SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Imbruvica™
Name of Active Ingredient(s)	JNJ-54179060 (ibrutinib)

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Status: Approved
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Prepared by: Janssen Research & Development, LLC

Protocol No.: PCI-32765MCL2001

Title of Study: A Phase 2, Multicenter, Single-Arm Study to Evaluate the Efficacy and Safety of Single-Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy

Study Name: SPARK

EudraCT Number: 2012-000711-88

NCT No.: NCT01599949

Clinical Registry No.: CR100847

Coordinating Investigators:

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Study Center(s): Study centers in the following countries enrolled subjects into this study: Belgium (n=1 study center), France (n=2), Israel (n=6), Poland (n=1), Russia (n=4), United Kingdom (n=2), and United States (n=22).

Publication (Reference): None

Study Period: Study initiated: 17 July 2012; Clinical cutoff: 29 April 2014; Database lock: 20 June 2014

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 mantle cell lymphoma (MCL) who received at least 1 prior rituximab-containing chemotherapy regimen and who progressed after bortezomib therapy.

The secondary objectives were to evaluate the duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety of ibrutinib; to characterize the pharmacokinetics of ibrutinib after oral dosing; to explore the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information; to evaluate patient reported outcomes (PRO) utilizing the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) and EuroQol (EQ-5D); and to identify biomarkers that alter B-cell receptor (BCR) signaling or activate alternative signaling pathways and to explore their association with response to ibrutinib.

Methodology: This was a Phase 2, multicenter, single-arm study to evaluate the efficacy and safety of single-agent ibrutinib in subjects with histologically documented MCL. Eligible subjects were required to have a diagnosis of MCL confirmed by central review, to have received at least 1 prior rituximab-containing chemotherapeutic regimen, and to have documented progressive disease after at least 2 cycles of single-agent or combination bortezomib therapy. All eligible subjects were to receive continuous treatment with ibrutinib 560 mg orally once per day in 21-day treatment cycles until disease progression, relapse after complete response (CR), unacceptable toxicity, or study end, whichever occurred first. After treatment was discontinued, subjects were to be followed-up for survival status, use of subsequent therapy, and occurrence of other malignancies.

Systemic chemotherapy, anticancer immunotherapy, systemic corticosteroids, experimental therapy, and radiotherapy were prohibited. A subject was excluded if it was known that he or she would require concomitant treatment with strong CYP3A4/5 inhibitors or, beginning with Amendment INT-1, anticoagulation therapy with warfarin or equivalent vitamin K antagonists.

Disease assessments for the primary analysis were performed by central radiologic review by an IRC. Supportive analyses were based on investigator review. No interim efficacy analyses were performed.

Number of Subjects: The study was designed to enroll 110 subjects in order to attain 101 response-evaluable subjects. One-hundred-twenty subjects were ultimately enrolled, yielding 110 response-evaluable subjects. All subjects received study drug. Safety population: n=120; all-treated population: n=120.

Diagnosis and Main Criteria for Inclusion: Pathologically-confirmed diagnosis of MCL by central review and measurable disease per computed tomography (CT). Additionally, subjects were to have received at least 1 prior rituximab-containing chemotherapeutic regimen and documented progressive disease during or after bortezomib therapy based on Revised Response Criteria for Malignant Lymphoma (Cheson 2007[*]).

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib was provided as a hard gelatin capsule oral formulation containing 140 mg of the active ingredient and administered at a dose of 560 mg daily. Study drug from the following manufacturing lots was provided: L0308541, L0308792, L0400218, L0404313.

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

Duration of Treatment: Subjects were to receive continuous daily treatment until disease progression, relapse after CR, unacceptable toxicity, or until the end of the study, whichever occurred first. The end of the study was planned to occur 2 years after enrollment of the last subject.

Criteria for Evaluation:

[*] Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586.

