SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Imbruvica™ (United States)/Not applicable (European Union/Rest of World)
Name of Active Ingredient(s)	JNJ-54179060 (ibrutinib)

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Status: Approved

Date: 16 May 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: PCI-32765DBL1002

Title of Study: A Phase 1b Study Combining Ibrutinib with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects with CD20-Positive B-Cell Non-Hodgkin Lymphoma (NHL)

EudraCT Number: 2012-000546-35

NCT No.: NCT01569750

Clinical Registry No.: CR100844

Coordinating Investigator: Anas Younes, MD – Memorial Sloan-Kettering Cancer Center, New York, NY, United States

Study Center(s): United States (4 sites) and France (2 sites)

Publications (References):

Younes A, Flinn I, Berdeja J, et al. Combining ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP): updated results from a Phase 1b study in treatment-naïve patients with CD20-positive B-Cell non-Hodgkin's lymphoma (NHL). 55th ASH Annual Meeting and Exposition, December 7-10, New Orleans, LA. American Society of Hematology 2013;Abstract 852.

Younes A, Flinn I, Berdeja JG, et al. Phase Ib study combining ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with CD20-positive B-cell non-Hodgkin lymphoma (NHL). J Clin Oncol. 2013;31(suppl; Abstract 8502).

Study Period: 22 June 2012 (first subject consented) – 05 September 2013 (last subject completed the End-of-Treatment visit; follow up ongoing). Database lock: 14 October 2013.

Phase of Development: 1b

Objectives: The primary objective was to determine the recommended Phase 2 dose and to assess dose-limiting toxicities (DLTs) of ibrutinib in combination with standard R-CHOP in subjects with CD20-positive B-cell NHL (diffuse large B-cell lymphoma [DLBCL], mantle cell lymphoma [MCL], and follicular lymphoma [FL]). Secondary objectives were to document the overall response rate (ORR; complete response [CR] + partial response [PR]) of the ibrutinib and R-CHOP combination in the overall population and in subjects with DLBCL, assess the pharmacokinetics of ibrutinib in the presence of

R-CHOP and explore a potential drug-drug interaction between ibrutinib and vincristine, assess pharmacodynamic markers of ibrutinib in peripheral blood mononuclear cells, and explore biomarkers predictive of response to the combination regimen.

Methodology: This was a Phase 1b, open-label, non-randomized, multicenter, dose-escalation (Part 1) and expansion (Part 2) study to establish the recommended Phase 2 dose of ibrutinib combined with standard R-CHOP in adults with CD20-positive treatment-naïve B-cell NHL (DLBCL, MCL, and FL) for whom R-CHOP was an appropriate therapy. The study included a Pretreatment (screening) period of up to 28 days before enrollment; an Open-label treatment period (up to 6 cycles of ibrutinib and R-CHOP; ending at the End-of-Treatment visit); and a Posttreatment Follow-up period until the end of study (maximum of up to 1 year after the last subject has completed the End-of-Treatment visit). During the dose escalation period, subjects were assigned to cohorts of increasing oral daily doses of ibrutinib (280, 420, and 560 mg/day) administered in combination with R-CHOP. Using a standard 3+3 dose escalation design, the maximum tolerated dose (MTD), defined as the highest dose of the combination regimen at which ≤33% of subjects experience DLT, was assessed in Cycle 1. A Study Evaluation Team; consisting of the principal investigators, sponsor medical monitors, and the sponsor's clinical pharmacologist, or their designees; reviewed all available data upon completion of the first cycle for all subjects at each dose cohort to determine DLTs. Once the recommended Phase 2 dose was determined, approximately 15 subjects with newly diagnosed DLBCL were to be entered into an expansion cohort at the dose level selected to further assess the safety, pharmacokinetics, pharmacodynamics, pharmacogenomics, and activity of the combination. Subjects whose disease had not progressed at the end of Cycle 1 were to continue to receive ibrutinib and R-CHOP up to a maximum of 6 cycles. During the Posttreatment Follow-up period, long-term safety, survival status, disease progression, and subsequent lymphoma therapy were to be collected. The study will end 1 year after the last subject has completed the End-of-Treatment visit.

