SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-54179060 (ibrutinib)

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Prepared by:	Janssen Research & Development, LLC

Protocol No.: PCI-32765LYM1003

Title of Study: A Drug-Drug Interaction Study of Ibrutinib With Moderate and Strong CYP3A Inhibitors in Patients With B-cell Malignancy

NCT No.: NCT02381080

Clinical Registry No.: CR106609

Coordinating Investigator(s): Dr. Alexander Myasnikov, MD

Study Center(s): Russian Federation (3 sites), Spain (2 sites), Canada (1 site)

Study Period: 21 May 2015 - 24 June 2016

Phase of Development: Phase 1

Objectives:

Primary Objective

The primary objective of this study was to assess the effect of the moderate CYP3A inhibitor erythromycin and the strong CYP3A inhibitor voriconazole on the steady-state pharmacokinetics (PK) of repeated oral doses of ibrutinib in patients with B-cell malignancy.

Secondary Objectives

The secondary objectives of this study were:

- To assess the safety of ibrutinib when dosed concomitantly with voriconazole (a strong CYP3A inhibitor) in patients with B-cell malignancy
- To assess the safety of ibrutinib when dosed concomitantly with erythromycin (a moderate CYP3A inhibitor) in patients with B-cell malignancy
- To assess the steady state PK of erythromycin and voriconazole in patients with B-cell malignancy when combined with ibrutinib

[redacted]

Methodology: This was an open-label, multicenter, CYP3A drug-drug interaction (DDI) study of ibrutinib with the CYP3A inhibitors erythromycin and voriconazole in patients with B-cell malignancy. The subject population was to be comprised of patients with B-cell malignancy including chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), follicular lymphoma (FL), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM) or mantle cell lymphoma (MCL), who met all the inclusion criteria and none of the exclusion criteria.

The study consisted of a 28-day screening phase and a Treatment Phase consisting of six 28-day treatment cycles. Drug-drug interaction potential and clinical safety was assessed during the first treatment cycle. During the consecutive treatment cycles (maximal duration of 6 months from first intake of study drug) clinical safety was assessed and documented, and efficacy was documented.

During Cycle 1, subjects assigned to Part 1 of the study took ibrutinib 560 mg once daily (QD) from Days 1-4 and had steady state PK assessments on Day 4. On Days 5-11, subjects took ibrutinib 140 mg QD in combination with erythromycin 500 mg thrice-a-day (TID, on Days 5-10 and morning dose on Day 11) and had steady state PK assessments on Day 11. On Days 12-13, subjects took ibrutinib 140 mg QD and on Days 14-18 took ibrutinib 560 mg QD. On Days 19-25, subjects took ibrutinib 140 mg QD in combination with voriconazole 200 mg twice a day (BID) and had steady state PK assessments on Day 25. On Days 26-27, subjects took ibrutinib 140 mg QD and on Day 28 subjects continued on ibrutinib 420 mg QD or ibrutinib 560 mg QD (depending on the underlying subtype of B-cell malignancy).

An End-of-Treatment (EoT) Visit was scheduled within 30 days after the last dose of study drug for all subjects discontinuing treatment in this study before the end of the 6-month Treatment Phase for any reason, except for loss to follow-up, death, or withdrawal of consent for study participation.

There were 2 planned parts of this study:

- Part 1 determined the extent of DDI for the CYP3A inhibitors erythromycin and voriconazole with ibrutinib at a dose level of 140 mg in patients with B-cell malignancy. Up to 26 subjects were to take part in Part 1 of the study to ensure up to 22 subjects were evaluable for assessment of the DDI factor. During Part 1 an adaptive design was applied with interim review of safety and PK information after 6 and 12 subjects had been enrolled.
- Part 2 was optional and could occur when the extent of the geometric mean area under the concentration-time curve (AUC) ratio of ibrutinib was <4 fold in Part 1 for either concomitant administration of erythromycin or voriconazole.

After up to 26 subjects completed Cycle 1 in Part 1 of the study a review of all available PK and safety data were to be conducted by the Study Evaluation Team (SET). Pending the DDI factor for ibrutinib, AUC observed, and in absence of significant safety concerns a decision was to be made to proceed with Part 2 of the study.

Number of Subjects (planned and analyzed): A total of 26 subjects were planned for Part 1 of the study to ensure up to 22 subjects were available to provide estimation on the magnitude of interaction effect. As planned, 26 subjects were enrolled and analyzed in the study.

