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ORIGINAL ARTICLE

Ibrutinib does not have clinically relevant interactions with oral contraceptives or substrates of CYP3A and CYP2B6

Jan de Jong[1] | Anna Mitselos[2] | Wojciech Jurczak[3] | Raul Cordoba[4,5,6] | Carlos Panizo[7,8] | Tomasz Wrobel[9] | Monika Dlugosz-Danecka[3] | James Jiao[10] | Juthamas Sukbuntherng[11] | Daniele Ouellet[12] | Peter Hellemans[2]

[1]Clinical Pharmacology, Janssen Research & Development LLC, San Diego, CA, USA

[2]Clinical Research Oncology, Janssen Research & Development LLC, Beerse, Belgium

[3]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland

[4]Lymphoma Unit, Department of Hematology, Fundacion Jimenez Diaz University Hospital, Madrid, Spain

[5]Health Research Institute IIS-FJD, Madrid, Spain

[6]START Madrid, Phase 1 Clinical Trials Unit, Madrid, Spain

[7]Department of Hematology, Clínica Universidad de Navarra, Pamplona, Spain

[8]Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain

[9]Department and Clinic of Hematology, Blood Neoplasms, and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland

[10]Clinical Pharmacology, Janssen Research & Development LLC, Raritan, NJ, USA

[11]Pharmacyclics LLC, an AbbVie company, Sunnyvale, CA, USA

[12]Clinical Pharmacology, Janssen Research & Development LLC, Spring House, PA, USA

Abstract

Ibrutinib may inhibit intestinal CYP3A4 and induce CYP2B6 and/or CYP3A. Secondary to potential induction, ibrutinib may reduce the exposure and effectiveness of oral contraceptives (OCs). This phase I study evaluated the effect of ibrutinib on the pharmacokinetics of the CYP2B6 substrate bupropion, CYP3A substrate midazolam, and OCs ethinylestradiol (EE) and levonorgestrel (LN). Female patients (N = 22) with B-cell malignancies received single doses of EE/LN (30/150 μg) and bupropion/midazolam (75/2 mg) during a pretreatment phase on days 1 and 3, respectively (before starting ibrutinib on day 8), and again after ibrutinib 560 mg/day for ≥ 2 weeks. Intestinal CYP3A inhibition was assessed on day 8 (single-dose ibrutinib plus single-dose midazolam). Systemic induction was assessed at steady-state on days 22 (EE/LN plus ibrutinib) and 24 (bupropion/midazolam plus ibrutinib). The geometric mean ratios (GMRs; test/reference) for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) were derived using linear mixed-effects models (90% confidence interval within 80%-125% indicated no interaction). On day 8, the GMR for midazolam exposure with ibrutinib coadministration was ≤ 20% lower than the reference, indicating lack of intestinal CYP3A4 inhibition. At ibrutinib steady-state, the C_{max} and AUC of EE were 33% higher than the reference, which was not considered clinically relevant. No substantial changes were noted for LN, midazolam, or bupropion. No unexpected safety findings were observed. A single dose of ibrutinib did not inhibit intestinal CYP3A4, and repeated administration did not induce CYP3A4/2B6, as assessed using EE, LN, midazolam, and bupropion.

Abbreviations: AE, adverse event; AIHA, autoimmune hemolytic anemia; AUC, area under the plasma concentration-time curve; BTK, Bruton's tyrosine kinase; CI, confidence interval; CLL, chronic lymphocytic leukemia; C_{max}, maximum plasma concentration; ECOG, Eastern Cooperative Oncology Group; EE, ethinylestradiol; GMR, geometric mean ratio; LN, levonorgestrel; MCL, mantle cell lymphoma; MPR, metabolite-to-parent ratio; MZL, marginal zone lymphoma; OCs, oral contraceptives; PD, progressive disease; PK, pharmacokinetics; QD, once daily; R/R, relapsed/refractory; SAE, serious adverse event; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event; T_{max}, time to maximum plasma concentration; WM, Waldenström's macroglobulinemia.

Part of the study results were presented as a poster at the 2019 American College of Clinical Pharmacology Annual Meeting in Chicago, IL, USA.

Principal Investigator: The authors confirm that the Principal Investigator for this paper is Professor Wojciech Jurczak, MD, and that he had direct clinical responsibility for patients.

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Correspondence
Peter Hellemans, Clinical Research Oncology, Janssen Research & Development LLC, Beerse, Belgium.
Email: phellema@its.jnj.com

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1 | INTRODUCTION

Ibrutinib, a first-in-class, oral covalent inhibitor of Bruton's tyrosine kinase (BTK), has been approved in the United Sates for the treatment of adult patients with various B-cell malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia (WM), previously treated mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL), and chronic graft-vs-host disease after failure of one or more lines of systemic therapy.[1] In Europe, ibrutinib is approved for treatment of CLL, MCL, and WM.[2]

Following oral administration, ibrutinib is absorbed completely from the gastrointestinal tract and metabolized in the liver and intestines.[3] Metabolism occurs mostly by cytochrome P450 (CYP)3A enzymes. The resultant metabolite is PCI-45227, a dihydrodiol metabolite that reversibly inhibits BTK with approximately 15-times lower activity compared with that of ibrutinib.[1,4] In healthy adults, the absolute bioavailability of ibrutinib (560 mg) is low and ranges from 3.9% under fasting conditions to 8.4% under fed conditions.[5] Extensive first-pass metabolism, rather than poor absorption, is considered to be the main reason for low bioavailability of ibrutinib.[3,5] In agreement with a major role of CYP3A in ibrutinib metabolism, inhibitors or inducers of CYP3A enzymes were shown to alter the exposure of ibrutinib both in healthy adults and in patients with B-cell malignancies.[6,7] A study using physiologically based pharmacokinetic modeling predicted the interaction potential of mild-to-strong CYP3A4 inhibitors and strong-to-moderate CYP3A4 inducers with ibrutinib, based on which the dose recommendations for ibrutinib in combination with the CYP3A4 perpetrators were formulated and approved for labeling.[8]

In vitro data suggest that CYP3A and CYP2B6 may be induced at concentrations lower than 50 times clinically relevant levels (unpublished data on file, Janssen R&D, LLC). Thus, a clinically relevant induction of CYP3A and CYP2B6 (or other enzymes and transporters regulated via the constitutive androstane receptor) during treatment with ibrutinib could not be excluded. With respect to the inhibitory potential of ibrutinib, the CYP3A inhibition constant (Ki) value obtained from the in vitro studies (unpublished data on file, Janssen R&D, LLC) was over 50 times higher than clinically relevant systemic concentrations, leading to the conclusion that a clinically relevant systemic CYP3A inhibition upon ibrutinib dosing could be excluded. However, the in vitro CYP3A Ki value was not above the theoretical maximum concentration reached in the gut with daily oral dosing of ibrutinib, indicating that a clinically relevant CYP3A inhibition at the gut level could not be excluded.

