatigue (5.5%). Treatment-emergent serious adverse events were reported in 48.2% of subjects, most commonly (≥5% of subjects) pneumonia and pyrexia (6.4% each).

Thirteen (11.8%) subjects had TEAEs contributing to study treatment discontinuation. Seven subjects (6.4%) had adverse events (AEs) as the primary reason of discontinuation, with subdural hematoma being the most frequent with 2 subjects (1.8%).

In this study, 8 subjects died during the treatment period or within 30 days of the last dose of ibrutinib.

Hemorrhagic events were reported in 37 subjects (33.6%). Treatment-emergent major hemorrhagic events were reported for 4 subjects (3.6%), with subdural hematoma being the most frequent (2 subjects, 1.8%).

Tumor lysis syndrome (Grade 3) was reported in 1 subject (0.9%).

Atrial fibrillation was reported in 10 (9.1%) subjects, of which 7/10 subjects recovered or resolved. Grade 3 or 4 atrial fibrillation was reported for 4 subjects (3.6%). All 4 subjects recovered, however none of the 4 subjects required dose reduction or discontinuation due to this event.

Clinical laboratory data, including hematology and serum chemistry did not reveal any new safety signals.

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

CONCLUSION(S): Treatment with single-agent ibrutinib at a dose of 560 mg/day in subjects with CIT-refractory FL achieved durable responses, with an ORR of 20.9%. Statistically, ORR did not meet the primary objective of the study. However, ibrutinib treatment clearly showed substantial clinical benefits as supported by DOR, resolution of symptoms, TTNT, and OS. Safety results in this study were consistent with the current known profile of ibrutinib; the majority of AEs reported were Grade 1 or 2. There were no new safety signals identified from this study. The observed ibrutinib plasma concentrations were consistent with previous assessments. In subjects with CIT-refractory FL who have limited treatment options, treatment with ibrutinib resulted in a clinical benefit with an acceptable safety profile.

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