Number of Subjects (planned and analyzed): Thirty-three subjects planned and enrolled (17 subjects in Part 1, 16 subjects in Part 2). Subject disposition is provided below.

Subject Disposition and Treatment Completion/Withdrawal Information by Planned Dose Level; All Treated Population (Study PCI-32765DBL1002)

	R-CHOP + Ibrutinib				
	Part 1			Part 2	
	280 mg	420 mg	560 mg	560 mg	Combined
Population: all treated[a]	7	4	6	16	33
Received ibrutinib	7 (100.0%)	4 (100.0%)	6 (100.0%)	15 (93.8%)	32 (97.0%)
Completed Cycle 1 (DLT evaluation)	6 (85.7%)	4 (100.0%)	6 (100.0%)	15 (93.8%)	31 (93.9%)
Completed treatment[b]	6 (85.7%)	4 (100.0%)	5 (83.3%)	14 (87.5%)	29 (87.9%)
Premature treatment discontinuation	1 (14.3%)	0	1 (16.7%)	2 (12.5%)	4 (12.1%)
Reason for discontinuation					
Adverse event	0	0	1 (16.7%)	2 (12.5%)	3 (9.1%)
Noncompliance with study drug	1 (14.3%)	0	0	0	1 (3.0%)

[a] All treated population includes all subjects who received at least 1 dose of any of the 6 study drugs (ibrutinib, rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone).
[b] Completed 6 cycles of treatment as indicated on the end of treatment CRF.
Note: Percentage is based on the number of subjects treated.

Diagnosis and Main Criteria for Inclusion:

Key inclusion criteria: 18 years of age or older; histopathologically-confirmed CD20-positive B-cell NHL disease (DLBCL, MCL, or FL); Stage I_{AX} (single lymph node mass ≥10 cm in diameter) to Stage IV disease; at least 1 measurable site of disease based on the Revised Response Criteria for Malignant Lymphoma; Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2; adequate bone marrow, liver, and renal function as specified in the protocol. Key exclusion criteria: prior treatment with a Bruton's tyrosine kinase inhibitor, prior extended radiotherapy for lymphoma;

>150 mg/m^2 of prior doxorubicin; prior multidrug chemotherapy for lymphoma; history of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug; major surgery within 3 weeks before enrollment; known bleeding diatheses or platelet dysfunction disorders (Amendment INT-1 onwards), or required therapeutic anticoagulation.

Test Product, Dose and Mode of Administration, Batch No.: Subjects were assigned to cohorts of increasing daily doses of ibrutinib (self-administered: 280, 420, or 560 mg; Cycle 1 Day 3 onwards) in combination with R-CHOP (rituximab 375 mg/m^2 intravenously [IV], cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV [maximum total of 2 mg], and prednisone 100 mg orally) for up to 6 cycles (21 days/cycle). R-CHOP was to be given on the first day of every treatment cycle (prednisone given on Days 1 to 5). The sponsor only supplied ibrutinib (batch number: L0307693); all other drugs were provided through a local pharmacy.