Statement 1: What is already known about this subject

- Ibrutinib, a first-in-class, oral covalent inhibitor of Bruton's tyrosine kinase approved for the treatment of B-cell malignancies, is a sensitive CYP3A substrate.
- In vitro data suggest that systemic concentrations of ibrutinib might induce CYP2B6 and CYP3A, while intestinal concentrations might inhibit CYP3A locally.
- Ibrutinib is a potential teratogen.

Statement 2: What this study adds

- Repeated administration of ibrutinib 560 mg did not induce the metabolism of CYP2B6 substrate bupropion, CYP3A substrate midazolam, or oral contraceptives ethinylestradiol and levonorgestrel.
- A single administration of ibrutinib did not inhibit intestinal CYP3A.
- No unexpected safety issues were seen with ibrutinib coadministered with study drugs.

These interactions had not been studied in vivo and their impact on medications that are CYP3A and CYP2B substrates remained uncertain, which originally led to precautionary language in the European Summary of Product Characteristics for ibrutinib. Simulations using the above-referenced ibrutinib physiologically based pharmacokinetic model,[8] this time with ibrutinib as a perpetrator, suggested that ibrutinib concentrations along the intestinal tract, although capable of increasing systemic concentrations of the CYP3A probe midazolam to some extent, did not reach the level of a weak CYP3A inhibitor, that is, the predicted midazolam area under the plasma concentration-time curve (AUC) increase in the presence of a single dose of ibrutinib was ≤ 25% (unpublished data on file, L. de Zwart, Janssen R&D internal report, 2014).

Midazolam and bupropion are sensitive probes for CYP3A and CYP2B6, respectively,[9,10] and have been used in this study to assess the effect of ibrutinib on the activity of CYP3A and CYP2B6 enzymes. Midazolam is a short-acting benzodiazepine central nervous system depressant, metabolized primarily to 1-OH-midazolam by CYP3A4. Bupropion is an aminoketone antidepressant metabolized by CYP2B6 to 4-OH-bupropion. Both are guideline-recommended probes for drug-drug interaction assessments.[9,10]

To address a post-authorization measure from the Committee for Medicinal Products for Human Use requesting a drug-drug

interaction study with oral contraceptives (OCs), we tested OCs specifically to identify if any induction effect perpetrated by ibrutinib (CYP3A or otherwise) might result in clinically relevant lowering of OC exposure when coadministered with ibrutinib.[11-13] Because ibrutinib is a potential teratogen,[1,4,14] effective contraception use is required in women of childbearing potential who are treated with ibrutinib. It is not known whether ibrutinib may affect the exposure, and therefore, effectiveness of hormonal OCs.

This study assessed the effect of ibrutinib (as a potential perpetrator) on the pharmacokinetics (PK) of OCs (levonorgestrel [LN] and ethinylestradiol [EE]),[15] the CYP2B6 substrate bupropion, and the CYP3A substrate midazolam in female patients with B-cell malignancies.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients eligible for enrollment were females ≥ 18 years of age with histologically or cytologically confirmed B-cell malignancy including CLL/SLL, WM, relapsed or refractory MCL following ≥ 1 prior line of systemic therapy, or MZL after failure of ≥ 1 anti-CD20-based therapy. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.

Key exclusion criteria included history of stroke or intracranial hemorrhage within 6 months before the first dose of ibrutinib and any unresolved toxicities from prior anticancer therapy. Additionally, the study excluded patients requiring continuous treatment with strong and moderate CYP3A and CYP2B6 inhibitors or inducers, or with drugs that are not allowed to be combined with study drugs, patients who had prior exposure to ibrutinib or other BTK inhibitors, and those who had an uncontrolled active systemic infection or any other medical condition that could compromise patient safety or impact the absorption/metabolism of ibrutinib.

2.2 | Study design

This was a phase I, open-label, multicenter, single-sequence study (NCT03301207) conducted from 31 October 2017 to 4 December 2018 in Poland and Spain (two sites each). The objectives of the study were to assess: (a) the effects of repeated dosing of ibrutinib on the single-dose PK of hormonal OCs (EE and LN), the CYP2B6 substrate bupropion, and the CYP3A substrate midazolam; (b) the effect of single-dose ibrutinib on the single-dose PK of the CYP3A4 probe midazolam; (c) the steady-state exposure of ibrutinib in the presence of probe drugs; (d) the safety of ibrutinib alone and in the presence of OCs and probe drugs.

The study consisted of a 28-day screening phase, a 7-day pretreatment phase (days 1-7; assessments of OCs and probe drug systemic levels before ibrutinib administration), a treatment phase including a PK assessment period (days 8-26; assessment of OCs and probe drug systemic levels after repeated ibrutinib 560 mg/day administration for ≥ 2 weeks), and a follow-up period (day 27 to the end of six 28-day cycles; continued treatment with single-agent ibrutinib; Table 1). The drug-drug interactions were investigated during the first treatment cycle, and therefore, drugs and substances known to affect the PK of ibrutinib, OCs, and CYP probe drugs were prohibited from 7 days before ibrutinib administration through day 26 of cycle 1 when the PK sample collection was completed. To minimize the chance of confounding the OC drug exposure, the midazolam/bupropion cocktail was dosed 48 hours after administration of OC. Antitumor activity and clinical safety of ibrutinib was monitored throughout the study. After completion of the 6-month treatment period, patients who derived clinical benefit from ibrutinib could continue treatment with ibrutinib in a rollover long-term extension study (NCT01804686).

