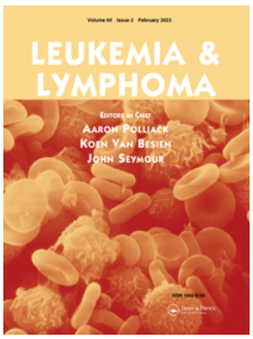

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ORIGINAL ARTICLE

A phase 1, open-label, randomized drug–drug interaction study of zanubrutinib with moderate or strong CYP3A inhibitors in patients with B-cell malignancies

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ABSTRACT

BTK inhibitor exposure increases significantly when coadministered with CYP3A inhibitors, which may lead to dose-related toxicities. This study explored the pharmacokinetics, efficacy, and safety of zanubrutinib when coadministered with moderate or strong CYP3A inhibitors in 26 patients with relapsed or refractory B-cell malignancies. Coadministration of zanubrutinib (80 mg BID) with moderate CYP3A inhibitors fluconazole and diltiazem or zanubrutinib (80 mg QD) with strong CYP3A inhibitor voriconazole resulted in comparable exposures to zanubrutinib (320 mg QD) with $AUC_{0\text{-}24h}$ geometric least squares mean ratios approaching 1 (0.94, 0.81, and 0.83, for fluconazole, diltiazem, and voriconazole, respectively). The most common treatment-emergent adverse events were contusion (26.9%), back pain (19.2%), constipation and neutropenia (15.4% each), and rash, diarrhea, and fall (11.5% each). This study supports current United States Prescribing Information dose recommendations for the coadministration of reduced-dose zanubrutinib with moderate or strong CYP3A inhibitors and confirms the favorable efficacy and safety profile of zanubrutinib.

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Zanubrutinib; BTK; DDI; CYP3A; pharmacokinetics

Introduction

Bruton tyrosine kinase (BTK) is expressed in B-lymphocytes at various stages of development; BTK activation triggers signaling events involved in cell proliferation and survival. Aberrant BTK activation is a feature observed in several B-cell malignancies and thought to be important for their pathogenesis. BTK inhibition is now an established treatment strategy for various B-cell malignancies [1,2].

Zanubrutinib, a second-generation covalent BTK inhibitor (BTKi), is approved globally or is under review globally for various B-cell malignancies, including for the treatment of patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL), R/R marginal zone lymphoma (MZL), Waldenström macroglobulinemia (WM), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [3]. Compared with ibrutinib, the first-in-class covalent BTKi, zanubrutinib has improved selectivity for inhibiting BTK versus other receptor tyrosine kinases [4–13]. This improved selectivity is consistent with reduced side effects and improved tolerability in patients with WM and CLL compared with ibrutinib in phase 3 studies [14–16].

In patients with B-cell malignancies, caution must be exercised when concomitantly administering BTKi with strong CYP3A inhibitors like azole antifungals (e.g. voriconazole, posaconazole) [17–20]. A drug–drug interaction (DDI) study in healthy volunteers evaluating the coadministration of ibrutinib with the strong CYP3A inhibitor ketoconazole found a 29-fold increase in ibrutinib C_{max} and a 24-fold increase in AUC [17]. DDI studies of acalabrutinib, a second-generation BTKi, with the coadministration of the strong CYP3A inhibitor itraconazole in healthy volunteers resulted in a 3.9-

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fold increase in C_{max} and a 5.1-fold increase in AUC [18]. The United States Prescribing Information (USPI) recommends avoiding coadministration of strong CYP3A inhibitors with ibrutinib and acalabrutinib, except for voriconazole and posaconazole with ibrutinib dose reductions [17,18].

Zanubrutinib is metabolized by CYP3A, and CYP3A inhibitors can modulate its exposure. A DDI study in healthy patients assessing the coadministration of zanubrutinib with the strong CYP3A inhibitor itraconazole resulted in zanubrutinib C_{max} and AUC increasing by 2.6-fold and 3.8-fold, respectively [21]. Physiologically based pharmacokinetic (PBPK) simulations suggest that when coadministered with multiple doses of a moderate CYP3A inhibitor (e.g. fluconazole, diltiazem, erythromycin), zanubrutinib C_{max} and AUC may increase by approximately 2- to 3-fold. The USPI requires no dose reduction when coadministering zanubrutinib with mild CYP3A inhibitors and 2- and 4-fold reductions with moderate/strong CYP3A inhibitors without dose interruptions [3]. Coadministration of zanubrutinib with CYP3A inhibitors is a clinical benefit that allows for continuation of zanubrutinib if patients require moderate/strong CYP3A inhibitor treatment [3].