Diagnosis and Main Criteria for Inclusion: The subject population comprised of patients with B-cell malignancy including CLL/SLL, MCL, FL, WM, or MZL, who met all the inclusion criteria and none of the exclusion criteria.

Male and female subjects, 18 years or older, with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and with relapsed or refractory disease after at least 1 prior line of systemic therapy were eligible for enrollment in this study.

Test Product and Reference Therapy, Dose and Mode of Administration, Batch No.:

The information for study drugs is provided in the table below:

Study Drugs Information (Study PCI-32765LYM1003**)**

Study Drug	Description, dose and mode of administration	[redacted]	[redacted]	[redacted]
Ibrutinib	white opaque, size 0, hard gelatin capsules containing 140 mg ibrutinib			
Erythromycin	white, oblong, film-coated tablet with a curved double-sided scoreline containing 500 mg erythromycin stearate			
Voriconazole	white to off-white, oval shaped, unscored, film-coated tablets containing 200 mg voriconazole, debossed with “TEVA” on one side and “5290” on the other side			

Duration of Treatment: The study consisted of a 28-day screening phase and a Treatment Phase consisting of six 28-day treatment cycles.

Criteria for Evaluation: Pharmacokinetic parameters (C_{max}, C_{min}, t_{max}, AUC_{0-24h}, metabolite to parent ratio [M/P] ratio) were derived from plasma concentration versus time data for ibrutinib and PCI-45227 metabolite. The PK parameter determined for voriconazole was $AUC_{(0-6h)}$ and those for erythromycin were C_{0h} (on Day 5) and C_{0h} and C_{2h} (on Day 11).

Assessment of antitumor activity in this study by means of computed tomography (CT) imaging and positron emission tomography (PET) scans was performed in this study at discretion of the Investigator after 3 and 6 cycles of treatment. Imaging assessments throughout the study were performed using the same imaging modality used to assess disease at baseline. Other assessments to assess antitumor activity (eg bone marrow biopsies or aspirates, serum β2-microglobulin levels, serum immunoglobulin levels and others) were performed at the discretion of the Investigator. Subjects with MCL, MZL, and FL were assessed for response according to Revised Response Criteria for Malignant Lymphoma and subjects with CLL/SLL were evaluated according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL). Subjects with WM were evaluated in accordance with the modified consensus criteria adapted from the VIth International Workshop on WM.

[redacted]

[redacted]

The study evaluations of safety and tolerability included adverse events (AEs), clinical laboratory tests, physical examinations, electrocardiograms (ECGs), vital signs, and ECOG performance status. Any clinically significant abnormalities persisting at the end of the study/early withdrawal were followed by the investigator until resolution or until a clinically stable endpoint was reached.

Statistical Methods:

The statistical analysis was performed using Statistical Analysis Software (SAS), Version 9.3.

Sample Size

The study applied an adaptive approach to enroll subjects in Part 1 of the study. Six and 12 PK evaluable subjects were planned for the first and second SET meetings, respectively, to review safety and PK data. A maximum number of 26 subjects with 22 PK evaluable subjects were planned for Part 1 of the study to provide estimation on the magnitude of interaction effect.

The maximum number of 26 subjects with 22 PK evaluable subjects for Part 1 of the study was estimated based on similar study data (CLL1002) which indicated the intrasubject coefficient of variations (CVs) were approximately 31% for C_{max} and 41% for AUCs of ibrutinib. With an intrasubject CV of 31% for C_{max}, a sample size of 22 subjects was deemed sufficient for the point estimates of the geometric mean ratios (GMRs) of C_{max} of ibrutinib, with and without coadministration of the CYP3A inhibitor voriconazole, to fall within 85% and 117% of the true value, with 90% confidence. With an intrasubject CV of 41% for AUC, a sample size of 22 subjects was sufficient for the point estimates of the GMRs of AUC of ibrutinib, with and without coadministration of the CYP3A inhibitor voriconazole, to fall within 82% and 122% of the true value, with 90% confidence.

Analysis

Interim

An interim analysis was conducted after all subjects had completed Cycle 1 in Part 1 of the study to mainly assess the primary objective of drug interaction. The final analysis was completed when all subjects had completed the study and included subjects enrolled in Part 1 and the optional Part 2.

Efficacy

Disease response evaluation data were captured in the electronic case report form (eCRF) and were analyzed descriptively per subject histology. These data were used to derive if subjects were receiving a clinical benefit from ibrutinib monotherapy.