The study protocol was reviewed and approved by an independent ethics committee at each study site. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients provided their written informed consent to participate in the study.

2.3 | Study treatments

During the 7-day pretreatment phase (days 1-7 before starting ibrutinib treatment), systemic baseline levels of OCs and probe drugs were assessed by administering a single dose of EE (30 μg) and LN (150 μg) on day 1, and a single dose of bupropion (75 mg) and a single dose of midazolam (2 mg) on day 3 (Table 1), followed by a 4-day washout phase. During the treatment phase (days 8-26), ibrutinib was administered at 560 mg once daily (QD) regardless of the recommended ibrutinib dose based on indication. During intensive PK sampling (days 1, 3, 8, 22, and 24), all study drugs were administered orally at the study site in the morning, approximately 30 minutes before starting a standardized low-fat breakfast, which had to be consumed within 20 minutes. On all other days, ibrutinib was self-administered at home approximately 30 minutes before breakfast in the morning. From day 27 onward, ibrutinib was taken with or without food.

To assess intestinal CYP3A inhibition in the presence of ibrutinib, a single dose of midazolam (2 mg) was given together with ibrutinib (560 mg) on day 8. Assessment of systemic levels of OCs and probe drugs was conducted during repeated daily dosing with 560 mg of ibrutinib, by administering single doses of EE/LN and bupropion/midazolam on days 22 and 24, respectively (Table 1). From day 27 onward, patients with MCL or MZL received 560 mg of ibrutinib QD and patients with CLL/SLL or WM were given 420 mg of ibrutinib QD, in accordance with the dose level approved for each type of malignancy per the ibrutinib prescribing information.[1,2]

2.4 | Study assessments

Plasma samples for PK measurements were collected on days 1, 3, 8, 22, and 24 and analyzed for ibrutinib and PCI-45227 (days 8, 22, 24),

TABLE 1 Treatment schedule and PK assessments

Study phase	Day	Ibrutinib treatment	Additional treatment	PK assessments
Pretreatment: days 1-7	1	--	EE 30 μg and LN 150 μg	Aim: baseline systemic levels of OC and probe drugs PK sampling: - EE/LN: days 1-4 over a 72-hour period - Midazolam/1-OH-midazolam: days 3-4 over a 24-hour period - Bupropion/4-OH-bupropion: days 3-5 over a 58-hour period
	3	--	Bupropion 75 mg and midazolam 2 mg	
Treatment: days 8-26	8	560 mg QD	Midazolam 2 mg	Aim: intestinal CYP3A inhibition by midazolam in the presence of a single dose of ibrutinib PK sampling: day 8 over a 12-hour period
	9-21	560 mg QD	--	--
	22	560 mg QD	EE 30 μg and LN 150 μg	Aim: systemic levels of OCs at ibrutinib steady-state PK sampling: days 22-25 over a 72-hour period
	23	560 mg QD	--	--
	24	560 mg QD	Bupropion 75 mg and midazolam 2 mg	Aim: systemic levels of probe drugs at ibrutinib steady-state PK sampling: - Midazolam/1-OH-midazolam: days 24-25 over a 24-hour period - Bupropion/4-OH-bupropion: days 24-26 over a 58-hour period
	25, 26	560 mg QD	--	--
Follow-up: day 27 to the end of six cycles	≥ 27	560 mg QD or 420 mg QD[a]	--	--

Abbreviations: CLL, chronic lymphocytic leukemia; EE, ethinylestradiol; LN, levonorgestrel; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

[a]Patients with mantle cell lymphoma or marginal zone lymphoma received 560 mg of ibrutinib QD and patients with CLL/SLL or WM received 420 mg of ibrutinib QD.

EE/LN (days 1-4 and 22-25, over a 72-hour period), bupropion and its metabolite 4-OH-bupropion (days 3-5 and 24-26, over a 58-hour period), and midazolam and its metabolite 1-OH-midazolam (days 3-4 and 24-25, over a 24-hour period, and on day 8 over a 12-hour period).

Plasma samples were analyzed using validated, specific, and sensitive liquid chromatography coupled with tandem mass spectrometry methods (PPD® Laboratories, Middleton, WI, USA and Frontage Laboratories Inc, Exton, PA, USA). The quantification range was 0.500-250 ng/mL for ibrutinib and its metabolite, 0.100-100 ng/mL for midazolam and 1-OH-midazolam, 0.500-250 ng/mL for bupropion, 1.00-500 ng/mL for 4-OH-bupropion, 2.00-500 pg/mL for EE and 0.050-25 ng/mL for LN.

The following PK parameters were assessed: maximum observed analyte concentration (C_{max}); time to reach the C_{max} (T_{max}); AUC from 0 to specific timepoint ($AUC_{0\text{-}t;}$ t = 0-12 h, 0-24 h, 0-58 h, and 0-72 h, depending on analyte), from 0 to last measurable concentration (AUC_{last}) and from 0 to infinite time (AUC_{∞}); and apparent terminal elimination half-life ($t_{1/2term}$).

Safety evaluations included treatment-emergent adverse events (TEAEs), clinical laboratory tests, physical examination, vital signs, electrocardiograms, concomitant medication usage, and ECOG performance status. TEAEs reported throughout the study were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0, and graded per NCI-CTCAE, Version 4.03.

Ibrutinib antitumor activity was assessed by the investigators in accordance with Revised Response Criteria for Malignant Lymphoma (for MCL and MZL),[16] International Workshop on Chronic Lymphocytic Leukemia guidelines (iwCLL; for CLL/SLL),[17] and modified consensus criteria adapted from the sixth International Workshop on Waldenström's Macroglobulinemia (for WM).[18]

2.5 | Statistical methods

A sample size of approximately 18 patients was planned, enabling the study to provide a reliable estimate of the magnitude and variability of the interaction. Patients who were not considered PK-evaluable due to missing PK assessments could be proactively replaced during the course of the study. In this study, there were three patients who were not considered PK-evaluable and these patients were proactively replaced, and one extra patient was enrolled, given the flexibility in sample size.

The primary PK parameters for statistical analysis were C_{max} and AUC; 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 variation were derived from the model. The geometric mean ratio (GMR) and the 90% confidence interval (CI) of the PK parameters of each probe drug (and metabolite for midazolam and bupropion) with and without

ibrutinib coadministration were constructed through back-transformation based on the model.