Efficacy:

The primary endpoint was ORR, defined as the proportion of evaluable subjects who achieved CR or partial response (PR) as assessed by the IRC based upon the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Response assessments were to be performed every 9 weeks for the first 15 months from the start of ibrutinib treatment, and thereafter, every 24 weeks until disease progression, death, or study end, whichever occurred first. Subjects were contacted every 9 weeks after documentation of disease progression to assess survival status and use of subsequent anti-MCL therapies. The FACT-Lym and EQ-5D-5L PRO instruments were administered during the Treatment Phase or until documentation of disease progression, death, or study end.

Safety:

Safety evaluations included monitoring of adverse events following signing of the informed consent form, clinical laboratory tests (hematology, serum chemistry, coagulation, serum immunoglobulin [IgG, IgM, IgA] and beta2-microglobulin), focused physical examination, vital sign measurements, Eastern Cooperative Oncology Group performance status, and cardiac assessments (electrocardiogram and echocardiogram/ multiple uptake gated acquisition [MUGA]).

Pharmacokinetics:

Venous blood samples were to be collected on Day 1 of Cycle 1 and Cycle 2 before dosing, and at 1, 2, and 4 hours postdose. Plasma was to be analyzed to determine concentrations of ibrutinib and the metabolite PCI-45227 using a validated, specific, and sensitive liquid chromatography/tandem mass spectrometry (LC-MS/MS). Ibrutinib plasma concentrations were graphically explored for consistency with previous studies.

Biomarkers:

Tumor (from lymph node biopsies or diagnostic biopsy tissue collected during Screening, but prior to Day 1 of Cycle 1), blood, and bone marrow aspirate or biopsy was evaluated to identify markers predictive of response to ibrutinib. A lymph node biopsy sample and a bone marrow aspirate for biomarker evaluations were required at progression, if feasible. Results of biomarker analyses will be reported separately.

Statistical Methods:

Assuming a 56% ORR for ibrutinib, 101 response-evaluable subjects are required to have 90% power to declare that the ORR is 40% or higher at the 1-sided significance level of 0.025. The response-evaluable population included all treated subjects who had at least 1 adequate post-baseline efficacy assessment and measurable MCL at baseline.

No interim efficacy analysis was planned or conducted. The final analysis for the primary endpoint, ORR, was conducted using the response-evaluable population and was based upon a clinical cutoff date approximately 1 year after enrollment of the last subject. The 95% confidence interval (CI) for the ORR was calculated using normal approximation to the binomial distribution. The null hypothesis was tested at the overall significance level of 0.025 (1-sided) and rejected if the lower bound of the CI exceeded 40%. Subgroup analyses were predefined. Descriptive summaries of time to response (TTR) and time to best response (TBR) were provided for subjects who achieved a CR or PR. The distribution of DOR (CR+PR), PFS, and OS were estimated using the Kaplan-Meier method based on the all-treated population.

For the FACT-Lym and EQ-5D-5L PRO assessments, descriptive statistics (mean, standard deviation, median, and range) were calculated for the raw data and for changes from baseline at each time point, as well as for changes from baseline to the last value. Time to worsening and time to improvement in the

Lym subscale were examined using Kaplan-Meier methods. Worsening and improvement in the Lym subscale were defined as a ≥5 point reduction or increase from baseline in the Lym subscale. Missing FACT-Lym assessments were imputed using the last observation carried forward method. Subjects who did not meet the definition of worsening/improvement were censored at the last PRO assessment.

Safety analyses were based on the treatment-emergent period, which began with the first dose of study drug and continued until 30 days after the last dose of study drug, or until the start of a subsequent systemic anti-MCL therapy. Adverse events that occurred >30 days after the last dose of study drug were included if considered related to study drug. Detailed tabulations of safety data (adverse events and clinical laboratory tests) were provided for all subjects who received study drug (safety population). The number and percentage of subjects with adverse events were summarized. Summaries of other safety parameters were provided.

For pharmacokinetic analyses, observed ibrutinib plasma concentrations were graphically explored for consistency with previous studies. To achieve this aim, graphical presentations were overlaid with model-based simulations derived from a previously developed pharmacokinetic model for ibrutinib.