Anticancer agents can be concomitantly prescribed with antibacterial and/or antifungal agents, some of which are CYP3A inhibitors. Of these, clarithromycin, fluconazole, and voriconazole are approved in multiple countries and often prescribed throughout zanubrutinib trials. The concurrent use of calcium channel blockers (e.g. diltiazem) can inhibit CYP3A activity and potentially impact zanubrutinib exposures.

This phase 1 study was conducted to explore the DDI potential on steady-state zanubrutinib pharmacokinetics (PK) when coadministered with moderate (fluconazole and diltiazem) or strong (voriconazole and clarithromycin) CYP3A inhibitors in patients with R/R B-cell malignancies and to evaluate USPI dose recommendations.

Materials and methods

Study design and population

This was a multicenter, phase 1, open-label, randomized clinical DDI study of zanubrutinib that enrolled patients with R/R B-cell malignancies in Australia from November 2020 to February 2022 (NCT04551963). This study was designed, conducted, and monitored according to sponsor procedures, and complies with the ethical principles of Good Clinical Practice, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Declaration of Helsinki, and local regulatory requirements. All patients provided written, informed consent before study entry. The independent ethics committees/institutional review boards reviewed and approved the protocol at the respective study centers.

The study comprised an initial screening phase (up to 28 days), a DDI PK study in Cycle 1 (30 days) as part of a treatment phase of 6 treatment cycles (Cycles 2 to 6; 28-day cycles), and a safety follow-up phase or rollover to a long-term extension study (BGB-3111-LTE1; NCT04170283). In the PK study (Cycle 1), patients were randomized to Arm A or B to assess the effects of CYP3A inhibitors (fluconazole, diltiazem, voriconazole, and clarithromycin) on zanubrutinib PK. Efficacy was investigated during Cycles 2 to 6. Safety was investigated throughout the study. Patients who continued to derive clinical benefit from zanubrutinib with acceptable tolerability at the end of the treatment phase (6 cycles) were eligible to receive zanubrutinib monotherapy under the rollover extension study. Patients who discontinued treatment before 6 cycles were eligible to be followed posttreatment for survival in the rollover extension study.

Male or female patients with B-cell malignancies aged $\geq$18 years with histologically or cytologically confirmed CLL/SLL, MCL, WM, or MZL who had received $\geq$1 prior line of systemic therapy and a baseline Eastern Cooperative Oncology Group performance status of 0 to 1 were eligible. Patients with WM met $\geq$1 criterion for treatment according to an adapted consensus panel criteria of the Sixth International Workshop on WM [22,23]. Patients with MZL had failed an anti-CD20 monoclonal antibody-containing chemotherapy regimen. Exclusion criteria included known hypersensitivity or contraindication to zanubrutinib, diltiazem, fluconazole, clarithromycin, or voriconazole; prior exposure to zanubrutinib or other BTKi; requirement of chronic treatment with moderate/strong CYP3A inhibitors or inducers or with drugs that were not allowed to be combined with diltiazem, clarithromycin, fluconazole, or voriconazole; history of stroke or intracranial hemorrhage (within 6 months of treatment start); and having received any antitumor therapy within 3 weeks of initiating study drug.

Treatments

Arm A (moderate CYP3A inhibitors)

Patients received zanubrutinib (320 mg) once daily (QD) on Days 1 to 3, fluconazole (400 mg) QD and zanubrutinib (80 mg) twice daily (BID) on Days 4 to 10,

zanubrutinib (80 mg) BID on Days 11 and 12, zanubrutinib (320 mg) QD on Days 13 to 21, diltiazem (180 mg) QD with zanubrutinib (80 mg) BID on Days 22 to 28, and zanubrutinib (80 mg) BID on Days 29 and 30 (Supplemental Figure 1).

On PK sampling days (Days 3 [zanubrutinib monotherapy], 10 [with fluconazole], and 28 [with diltiazem]), zanubrutinib was administered 30 min after a low-fat breakfast. Morning doses of fluconazole and diltiazem were administered together with zanubrutinib on PK sampling days. On days where PK samples were not collected, zanubrutinib could be taken with or without food [3].