PK parameters were determined for each analyte in the absence (reference) and presence (test) of ibrutinib by noncompartmental analysis (Venn Life Sciences, Breda, Netherlands) using the validated computer program Phoenix™ WinNonlin® (version 6.2.1; Certara USA, Inc, Princeton, NJ, USA).

For each analyte, all patients who had sufficient and interpretable PK assessments to calculate the noncompartmental PK parameters were included in the statistical analysis (PK population). The safety population included all patients who received ≥ 1 dose of study drugs (ibrutinib, OCs, and probe drugs).

3 | RESULTS

3.1 | Disposition and baseline demographic characteristics

Among 22 patients enrolled, median (range) age was 64 (44-86) years; all patients were white, with median body mass index (range) of 26.6 (19-34) kg/m^2. The majority of patients were diagnosed with CLL (59.1%) and had an ECOG performance status of 0 (59.1%; Table 2). Seventeen (77.3%) patients had received prior systemic cancer therapies that were stopped before the start of this study per protocol.

TABLE 2 Patient demographic and baseline characteristics

	N = 22
Age, median (range), years	64 (44-86)
White, n (%)	22 (100)
Ethnicity, n (%)	
Not Hispanic or Latino	20 (91)
Hispanic or Latino	1 (4.5)
Unknown	1 (4.5)
Weight, median (range), kg	68.5 (49-88)
BMI, median (range), kg/m^2	26.6 (19-34)
ECOG score, n (%)	
0	13 (59)
1	9 (41)
Diagnosis type, n (%)	
CLL	13 (59)
MZL[a]	4 (18)
R/R MCL[b]	3 (14)
WM	2 (9)

Abbreviations: BMI, body mass index; CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

[a]After failure of anti-CD20-based therapy.

[b]After failure of ≥ 1 prior systemic therapy.

All 22 patients were treated with study drugs (ibrutinib, OCs, or probe drugs) and 19 (86.4%) completed the PK assessment phase by day 26. Among three patients, who did not complete PK assessments, one died due to progressive disease (PD) on day 19, one did not receive the second bupropion dose on day 24 due to a late report of medical history of seizure (an exclusion criterion per protocol) but received full dose of midazolam and OCs, and one required ibrutinib dose interruptions during cycle 1 because of grade 3 pneumonia, and was not dosed with midazolam and bupropion on day 24 but received full dose of OCs on day 22. Seventeen (77.3%) patients completed the six treatment cycles and rolled over to the long-term extension study. Five (22.7%) patients discontinued study treatment (TEAE, n = 2 [including a serious AE of autoimmune hemolytic anemia (AIHA) leading to death]; PD, n = 1; death due to PD, n = 2).

3.2 | Pharmacokinetic assessments

Plasma concentration-time profiles of OCs, probe drugs, and their metabolites when administered alone or together with ibrutinib are presented in Figure 1A-F; the corresponding PK parameters are summarized in Table 3. Table 4 presents statistical analyses of PK parameters, and Figure 2A-F depicts the individual and mean exposures for each analyte in the absence/presence of ibrutinib. Plasma concentrations of ibrutinib and its metabolite PCI-45227 are reported in Table S1.

3.2.1 | Oral contraceptives: ethinylestradiol and levonorgestrel

In the presence of ibrutinib, mean EE plasma concentrations were modestly higher, compared with EE given alone. The mean C_{max} increased from 81 pg/mL for EE alone to 107 pg/mL when coadministered with ibrutinib and was reached 1 hour postdose for both assessments (Figure 1A, Table 3). Based on GMRs, C_{max}, AUC_{last}, and AUC_{∞} were 33%, 38%, and 33% higher, respectively, compared with EE dosed alone (Table 4).

For LN, mean plasma concentrations and associated PK parameters did not change substantially in the presence of ibrutinib (Figure 1B, Table 3). The test vs reference GMRs for C_{max}, $AUC_{0\text{-}72h}$, and AUC_{last} were 110%, 99%, and 100%, respectively, with 90% CIs within the 80%-125% range (Table 4). Due to the long half-life of LN, relatively high plasma concentrations were still observed at 72 hours postdose, which was the last sampling timepoint. Therefore, the percentage of AUC_{∞} calculated by extrapolation ($\%AUC_{\infty,ex}$) in many cases exceeded 20%, causing corresponding AUC_{∞} values to be excluded from descriptive and inferential statistics. As a result, valid AUC_{∞} values were only available for six patients dosed with LN alone and five patients dosed with LN in the presence of ibrutinib; only three patients had values for both treatments. For this reason, exposure assessment was based on AUC_{last} (vs AUC_{∞}).

