SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K. *
Name of Investigational Product	PCI-32765

* This study was conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the report to represent Janssen Pharmaceutical K.K.

Status: Approved

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Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: PCI-32765-JPN-101

Title of Study: A Phase 1 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 in Subjects With Recurrent Mature B-Cell Neoplasms

NCT No.: NCT01704963

Clinical Registry No.: CR100896

Principal Investigator(s): No coordinating investigator.

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Study Center(s): Four study centers in Japan

Publication (Reference): *Primary analysis results*: Tobinai K, Ogura M, Ishizawa K, et al. Safety and tolerability of ibrutinib monotherapy in Japanese patients with relapsed/refractory B cell malignancies. Int J Hematol. 2016; 103(1): 86-94.

Study Period: 18 September 2012 (Date of first subject signed informed consent) to 1 February 2017 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 1

Objectives: The primary objective of this study was to evaluate the safety and tolerability of ibrutinib in Japanese subjects with recurrent mature B-cell neoplasms. The secondary objectives were to evaluate the pharmacokinetic (PK) profile of ibrutinib and its dihydrodiol metabolite of the parent compound PCI-32765 (PCI-45227), measure BTK active site occupancy as a pharmacodynamic parameter, and evaluate tumor response. The exploratory objectives were to explore pharmacogenomics and other biomarkers as deemed necessary.

Methodology: This was an open-label Phase 1 multicenter dose-escalation study, conducted in Japan, with 3 cohorts (Cohort 1, Cohort 2 and chronic lymphocytic leukemia or small lymphocytic lymphoma

[CLL/SLL] Cohort). Cohort 1 was divided into two phases: a single dose phase and a multiple dose (MD) phase. In the single dose phase, subjects with recurrent mature B-cell neoplasms received ibrutinib 140 and 280 mg with a washout period between dose levels. After a second washout period, subjects then entered the MD phase to receive 420 mg ibrutinib once daily for 35 days during Cycle 1 and for 28 days in subsequent cycles. In Cohort 2, subjects with recurrent mature B-cell neoplasms received ibrutinib 560 mg once daily for 35 days during Cycle 1 and for 28 days in subsequent cycles. Enrollment in Cohort 2 started after the tolerability was confirmed in cohort 1. Based on the tolerability of ibrutinib 420 mg in Cohort 1, the protocol was amended to add a new cohort (CLL/SLL Cohort), which enrolled subjects with only CLL/SLL, to further investigate the safety and tolerability of ibrutinib in Japanese patients with relapsed/refractory CLL/SLL, wherein subjects received ibrutinib 420 mg, once daily.

Tolerability was evaluated based on dose-limiting toxicities (DLTs) during the single dose phase and Cycle 1 of the MD phases for Cohort 1, and during Cycle 1 for Cohort 2 and the CLL/SLL Cohort. Subjects could remain on treatment until disease progression, the investigator no longer considered the treatment to be tolerable, or other reasons as listed in the discontinuation criteria.

The study was started on 18 September 2012 (first subject signed informed consent). The primary analysis of this study was conducted with a clinical data cutoff date of 5 June 2014, when the last subject completed Cycle 6. Five amendments to the protocol were made after the primary analysis. In these protocol amendments, for an indication that had marketing approval, subjects with CLL and SLL continued the study with a status of 'postmarketing'. These subjects were to complete the postmarketing study only after the institution was ready to prescribe the drug as a market product. Subjects with subtypes other than CLL/SLL were to end this study at the time when marketing approval was obtained for the indication.

Number of Subjects (planned and analyzed): Planned: A maximum of 27 subjects were to be enrolled in this study. Analyzed: 18 subjects provided informed consent and 15 subjects received ibrutinib.

Diagnosis and Main Criteria for Inclusion: The study population consisted of adults with recurrent mature B-cell neoplasms, excluding plasma cell neoplasm and diffuse large B-cell lymphoma (DLBCL), who had measurable disease.

