SYNOPSIS

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

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Status: Approved

Date: 4 July 2019

Prepared by: Janssen Research & Development, LLC

Protocol No.: 54179060CLL1017

Title of Study: A Drug-Drug Interaction Study to Evaluate the Effect of Ibrutinib on the Pharmacokinetics of Oral Contraceptives, CYP2B6, and CYP3A4 Substrates in Female Subjects with B Cell Malignancy

EudraCT Number: 2017-000496-84

NCT No.: NCT03301207

Clinical Registry No.: CR108347

Principal Investigator: Professor Wojciech Jurczak, MD, PhD, Malopolskie Centrum Medyczne, [redacted] Poland

Study Centers: Poland and Spain (2 sites each)

Publication (Reference): None

Study Period: 31 October 2017 (Date first subject signed informed consent) to 4 December 2018 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 1

Objectives:

Primary Objectives:

- To evaluate the effects of repeat dosing of ibrutinib on the single-dose pharmacokinetics (PK) of oral contraceptives (OC) (ethinylestradiol [EE] and levonorgestrel [LN]), the cytochrome P450 (CYP) 2B6 probe bupropion, and the CYP3A4 probe midazolam, in female subjects with B cell malignancy.
- To evaluate the effects of single-dose ibrutinib on the single-dose PK of the CYP3A4 probe midazolam in female subjects with B cell malignancy.

Secondary Objectives:

- To assess the steady-state exposure of ibrutinib in the presence of probe drugs in female subjects with B cell malignancy.

- To evaluate the safety of ibrutinib alone and in the presence of OC and probe drugs.

Methodology: This was a Phase 1, open-label, multicenter study of female subjects with B cell malignancy to assess the effect of repeat dosing of ibrutinib on the PK of OC (EE and LN) and CYP2B6 and CYP3A4 probe drugs (bupropion and midazolam, respectively). The study consisted of 3 phases: a 28-day Screening Phase to determine eligibility, a 7-day Pretreatment Phase (Study Days 1 to 7), and a Treatment Phase consisting of a PK assessment period (Study Days 8 to 26) and follow-up period (from Study Day 27 to the end of Cycle 6).

Drug-drug interaction (DDI) potential was assessed by data collected during the first treatment cycle where the PK objectives from this study were answered. Assessment of systemic levels of the OC and probe drugs was conducted at baseline during the 7-day Pretreatment Phase (ie, before starting treatment with ibrutinib) and during the Treatment Phase after repeated dosing with ibrutinib at a dose of 560 mg daily for approximately 2 weeks.

Throughout the study, safety and efficacy was assessed. Ibrutinib was administered orally once daily in treatment cycles of 28 days starting on Study Day 8 (Cycle 1 Day 1). The maximal duration of ibrutinib treatment in this study was 6 months from the first dose. Subjects who continued to derive clinical benefit (in the absence of unacceptable toxicity) at the end of the 6-month period ended participation in this study, completed an end of treatment (EoT) visit (approximately 1 month after Cycle 6 Day 1), then continued ibrutinib treatment without interruption under the extension study protocol, PCI-32765CAN3001. Subjects who discontinued treatment prior to the completion of the 6-month Treatment Phase (except lost to follow-up, death, or withdrawal of consent for study participation) completed the EoT visit within 30 days after the last dose of study drug (ibrutinib, OC or probe drugs, whichever was last).

The end of study was defined as the last study-related assessment for the last subject on study at the end of the 6-month treatment period.

Number of Subjects (planned and analyzed): Planned subjects: 18 and Analyzed subjects: 22

Diagnosis and Main Criteria for Inclusion: Female subjects, 18 years or older, with histologically or cytologically confirmed B-cell malignancy including chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), or marginal zone lymphoma (MZL), with Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Subjects with MCL had relapsed or refractory disease after at least 1 prior line of systemic therapy and subjects with MZL had failed at least one anti-CD20 based therapy. Use of CYP inhibitors/inducers or drugs known to affect the PK of study drug (ibrutinib, OC, and probe drugs) was not allowed at specified times during the course of the study.