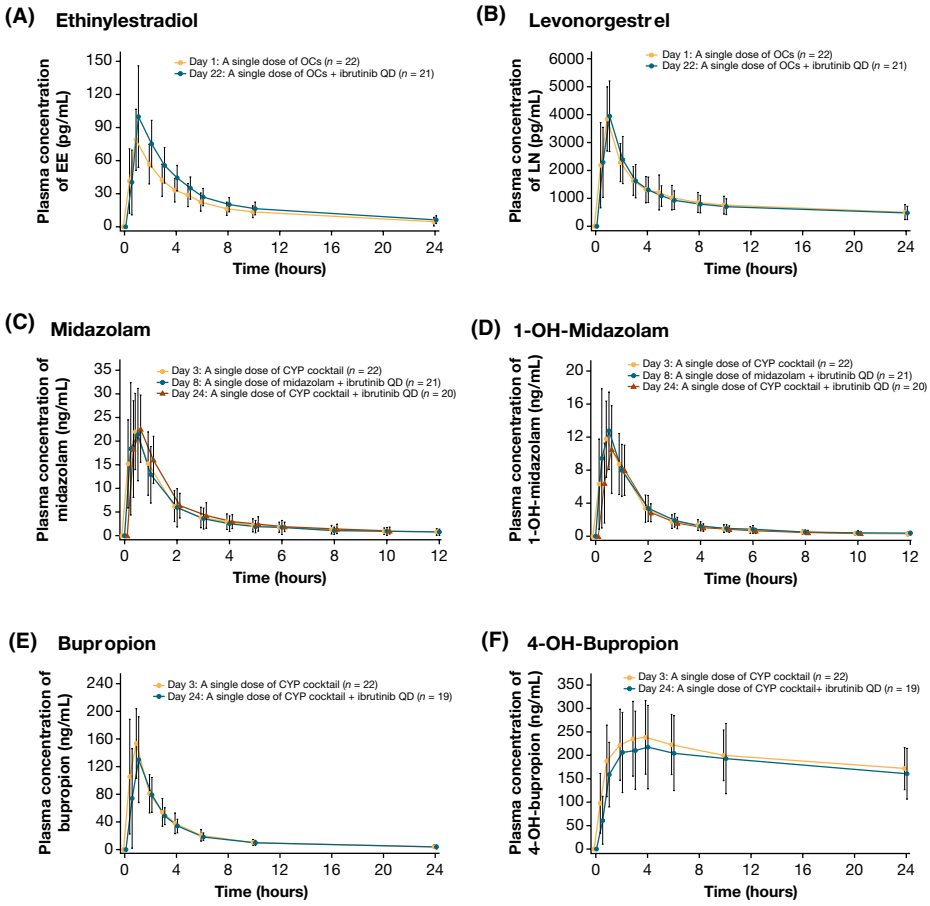

FIGURE 1 Mean plasma concentration-time curves: (A) ethinylestradiol; (B) levonorgestrel; (C) midazolam; (D) 1-OH-midazolam; (E) bupropion; (F) 4-OH-bupropion. [a]AUC_{last} is presented because AUC_{∞} was not calculable for > 50% of samples. AUC_{∞}, area under the plasma concentration-time curve from 0 to infinite time; AUC_{last}, area under the plasma concentration-time curve from 0 to last measurable concentration; EE, ethinylestradiol; LN, levonorgestrel; OCs, oral contraceptives; QD, once daily

3.2.2 | Midazolam and 1-OH-midazolam

Mean midazolam plasma concentrations vs time curves were similar on day 3 (drug probes alone), day 8 (after first dose of ibrutinib), and day 24 (in the presence of steady-state ibrutinib). A similar trend was observed with 1-OH-midazolam (Figure 1C-D, Table 3). After the administration of a single dose of ibrutinib (day 8), based on the GMRs, $AUC_{0\text{-}12h}$ and AUC_{∞} for midazolam were reduced by 12% (90% CI within the 80%-125% range) and 20% (lower boundary of 90% CI was 72%), respectively, compared with midazolam administered alone (Table 4). In the presence of steady-state ibrutinib, based on the GMRs, midazolam $AUC_{0\text{-}24h}$, AUC_{last}, and AUC_{∞} were 15%, 14%, and 14% higher, respectively, than those noted for midazolam alone, with the upper boundaries of the 90% CIs just above 125%.

Following administration of a single dose of ibrutinib (day 8), per GMRs, 1-OH-midazolam C_{max}, $AUC_{0\text{-}12h}$, and AUC_{∞} were 8%, 3%, and 8% higher, respectively, with corresponding GMR 90% CIs within the 80%-125% range, compared with midazolam administered alone. On day 24, in the presence of steady-state ibrutinib, 1-OH-midazolam C_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, and AUC_{∞} were 10%, 5%, 8%, and 10% lower, respectively; the GMR 90% CIs were within the 80%-125% range for $AUC_{0\text{-}24h}$ and AUC_{last}, and the lower boundaries of the 90% CIs were just below 80% for C_{max} (78%) and AUC_{∞} (76%; Table 4).

The metabolite-to-parent ratios (MPRs) for C_{max}, $AUC_{0\text{-}12h}$, and AUC_{∞} were 11%, 18%, and 35% higher, respectively, when midazolam was administered with a single dose of ibrutinib, compared with midazolam alone. The MPRs for C_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, and AUC_{∞} were 13%, 17%, 19%, and 19% lower, respectively, when midazolam was administered at steady-state of ibrutinib on day 24, compared with midazolam dosed alone (Tables 3 and 4).

3.2.3 | Bupropion and 4-OH-bupropion

Mean bupropion plasma concentration vs time profiles were similar for bupropion given alone and in the presence of ibrutinib (Figure 1E-F, Table 3), as was the case for 4-OH-bupropion. With ibrutinib coadministration, bupropion C_{max}, $AUC_{0\text{-}58h}$, AUC_{last}, and AUC_{∞} were 11%, 8%, 8%, and 14% lower, respectively, compared with values obtained for bupropion given alone. The corresponding

TABLE 3 Pharmacokinetic parameters derived from plasma-concentration profiles

Test	Day	C_{max} mean (SD) ng/mL	MPR C_{max} mean (SD) %	T_{max} median (range) hours	AUC_{∞} mean (SD) ng·h/mL	MPR AUC_{∞} mean (SD) %	$T_{1/2term}$ mean (SD) hours
		Ethinylestradiol					
Alone	1	81 (26)[a]	--	1.0 (0.5-2.0)	547 (234)[a]	--	8.9 (4.2)
At steady-state ibrutinib	22	107 (35)[a]	--	1.0 (0.5-3.0)	706 (230)[a]	--	11 (4.2)
		Levonorgestrel					
Alone	1	3.9 (1.1)	--	1.0 (0.5-2.0)	41 (18)[b]	--	41 (20)
At steady-state ibrutinib	22	4.2 (1.1)	--	1.0 (0.5-2.0)	39 (16)[b]	--	43 (24)
		Midazolam					
Alone	3	24 (8.4)	--	0.5 (0.3-1.0)	56 (29)	--	5.5 (1.9)
With one dose of ibrutinib	8	25 (12)	--	0.5 (0.3-0.6)	42 (22)	--	4.6 (2.2)[b]
At steady-state ibrutinib	24	24 (6.8)	--	0.5 (0.3-1.0)	60 (27)	--	5.4 (2.1)
		1-OH-midazolam					
Alone	3	12 (4.5)	53 (21)	0.5 (0.3-1.0)	27 (11)	51 (23)	6.1 (2.8)
With one dose of ibrutinib	8	14 (6.3)	61 (33)	0.5 (0.3-0.6)	27 (10)	75 (41)	4.1 (1.0)[c]
At steady-state ibrutinib	24	11 (4.9)	45 (13)	0.5 (0.3-1.0)	24 (10)	40 (16)	5.9 (2.8)
		Bupropion					
Alone	3	162 (60)	--	1.0 (0.5-1.2)	682 (234)	--	14 (4.5)
At steady-state ibrutinib	24	147 (62)	--	1.0 (0.5-2.0)	553 (160)	--	14 (3.8)
		4-OH-bupropion					
Alone	3	246 (78)	164 (88)	4.0 (2.0-24.0)	8871 (2402)[b]	1498 (532)[b]	38 (27)
At steady-state ibrutinib	24	226 (89)	170 (104)	4.0 (2.0-24.0)	8090 (2822)[b]	1461 (559)[b]	34 (11)