Inclusion criteria included recurrent mature B-cell neoplasms including CLL/SLL, mantle cell lymphoma (MCL), and follicular lymphoma (FL); measurable disease (for Non-Hodgkin's lymphoma [NHL] bi-dimensional disease ≥2 cm diameter in at least one dimension and for CLL ≥5,000 leukemia cells/mm^3); failed ≥1 previous treatment and no standard therapy was available; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib capsules were provided as a gray, size 0 hard gelatin capsule containing 140 mg of ibrutinib. Subjects in Cohort 1 received single oral doses of ibrutinib at 140 mg and 280 mg before receiving daily oral doses of 420 mg/day. Subjects in Cohort 2 and those in the CLL/SLL Cohort received daily oral doses of ibrutinib at 560 mg/day and 420 mg/day, respectively. Subjects were instructed to take each dose of ibrutinib at least 30 minutes before a meal and at least 2 hours after a meal at approximately the same time each day. The following lot numbers of ibrutinib were used in this study: L0307693, L0308266, L0403953, and L0501945.

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

Duration of Treatment: Subjects in Cohort 1 received a single oral dose of ibrutinib at 140 mg followed by a 72 to 168 hour washout period, and then received a single oral dose of ibrutinib at 280 mg. After a 72 to 168 hour second washout period, subjects in Cohort 1 received daily oral doses of 420 mg/day for 35 days in Cycle 1 and for 28 days in Cycle 2 and every cycles thereafter. Subjects in Cohort 2 and those in the CLL/SLL Cohort received daily oral doses of ibrutinib at 560 mg/day and 420 mg/day, respectively, every day for 35 days in Cycle 1 and for 28 days in Cycle 2 and every cycles thereafter.

Subjects could remain on treatment until disease progression, the investigator no longer considered the treatment to be tolerable, or other reasons as listed in the discontinuation criteria. Subjects who had not progressed at the end of the study, switched to marketing-approved ibrutinib (IMBRUVICA®) treatment.

Criteria for Evaluation: An update of adverse events (AEs), clinical laboratory, electrocardiogram (ECG), and efficacy assessments was performed for the final analysis. The definitions and analysis methods used for the safety and efficacy analysis in this report are the same as those used for the primary clinical study report (CSR) for study PCI-32765-JPN-101.

Statistical Methods: The AEs recorded by the investigators in the case report form (CRF) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0; note that the version of MedDRA is not the same as that used for the primary analysis (Version 16.1).

All subjects were evaluated for tumor response according to the International Working Group (IWG) Revised Criteria for Malignant Lymphoma or the Guidelines for the diagnosis and treatment of CLL. The best tumor response and its related parameters (eg, time to response [TTR], duration of response [DOR]) were presented for each subject. The overall response rate (ORR) was defined as the proportion of subjects with a best response of either complete response (CR) or partial response (PR) in the response evaluable population.

RESULTS:

The results of the final analysis of this study are presented in this CSR. The results for the primary analysis were reported in the CSR with a clinical data cutoff date of 5 June 2014.

STUDY POPULATION:

In this study, 15 subjects received ibrutinib. Of these, 3 subjects in Cohort 1 and 6 subjects in the CLL/SLL Cohort received ibrutinib at 420 mg/day, and 6 subjects in Cohort 2 received ibrutinib at 560 mg/day. With regard to histological subtypes of B-cell neoplasms, 2 of 3 subjects in Cohort 1 had CLL/SLL and the remaining 1 subject had FL. Of the 6 subjects in Cohort 2, 3 subjects had CLL/SLL, 2 subjects had MCL, and 1 subject had mucosa-associated lymphoid tissue (MALT) lymphoma.

At the final analysis, all 15 subjects had discontinued from the study treatment. Eight subjects (53.3%, of which 7 subjects had CLL/SLL and 1 subject had MCL), who were still on ibrutinib treatment at the end of the study, were offered continued access to marketing-approved ibrutinib, and all subjects chose to continue ibrutinib treatment. Six subjects (2 subjects each in Cohort 1, Cohort 2, and the CLL/SLL Cohort) discontinued from the study treatment due to progressive disease and 1 subject in the CLL/SLL Cohort discontinued from the study treatment due to an unacceptable toxicity.

During the study, major protocol deviations were reported in 2 subjects. One subject in the CLL/SLL Cohort had a deviation that was categorized as “received the wrong treatment or incorrect dose” (as reported at the primary analysis). One additional subject in Cohort 2 did not take the study agent for 14 days and this deviation was categorized as “other”.

