SYNOPSIS

Name of Sponsor/Company	Janssen Global Services, LLC*
Name of Finished Product	IMBRUVICA®
Name of Active Ingredient(s)	PCI-32765; JNJ-54179060 (ibrutinib)

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Status: Approved

Date: 23 January 2015

Prepared by: Janssen Global Services, LLC

Protocol No.: PCI-32765MCL4001

Title of Study: An Open-Label Treatment Use Protocol for Ibrutinib (PCI-32765) in Subjects With Relapsed or Refractory Mantle Cell Lymphoma

NCT No.: NCT01833039

Clinical Registry No.: CR101862

Study Center(s): Subjects were enrolled from 38 sites in the United States of America (USA).

Publication (Reference): None available at the time of this report.

Study Period: Study initiation date: 15 May 2013 (study initiated in USA). Study completion date: 02 April 2014 (Study Completed in USA). Database lock: 18 June 2014.

Phase of Development: 4

Objective: The objective of this study was to provide early access to ibrutinib treatment and collect additional safety data while ibrutinib was not commercially available for patients with relapsed or refractory mantle cell lymphoma (MCL).

Methodology: This was a multicenter, open-label, early access treatment protocol of single-agent ibrutinib in subjects with relapsed or refractory MCL who resided in areas where ibrutinib was not yet commercially available through local healthcare providers, and who were not eligible for enrollment in another ongoing clinical study of ibrutinib. Eligible subjects received 560 mg of oral ibrutinib once daily continuously on 28-day cycles until disease progression, occurrence of unacceptable toxicity, the subject was no longer receiving clinical benefit, or the end of study.

The end of study in the USA occurred when the Food and Drug Administration (FDA) approval was received and ibrutinib was available by a doctor's prescription (ie, commercially available and reimbursement granted). This global study protocol may be initiated in other countries as well and will be considered completed when the last study assessment for the last participating subject is completed.

Number of Subjects (planned and analyzed):

Planned: The number of subjects eventually enrolled was determined by medical need and the timing of health authority approval and reimbursement authorization for the use of ibrutinib.

Analyzed: A total of 149 subjects were enrolled; all 149 subjects were included in the analyses.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were required to be 18 years of age or older with a diagnosis of MCL, with relapsed or refractory disease after prior therapy, based on investigator assessment. Other key inclusion criteria at baseline were Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, absolute neutrophil count (ANC) $\geq 750/mm^3$ independent of growth factor support, and platelets $\geq 50{,}000/mm^3$ independent of transfusion support. Subjects were excluded from this study if they were eligible for another ongoing clinical study of ibrutinib or were enrolled in another interventional clinical study with therapeutic intent.

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib capsules containing 140 mg of micronized ibrutinib (lot number 4367268) were provided by the sponsor. Subjects were instructed to take 560 mg of oral ibrutinib (4 capsules) once daily continuously during the 28-day treatment cycles.

Reference Therapy, Dose and Mode of Administration, Batch No.: No reference therapy was used in this open-label early access protocol.

Duration of Treatment: Subjects received open-label treatment with ibrutinib until it became available by a doctor's prescription (ie, commercially available and reimbursement in that country was granted).

Criteria for Evaluation:

Efficacy Endpoints: There were no efficacy endpoints in this study. To determine whether continued treatment with ibrutinib was warranted and guide end of treatment decisions, investigators recorded assessments of disease progression at each cycle.

Safety Endpoints: Safety assessments were based on reported adverse events, clinical laboratory tests (hematology and serum chemistry), lymphocytosis, physical examinations, and ECOG performance status. Adverse events were collected only if they were serious, Grade 3 or higher, or events of special interest. Major hemorrhage (including intracranial hemorrhage) was an adverse event of special interest and was defined as any hemorrhagic event that was Grade 3 or higher in severity or that resulted in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

Statistical Methods:

Safety was analyzed by using the incidence and severity of adverse events, laboratory tests, vital signs, physical examinations, and ECOG performance status. All safety analyses were based on the safety analysis set. Treatment-emergent adverse events were summarized by system organ class and preferred terms, by National Cancer Institute common toxicity criteria for adverse events (NCI-CTCAE, version 4.03), by relationship to study drug, and by action taken. Clinical laboratory results were summarized by using descriptive statistics and change from baseline to the worst grade during the treatment was provided as shift tables.

