SYNOPSIS

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

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

Status: Approved

Date: 18 February 2019

Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: 54179060LEU1001

Title of Study: Phase 1 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Subjects With Treatment-naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

NCT No.: NCT02556892

Clinical Registry No.: CR107620 54179060LEU1001

Principal Investigator(s): Hirohiko Shibayama, MD, PhD - Osaka University Hospital, [redacted] Japan

Study Center(s): 5 study sites in Japan

Publication (Reference): None

Study Period: 3 July 2015 (Date first subject signed informed consent) to 22 August 2018 (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 investigate the safety of ibrutinib in Japanese subjects with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The secondary objectives were to evaluate the pharmacokinetic (PK) profile of ibrutinib and its metabolite PCI-45227, and to evaluate tumor response (overall response rate [ORR] and time to response). The exploratory objective was to evaluate progression-free survival (PFS) and overall survival (OS).

Methodology: This was a Phase 1 open-label multicenter study to investigate the safety and evaluate the PK and efficacy of single agent ibrutinib 420 mg once daily in Japanese subjects with treatment-naive CLL/SLL. Eligible subjects in the study were patients aged between 20 and 70 years who were not candidates for frontline chemotherapy with fludarabine or cyclophosphamide, and patients aged 70 years or older. All subjects were to receive ibrutinib 420 mg orally once daily on a 28-day cycle until disease progression, the investigator considered the treatment to be no longer tolerated, or the subject met any of the discontinuation criteria.

The end of the whole study was defined as one of the following time points, whichever came first: when all patients discontinued the study, when ibrutinib was approved by the Japanese Ministry of Health, Labour and Welfare (MHLW) as an indication for patients with treatment-naive CLL/SLL, or if the sponsor discontinued the study. The first clinical cutoff of the study occurred on 2 May 2016 at the time point when the first 6 subjects completed the efficacy assessment on Day 1 of Cycle 7. The second clinical cutoff occurred on 21 July 2017 at the time point when the tumor responses were confirmed from the 6 subjects. The primary analysis was conducted at the timepoint when all 8 subjects completed the Cycle 7 Day 1 assessments with a clinical data cutoff date of 4 December 2017. The Clinical Study Report (CSR) for the primary analysis was completed on 6 February 2018. The final analysis at the study

closure was conducted with a clinical data cutoff date of 22 August 2018 after receiving the marketing approval for the treatment of patients with treatment-naive CLL/SLL from MHLW on 2 July 2018. No protocol amendment was made after the primary analysis.

Number of Subjects (planned and analyzed): Planned: 8 eligible subjects were to be enrolled in the study. Analyzed: 8 subjects.

Diagnosis and Main Criteria for Inclusion: Key eligibility criteria included: men or women aged 20 years or older, patients aged between 20 and 70 years who were not candidates for frontline chemotherapy with fludarabine or cyclophosphamide; diagnosis of CLL/SLL that met the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria; active disease meeting at least one of the IWCLL criteria for requiring treatment; measurable disease >1.5 cm at the longest diameter; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

Test Product, Dose and Mode of Administration, Batch No.: The ibrutinib capsule supplied for the study was formulated as a gray, size 0 hard gelatin capsule containing 140 mg of ibrutinib. Subjects were instructed to take 3 capsules of ibrutinib (at a dose of 420 mg) orally once daily, starting at Day 1 of Cycle 1. Four lot numbers of ibrutinib (L0408980C, L0503302A, L0503928A, and L0507141A) were used in the study.

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

Duration of Treatment: The treatment duration was from the time when the first dose of ibrutinib was administered until disease progression, the investigator considered the treatment to be no longer tolerated, or the subject met any one of the discontinuation criteria. The follow-up duration was to be from the end of the last dose of study agent until 30 days after the last dose of study agent or the start of subsequent anti-CLL/SLL therapy, whichever came first.

Criteria for Evaluation and Statistical Methods:

Updates of adverse events (AEs), clinical laboratory results, and efficacy assessments were 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 CSR for Study 54179060LEU1001.

RESULTS:

The results of the final analysis of the study are presented in this CSR. The results for the primary analysis were reported in the CSR dated 6 February 2018.

STUDY POPULATION:

In the study, 8 subjects provided informed consent and received ibrutinib. At the final analysis, all 8 subjects discontinued the study treatment. Most of the reasons for treatment discontinuation were study termination by the sponsor (6 subjects) due to the marketing approval of ibrutinib for the treatment of patients with treatment-naive CLL/SLL from MHLW. Of those 6 subjects, 2 subjects discontinued the ibrutinib treatment by the final analysis and 4 subjects were still on the ibrutinib treatment at the final analysis and continued treatment with commercially available ibrutinib (IMBRUVICA®). One subject (12.5%) discontinued treatment due to death from cardiac arrest. The reason for treatment discontinuation of the remaining 1 subject (12.5%) was physician decision. The subject required inpatient rehabilitation in another hospital due to progression of underlying Parkinson's disease.

No major protocol deviations were reported in the study.

The median duration of ibrutinib treatment was 32.20 months (range, 10.4-35.9 months) and the median relative dose intensity was 98.52% (range, 60.2%-100.0%).

EFFICACY RESULTS:

Results at the final analysis were generally consistent with the primary analysis.

The ORR (ie, complete response [CR] or partial response [PR]) in the efficacy-evaluable population was 87.5% (7/8 subjects; 95% confidence interval [CI]: 47.3%, 99.7%). The median time to initial response in these subjects was 5.42 months (range, 1.9-20.2 months). Regarding the best objective response, 1 subject (12.5%) had CR, 6 subjects (75.0%) had PR, and 1 subject (12.5%) had partial response with lymphocytosis (PRL).

The median PFS was not estimable. The range of PFS was 10.9 to 35.0+ months (the symbol "+" indicates censored data).