Arm B (strong CYP3A inhibitors)

Patients received zanubrutinib (320 mg) QD from Days 1 to 3, voriconazole (total daily dose of 400 mg) BID with zanubrutinib (80 mg) QD on Days 4 to 10, zanubrutinib (80 mg) QD on Days 11 and 12, zanubrutinib (320 mg) QD from Days 13 to 21, clarithromycin (total daily dose of 500 mg) BID with zanubrutinib (80 mg) QD on Days 22 to 28, and zanubrutinib (80 mg) QD on Days 29 and 30 (Supplemental Figure 1).

On PK sampling days (Days 3 [zanubrutinib monotherapy], 10 [with voriconazole], and 28 [with clarithromycin]), zanubrutinib was administered 30 min after a low-fat breakfast. When coadministered, the morning dose of voriconazole was administered 1 h before a low-fat breakfast and zanubrutinib was administered 30 min after the low-fat breakfast; the morning dose of clarithromycin was administered together with zanubrutinib. On days where PK samples were not collected, zanubrutinib could be taken with or without food [3].

Study assessments

Pharmacokinetic sample analysis

Serial blood samples were collected with zanubrutinib alone and combined with fluconazole, diltiazem, voriconazole, and clarithromycin for the measurement of zanubrutinib plasma concentrations. Plasma samples were collected to assess steady-state zanubrutinib PK during Cycle 1 on Days 3, 10, and 22 (predose only), and Day 28 at the following timepoints: predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 h postdose.

Plasma concentrations of zanubrutinib were determined using a validated liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) method by WuXi AppTec (Shanghai) Co., Ltd. Protein precipitation was utilized to extract the analyte and internal standard from human plasma containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) as an anticoagulant. The calibration range was 1.00–1000 ng/mL for the plasma zanubrutinib concentration with a lower limit of quantification of 1.00 ng/mL.

Safety assessments

Safety was assessed by monitoring and recording of adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, and vital signs. Safety was measured by the incidence, timing, and severity of treatment-emergent adverse events (TEAEs), according to the National Cancer Institute Common Terminology Criteria for AEs Version 5.0 (CTCAE v5.0). AEs were classified based on Medical Dictionary for Regulatory Activities Version 24.0.

Efficacy assessments

For patients with MCL, MZL, or SLL, response was assessed and categorized per Lugano Classification for non-Hodgkin lymphoma [24]. For patients with CLL, disease response was determined according to the 2018 International Workshop on CLL guidelines with modification for treatment-related lymphocytosis [24,25]. Response in patients with WM was evaluated using an adaptation of the consensus panel criteria updated at the Sixth International Workshop [22,23].

Pharmacokinetic analyses

Noncompartmental analysis was conducted using Phoenix® WinNonlin™ version 8.2 (Certara USA, Inc). The following PK parameters were assessed for zanubrutinib: C_{max}, time to reach C_{max} (T_{max}), area under plasma concentration-time curve (AUC_{0-t}) from 0 to the time of the last quantifiable concentration (up to 10 h postdose), AUC from 0 to 24 h (AUC_{0-24h}), and apparent terminal elimination half-life ($t_{1/2}$) on Day 3 in the absence of CYP3A inhibitors and on Days 10 and 28 in the presence of CYP3A inhibitors. AUC was extrapolated to 24 h postdose for the once-a-day dose regimen; for the twice-a-day dose regimen, AUC_{0-24h} was estimated as twice that of AUC_{0-12h}. The PK evaluable analysis set included all patients who received $\geq$1 dose of zanubrutinib and had evaluable PK data ($\geq$1 PK parameter can be calculated).

Statistical analysis

The geometric least square mean (GLSM) ratios of PK parameters of zanubrutinib with and without coadministration of the CYP3A inhibitors and the associated 90% confidence interval were constructed from a mixed effects model of log-transformed PK

parameters. The model included treatment as a fixed effect and patient as a random effect. Analyses of PK parameters were performed in a model for each comparison of geometric means in each arm separately. The GLSM and their ratios were obtained by taking the exponential of the corresponding estimates of least square means and their differences on the natural logarithmic scale, where ratio = test/reference. For the analyses of each parameter, patients must have valid values in all 3 periods to be included. The study sample size was based on precedent set by other PK studies of a similar nature and was not based on power calculations. Thirteen patients with B-cell malignancies were enrolled in each arm, with the expectation that 12 in each arm would complete the study.