RESULTS:

STUDY POPULATION:

One hundred twenty subjects were enrolled and all received 1 or more dose of study treatment. As of the clinical cutoff, 81 (67.5%) subjects had discontinued study treatment; 53 (44.2%) due to disease progression and 8 (6.7%) due to adverse events. Thirty-nine (32.5%) subject were continuing to receive study treatment.

The median age of the all-treated population was 67.5 years (range: 35 to 85 years), with 62.5% of subjects ≥65 years. Most subjects were men (86.7%) and 94.2% were white. The majority of subjects (77.5%) had Stage IV disease at study entry, and blastoid histology was present for 9.2% of subjects. The median number of prior lines of systemic anti-MCL therapy was 2 (range 1 to 8 lines), and all subjects received prior treatment with rituximab and bortezomib. Other prior therapies included hyper-CVAD (15.8% of subjects), CHOP/R-CHOP (40.0%), and stem cell transplantation (33.3%).

EXPOSURE:

The median duration of treatment was approximately 8.0 months (range: 0.5 to 20.9 months), and 42.5% of subjects received ≥18 cycles. Median relative dose intensity was 96.5%. Eight (6.7%) subjects had dose reductions, most commonly due to neutropenia (3 subjects). Three (2.5%) subjects required 2 dose reductions.

EFFICACY RESULTS:

Overall Response Rate

The IRC-assessed ORR (CR+PR) was 62.7% (95% CI: 53.7%, 71.8%) for the response-evaluable population (n=110). The lower bound of the 95% CI exceeded 40% (1-sided p-value <0.001), thus meeting the primary goal of the study. The CR rate was 20.9% (95% CI: 13.3%, 28.5%). The ORR was generally consistent across most of the subgroups examined.

Secondary Efficacy Analyses

- Median TTR by IRC was 2.1 months (range: 1.3 months to 6.3 months). Median DOR by the IRC was 14.9 months (95% CI: 12.4 months to not estimable).
- Median PFS by the IRC was 10.5 months (95% CI: 4.4 months to 15.0 months); 47% of subjects remained progression-free and alive at 1 year.
- Median OS was not reached; 61% of subjects were alive at 18 months after a median follow-up of 14.9 months.

PHARMACOKINETIC RESULTS: There was a substantial overlap between the observed ibrutinib plasma concentrations and the predicted values based on the previous pharmacokinetic model, indicating that the pharmacokinetic behavior in this study was reasonably consistent with the previous assessments.

PATIENT-REPORTED OUTCOMES RESULTS:

*FACT-Lym***:** Improved patient functioning was demonstrated by positive mean changes through Week 61 for all post-baseline assessments of the lymphoma subscale. Based on a change of at least 5 points, 67 (61.5%) subjects achieved a clinically meaningful improvement in lymphoma symptoms during the Treatment Phase versus 39 (35.8%) subjects who experienced a clinically meaningful worsening.

EQ-5D: The mean (SD) Visual Analog Scale (VAS) score at baseline was 68.77 (22.25) with a range of 10 to 100, indicating that a wide variability and heterogeneity of responses was captured using this measure. Utility values followed the same pattern. Both VAS and utility values showed improvement patterns during treatment similar to the pattern observed for the FACT-Lym assessment.

SAFETY RESULTS: Safety data were based on treatment-emergent period unless otherwise noted. The safety population (n=120) included all subjects who received at least 1 dose of study drug.