Pharmacokinetics

Individual and mean plasma ibrutinib and PCI-45227 concentration-time profiles were plotted for each treatment. Plasma concentration data at each timepoint were summarized with mean, median, geometric mean, minimum, maximum, standard deviation (SD) and CV (%) for each treatment. All estimated PK parameters of ibrutinib and PCI-45227 were summarized for each treatment with mean, median, geometric mean, minimum value, maximum value, SD, and %CV.

Statistical analysis for drug interaction between ibrutinib and erythromycin included only those subjects who had PK-parameter estimations of ibrutinib for both periods (ibrutinib 560 mg administered alone on Day 1-Day 4 and ibrutinib 140 mg administered in combination with erythromycin on Day 5-Day 11). Similarly, statistical analysis for drug interaction between ibrutinib and voriconazole included only those subjects who had PK-parameter estimations of ibrutinib for both periods (ibrutinib 560 mg administered alone on Day 1-Day 4 and ibrutinib 140 mg administered in combination with voriconazole on Day 19-Day 25). The primary PK parameters of interest were dose-normalized AUC_{0-24h} and dose-normalized C_{max} of ibrutinib. The GMRs of PK parameters of ibrutinib with and without coadministration of the inhibitors (erythromycin or voriconazole) and the associated 90% confidence

intervals (CI) was constructed based on the least square means and intrasubject CV from a mixed effects model of log-transformed PK parameters. Similar analysis was performed based on non-dose-normalized PK parameters of ibrutinib.

[redacted]

[redacted]

[redacted]

Safety

Safety analysis was performed on treated population. The safety parameters to be analyzed were the incidence, intensity, and type of AEs, clinically significant changes in the subject's physical examination findings, ECGs, vital signs measurements, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment were tabulated.

RESULTS:

STUDY POPULATION:

The subject population was comprised of patients with B-cell malignancy including CLL/SLL, MCL, FL, WM, or MZL, who met all the inclusion criteria and none of the exclusion criteria described in the protocol. Overall, 26 subjects were enrolled in Part 1 of the study and Part 2 was not conducted. Of the 26 enrolled subjects in Part 1, all 26 subjects completed the PK part and 23 subjects (88.5%) completed the Treatment Phase (6 Cycles) of the study. Three subjects (11.5%) prematurely terminated the study, 2 subjects (7.7%) discontinued due to AEs (1 death), and 1 subject (3.8%) discontinued due to progressive disease after 3 cycles of therapy.

Of the 26 subjects enrolled, there were 13 men and 13 women. The median age was 64.5 years (range 50 to 88 years of age, inclusive). The median body mass index (BMI) was 24.68 kg/m^2 (range 20.0 to 39.2 kg/m^2). Twelve subjects (46.2%) had a reported baseline ECOG performance score of 0 and 14 subjects (53.8%) had a reported baseline ECOG performance score of 1.

The population evaluable for safety included all subjects who received at least 1 dose of study drugs. All 26 subjects were included in the safety analysis. The PK analysis of ibrutinib in the presence of erythromycin and voriconazole involved 25 and 26 subjects, respectively.

PHARMACOKINETIC RESULTS:

Ibrutinib

The [redacted], C_{max}, and AUC_{0-24h} observed after treatment with ibrutinib 140 mg in the presence of erythromycin or voriconazole were numerically lower and higher, respectively, compared to after treatment with ibrutinib alone at the dose of 560 mg. For all 3 treatments, the median t_{max} was 2 hours.

Based on the GMR, C_{max} and AUC_{0-24h} of ibrutinib were decreased by 16% and 25%, respectively, after treatment with 140 mg ibrutinib in the presence of erythromycin [redacted] as compared to treatment with 560 mg ibrutinib alone [redacted]

Based on the GMR, the C_{max} and AUC_{0-24h} of ibrutinib were increased by 68% and 43%, respectively, after treatment with 140 mg ibrutinib in the presence of voriconazole [redacted] as compared to treatment with 560 mg ibrutinib alone [redacted]

Pharmacokinetics of ibrutinib

Pharmacokinetics of ibrutinib (mean±SD, t_{max}: median (range))	Day 4 Ibrutinib 560 mg QD alone [redacted]	Day 11 Ibrutinib 140 mg QD + erythromycin 500 mg TID [redacted]	Day 25 Ibrutinib 140 mg QD + voriconazole 200 mg BID [redacted]
n [redacted]	26 [redacted]	26[a] [redacted]	26 [redacted]
C_{max} (ng/mL) [redacted]	89.4±67.1 [redacted]	75.5±47.9 [redacted]	129±63.4 [redacted]
AUC_{0-24h} (ng.h/mL) [redacted]	470±350 [redacted]	397±420 [redacted]	559±251 [redacted]

[redacted]

n= 25 for C_{max}, t_{max} and AUC_{0-24h}

After dose normalization (to an ibrutinib dose of 560 mg), the dose-normalized C_{max} and AUC_{0-24h} of ibrutinib were increased by 3.4-fold and 3.0-fold, respectively, after treatment with ibrutinib in the presence of erythromycin [redacted] as compared to treatment with ibrutinib alone [redacted] based on the GMR.