There were no efficacy endpoints in this study. Disease evaluations were conducted to guide decisions about continuing ibrutinib. The distribution of progression-free survival (PFS), based upon the investigator opinion, was estimated by using the Kaplan-Meier method.

RESULTS:

STUDY POPULATION:

Of the 149 subjects enrolled, 99 (66.4%) discontinued the study when ibrutinib received market authorization in the USA. Fifty (33.6%) subjects discontinued the study due to other reasons, most commonly due to disease progression (20 subjects; 13.4%) or death (12 subjects; 8.1%); 4 (2.7%) subjects discontinued the study due to adverse events. Of the 12 subjects who discontinued due to death, 11 of the deaths were due to treatment-emergent adverse events and 1 was due to an adverse event that started before study treatment. The cause of death reported by the investigator for these 12 deaths was

progressive disease (MCL) for 8 subjects, septic shock for 3 subjects, and dyspnea for 1 subject. Upon sponsor review of the event narratives, 11 of these 12 deaths occurred in the setting of progressive disease; the remaining death was due to septic shock that the investigator reported was possibly related to study drug. Mean (SD) time on study was 4.5 (2.0) months, the range was 0.2 to 8.6 months, and the median was 4.7 months. Mean (SD) duration of ibrutinib treatment was 3.5 (1.7) months, the range was 0.0 to 7.7 months, and the median was 3.7 months.

EFFICACY RESULTS:

There were no efficacy endpoints in this study.

SAFETY RESULTS:

No new safety signals were observed in this study. Adverse events were collected only if they were serious, Grade 3 or higher, or events of special interest. The overall safety profile for this study is shown in the table below. Of the 149 subjects enrolled:

- Grade 3 or higher treatment-emergent adverse events were reported for 59 (39.6%) subjects and were considered to be drug-related for 28 (18.8%) subjects.
- Treatment-emergent serious adverse events were reported for 46 (30.9%) subjects; they were considered to be drug-related for 17 (11.4%) subjects and were grade 3 or higher for 40 (26.8%) subjects.
- Treatment-emergent adverse events leading to death were reported for 20 (13.4%) subjects, including 11 (7.4%) subjects whose treatment-emergent adverse event leading to death was reported as the reason for study discontinuation.
- Treatment-emergent adverse events led to treatment discontinuation for 10 (6.7%) subjects.

Overall Summary of All (Collected) Treatment-emergent Adverse Events; Safety Analysis Set (Study PCI-32765MCL4001)

	Ibrutinib
Population: safety	149
Any AE	64 (43.0%)
Drug related	31 (20.8%)
Grade ≥ 3 AE	59 (39.6%)
Drug related	28 (18.8%)
Any SAE	46 (30.9%)
Drug related	17 (11.4%)
Grade ≥ 3	40 (26.8%)
AE leading to treatment discontinuation	10 (6.7%)
Drug related	1 (0.7%)
AE leading to death	20 (13.4%)
Drug related	1 (0.7%)

Note: The only adverse events collected in this study were serious, grade 3 or higher, and events of special interest (major hemorrhages).
Note: Percentages calculated with the number of all treated subjects as denominator

Grade 3 or higher treatment-emergent adverse events that were reported for more than 2% of subjects were as follows: neutropenia in 10 (6.7%) subjects; progressive disease (MCL) in 8 (5.4%) subjects, dyspnea in 6 (4.0%) subjects; anemia, pneumonia, and thrombocytopenia each in 5 (3.4%) subjects; and abdominal pain and leukocytosis each in 4 (2.7%) subjects.

Treatment-emergent serious adverse events that were reported for more than 2% of subjects were as follows: progressive disease (MCL) in 8 (5.4%) subjects; pneumonia in 6 (4.0%) subjects; dyspnea in 5 (3.4%) subjects; and abdominal pain in 4 (2.7%) subjects.

A nonfatal serious adverse event of atrial fibrillation was reported for 3 (2.0%) subjects and nonfatal serious adverse events of palpitations and atrial flutter were reported for 1 (0.7%) subject. During hospitalization for other serious adverse events, 4 additional subjects had nonfatal atrial fibrillation that was neither serious nor Grade 3 or higher and thus was not reported as a treatment-emergent adverse event. All of the cases of atrial fibrillation or atrial flutter were reported in subjects with known cardiac risk factors. No subject discontinued study drug due to these events.