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

Duration of Treatment: Approximately 18 weeks (up to 6 cycles of ibrutinib+R-CHOP)

Criteria for Evaluation: Efficacy: computed tomography (CT) scans with IV contrast of the neck, chest, abdomen, and pelvis and whole body positron emission tomography scans (magnetic resonance imaging for sites of disease that could not be adequately imaged using CT). Disease response was assessed according to the Revised Response Criteria for Malignant Lymphoma. Pharmacokinetics: Blood samples were collected (predose and at various timepoints postdose up to 24 hours during Cycles 1 and 2, and predose during Cycles 3 and 4 and at the End-of-Treatment visit) from all subjects. Plasma samples were analyzed to determine concentrations of ibrutinib (and its metabolites) and vincristine using a validated, specific, and sensitive (eg, liquid chromatography-mass spectrometry [LC-MS]) method. Pharmacodynamics/Biomarkers: Tumor (from lymph node biopsies or diagnostic biopsy tissue collected during screening), blood, and bone marrow aspirate or biopsy was evaluated in all subjects to identify markers predictive of response to ibrutinib. Pharmacogenomics: a blood sample was collected to allow for pharmacogenomic research, where local regulations permit (participation was optional). Safety (assessments repeated as necessary): adverse events, clinical laboratory tests (hematology, serum chemistry, coagulation, bleeding time [Amendment INT-1 onwards; at screening and end of Cycle 1], and serum or urine pregnancy testing), physical examinations (including vital signs [heart rate, blood pressure, and temperature], weight evolution, and ECOG performance status evaluations), concomitant medication usage, baseline left ventricular ejection fraction measurement by multiple-gated acquisition scan or echocardiography (required in all subjects), and electrocardiogram findings.

Statistical Methods: No formal power calculations were performed to pre-determine sample size. The MTD was determined based on the "3+3" rules for dose escalation (if sites identified 4 eligible subjects, all 4 subjects could be enrolled). Three ibrutinib dose levels (ie, 280, 420, and 560 mg) in combination with R-CHOP were planned. Approximately 33 subjects were to be enrolled in the study. No formal hypothesis testing was made. Descriptive statistics were provided for efficacy, safety, pharmacokinetics, pharmacodynamics, as well as other endpoints. Summary statistics for continuous variables include the mean, standard deviation, median, and range. Categorical data was presented as frequencies and percentages. The number and percent of subjects with an overall response (CR+PR) was presented.

RESULTS:

STUDY POPULATION: Thirty-three subjects from 6 centers in the United States (4 sites) and France (2 sites) were enrolled. The all treated population was balanced by sex (51.5% males, 48.5% females), with over half (54.5%) of the subjects less than 65 years of age (median age: 61.0 years; range: 22 to 81 years) and the majority (75.8%) of subjects were white. Most subjects (87.9% [29/33 subjects]) entered the study with an ECOG performance status score of 0 or 1. Thirty-two of 33 subjects (97.0%) received at least 1 dose of the ibrutinib+R-CHOP combination; 1 subject received only rituximab and was withdrawn from the study due to a Grade 3 rituximab infusion reaction. Among all treated subjects who

received the ibrutinib+R-CHOP combination, the median treatment duration was 18.0 weeks; median time on study was 7.1 months at the clinical cutoff.

PHARMACOKINETIC RESULTS: Ibrutinib maximum observed plasma concentration (C_{max}) and area under the plasma-concentration versus time curve (AUC) increased across the dose range tested and were higher during Cycle 2 compared with Cycle 1. Accumulation ratios varied from 2.17 to 8.60. PCI-45227 (dihydrodiol metabolite of ibrutinib) C_{max} and AUC increased across the dose range tested. C_{max} increased slightly from Cycle 1 to Cycle 2; whereas, the area under the plasma-concentration versus time curve from time 0 to the last assessment (AUC_{last}) increased 1.8- to 3.5-fold from Cycle 1 to Cycle 2. Metabolite/parent ratios decreased somewhat from Cycle 1 to Cycle 2 for both C_{max} and AUC. Vincristine pharmacokinetics did not appear to be affected by ibrutinib when Cycle 1 Day 1 kinetics (without ibrutinib) were compared with Cycle 2 Day 1 (with ibrutinib).