After dose normalization (to an ibrutinib dose of 560 mg), the dose-normalized C_{max} and AUC_{0-24h} of ibrutinib were increased by 6.7-fold and 5.7-fold, respectively, after treatment with ibrutinib in the presence of voriconazole [redacted] as compared to treatment with ibrutinib alone [redacted] based on the GMR.

Pharmacokinetics of ibrutinib, dose-normalized to a 560 mg ibrutinib dose

Pharmacokinetics of ibrutinib (mean ± SD)	Day 4 Ibrutinib 560 mg QD alone [redacted]	Day 11 Ibrutinib 140 mg QD + erythromycin 500 mg TID [redacted]	Day 25 Ibrutinib 140 mg QD + voriconazole 200 mg BID [redacted]
n [redacted]	26 [redacted]	26[a] [redacted]	26 [redacted]
C_{max} (ng/mL)	89.4±67.1	302±192	516±254
AUC_{0-24h} (ng.h/mL)	470±350	1587±1679	2234±1004

[redacted]

[a] n=25 for C_{max}, t_{max} and AUC_{0-24h}

PCI-45227

The ratio of AUC_{0-24h} between PCI-45227 (metabolite) and ibrutinib (parent) was lower when 140 mg ibrutinib was coadministered with erythromycin (0.46±0.25) or with voriconazole (0.37±0.17) compared to the administration of 560 mg ibrutinib alone (1.20±0.54). The ratio of C_{max} between PCI-45227 and ibrutinib was lower when 140 mg ibrutinib was coadministered with erythromycin (0.28±0.18) or with voriconazole (0.18±0.09) compared to the administration of 560 mg ibrutinib alone (0.90±0.39).

Pharmacokinetics of PCI-45227

Pharmacokinetics of PCI-45227 (mean±SD, t_{max}: median (range))	Day 4 Ibrutinib 560 mg QD alone [redacted]	Day 11 Ibrutinib 140 mg QD + erythromycin 500 mg TID [redacted]	Day 25 Ibrutinib 140 mg QD + voriconazole 200 mg BID [redacted]
n	26	26[a]	26
[redacted]	[redacted]	[redacted]	[redacted]
C_{max} (ng/mL)	69.1±38.4	19.7±15.6	22.2±13.1
[redacted]	[redacted]	[redacted]	[redacted]
AUC_{0-24h} (ng.h/mL)	556±430	204±261	220±152
M/P C_{max}	0.90±0.39	0.28±0.18	0.18±0.09
M/P AUC_{0-24h}	1.20±0.54	0.46±0.25	0.37±0.17

[a]: n=25 for Cmax, tmax and AUC0-24h

After dose normalization compared to the administration of ibrutinib alone, the concomitant administration with erythromycin and voriconazole resulted in an increase of the PCI-45227 mean PK parameters with ratio of mean AUC of 1.46 and 1.58, respectively.

Pharmacokinetics of PCI-45227 dose-normalized to a 560 mg ibrutinib dose

Pharmacokinetics of PCI-45227 (mean±SD)	Day 4 Ibrutinib 560 mg QD alone [redacted]	Day 11 Ibrutinib 140 mg QD + erythromycin 500 mg TID [redacted]	Day 25 Ibrutinib 140 mg QD + voriconazole 200 mg BID [redacted]
n	26	26[a]	26
[redacted]	[redacted]	[redacted]	[redacted]
C_{max} (ng/mL)	69.1±38.4	78.7±62.4	88.8±52.5
AUC_{0-24h} (ng.h/mL)	556±430	814±1043	879±610

[a] n=25 for C_{max} and AUC_{0-24h}

[redacted]

[redacted]

[redacted]

[redacted]

SAFETY RESULTS:

All subjects who received at least 1 dose of the study drug were included in the safety analysis. Of the 26 subjects dosed, 22 subjects (84.6%) experienced at least 1 treatment-emergent adverse event (TEAE), of which 19 subjects (73.1%) had TEAEs considered related to the study drugs by the investigator. Treatment-emergent AEs of Grade ≥3 were experienced by 13 subjects (50.0%). Serious adverse events (SAEs) were experienced by 4 subjects (15.4%). Treatment-emergent AEs leading to treatment discontinuation were experienced by 2 subjects (7.7%).