Median duration of ibrutinib exposure in the MD phase of Cohort 1 was 22.31 months (range, 5.9-45.6 months). Median durations of ibrutinib exposure in Cohort 2 and the CLL/SLL Cohort were 42.74 months (range, 17.3-49.1 months) and 23.16 months (range, 4.8-36.3 months), respectively.

Median relative dose intensities in Cohort 1, Cohort 2, and the CLL/SLL Cohort were 99.78% (range, 97.2-100.0%), 96.22% (range, 53.5-99.9%), and 97.56% (range, 56.0-100.0%), respectively.

In Cohort 1, 1 of 3 subjects (33.3%) had a dose delay for 7 or more continuous days. No subjects had a dose reduction in Cohort 1. In Cohort 2, 4 of 6 subjects (66.7%) had a dose delay for 7 or more continuous days. Four subjects (66.7%) had a dose reduction in Cohort 2. In the CLL/SLL Cohort, 3 of

6 subjects (50.0%) had a dose delay for 7 or more continuous days. Two subjects (33.3%) had a dose reduction in the CLL/SLL Cohort.

In 8 subjects with relapsed or refractory CLL or SLL who received 420 mg/day ibrutinib (6 subjects in the CLL/SLL Cohort and 2 subjects in Cohort 1), median duration of exposure in the MD phase was 27.01 months and median relative dose intensity was 97.66%.

EFFICACY RESULTS:

Efficacy analyses were performed based on the response evaluable population, which was defined as all subjects who received at least 1 dose of study agent and had at least 1 adequate postbaseline tumor assessment. The response evaluable population consisted of 15 subjects. Efficacy analyses were also performed using a subgroup of 8 relapsed or refractory CLL/SLL subjects who received 420 mg/day ibrutinib (6 subjects in the CLL/SLL Cohort and 2 subjects in Cohort 1).

At the final analysis, ORR was 86.7% (13 of 15 subjects) (95% confidence interval [CI]: 59.5; 98.3) across all cohorts: 66.7% of subjects who received 420 mg/day in Cohort 1 and 100.0% of subjects who received 560 mg/day in Cohort 2. The 95% CI was based on exact binomial distribution. In 8 subjects with relapsed or refractory CLL/SLL who received 420 mg/day, the ORR was 87.5% (95% CI: 47.3, 99.7) of subjects, demonstrating the efficacy of ibrutinib 420 mg/day in subjects with relapsed or refractory CLL/SLL.

At the final analysis, median TTR across all cohorts was 2.48 months, ranging from 1.9 to 15.0 months. Despite the extended duration of ibrutinib exposure since the primary analysis, median DOR based on Kaplan-Meier estimates could not be estimated at the final analysis; 8 of 13 responders (CR or PR) remained progression free and were censored. Including the censored data, a DOR of more than 24 months was observed for 8 subjects and a DOR of more than 36 months was observed for 6 subjects, indicating that these responses were durable.

SAFETY RESULTS:

Summaries of AEs and other safety data were performed based on the all-treated analysis population included subjects who received at least 1 dose of ibrutinib. In this study, the all-treated analysis set consisted of 15 subjects.

The results of the safety assessments for the final analysis were consistent with those observed at the primary analysis. No new safety signals were observed during the 32 months since the primary analysis.

At the final analysis, all 15 subjects experienced at least 1 treatment-emergent adverse event (TEAE). Commonly reported TEAEs of any Grades were viral upper respiratory tract infection (10 subjects, 66.7%), neutropenia (9 subjects, 60.0%), anemia and rash (8 subjects, 53.3% each), C-reactive protein increased (7 subjects, 46.7%), diarrhea, blood bilirubin increased, and pyrexia (6 subjects, 40.0% each), and leukopenia, thrombocytopenia, stomatitis, and dry skin (5 subjects, 33.3% each). TEAEs of Grade 3 or higher by toxicity grade were reported in 10 subjects (66.7%). All Grade 3 or higher TEAEs were reported as resolved or resolving.