Mean Ibrutinib Pharmacokinetic Parameters Following Once Daily Oral Administration of Ibrutinib (Study PCI-32765DBL1002: Pharmacokinetics Data Analysis Set)[a]

	280 mg		420 mg		560 mg	
Parameter	Cycle 1 Day 3 N=6	Cycle 2 Day 1 N=5	Cycle 1 Day 3 N=4	Cycle 2 Day 1 N=7	Cycle 1 Day 3 N=19	Cycle 2 Day 1 N=18
t_{max} (h)[b]	3.0 (0.5 – 8.0)	4.0 (1.0 – 6.3)	2.0 (1.0 – 2.0)	2.0 (1.0 – 3.0)	2.0 (1.0 – 24.0)	2.0 (0.0 – 3.0)
C_{max} (ng/mL)	44.4 (16.4)	80.3 (28.9)	92.0 (86.8)	190 (135)	147 (125)	187 (198)
DN_C_{max} (ng/mL)	88.9 (32.8)	161 (57.7)	123 (116)	253 (180)	147 (125)	187 (198)
AUC_{24} (ng.h/mL)	NAs	619 (278)	NAs	762 (465)[c]	502 (332)	1014 (785)[e]
DN_AUC_{24} (ng.h/mL)	NAs	1238 (557)	NAs	1016 (620)[c]	502 (332)	1014 (785)[e]
AUC_{last} (ng.h/mL)	150 (48.1)	619 (278)	322 (280)	785 (429)	554 (406)	882 (741)
DN_AUC_{last} (ng.h/mL)	300 (96.0)	1238 (557)	429 (373)	1047 (572)	554 (406)	882 (741)
Acc Ratio	NA	4.36 (1.12)	NA	8.60 (8.92)[d]	NA	2.17 (2.00)[f]

DN=dose normalized to 560 mg; NAs=not assessable; no 24 hour samples; Acc Ratio=$AUC_{last, C2D1}/AUC_{last, C1D3}$; NA=not applicable
[a] Ibrutinib was given once daily orally from Cycle 1 Day 3 onwards to allow for analysis of potential drug-drug interactions between ibrutinib and vincristine (Cycle 1 Day 1 compared with Cycle 2 Day 1). Ibrutinib was given once daily orally from Day 1 onwards for consecutive cycles. [b] Median (range) [c] N=6 [d] N=4 [e] N=14 [f] N=17

SAFETY RESULTS: Three DLTs were reported during the study (280 mg: Grade 3 transient syncope and Grade 3 periorbital cellulitis; 560 mg: Grade 2 gastritis), however, the MTD was not reached. The recommended Phase 2 dose was established at 560 mg ibrutinib once daily in combination with R-CHOP in treatment-naïve subjects with NHL. In the all treated population, all subjects had at least 1 adverse event. The most frequently reported adverse events (≥30%) were related to (i) the hematopoietic system with neutropenia (75.8%), thrombocytopenia (63.6%), and anemia (42.4%); (ii) the gastrointestinal system with nausea (69.7%), vomiting (60.6%), constipation (42.4%), and diarrhea (39.4%); (iii) the nervous system with peripheral sensory neuropathy (30.3%); and (iv) general disorders such as fatigue (45.5%) and headache (33.3%). No ibrutinib adverse events of special interest (ie, major hemorrhage or intracranial bleeding) were reported. Grade 3 or higher adverse events were reported in 81.8% of subjects, and were primarily hematologic with neutropenia (72.7%), febrile neutropenia (18.2%), thrombocytopenia (21.2%), and anemia (18.2%) the most commonly reported. No other Grade 3 or higher adverse events occurred in ≥7% of subjects. Treatment-emergent serious adverse events were reported in almost half (48.5%) of subjects in the all treated population. The most frequently (>3%) reported treatment-emergent serious adverse events were febrile neutropenia (18.2%) and hypotension (6.1%). All other serious adverse events were reported in 1 subject each. One subject who received 560 mg ibrutinib+R-CHOP during the dose expansion phase of the study committed suicide during Cycle 6, which was considered by the investigator as not related to any of the study drugs. Among those subjects treated with the 560 mg ibrutinib+R-CHOP combination, the majority (95.2% [20/21]) of subjects (100.0% [18/18] of DLBCL subjects) tolerated 6 cycles of R-CHOP treatment and most adverse