The most commonly reported TEAEs (>5% subjects) by preferred terms were diarrhea (26.9% of subjects), neutropenia (23.1% of subjects), abdominal pain, thrombocytopenia, fatigue, pyrexia (15.4% of subjects each), nasopharyngitis, dry mouth, anemia, cough, dyspnea, hypertension (11.5% of subjects each), and respiratory tract infection, urinary tract infection, constipation, edema, edema peripheral, petechiae, purpura, rash maculo-papular, atrial fibrillation, decreased appetite (7.7% of subjects each). Grade 3 or higher TEAEs were reported for 50.0% subjects in this study. The most commonly reported Grade 3 or higher TEAEs in the study were neutropenia (23.1%) and hypertension (7.7%).

Overall, SAEs were experienced by 15.4% of subjects enrolled in the study. All of these treatment-emergent SAEs reported Grade ≥3 as the worst toxicity grade. Drug-related treatment-emergent SAEs were reported for 7.7% of subjects. The treatment-emergent SAEs reported in the study by preferred term were: upper respiratory tract infection, atrial fibrillation, cardiac failure, performance status decreased, thrombocytopenia, herpes zoster disseminated, and appendicitis.

There was 1 death (performance status decreased) reported in this study which occurred in an overall context of progressive disease. This subject reported several SAEs (atrial fibrillation, cardiac failure, performance status decreased, and thrombocytopenia) at separate timepoints prior to death.

EFFICACY RESULTS:

Of the 26 enrolled subjects, 6 subjects had MCL, 14 subjects had CLL, 2 subjects each had FL and SLL, and 1 subject each had WM and MZL as the reported lymphoma subtype. Of the 26 enrolled subjects at EoT 1 subject had a complete response, 17 subjects had a partial response, 5 subjects had stable disease, 2 subjects had progressive disease (one subject after 3 cycles of therapy and one subject after 6 cycles of therapy), and 1 subject was considered not evaluable for response. Of the 26 subjects enrolled in this study, 22 subjects continued treatment with ibrutinib in the roll-over extension study PCI-32765CAN3001.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor, but it was decided to not enroll Part 2. Although the DDI factor for AUC was <4 with erythromycin (GMR=3.0) and >4 for voriconazole

(GMR=5.7), exposure ranges for both combination treatments were comparable to the range observed with ibrutinib 560 mg alone.

CONCLUSION(S):

- Based on GMR, C_{max}, and AUC_{0-24h} of ibrutinib were increased by 3.4-fold and 3.0-fold, respectively, in the presence of erythromycin as compared to treatment with ibrutinib alone.
- Based on GMR, $C_{max,}$ and AUC_{0-24h} of ibrutinib were increased by 6.7-fold and 5.7-fold, respectively, after treatment with ibrutinib in the presence of voriconazole as compared to treatment with ibrutinib alone.
- Based on GMR, with the daily dose of 140 mg of ibrutinib coadministered with moderate or strong CYP3A inhibitors, the ibrutinib [redacted] C_{max} and AUC_{0-24h}, were respectively 16% and 25% lower in combination with erythromycin and 68% and 43% higher in combination with voriconazole, as compared to treatment with 560 mg ibrutinib alone. These differences are not considered clinically relevant.
- The observed interactions are in line with physiologically-based pharmacokinetic (PBPK) predicted values and therefore do not warrant revision of existing dose recommendations for concomitant administration of 140 mg ibrutinib with strong or moderate CYP3A inhibitors.
- The coadministration of erythromycin or voriconazole with ibrutinib had minimal effect on dose-normalized C_{max} of PCI-45227 (metabolite of ibrutinib), whereas AUC increased less than 2-fold compared to the PCI-45227 levels measured when ibrutinib was taken alone. The metabolite to parent ratio decreased from 0.90 and 1.20 for C_{max} and AUC_{0-24h} after ibrutinib alone, to 0.28 and 0.46 when ibrutinib was coadministered with erythromycin, and to 0.18 and 0.37 for ibrutinib with voriconazole.
- The overall safety profile observed is in alignment with prior observations of ibrutinib treatment in patients with B-cell malignancies. No unexpected safety events were observed and no major hemorrhage events occurred.

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