Test Product, Dose and Mode of Administration, Batch No.: The information for study drugs is provided in the table below:

Study Drug Information (Study 54179060CLL1017)

Study Drug	Description, dose and mode of administration	Reference No.	Bulk Lot No.	Expiration date
Ibrutinib	grey, size 0, hard gelatin capsules containing 140 mg ibrutinib	4374774	L0507141A	Apr 2019
Ethinylestradiol/levonorgestrel	Marketed formulation: Microgynon 30 tablet containing 30 µg EE and 150 µg LN	4374657	64535A	30 Nov 2021
Bupropion	Marketed formulation: tablet containing 75 mg bupropion	4374775	3081015	31 Oct 2019
Midazolam	Marketed formulation: 1 mL of midazolam oral solution (30-mL bottles containing 2 mg midazolam/mL)	4374776	S24981	31 Jul 2020

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

Duration of Treatment: The study consisted of a 28-day Screening Phase, a 7-day Pretreatment Phase (Study Days 1 to 7), and a Treatment Phase consisting of a PK assessment period (Study Days 8 to 26) and follow-up period (from Study Day 27 to the end of Cycle 6). The maximal duration of ibrutinib treatment in this study was 6 months from the first ibrutinib dose after which the subjects could continue treatment under the extension study protocol PCI-32765CAN3001.

Criteria for Evaluation:

Pharmacokinetic Evaluations

Based on the individual plasma concentration-time data, using the actual sampling times, the following PK parameters were to be derived:

Ibrutinib and metabolite PCI-45227:

Study Day 8, Study Day 22, and Study Day 24: concentration by timepoint

EE, LN, midazolam and its metabolite 1-OH-midazolam, bupropion and its metabolite 4-OH-bupropion:

Study Day 1: EE/LN

Study Day 3: midazolam, 1-OH-midazolam, bupropion, 4-OH-bupropion

Study Day 8: midazolam, 1-OH-midazolam

Study Day 22: EE/LN

Study Day 24: midazolam, 1-OH-midazolam, bupropion, 4-OH-bupropion:

- C_{max}, t_{max}, $AUC_{0\text{-}12h}$ (midazolam, 1-OH-midazolam Days 3 and 8 only), $AUC_{0\text{-}24h}$ (midazolam, 1-OH-midazolam Days 3 and 24 only), $AUC_{0\text{-}72h}$ (EE/LN only), $AUC_{0\text{-}58h}$ (bupropion and 4-OH-bupropion only), AUC_{last}, AUC_{∞}, λ_z, $t_{1/2term}$
- CL/F (only for parent compounds EE, LN, midazolam, and bupropion)
- Ratio $C_{max,}$ metabolite/parent, Ratio $AUC_{0\text{-}t}$*, metabolite/parent, Ratio AUC_{last}, metabolite/parent, Ratio $AUC_{\infty,}$ metabolite/parent (metabolite/parent=1-OH-midazolam/midazolam, 4-OH-bupropion/bupropion)
- Ratio $C_{max,}$ test/reference, Ratio $AUC_{0\text{-}t}$*, test/reference, Ratio AUC_{last}, test/reference, Ratio $AUC_{\infty,}$ test/reference (test/reference=probe drug in presence of ibrutinib/probe drug alone)
- Ratio $C_{max,}$ test/reference, Ratio $AUC_{0\text{-}t}$*, test/reference, Ratio AUC_{last}, test/reference, Ratio $AUC_{\infty,}$ test/reference (test/reference= OC in presence of ibrutinib/OC alone)

  *t=12, 24, 58, or 72 hours as noted in the first bullet above.

Safety Evaluations

The safety of ibrutinib was assessed by abnormal physical examinations, ECOG performance status, laboratory tests, vital signs, electrocardiograms (ECGs), adverse events (AEs) monitoring, and concomitant medication usage. The severity of AEs was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.03). Major hemorrhage was identified as an AE of special interest and required enhanced reporting and data collection. All AEs were recorded in source documents. After Cycle 2 Day 1, AE data collection on the electronic case report form (eCRF) was limited to serious adverse events (SAEs), Grade ≥3 AEs, AEs leading to ibrutinib dose interruption/withdrawal/dose reduction and concomitant medication associated with these events. Any

clinically significant abnormalities persisting at the EoT or early withdrawal were followed by the investigator until resolution or until a clinically stable endpoint was reached or until the end of the study.

Efficacy Evaluations

Antitumor activity was assessed by means of computed tomography (CT) imaging and positron emission tomography (PET) scans. Imaging assessments throughout the study were performed using the same imaging modality used to assess disease at baseline. Other assessments of 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 lymphoma were assessed for response according to Revised Response Criteria for Malignant Lymphoma (2014). Subjects with CLL/SLL were evaluated according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL 2008) with subsequent modification that treatment-related lymphocytosis was not considered as disease progression and clarification of IWCLL criteria for a partial response to therapy. Subjects with WM were evaluated in accordance with the modified consensus criteria adapted from the VIth International Workshop on WM (NCCN guidelines on WM, 2017).