Secondary tumors were reported as serious adverse events for 2 (1.3%) subjects: 1 subject with gastric adenocarcinoma and 1 subject with intraductal proliferative breast lesion (invasive ductal carcinoma). A treatment-emergent serious adverse event of acute renal failure or acute on chronic renal failure was reported for 4 (2.7%) subjects; the investigator assessed relatedness to ibrutinib as unrelated for 2 subjects and possibly related for 2 subjects. There were no reports of ocular or hepatobiliary adverse events.

Of the 21 deaths reported, 20 (13.4%) deaths occurred within 30 days of the last dose of ibrutinib and 1 (0.7%) death occurred 70 days after the last dose of ibrutinib. For 12 (8.1%) subjects who died within 30 days of the last dose of ibrutinib, death was reported as the reason for study discontinuation. The most commonly reported treatment-emergent adverse event leading to death was progressive disease in 10 (6.7%) subjects, which included 8 (5.4%) subjects with events reported as MCL and 2 (1.3%) subjects with events reported as non-Hodgkin's lymphoma. Other treatment-emergent adverse events leading to death were as follows: septic shock in 3 (2.0%) subjects; and gastric adenocarcinoma, pneumonia, dyspnea, respiratory failure, leukocytosis, cardiorespiratory arrest, and Parkinson's disease each in 1 (0.7%) subject.

Upon sponsor review of the event narratives, 16 (10.7%) treatment-emergent adverse events leading to death occurred in the setting of progressive disease and the remaining 4 (2.7%) events (septic shock, gastric adenocarcinoma, pneumonia, and Parkinson's disease) were not in the setting of progressive disease. One (0.7%) treatment-emergent adverse event leading to death (septic shock) was reported by the investigator to be possibly related to study drug.

Investigators reported that treatment-emergent adverse events led to ibrutinib dose withholding for 20 (13.4%) subjects overall, most commonly due to neutropenia in 4 (2.7%) subjects, pneumonia in 3 (2.0%) subjects, and dehydration in 2 (1.3%) subjects. No treatment-emergent adverse event led to ibrutinib dose reduction. However, 2 subjects received reduced doses of ibrutinib due to events that were not reported as treatment-emergent adverse events.

Treatment-emergent major hemorrhages (including intracranial hemorrhage) were reported for 2 (1.3%) subjects: 1 subject with Grade 2 intracranial hemorrhage in the setting of lymphocytosis that was considered probably related to ibrutinib and 1 subject with Grade 3 anemia that resulted from hemorrhage and required transfusion of 2 units of packed red blood cells and was considered not related to ibrutinib. These events occurred without precedent trauma or anticoagulation exposure.

There was no evidence of a clinically meaningful effect of ibrutinib on vital signs or chemistry laboratory values. Grade 4 decreased absolute neutrophil count was observed in 3 (2.1%) subjects and Grade 4 decreased platelets was observed in 1 (0.7%) subject. Investigators reported a treatment-emergent hematologic adverse event CTCAE Grade 3 or higher for 17 (11.4%) subjects, including 10 (6.7%) with neutropenia, 5 (3.4%) with anemia, and 5 (3.4%) with thrombocytopenia.

Of the 141 subjects with at least one post-baseline absolute lymphocyte count measurement, 29 (20.6%) subjects had lymphocytosis during the study. The median time from first dose of ibrutinib to onset of lymphocytosis in these subjects was 4.1 weeks and the mean (SD) was 6.1 (6.1) weeks. The median time from the first dose to peak ALC in these subjects was 7.7 weeks and the mean (SD) was 9.0 (8.2) weeks.

Lymphocytosis resolved in 12 of 29 subjects (41.4%), at a median of 13.1 weeks (95% CI, 4.1 to 19.9) after onset. As noted above, median duration of study participation in the USA was 4.7 months. One (0.7%) subject developed leukostasis with intracranial hemorrhage in the setting of lymphocytosis.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSIONS:

This early access treatment protocol provided a mechanism for patients with relapsed and refractory MCL to receive ibrutinib prior to its approval in the USA. A total of 111 subjects with relapsed or refractory MCL received ibrutinib in the registration trial (PCYC-1104-CA) and an additional 149 subjects with relapsed or refractory MCL were exposed to ibrutinib for a median of 3.7 months in this early access treatment protocol. The safety profile for ibrutinib that was observed in this cohort was consistent with that observed during the registration trial for MCL. No new safety signals were observed with ibrutinib treatment in this population of patients who were predominantly refractory to previous MCL treatments.

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