Abbreviations: AUC_{∞}, area under the plasma concentration-time curve from 0 to infinite time; AUC_{last}, area under the plasma concentration-time curve from 0 to last measurable concentration; C_{max}, maximum observed analyte concentration; MPR, metabolite-to-parent ratio; SD, standard deviation; $T_{1/2term}$, apparent terminal elimination half-life; T_{max}, time to maximum plasma concentration.

[a]The unit for C_{max} and AUC for EE is pg/mL and pg·h/mL, respectively.

[b]AUC_{last} is presented because AUC_{∞} was not calculable for > 50% of samples.

[c]On day 8 the last sample was taken at 12 hours postdose, while on days 3 and 24 sampling continued for 24 hours.

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%) and AUC_{∞} (78%).

For 4-OH-bupropion, based on the GMRs, C_{max}, $AUC_{0\text{-}58h}$, and AUC_{last} were 9%, 11%, and 11% lower, respectively, in the presence of ibrutinib, compared with 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 $AUC_{0\text{-}58h}$ and AUC_{last} (78%).

Bupropion MPRs were similar in the absence and presence of ibrutinib (Tables 3 and 4). Due to the longer half-life for 4-OH-bupropion, AUC_{∞} could only be determined accurately for five patients based on the PK sampling up to 58 hours postdose and was, therefore, replaced by AUC_{last} for data reporting.

3.3 | Safety

Of the 22 patients in the safety population, 20 (90.9%) experienced ≥ 1 TEAE (Table 5). The most common TEAEs (≥ 10% patients) were urinary tract infection, diarrhea, and anemia (each 22.7%), neutropenia and thrombocytopenia (each 18.2%). Grade ≥ 3 TEAEs were reported in 15 (68.2%) patients, with anemia (22.7%), neutropenia (18.2%), and thrombocytopenia (13.6%) being most common (Table 4). Fifteen (68.2%) patients had TEAEs considered by the investigator to be related to ibrutinib, including diarrhea (18.2%), neutropenia (18.2%), and thrombocytopenia (9.1%). The most common ibrutinib-related grade ≥ 3 TEAE was neutropenia, reported in four (18.2%) patients.

TEAEs leading to permanent discontinuation of ibrutinib were experienced by two patients (grade 3 intracranial hemorrhage and grade 5 AIHA). Intracranial hemorrhage was considered ibrutinib-related; the patient was hospitalized and improved following treatment with osmotherapy and antiepileptic drugs. AIHA is a common comorbidity in patients with non-Hodgkin lymphoma[19] and was deemed unrelated to ibrutinib. The patient with AIHA (initially grade 3) also experienced grade 1 pyrexia and grade 2 urinary tract infection and received treatment with darbepoetin alfa, methylprednisolone, antibiotics, and acyclovir while in the hospital. The pyrexia and urinary tract infection resolved, but the AIHA worsened to grade 4.

TABLE 4 GMRs of C_{max} and AUC_{∞} of study drugs and their metabolites (test/reference)

Ibrutinib	Drug *Metabolite*	C_{max} N	 GMR, % (90% CI)	AUC_{∞} N	 GMR, % (90% CI)	AUC change with ibrutinib
Single dose	Midazolam	21	98 (88-109)	17	80 (72-89)	Decreased
	1-OH-midazolam	*21*	*108 (96-122)*	*15*	*108 (96-121)*	*Similar*
	MPR	*21*	*111 (101-121)*	*13*	*135 (117-156)*	*Increased*
Steady-state	Ethinylestradiol	21	133 (120-147)	18	133 (122-144)	Increased
Steady-state	Levonorgestrel	21	110 (99-122)	20	100[a] (88-113)	Similar
Steady-state	Midazolam	20	105 (96-115)	17	114 (104-126)	Similar
	1-OH-midazolam	*20*	*90 (78-103)*	*15*	*90 (76-107)*	*Similar*
	MPR	*20*	*87 (77-97)*	*15*	*81 (68-97)*	*Similar*
Steady-state	Bupropion	19	89 (74-108)	17	86 (78-94)	Similar
	4-OH-bupropion	*19*	*91 (82-101)*	*19*	*89[a] (78-101)*	*Similar*
	MPR	*19*	*101 (85-119)*	*19*	*96[a] (88-105)*	*Similar*

Abbreviations: AUC_{last}, area under the plasma concentration-time curve from 0 to last measurable concentration; AUC_{∞}, area under the plasma concentration-time curve from 0 to infinite time; CI, confidence interval; C_{max}, maximum observed analyte concentration; GMR, geometric mean ratio (test/reference); MPR, metabolite-to-parent ratio.

[a]AUC_{last} is presented because AUC_{∞} was not calculable for > 50% of profiles.