Statistical Methods:

Sample Size: Approximately 18 subjects were planned to be enrolled to account for a potential greater intrasubject variability for this patient study. The sample size calculation was based on statistical estimation enabling the study to provide an estimate with reasonable precision on the magnitude of the interaction. If the number of subjects evaluable for PK in the Treatment Phase up to Study Day 26 (Cycle 1 Day 19) dropped below 12, additional subjects could be enrolled.

In previous DDI studies conducted by the sponsor in healthy subjects, the intrasubject coefficient of variation (CV) for the OC, probe drugs, and their metabolites investigated in the study ranged from 12.66% to 25.08% for C_{max} and 11% to 15.97% for AUC.

Assuming an intrasubject CV of 26% among the OC and probe drugs for AUCs and C_{max}, a sample size of 12 subjects would be sufficient for the point estimate of the geometric mean ratio (GMR) of AUC and C_{max} of the OC and probe drugs with and without ibrutinib, to fall within 83% and 120% of the true value with 90% confidence.

Pharmacokinetic Analyses

Descriptive statistics were provided for the plasma concentrations of ibrutinib and its metabolite PCI-45227, the OC and probe drugs and their metabolites, and for the derived PK parameters, as applicable. The primary PK parameters of interest for statistical analysis were C_{max}, AUC_{last}, $AUC_{0\text{-}t}$, and AUC_{∞} of the parent compounds EE, LN, the CYP cocktail, midazolam, and bupropion. For each analyte, all subjects who had sufficient and interpretable PK assessments to calculate the non-compartmental PK parameters were included in the statistical analysis. The PK statistical analysis was performed using Statistical Analysis Software (SAS), Version 9.3.

Statistical analysis was performed for the PK parameters of each of the following analytes of the OC and probe drugs:

- EE and LN
- The probe drugs and metabolites: midazolam and its metabolite 1-OH-midazolam and bupropion and its metabolite 4-OH-bupropion

Linear mixed effects models were applied to log-transformed PK parameter data with treatment as fixed-effect and subject as random-effect. The least square means and intrasubject CV were derived from the model. The GMR and the 90% confidence interval (CI) of the PK parameters of each probe drug (and metabolite for midazolam and bupropion) with and without co-administration of ibrutinib were then constructed through back-transformed results based on the model.

The PK parameters of the metabolites of the probe drugs and the metabolite to parent ratios (MPRs) for C_{max}, AUC_{0-t}, AUC_{last}, and AUC_{∞} were analyzed in a similar way as above.

Safety Analyses

All subjects who received at least 1 dose of study drug (ibrutinib, OC, or probe drugs) were analyzed for safety. Treatment-emergent AEs (TEAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0). The safety parameters to be analyzed included the incidence, intensity, type of AEs, abnormal physical examination findings, ECOG, ECGs, vital signs measurements, clinical laboratory test, and concomitant medication results. Exposure to study drugs and reasons for discontinuation of study treatment were tabulated.

Efficacy Analyses

Disease response evaluation data were analyzed descriptively according to B-cell histology. These data were used to determine if subjects were receiving clinical benefit from ibrutinib monotherapy and qualified to enroll in the long-term extension study (PCI-32765CAN3001) after participation in this study.

RESULTS:

STUDY POPULATION:

Overall, 22 subjects were enrolled (including 13 [59.1 %] subjects with CLL, 4 [18.2%] subjects with MZL, 3 [13.6%] subjects with MCL and 2 [9.1%] subjects with WM) and treated with study drug (ibrutinib, OC [EE and LN] or probe drugs [bupropion and midazolam]). Of 22 subjects dosed, 19 (86.4%) subjects completed the PK assessment period up to Study Day 26 (Cycle 1 Day 19) and 3 (13.6%) subjects did not complete the PK assessment period up to Study Day 26 (Cycle 1 Day 19) due to the following reasons: one subject prematurely discontinued the study due to progressive disease and died before completing the PK assessment period; one subject did not receive a bupropion dose on Cycle 1 Day 17 due to a late report of medical history condition of seizure (due to meningioma) but subject completed the 6-month treatment period with ibrutinib; and one subject had ibrutinib dose interruptions due to Grade 3 SAE of pneumonia and did not receive probe drugs on Cycle 1, Day 17. The subject did not complete the study due to progressive disease as assessed on Cycle 4 Day 1.