The median OS was not estimable. The range of OS was 10.9 to 35.9+ months.

Regarding the proportion of sustained hematological improvement, 3 of 8 subjects (37.5%) had platelet counts of $\leq 100 \times 10^9$/L at baseline and 2 (66.7%) of them had a sustained improvement. Three (37.5%) of 8 subjects had hemoglobin of ≤11 g/dL at baseline and all 3 (100%) had a sustained improvement.

SAFETY RESULTS:

There were no unexpected increases in the numbers of subjects with treatment-emergent adverse events (TEAEs) during the additional 8 months follow up from the primary analysis to the final analysis. Safety data from the 8 subjects in the safety population indicated that ibrutinib was generally well tolerated in Japanese subjects with treatment-naive CLL. Most AEs were Grade 1 or 2 in severity and clinically manageable:

- All 8 subjects had at least 1 TEAE. The most common TEAE (reported in at least 3 subjects) was platelet count decreased (6 subjects, 75.0%), followed by upper respiratory tract infection and lymphocyte count increased (4 subjects, 50.0% each), and diarrhea, nasopharyngitis, rash, and edema peripheral (3 subjects, 37.5% each).
- Four (50.0%) of 8 subjects had at least 1 Grade 3 or higher TEAE. Grade 3 or higher TEAEs were lung infection and neutrophil count decreased (2 subjects, 25.0% each), cellulitis, pneumonia, aspartate aminotransferase (AST) increased, muscle hemorrhage, femoral neck fracture, hypertension, hypokalemia, Parkinson's disease, cardiac arrest, and tibia fracture (1 subject, 12.5% each). Except for hypertension and Parkinson's disease, the remaining Grade 3 or 4 TEAEs resolved at the final analysis. The cardiac arrest was Grade 5.
- One subject had a TEAE of cardiac arrest leading to death after 10.9 months of treatment. The event was considered unrelated to the study agent. Except for the event of cardiac arrest described above, no other TEAEs leading to discontinuation of study agent were reported in the study.
- Eight serious TEAEs were reported in 4 (50.0%) of 8 subjects: 1 subject had pneumonia, 1 subject had muscle hemorrhage, lung infection, and neutrophil count decreased, 1 subject had cardiac arrest, and 1 subject had cellulitis, femoral neck fracture, and tibia fracture. Except for cardiac arrest that resulted in death, all serious TEAEs resolved at the final analysis. One subject required a dose reduction twice for serious muscle hemorrhage and serious neutrophil count decreased.
- Treatment-emergent hemorrhagic events were reported in 5 (62.5%) of 8 subjects. Except for 1 event, which was muscle hemorrhage, all treatment-emergent hemorrhagic events were assessed as Grade 1 or 2. The muscle hemorrhage that occurred in 1 subject (12.5%) was assessed as a Grade 3 drug-related serious adverse event (SAE). No subjects experienced central nervous system (CNS) hemorrhage/hematoma.

- Treatment-emergent AEs classified in the system organ class (SOC) of "Infections and infestations" were reported in 6 (75.0%) of 8 subjects. No new events of Grade 3 or higher were reported after the primary analysis.
- Treatment-emergent hematologic AEs were reported in 3 (37.5%) of 8 subjects. None of these TEAEs were reported as SAEs or assessed as Grade 3 or higher in severity.
- No TEAEs in the SOC of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" were reported in the study.
- Three (37.5%) of 8 subjects had TEAEs in the SOC of "Cardiac disorders" (atrial fibrillation, cardiac arrest, and palpitations; 1 subject, 12.5% each). Except for the cardiac arrest that resulted in death, these events were reported as nonserious TEAEs and assessed as Grade 2 in severity.
- Six (75.0%) of 8 subjects had TEAEs classified in the SOC of "Skin and subcutaneous tissue disorders" and of these, 3 subjects (37.5%) were reported with rash. None of these TEAEs were reported as SAEs or assessed as Grade 3 or higher in severity.
- Treatment-emergent AEs in the SOC of "Eye disorders" were reported in 2 (25.0%) of 8 subjects. None of these events were reported as SAEs or assessed as Grade 3 or higher in severity.
- Treatment-emergent AEs in the SOC of "Gastrointestinal disorders" were reported in 6 (75.0%) of 8 subjects. None of these TEAEs were reported as SAEs or assessed as Grade 3 or higher in severity.
- Two (25.0%) of 8 subjects had TEAEs in the SOC of "Renal and urinary disorders". These events were reported as nonserious and assessed as Grade 2.
- TEAEs in the high level group term (HLGT) of vascular hypertensive disorders (hypertension) were reported in 2 (25.0%) of 8 subjects. These events were reported as nonserious and the worst grades for each subject were Grade 2 and 3.
- Treatment-emergent shifts in hematology values from baseline to Grade 3 or 4 were reported in 3 (37.5%) of 8 subjects: 1 subject (12.5%) had a Grade 3 decrease in leukocytes and a Grade 4 decrease in neutrophils, 1 subject (12.5%) had a Grade 3 decrease in lymphocytes, and the other subject had a Grade 4 decrease in neutrophils.
- Treatment-emergent shifts in serum chemistry values from baseline to Grade 3 or 4 were reported in 2 (25.0%) of 8 subjects: 1 subject (12.5%) had Grade 3 AST increased and potassium decreased, and the other subject had Grade 4 potassium increased. No shifts from baseline in prothrombin international normalized ratio (INR) were observed.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

The final results of Study 54179060LEU1001 were generally consistent with the primary analysis. No new safety signals were observed during the 8 months since the primary analysis. The results of the study indicate that ibrutinib at a dose of 420 mg/day showed favorable safety and efficacy profiles in Japanese subjects with treatment-naive CLL.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.