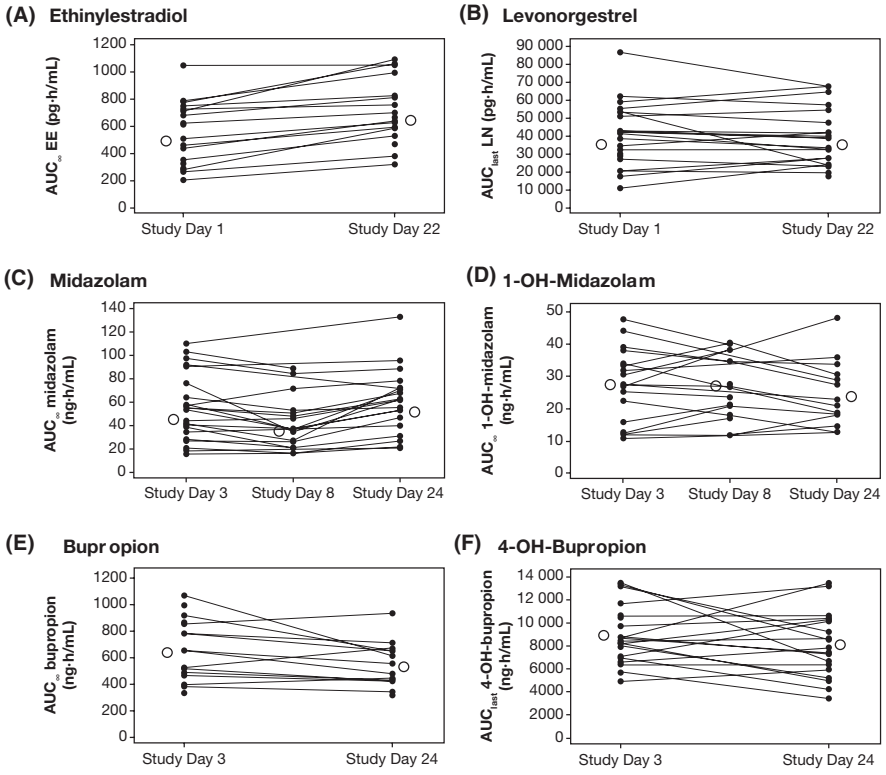

FIGURE 2 AUC scatterplots of study drugs and their metabolites alone and in the presence of ibrutinib: (A) ethinylestradiol; (B) levonorgestrel; (C) midazolam; (D) 1-OH-midazolam; (E) bupropion; (F) 4-OH-bupropion. Open circles represent mean values. AUC_{last} for levonorgestrel and 4-OH-bupropion is presented because AUC_{∞} was not calculable for > 50% of profiles. AUC_{∞}, area under the plasma concentration-time curve from 0 to infinite time; AUC_{last}, area under the plasma concentration-time curve from 0 to last measurable concentration

The patient discontinued ibrutinib and initiated subsequent anticancer treatment, and eventually died.

Five (22.7%) patients experienced TEAEs considered related to the OCs and probe drugs (midazolam and bupropion). All of these TEAEs were grade 2 except for one patient who had grade 3 neutropenia that was deemed related to OCs, probe drugs, and ibrutinib. This patient also had a grade 4 TEAE of neutropenia that was considered ibrutinib-related.

Serious AEs (SAEs) were experienced by 10 (45.5%) of patients and were mostly grade ≥ 3. Those reported in > 1 patient were pneumonia, anemia, and urinary tract infection (two patients each). Ibrutinib-related serious TEAEs occurred in five (22.7%)

TABLE 5 Safety summary (N = 22)

	Any grade n (%)	Grade ≥ 3 n (%)
TEAE	20 (90.9)	
TEAE related to study drugs	15 (68.2)	11 (50.0)
Serious TEAE	10 (45.5)	9 (49.9)
Serious TEAE related to study drugs	5 (22.7)	5 (22.7)
TEAE leading to permanent discontinuation of ibrutinib	2 (9.1)	2 (9.1)
TEAEs in > 5% of patients[a]		
Urinary tract infections	5 (22.7)	2 (9.1)
Anemia	5 (22.7)	5 (22.7)
Diarrhea	5 (22.7)	0
Neutropenia	4 (18.2)	4 (18.2)
Thrombocytopenia	4 (18.2)	3 (13.6)
Bronchitis	2 (9.1)	0
Tonsillitis	2 (9.1)	0
Upper respiratory tract infection	2 (9.1)	0
Pyrexia	2 (9.1)	0
Arthralgia	2 (9.1)	0
Cough	2 (9.1)	0

Abbreviations: OC, oral contraceptive; TEAE, treatment-emergent adverse event.

[a]TEAEs are for all study drugs (ibrutinib, OC, and probe drugs).

patients and included grade 3 events of anemia, fungal pneumonia, subdural hematoma, and urinary tract infection (all four in one patient), rectal hemorrhage, intracranial hemorrhage, and pneumonia (one patient each), and one grade 4 event of hyponatremia. None of the serious TEAEs were considered related to OCs or probe drugs.

Grade 3 serious bleeding events occurred in four patients, all of whom had underlying risk factors: (a) rectal hemorrhage after polypectomy (history of duodenal ulcers and diverticulitis); (b) muscle hemorrhage (subcutaneous injections of heparin); (c) post-traumatic subdural hematoma (history of hypertension and hemolytic anemia); (d) intracranial hemorrhage (history of hypertension and smoking). All these events, except muscle hemorrhage, were deemed ibrutinib-related.

Three patients experienced SAEs leading to death (cardiac arrest in context of PD, general physical health deterioration in context of PD, and autoimmune hemolytic anemia in one patient with CLL). None of the deaths were considered related to study treatments.

3.4 | Efficacy

Among the 17 patients who completed the study and rolled over to the long-term extension study to continue treatment with ibrutinib, 16 were evaluable for response: 1 patient had a complete response, 11 had a partial response, and 4 had stable disease. Of the five patients who did not complete the study, one had a complete response but discontinued ibrutinib treatment due to a serious TEAE of intracranial hemorrhage, one had PD, and three died during the study, one due to SAE, and two due to PD.

4 | DISCUSSION

This open-label, phase I multicenter study of female patients with B-cell malignancies investigated the effect of repeated dosing of ibrutinib on the PK of OCs (EE and LN) and CYP2B6 and CYP3A probe drugs (bupropion and midazolam, respectively), and of a single dose of ibrutinib on probe drug midazolam.

The mean C_{max} values of ibrutinib and PCI-45227 on day 24 (99.3 ng/mL and 71.2 ng/mL) were similar to those reported previously in patients with B-cell malignancies (89.4 ng/mL and 69.1 ng/mL) with the same ibrutinib dose under fed conditions.[6] The timing of the food intake (30 minutes after dosing ibrutinib) in another study in healthy participants [20] resulted in an approximate doubling of the ibrutinib AUC when compared with a schedule of fasting overnight with no food intake until 4 hours after ibrutinib administration. Ibrutinib and PCI-45227 trough levels were similar on days 22 and 24, indicating that steady-state levels had been reached prior to coadministration with the OC drugs (day 22) and the cocktail of midazolam and bupropion (day 24).