Of the 22 enrolled subjects, 17 subjects completed the study and transitioned to the long-term extension study, PCI-32765CAN3001. Five (22.7%) subjects discontinued study drug administration and did not complete the study. Three (13.6%) subjects were discontinued from study treatment due to progressive disease of which 2 (9.1%) subjects ultimately died (1 subject died before completing PK assessment period, 1 subject died after completion of Cycle 2 ibrutinib therapy) and 1 (4.5%) subject had progressive disease as assessed on Cycle 4 Day 1. Two (9.1%) subjects discontinued study treatment due to SAE (1 subject with SAE of autoimmune hemolytic anemia eventually died before completion of 3 cycles of ibrutinib therapy and after start of subsequent anticancer therapy of rituximab in combination with cyclophosphamide and 1 subject with SAE of intracranial hemorrhage).

The median age of subjects was 64 years (range 44 to 86 years of age, inclusive). The median body mass index (BMI) was 26.6 kg/m^2 (range 19 to 34 kg/m^2). Thirteen (59.1%) subjects had a reported baseline ECOG performance score of 0 and 9 (40.9%) subjects had a reported baseline ECOG performance score of 1.

PHARMACOKINETIC RESULTS:

Ethinylestradiol

Pharmacokinetic Parameter	Geometric Mean: EE/LN 30/150 µg alone Day 1 (reference)	Geometric Mean: EE/LN 30/150 µg + ibrutinib 560 mg qd Day 22 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	21[a]	21[b]			
C_{max} (pg/mL)	77.2	102	132.63	119.73 - 146.92	19.0
AUC_{last} (pg.h/mL)	413	571	138.18	120.66 - 158.25	24.1
AUC_{∞} (pg.h/mL)	488	647	132.54	121.75 - 144.28	13.5

[a] n=18 for AUC_{∞}

[b] n=19 for AUC_{last} and n=18 for AUC_{∞}

Based on the statistical evaluation, EE C_{max}, AUC_{last}, and AUC_{∞} were 1.33-fold, 1.38-fold, and 1.33-fold higher, respectively, in the presence of ibrutinib as compared to the OC drugs dosed alone. Mean $t_{1/2term}$ was slightly higher on Day 22 compared to Day 1, with values of 8.9 hours (OC drugs alone) and 11.0 hours (in the presence of ibrutinib).

The sensitivity analysis, where the Day 22 data for Subject [redacted] was excluded (subject showed low ibrutinib levels and experienced diverticulitis), showed very similar GMRs. Therefore, exclusion or inclusion did not impact the overall results. All tables and graphs in the report body include Subject [redacted] data.

Levonorgestrel

Pharmacokinetic Parameter	Geometric Mean: EE/LN 30/150 µg alone Day 1 (reference)	Geometric Mean: EE/LN 30/150 µg + ibrutinib 560 mg qd Day 22 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	21[a]	21[b]			
C_{max} (pg/mL)	3717	4087	109.94	99.12 - 121.95	19.4
AUC_{0-72h} (pg.h/mL)	36326	35867	98.74	87.88 - 110.93	21.7
AUC_{last} (pg.h/mL)	36105	35946	99.56	87.73 - 112.98	23.0
AUC_{∞} (pg.h/mL)	33820	46833	138.48	99.90 - 191.95	34.5

[a] n=6 for AUC_{∞}

[b] n=20 for AUC_{last} and n=5 for AUC_{∞}

Based on the statistical evaluation, for all parameters except for AUC_{∞}, LN in the presence of ibrutinib was found to be similar to LN alone. The test versus reference GMRs for C_{max}, AUC_{0-72h}, and AUC_{last} were 109.94%, 98.74%, and 99.56%, respectively, with 90% CIs within the 80%-125% range.

The sensitivity analysis, where the Day 22 data for Subject [redacted] was excluded (subject showed low ibrutinib levels and experienced diverticulitis), showed very similar GMRs. Therefore, exclusion or inclusion did not impact the overall results. All tables and graphs in the report body include Subject [redacted] data.

Mean $t_{1/2term}$ was similar, with values of 41.1 hours (OC drugs alone) and 43.2 hours (in the presence of ibrutinib).