No TEAEs leading to death were reported in this study. Serious TEAEs were reported in 5 subjects (33.3%) at the final analysis; the serious TEAEs were assessed as Grade 3 (stomatitis for 1 subject; bacterial infection for 1 subject; pneumonia, sepsis, and infection for 1 subject; pneumonia for 1 subject; and bile duct stone and pneumonia bacterial for 1 subject) and Grade 2 (decreased appetite for 1 subject). These serious events resolved except for 1 event of pneumonia, which was reported on 24 June 2014 and was resolving at the final analysis. With the exception of bacterial infection, bile duct stone, and 1 event of pneumonia, these serious TEAEs were considered to be related to the study agent. No new TEAEs leading to discontinuation were reported after the primary analysis (during which stomatitis was reported

in 1 subject). Nine subjects (60.0%) had their assigned dose reduced or delayed at least once due to a TEAE.

No subjects presented with major hemorrhage or intracranial hemorrhage defined in the protocol as being of special interest.

With regard to TEAEs from the system organ classes (SOCs) of Infections and Infestations, the most commonly reported TEAE was viral upper respiratory tract infection in 10 subjects (66.7%). With regard to infections and infection-related TEAEs of Grade 3 or higher, pneumonia and infection were reported in 2 subjects (13.3%) each, and bacterial infection, pneumonia bacterial, and sepsis were reported in 1 subject (6.7%) each. With the exception of infection (1 subject), these Grade 3 or higher infections were reported as serious TEAEs.

Hematologic TEAEs reported across the cohorts were neutropenia (9 subjects, 60.0%), anemia (8 subjects, 53.3%), and thrombocytopenia (5 subjects, 33.3%). Neutropenia reported in 4 subjects (26.7%) and thrombocytopenia reported in 1 subject (6.7%) were assessed as Grade 3 or higher in severity.

Rash was reported in 8 subjects (53.3%), and rash erythematous and rash papular were reported in 1 subject (6.7%) each. None of these events were assessed as Grade 3 or higher in severity.

TEAEs from the SOCs of Eye Disorders, Renal and Urinary Disorders, and Cardiac Disorders were reported in 7 subjects (46.7%), 4 subjects (26.7%), and 1 subject (6.7%), respectively; none of these events were assessed as Grade 3 or higher in severity nor reported as serious TEAEs. Furthermore, no TEAEs of other malignancies or leukostasis were reported in this study.

With regard to clinical laboratory evaluations, hematology shifts from baseline considered to be Grade 3 or 4 were Grade 3 decrease in hemoglobin reported in 3 subjects (20.0%), Grade 3 decrease in leukocytes reported in 1 subject (6.7%), Grade 3 and Grade 4 decreases in neutrophils reported in 2 subjects (13.3%) and 3 subjects (20.0%), respectively, and Grade 3 decrease in platelets reported in 3 subjects (20.0%). Serum chemistry shifts from baseline considered to be Grade 3 or 4 were Grade 3 decrease in phosphate reported in 2 subjects (13.3%), and Grade 3 increase in glucose, Grade 3 increase in magnesium, and Grade 3 increase in potassium reported in 1 subject (6.7%) each. Across all cohorts, an increase in prothrombin international normalized ratio from Grade 0 at baseline to Grade 1 in severity was reported in 5 subjects (33.3%).

Across the cohorts, 1 subject (6.7%) in the CLL/SLL Cohort had a QT corrected according to Fridericia's formula (QTcF) of >450 ms and ≤470 ms, and 2 subjects (13.3%) in the CLL/SLL Cohort had a QT corrected according to Bazett's formula (QTcB) of >450 ms and ≤470 ms. No increases in QTcF and QTcB of >30 ms from baseline were observed across the cohorts in the study.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

This study was conducted to evaluate the safety and tolerability of ibrutinib in Japanese subjects with recurrent mature B-cell neoplasms. Although the number of patients in the study was small, the safety profile in this study suggested that treatment with ibrutinib at doses of 420 mg/day and 560 mg/day was well-tolerated. In addition, these results were suggestive of a good and durable efficacy with ibrutinib.

Overall, the risk-benefit profile of ibrutinib treatment in Japanese patients with recurrent mature B-cell neoplasms is positive.

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