Our results demonstrated that coadministration of ibrutinib at steady-state with OCs did not lead to a decreased exposure of EE or LN, suggesting that OCs should remain effective when used during ibrutinib therapy. No obvious reason for the observed increase in EE C_{max} and AUC in the presence of ibrutinib can be given. Oral bioavailability of EE is 40%-60% and varies considerably between individuals,[15] suggesting that increased solubility in the stomach may have a positive effect on bioavailability.

However, as several studies reported that risk of venous thromboembolism increases with the use of combined OCs,[21] higher plasma concentration levels of EE seen after coadministration with ibrutinib may pose a potential safety concern. Based on the published evidence, the risk of venous thromboembolism varies with different types and doses of contraceptives.[22] To put the observed increase in EE exposure (33% for both C_{max} and AUC_{∞}) into perspective, an internal analysis compared several EE-containing products. Overall, these data indicate that regardless of the product, an increase of 33% for the mean C_{max} and AUC would fall within the established safe and efficacious exposure range (unpublished data on file, Janssen R&D, LLC).

Repeated administration of ibrutinib for 16 days neither induced nor inhibited metabolism of the CYP2B6 probe bupropion and CYP3A probe midazolam, as evidenced by all GMRs remaining within the 80%-125% range. Similarly, the exposure of midazolam and bupropion metabolites did not change substantially in the presence of steady-state ibrutinib. Although some 90% CIs were outside

the 80%-125% range, the observed effect sizes are not expected to have clinical relevance.

Midazolam and bupropion were selected because these drugs are recognized as sensitive probes of CYP3A4 and CYP2B6 activity, respectively.[9,10] Both probes are in the validated Geneva cocktail,[23] which includes 1 mg of midazolam and 25 of mg bupropion (in addition to multiple other CYP and transporter probes). As neither midazolam nor bupropion is an inhibitor or inducer of CYP activity, the probes are not expected to influence the respective PK of each drug. To allow for quantification of bupropion and its metabolite for at least 48 hours, and in the presence of induction, a higher dose was warranted. To our knowledge, other than in a conference abstract, administration of these two CYP probe drugs together at therapeutic doses has not been reported.[24]

Based on GMR for midazolam after single ibrutinib administration on day 8, AUC_{∞} was ≤ 20% lower compared with midazolam alone, and all GMRs were contained within the 80%-125% boundaries. Because single administration of ibrutinib did not result in an increased exposure of midazolam, it can be concluded that ibrutinib, at the highest therapeutic dose, does not inhibit intestinal CYP3A. The decrease in midazolam exposure following single doses of midazolam and ibrutinib cannot reflect CYP3A induction, as it takes several days for CYP de novo synthesis to take effect, and at least 10 days to reach the maximum effect.[25] As exposure of midazolam at ibrutinib steady-state did not decrease compared with that observed in the absence of ibrutinib, it can be concluded that ibrutinib did not cause CYP3A induction.

The safety profile of ibrutinib was consistent with previous safety data collected in patients with B-cell malignancies.[26-31] There were no unexpected safety events observed during the study. The most commonly reported TEAEs (> 5% of patients) were urinary tract infection, anemia, diarrhea (22.7% each), neutropenia, thrombocytopenia (18.2% each), bronchitis, tonsillitis, upper respiratory tract infection, pyrexia, arthralgia, and cough (9.1% each). The most common TEAEs considered related to ibrutinib by the investigator were diarrhea, neutropenia (18.2% each), and thrombocytopenia (9.1%). Four grade 3 serious bleeding events occurred in 4/22 patients (18%); three of these events were considered ibrutinib related. The frequency of hemorrhage grade ≥ 3 in clinical studies of ibrutinib in patients with B-cell malignancies ranged from 0% to 10%,[26-31] but some of these studies excluded patients with risks for bleeding.[27,28,31] High frequency of major hemorrhage in our study may have been due to the fact that all patients experiencing these events had underlying risk factors for bleeding.

5 | CONCLUSION

The results of this study demonstrated that repeated administration of ibrutinib for 14 days did not induce the metabolism of OC drugs EE and LN, CYP3A4 probe midazolam or CYP2B6 probe bupropion, and single administration of ibrutinib did not inhibit intestinal CYP3A4. No unexpected safety issues were noted with ibrutinib coadministered with any of the study drugs.

AUTHOR CONTRIBUTION

JdJ contributed to study design, data analysis/interpretation, and wrote the paper. AM and PH contributed to study design, data acquisition, analysis, and interpretation. DO, JJ, and JS contributed to study design and data analysis and interpretation. WJ, RC, CP, TW, and MD-D collected the data. All authors critically reviewed the subsequent drafts of the manuscript and approved the final version for submission. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DISCLOSURE

The authors declare the following conflicts of interest: JdJ, AM, JJ, DO, and PH are/were employees of Janssen Research & Development, LLC, and hold stock in the company. WJ has served as a consultant or in an advisory role for Janssen-Cilag, Acerta Pharma, Sandoz-Novartis, Celltrion, MEI Pharma, Roche, and Gilead Sciences and has received research funding from Janssen-Cilag, Acerta Pharma, Merck, Gilead Sciences, TG Therapeutics, Pfizer, Incyte, Bayer HealthCare Pharmaceuticals, Sandoz-Novartis, Roche, Celltrion, Takeda Pharmaceuticals, Affimed Therapeutics, and Epizyme. RC has served on speakers' bureaus and advisory boards for and has received travel funding from Janssen. CP has served as a consultant or advisor for Bristol Myers Squibb and Kyowa Kirin and has received travel funding from Roche Pharma. TW has served on advisory boards for Janssen-Cilag, Roche, Celgene, and Amgen and received research funding from Roche. MD-D has served on advisory boards for Servier, AbbVie, and Roche. JS is an employee of Pharmacyclics LLC, an AbbVie company, and holds stock in the company.

DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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