Midazolam

Pharmacokinetic Parameter	Geometric Mean: Midazolam 2 mg alone Day 3 (reference)	Midazolam 2 mg + Ibrutinib 560 mg single-dose, Day 8 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	22	21[a]			
C_{max} (ng/mL)	22.2	21.7	97.76	88.09 - 108.50	19.8
AUC_{0-12h} (ng.h/mL)	42.2	36.9	87.59	80.23 - 95.62	16.6
AUC_{∞} (ng.h/mL)[a]	48.3	38.7	80.05	71.85 - 89.18	18.3

Pharmacokinetic Parameter	Geometric Mean: Midazolam 2 mg alone Day 3 (reference)	Midazolam 2 mg + Ibrutinib 560 mg qd, Day 24 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	22	20			
C_{max} (ng/mL)	22.2	23.3	105.10	96.31 - 114.69	16.1
AUC_{0-24h} (ng.h/mL)	46.7	53.6	114.91	104.55 - 126.30	17.5
AUC_{last} (ng.h/mL)	46.2	52.7	113.91	103.61 - 125.22	17.5
AUC_{∞} (ng.h/mL)	48.3	55.3	114.45	104.07 - 125.87	17.6

[a] n=17 for AUC_{∞}.

Overall, midazolam exposure was not substantially changed in the presence of ibrutinib. After the first dose of ibrutinib, based on the GMRs, AUC_{0-12h}, and AUC_{∞} were 12% (90% CI within the 80%-125% range) and 20% lower (lower boundary of 90% CI=71.85%), respectively, as compared to midazolam alone. In the presence of steady-state ibrutinib, based on the GMRs, midazolam AUC_{0-24h}, AUC_{last}, and AUC_{∞} were 1.15-fold, 1.14-fold, and 1.14-fold higher, respectively, as compared to midazolam alone. The upper boundaries of the 90% CIs were just above 125%. C_{max} in the presence of ibrutinib (both after first dose and at steady-state) was similar compared to midazolam given alone.

Mean $t_{1/2term}$ was similar on all 3 occasions, with values of 5.5 hours (Day 3), 4.6 hours (Day 8), and 5.4 hours (Day 24).

1-OH-midazolam

Pharmacokinetic Parameter	Geometric Mean: Midazolam 2 mg alone Day 3 (reference)	Midazolam 2 mg + Ibrutinib 560 mg single-dose, Day 8 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	22[a]	21[b]			
C_{max} (ng/mL)	11.6	12.5	108.02	95.55 - 122.13	23.5
AUC_{0-12h} (ng.h/mL)	21.3	22.0	103.36	94.33 - 113.25	17.3
AUC_{∞} (ng.h/mL)	24.2	26.1	107.86	96.14 - 121.01	17.0
MPR $C_{max,}$ (%)	49.8	55.1	110.56	100.79 - 121.29	17.6
MPR AUC_{0-12h} (%)	48.1	56.6	117.68	106.54 - 130.00	18.9
MPR AUC_{∞} (%)	45.9	62.0	135.14	117.44 - 155.50	19.2

Pharmacokinetic Parameter	Geometric Mean: Midazolam 2 mg alone Day 3 (reference)	Midazolam 2 mg + Ibrutinib 560 mg qd, Day 24 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	22[a]	20[c]			
C_{max} (ng/mL)	11.6	10.4	89.89	78.12 - 103.42	26.3
AUC_{0-24h} (ng.h/mL)	23.1	22.0	95.26	84.77 - 107.05	21.7
AUC_{last} (ng.h/mL)	22.6	20.8	92.09	81.32 - 104.28	23.2
AUC_{∞} (ng.h/mL)	24.2	21.8	90.03	76.01 - 106.65	26.0
MPR $C_{max,}$ (%)	49.8	43.1	86.54	77.14 - 97.09	21.4
MPR AUC_{0-24h} (%)	47.1	39.1	83.11	74.02 - 93.32	21.5
MPR AUC_{last} (%)	46.6	37.7	81.03	71.00 - 92.48	24.7
MPR AUC_{∞} (%)	46.8	38.1	81.47	68.44 - 96.97	27.1

[a] n=19 for AUC_{∞} and MPR AUC_{∞}

[b] n=15 for AUC_{∞} and n=13 for MPR AUC_{∞}

c n=15 for AUC_{∞} and MPR AUC_{∞}

As for midazolam administration, 1-OH-midazolam exposure was not substantially changed in the presence of ibrutinib. On Day 8, after the first dose of midazolam, based on the GMRs, C_{max}, $AUC_{0-12h,}$ and AUC_{∞} were 1.08-fold, 1.03-fold, and 1.08-fold higher, respectively, with corresponding 90% CIs within the 80%-125% range, compared to midazolam alone. On Day 24, in the presence of steady-state ibrutinib, based on the GMRs, C_{max}, AUC_{0-24h}, AUC_{last}, and AUC_{∞} were 10%, 5%, 8%, and 10% lower, respectively, with 90% CIs within the 80%-125% range for AUC_{0-24h} and AUC_{last} and lower boundaries just below 80% for C_{max} (78.12%) and AUC_{∞} (76.01%).