Adverse events were experienced by 95.8% of subjects and 79.2% experienced an adverse event considered by the investigator to be related to study treatment. The most commonly reported adverse events (≥20% of subjects) included fatigue (43.3% of subjects), diarrhea (42.5%), cough (25.0%), thrombocytopenia (24.2%), neutropenia (23.3%), peripheral edema (23.3%), nausea (21.7%), pyrexia (20.8%), and muscle spasm (20.8%). Grade 3 or Grade 4 adverse events were reported for 60.8% of subjects, most commonly (≥5% of subjects) neutropenia (20.8% of subjects), thrombocytopenia (13.3%), pneumonia (9.2%), anemia (6.7%), and atrial fibrillation (5.0%). Serious adverse events were reported for 49.2% of subjects, most commonly (≥5% of subjects) pneumonia (11.7%) and febrile neutropenia (5.0%).

Twenty-three (19.2%) subjects died within 30 days after the last dose of study treatment; 13 (10.8%) were attributed by investigators primarily to disease progression and 10 (8.3%) primarily to adverse events, most commonly pneumonia (4 [3.3%] subjects). Note that 4 of the 10 subjects whose death was assessed as primarily due to an adverse event also experienced radiologic disease progression prior to death.

Adverse events contributed to treatment discontinuation for 20 (16.7%) subjects, with pneumonia (3 [2.5%] subjects) the only adverse event that contributed to treatment discontinuation for more than 2 subjects. Adverse events led to dose reduction for 8 (6.7%) subjects, most commonly neutropenia (3 [2.5%] subjects), diarrhea (2 [1.7%]), and stomatitis (2 [1.7%]).

Fifty-one (42.5%) subjects reported diarrhea. Most of these events were of Grade 1 or Grade 2 severity. Three (2.5%) subjects experienced Grade 3 or Grade 4 diarrhea. No subject had an adverse event of diarrhea that led to treatment discontinuation.

Adverse events in the Infections and infestations System Organ Class were reported for 80 (66.7%) subjects. The most frequently reported (≥10%) preferred terms included upper respiratory tract infection (17.5%), pneumonia (15.0%), sinusitis (12.5%), and urinary tract infection (10.0%). Twenty-seven (22.5%) subjects experienced Grade 3 or Grade 4 infections. Five (4.2%) subjects experienced Grade 5 infections. Pneumonia was the most frequently reported Grade 3 or higher adverse event.

Hemorrhagic adverse events were experienced by 45 (37.5%) of subjects; the vast majority were Grade 1 or Grade 2 events. The most commonly reported events were contusion (14.2% of subjects), epistaxis (6.7%), and petechiae (5.0%). Major hemorrhage was reported for 3 (2.5%) subjects. One subject experienced Grade 2 intracranial hemorrhage on [redacted] in the context of possible leukostasis (peripheral lymphocyte count 606 x 10^9/L). This event was resolved and treatment was restarted. One subject who was taking dalteparin experienced Grade 3 splenic hemorrhage. The subject underwent embolization of hemorrhaging splenic vessels and recovered from the event. The third subject developed subarachnoid hemorrhage after falling and [redacted]. Treatment was interrupted and never restarted. The outcome of the event was reported as recovering/resolving.

Atrial fibrillation was reported for 13 (10.8%) subjects, including 6 subjects with Grade 3 or Grade 4 atrial fibrillation. Two of the 13 subjects with atrial fibrillation also experienced atrial flutter. Eleven (9.2%) subjects reported other malignancies subsequent to initiation of ibrutinib treatment, primarily skin cancers (8 [6.7%] subjects). Also reported as other malignancies were lung adenocarcinoma, acute myeloid leukemia, and prostate cancer (1 subject each). All reports of other malignancies were considered not related to study drug by the investigator.

Clinical laboratory data, including hematology, serum chemistry, coagulation parameters, and immunoglobulins did not reveal any new safety signal.

STUDY LIMITATIONS: The single-arm study design that was used is typical for a Phase 2 oncology study. Within this context, there were no notable study limitations identified by the Sponsor.

CONCLUSION(S): Continuous treatment with ibrutinib 560 mg daily is well tolerated and produces rapid, durable, and robust response in subjects with MCL who received at least 1 prior rituximab-containing chemotherapy regimen and who progressed after bortezomib therapy. These findings support a favorable benefit/risk profile in this setting.

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