events were manageable with concomitant medications or dose modifications. Neutropenia was managed with colony stimulating factors. Single dose reductions of vincristine were reported most frequently (in 33.3% [11/33] of subjects) and among adverse events leading to treatment discontinuation, over half (55.6% [5/9 subjects]) of the events were neuropathy events that led to vincristine dose modification during later cycles of treatment. Cycle delays were reported in one-third (33.3% [11/33]) of subjects who received the ibrutinib+R-CHOP combination, with 21.2% (7/33) of subjects only requiring a single delay.

BIOMARKER, PHARMACODYNAMIC, AND PHARMACOGENOMIC RESULTS: Biomarker, pharmacodynamics, and pharmacogenomic results will be reported separately.

EFFICACY RESULTS: Efficacy analyses were based on the all treated and response evaluable analysis populations; no subjects were excluded from the efficacy analyses. The ibrutinib+R-CHOP combination demonstrated clinical activity across all dose cohorts in the all treated population (inclusive of subjects with treatment-naïve DLBCL, MCL, and FL) with an ORR of 85.7%, 100.0%, 95.2%, and 93.8% reported in the 280 mg, 420 mg, 560 mg, and combined dose cohorts, respectively. Among the 18 subjects with DLBCL who received the recommended Phase 2 dose of 560 mg ibrutinib once daily in combination with R-CHOP, a 100.0% ORR (15 CRs, 3 PRs) was achieved. Median duration of response, PFS, and overall survival could not be estimated at the time of this report.

Among the 13 subjects in the all treated population with DLBCL who had available immunohistochemistry subtyping data (Hans method, central laboratory), 9 subjects had GCB DLBCL and 4 subjects had non-GCB DLBCL. Excluding 1 non-evaluable subject in the 280 mg cohort (who was typed as GCB) and 1 subject who was discontinued from study treatment following a Grade 3 rituximab infusion reaction on Cycle 1 Day 1, the ORR was 100.0% regardless of subtype (9 CRs, 2 PRs; CR rate of 81.8% [9/11]). Both subjects who achieved a PR had the GCB subtype, leading to a CR rate of 71.4% (5/7) for those with the GCB subtype and 100% (4/4) for those with the non-GCB subtype. Among the 9 subjects who received 560 mg ibrutinib+R-CHOP, the CR rates were also 71.4% (5/7) for the GCB subtype and 100.0% (2/2) for the non-GCB subtype.

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

CONCLUSION(S): In the Phase 1 dose escalation part of this study, the recommended Phase 2 dose was established at 560 mg ibrutinib once daily in combination with R-CHOP in treatment-naïve subjects with NHL. The safety profile of this combination of 560 mg ibrutinib with standard R-CHOP was acceptable and consistent with, what has been reported for R-CHOP alone. In addition, the ibrutinib pharmacokinetic profile in combination with R-CHOP was similar to the ibrutinib monotherapy pharmacokinetic profile. Upon graphical exploration of ibrutinib and vincristine exposure, the data indicate that drug exposures were not altered by one another. The ibrutinib+R-CHOP combination demonstrated favorable efficacy, with an ORR of 100% in the 18 subjects with DLBCL who received the recommended Phase 2 dose regimen. Median duration of response, PFS, and overall survival data were not mature at the time of this report (median time on study of 7.1 months for all treated subjects [inclusive of DLBCL, MCL, and FL] and 5.6 months for all treated subjects with DLBCL). Based on the safety profile and the preliminary efficacy observed with the 560 mg ibrutinib+R-CHOP combination regimen in treatment-naïve subjects with DLBCL, further clinical development is warranted.

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