Mean $t_{1/2term}$ was similar on Day 3 and Day 24, with values of 6.1 hours and 5.9 hours, respectively. On Day 8 a slightly lower mean value was obtained, 4.1 hours.

Midazolam and 1-OH-midazolam exposure showed modest changes in the opposite direction. As a result, the MPRs for C_{max}, AUC_{0-12h}, and AUC_{∞} were 1.11-fold, 1.18-fold, and 1.35-fold higher, respectively, on Day 8 as compared to Day 3. The MPRs for C_{max}, AUC_{0-24h}, $AUC_{last,}$ and AUC_{∞} were 13%, 17%, 19%, and 19% lower, respectively, on Day 24 as compared to Day 3.

Bupropion

Pharmacokinetic Parameter	Geometric Mean: Bupropion 75 mg alone Day 3 (reference)	Geometric Mean: Bupropion 75 mg + Ibrutinib 560 mg qd, Day 24 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	22[a]	19[a]			
C_{max} (ng/mL)	152	136	89.44	74.25 - 107.74	34.8
AUC_{0-58h} (ng.h/mL)	572	528	92.35	82.78 - 103.03	19.8
AUC_{last} (ng.h/mL)	571	527	92.35	82.78 - 103.03	19.8
AUC_{∞} (ng.h/mL)	626	536	85.57	77.65 - 94.31	14.9

[a] n=17 for AUC_{∞}

Based on the statistical evaluation, no substantial changes in bupropion exposure were observed. Based on the GMRs, C_{max}, AUC_{0-58h}, AUC_{last}, and AUC_{∞} were 11%, 8%, 8%, and 14% lower, respectively, when comparing bupropion in the presence of ibrutinib to bupropion given alone. The corresponding 90% CIs were within the 80%-125% range for AUC_{0-58h} and AUC_{last} and lower boundaries just below 80% were observed for C_{max} (74.25%) and AUC_{∞} (77.65%).

Mean $t_{1/2term}$ values were similar on Day 3 and Day 24, with values of 13.9 hours and 14.0 hours, respectively.

4-OH-bupropion

Pharmacokinetic Parameter	Geometric Mean: Bupropion 75 mg alone Day 3 (reference)	Geometric Mean: Bupropion 75 mg + Ibrutinib 560 mg qd, Day 24 (test)	Geometric Mean Ratio, (%)	90% CI, (%)	Intrasubject CV, (%)
n	22[a]	19[b]			
C_{max} (ng/mL)	233	212	90.88	81.95 - 100.78	18.7
AUC_{0-58h} (ng.h/mL)	8571	7628	88.99	78.32 - 101.12	23.6
AUC_{last} (ng.h/mL)	8571	7616	88.86	78.20 - 100.98	23.6
AUC_{∞} (ng.h/mL)	9797	8666	88.46	65.49 - 119.47	22.6
MPR C_{max} (%)	144	145	100.58	84.82 - 119.28	31.3
MPR AUC_{0-58h} (%)	1404	1351	96.20	88.17 - 104.97	15.7
MPR AUC_{last} (%)	1408	1352	96.07	88.03 - 104.85	15.7
MPR AUC_{∞} (%)	2138	1771	82.87	64.64 - 106.25	24.2

[a] n=5 for AUC_{∞} and Ratio $AUC_{\infty, metabolite/parent}$.

[b] n=5 for AUC_{∞} and n=4 for Ratio $AUC_{\infty, metabolite/parent}$.

As for bupropion administration, no substantial changes in 4-OH bupropion exposure were observed. Based on the GMRs, C_{max}, AUC_{0-58h}, and AUC_{last} were 9%, 11%, and 11% lower, respectively, in the presence of ibrutinib, compared to bupropion given alone. The corresponding 90% CI for C_{max} was within the 80%-125% range and the lower boundary was just below 80% for AUC_{0-58h} (78.32%) and AUC_{last} (78.20%). As bupropion and 4-OH-bupropion exposures showed modest changes in the same direction, the MPRs were similar on Day 24 and Day 3.

Due to the longer half-life for 4-OH-bupropion, AUC_{∞} could only be determined accurately for 5 subjects based on the PK sampling up to 58 hours postdose, both on Day 3 and Day 24 ($\%AUC_{\infty, ex}$ >20% in many cases). Therefore, although the point estimates of the GMR ratios were fairly in line with the other

exposure parameters, the results for AUC_{∞} and MPR AUC_{∞} are shown for information purposes only and should be interpreted with caution. This is also reflected in the wide 90% CIs around the point estimates.