Safety analyses

The safety analysis set included all patients who received ≥1 dose of zanubrutinib. Safety and tolerability were assessed, where applicable, by incidence, severity, change from baseline values, and abnormal values for all relevant parameters, including AEs, laboratory parameters, vital signs, and physical examination.

Efficacy analyses

The population of primary interest for efficacy analyses is the safety analysis set. The overall response rate (ORR), complete response (CR) rate or complete metabolic response, and rate of very good partial response (VGPR) or better (for WM) were summarized. Patients with no postbaseline response assessment were considered nonresponders. Best responses were summarized (Table 1). Time to response (TTR) is defined as the time (weeks) from date of the first dose of zanubrutinib to the earliest qualifying response of MR or better for WM, to first earliest qualifying response of partial response (PR) with lymphocytosis or better for CLL, and to first earliest qualifying response of PR or better for other diagnoses. TTR was summarized by descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) for responders only.

Results

Demographics, baseline characteristics, and patient disposition

Twenty-six patients (13 Arm A; 13 Arm B) were enrolled in the study and received study treatment. All 26 completed Cycle 1, and 23 of 26 (88.5%) completed 6 cycles of study drug per protocol. Three (11.5%) patients discontinued from study treatment due to an AE, physician decision, or progressive disease (1 [3.8%] patient each). Twenty-one patients continued to receive zanubrutinib monotherapy under the rollover extension study (BGB-3111-LTE1; NCT04170283).

Demographic and baseline characteristics were comparable in both arms (Supplemental Table 1). Most patients had WM (61.5%) or MZL (19.2%), were white (88.5%), and male (69.2%). Median age was 72.5 years (53 to 83 years), and most patients were ≥65 years (76.9%).

Pharmacokinetics

In both arms, zanubrutinib was rapidly absorbed with a median T_{max} between 2 to 3 h following administration of zanubrutinib alone and zanubrutinib with moderate/strong CYP3A inhibitors, respectively (Figure 1). The coadministration of a reduced dose of zanubrutinib with moderate/strong CYP3A inhibitors resulted in lower mean steady-state zanubrutinib plasma concentrations as compared with zanubrutinib alone

Table 1. Disease response by the indication.

Response category	CLL ($n = 3$)	MCL ($n = 2$)	MZL ($n = 5$)	WM ($n = 16$)	Overall ($N = 26$)
Best overall response, n (%)					
CR	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (3.8)
VGPR	NA	NA	NA	2 (12.5)	2 (7.7)
PR	2 (66.7)	0 (0.0)	1 (20.0)	10 (62.5)	13 (50.0)
PR-L	1 (33.3)	NA	NA	NA	1 (3.8)
MR	NA	NA	NA	1 (6.3)	1 (3.8)
SD	0 (0.0)	0 (0.0)	2 (40.0)	3 (18.8)	5 (19.2)
Non-PD	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (7.7)
PD	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (3.8)
Overall response rate,[a] n (%)	3 (100.0)	1 (50.0)	1 (20.0)	13 (81.3)	18 (69.2)
Rate of CR or complete metabolic response, n (%)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (3.8)
Rate of VGPR or better for WM,[b] n (%)	NA	NA	NA	2 (12.5)	2 (12.5)

Notes: CLL: chronic lymphocytic leukemia; CR: complete response; MCL: mantle cell lymphoma; MR: minor response; MZL: marginal zone lymphoma; NA: not applicable; NHL: non-Hodgkin lymphoma; ORR: overall response rate; PD: progressive disease; PR: partial response; PR-L: partial response with lymphocytosis; SD: stable disease; VGPR: very good partial response; WM: Waldenström macroglobulinemia.
[a]ORR is defined as the proportion of patients with MR or better for WM, PR-L or better for CLL, and PR or better for NHL.
[b]VGPR or better is defined as the proportion of patients with VGPR or better for WM.

(320 mg). The steady-state PK parameters for zanubrutinib monotherapy or combined with moderate/strong CYP3A inhibitors are summarized (Table 2). The GLSM ratios were <1 for C_{max} and AUC_{0-24h} for the coadministration of zanubrutinib with moderate/strong CYP3A inhibitors, compared with zanubrutinib alone, suggesting that zanubrutinib exposures at reduced-dose levels upon concurrent administration with moderate/strong CYP3A inhibitors did not exceed exposures observed with zanubrutinib alone (320 mg; Table 3).