Mean $t_{1/2term}$ values were similar on Day 3 and Day 24, with values of 38.0 hours and 34.2 hours, respectively.

SAFETY RESULTS:

The population evaluable for safety included all subjects who received at least 1 dose of study drug. All 22 subjects were included in the safety analysis. Of the 22 subjects, 20 (90.9%) subjects experienced at least 1 TEAE, of which 15 (68.2%) subjects had TEAEs considered related to ibrutinib by the investigator. Treatment-emergent AEs leading to ibrutinib treatment discontinuation were experienced by 2 (9.1%) subjects.

The most commonly reported TEAEs (>5% of subjects) by preferred term (PT) were urinary tract infection, anemia, diarrhea (22.7% of subjects each), neutropenia and thrombocytopenia (18.2% of subjects each), bronchitis, tonsillitis, upper respiratory tract infection, pyrexia, arthralgia, and cough (9.1% of subjects each). Most subjects (68.2%) reported TEAEs of Grade 3 and 4 as the worst toxicity grade; nine (40.9%) subjects experienced Grade 3 TEAEs and 6 (27.3%) subjects experienced Grade 4 TEAEs. The most commonly reported Grade 3 or 4 TEAEs (>5% of subjects) were anemia (22.7%), neutropenia (18.2%), thrombocytopenia (13.6%), and urinary tract infection (9.1%).

The most commonly reported TEAEs considered related to ibrutinib by the investigator were diarrhea, neutropenia (18.2% of subjects each), and thrombocytopenia (9.1% of subjects).

Eight (36.4%) subjects had ibrutinib-related Grade 3 TEAEs (worst toxicity grade). The most commonly reported ibrutinib-related Grade 3 TEAE was neutropenia in 2 (9.1%) subjects.

Three (13.6%) subjects had ibrutinib-related Grade 4 TEAEs (neutropenia in 2 [9.1%] subjects and hyponatremia in 1 [4.5%] subject).

Five (22.7%) subjects experienced TEAEs that were considered related to the OC and probe drugs (midazolam and bupropion). All of the TEAEs reported were of Grade 2 toxicity except for 1 subject who experienced a Grade 3 TEAE of neutropenia which was considered to be related to the OC, probe drugs as well as to ibrutinib by the investigator. This subject also had Grade 4 TEAE of neutropenia which was considered related to ibrutinib only.

Serious adverse events (SAEs) were experienced by 10 of 22 (45.5%) subjects. None of the SAEs were considered related to the OC or probe drugs by the investigator. Except for 1 subject who reported a SAE of Grade 2, all SAEs reported were of Grade 3 or higher. Treatment-emergent SAEs which were reported in >1 subject included pneumonia, anemia, and urinary tract infection (2 subjects each).

Ibrutinib-related SAEs (all Grade ≥3) were reported for 5 of 22 (22.7%) subjects. Ibrutinib-related Grade 3 SAEs included anemia, pneumonia fungal, subdural hematoma (traumatic), urinary tract infection (all 4 events in 1 subject), rectal hemorrhage, hemorrhage intracranial, and pneumonia (1 subject each). An ibrutinib-related Grade 4 SAE of hyponatremia was reported in 1 subject.

Three subjects experienced SAEs leading to death (cardiac arrest, general physical health deterioration, and autoimmune hemolytic anemia). Of these 3 subjects, 2 subjects died in an overall context of disease progression and 1 subject died due to SAE of autoimmune hemolytic anemia. All 3 deaths were considered not related to study drugs by the investigator.

Major hemorrhage: Four subjects had bleeding events. The bleeding-related events were all of Grade 3 and included rectal hemorrhage, muscle hemorrhage, hemorrhage intracranial, and subdural hematoma. All were considered related to ibrutinib by the investigator except for muscle hemorrhage. All these bleeding events were reported as SAEs.

EFFICACY RESULTS:

Of the 22 subjects, 17 subjects reached EoT: 11 subjects had partial response, 4 subjects had stable disease, 1 subject had a complete response, and 1 subject was considered not evaluable for response. Of the 5 subjects who did not reach EoT, 1 subject had progressive disease as assessed on Cycle 4 Day 1, 1 subject had a complete response at Cycle 4 Day 1 (the subject was discontinued from the study due to Grade 3 SAE of intracranial hemorrhage during Cycle 5), and 3 subjects died during the study. Of the 3 deaths, 2 subjects died in the context of disease progression (1 subject died before completing the PK assessment period and 1 subject after completion of Cycle 2 of ibrutinib therapy) and 1 subject died due to SAE of autoimmune hemolytic anemia (before completion of 3 cycles of ibrutinib therapy and after start of subsequent anticancer therapy of rituximab in combination with cyclophosphamide). Of the 22 enrolled subjects, 17 subjects continued treatment with ibrutinib in the long-term extension study, PCI-32765CAN3001.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSIONS:

Repeated administration of ibrutinib for 14 days did not induce the metabolism of OC drugs EE/LN, CYP3A4 probe midazolam nor CYP2B6 probe bupropion, as evidenced by all GMRs remaining above the lower bound of the 80%-125% range. Single administration of ibrutinib did not inhibit intestinal CYP3A4, with midazolam GMRs between 80%-100%. None of the observed effect sizes were considered clinically relevant.

- Ethinylestradiol C_{max}, AUC_{last}, and AUC_{∞} were 1.33-fold, 1.38-fold, and 1.33-fold higher, respectively, in the presence of steady-state ibrutinib as compared to the OC drugs dosed alone.
- Levonorgestrel C_{max}, $AUC_{0\text{-}72h}$, and AUC_{last} were similar in the presence of steady-state ibrutinib (GMRs of 109.94%, 98.74%, and 99.56%, respectively, with 90% CIs within the 80%-125% range), compared to the OC drugs dosed alone. AUC_{∞} could only be determined accurately for 6 subjects (Day 1) and 5 subjects (Day 22) based on sampling up to 72 hours postdose ($\%AUC_{\infty,ex}$ > 20% in many cases).
- Midazolam exposure was not substantially changed in the presence of ibrutinib. After the first dose of ibrutinib, based on the GMRs, $AUC_{0\text{-}12h}$ and AUC_{∞} were 12% lower (90% CI within the 80%-125% range) and 20% lower (lower boundary of 90% CI=71.85%), respectively, as compared to midazolam alone. In the presence of steady-state ibrutinib, based on the GMRs, midazolam $AUC_{0\text{-}24h}$, AUC_{last}, and AUC_{∞} were 1.15-fold, 1.14-fold, and 1.14-fold higher, respectively, as compared to midazolam alone (upper boundary of 90% CI just above 125%). C_{max} in the presence of ibrutinib (both after first dose and at steady-state) was similar compared to midazolam given alone.
- 1-OH-midazolam exposure was not substantially changed either. After the first dose of ibrutinib, based on the GMRs, C_{max}, $AUC_{0\text{-}12h}$, and AUC_{∞} were 1.08-fold, 1.03-fold, and 1.08-fold higher, respectively, with corresponding 90% CIs within the 80%-125% range, compared to midazolam alone. In the presence of steady-state ibrutinib, based on the GMRs, C_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, and AUC_{∞} were 10%, 5%, 8%, and 10% lower, respectively, with 90% CIs within the 80%-125% range for $AUC_{0\text{-}24h}$ and AUC_{last} and lower boundaries just below 80% for C_{max} (78.12%) and AUC_{∞} (76.01%).
- Bupropion exposure was not substantially changed in the presence of ibrutinib. Based on the GMRs, C_{max}, $AUC_{0\text{-}58h}$, AUC_{last}, and AUC_{∞} were 11%, 8%, 8%, and 14% lower, respectively, when compared bupropion in the presence of steady-state ibrutinib to bupropion given alone. The corresponding 90% CIs were within the 80%-125% range for $AUC_{0\text{-}58h}$ and AUC_{last} and lower boundaries just below 80% were observed for C_{max} (74.25%) and AUC_{∞} (77.65%).

- 4-OH-bupropion exposure was not substantially changed either. Based on the GMRs, C_{max}, $AUC_{0\text{-}58h}$, and AUC_{last} were 9%, 11%, and 11% lower, respectively, in the presence of steady-state ibrutinib, compared to bupropion given alone. The corresponding 90% CI for C_{max} was within the 80%-125% range and the lower boundary was just below 80% for $AUC_{0\text{-}58h}$ (78.32%) and AUC_{last} (78.20%). AUC_{∞} could only be determined accurately for 5 subjects (both Day 3 and Day 24) based on sampling up to 58 hours postdose ($\%AUC_{\infty,ex}$ >20% in many cases).
- Major hemorrhage was identified as an AE of special interest and required enhanced reporting and data collection. There were 4 subjects that had serious bleeding events. All of these subjects had underlying risk factors for the development of the bleeds. No new or unanticipated safety concerns were identified. Findings from this study were consistent with the known benefit-risk profile of ibrutinib.

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