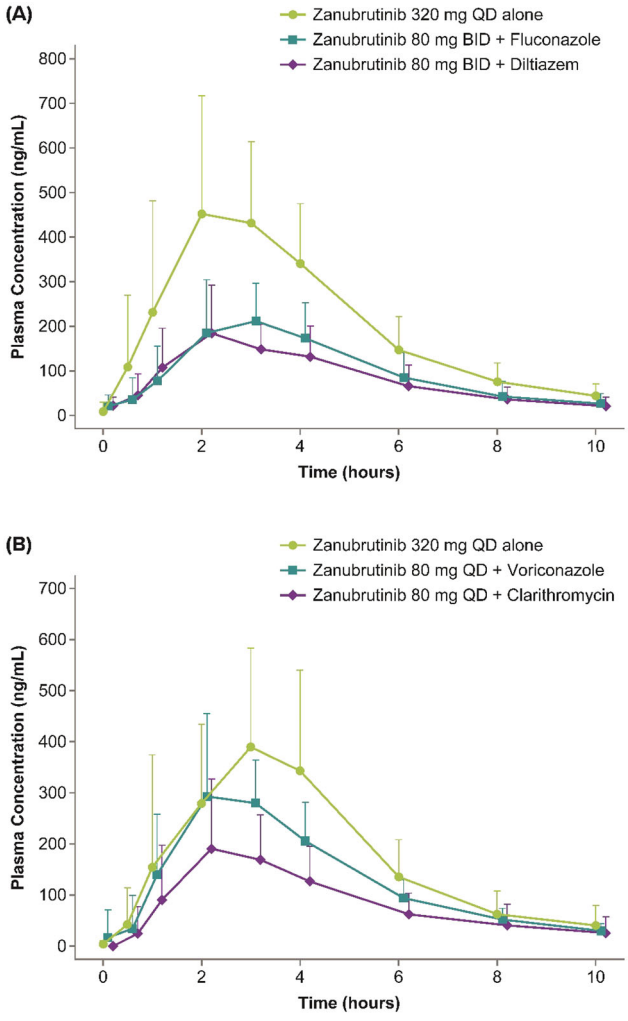

Figure 1. Zanubrutinib mean (+SD) steady-state plasma concentrations on a linear scale: monotherapy and with

Effect of fluconazole and diltiazem coadministration on zanubrutinib pharmacokinetics – Arm A

The GLSM ratios (90% CI) for AUC_{0-24h} and C_{max} were 0.94 (0.82–1.08) and 0.45 (0.35–0.58) for zanubrutinib with fluconazole and 0.81 (0.66–0.99) and 0.41 (0.32–0.51) for zanubrutinib with diltiazem, respectively, compared with zanubrutinib alone (Table 3). The magnitude of the interaction is illustrated in a dose-normalized presentation of the PK parameters (Table 4). The GLSM ratios (90% CI) for dose-normalized AUC_{0-24h} and C_{max} were 1.88 (1.63–2.16) and 1.81 (1.41–2.32), respectively, for zanubrutinib with fluconazole and 1.62 (1.33–1.98) and 1.62 (1.28–2.05) for zanubrutinib with diltiazem, respectively, compared with zanubrutinib alone.

Effect of voriconazole and clarithromycin coadministration on zanubrutinib pharmacokinetics – Arm B

The GLSM ratios (90% CI) for AUC_{0-24h} and C_{max} were 0.83 (0.65–1.06) and 0.82 (0.68–1.00) for zanubrutinib with voriconazole and 0.48 (0.40–0.58) and 0.50 (0.39–0.64) for zanubrutinib with clarithromycin, respectively, compared with zanubrutinib alone (Table 3). The GLSM ratios (90% CI) for dose-normalized AUC_{0-24h} and C_{max} were 3.30 (2.58–4.22) and 3.29 (2.70–4.01) for zanubrutinib with voriconazole and 1.92 (1.60–2.32) and 2.01 (1.57–2.57) for zanubrutinib with clarithromycin, respectively, compared with zanubrutinib alone (Table 4).

Table 2. Zanubrutinib steady-state pharmacokinetic parameters.

Arm	*N*	Treatment	AUC_{0-24h} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
Arm A	13	Zanubrutinib 320 mg QD alone	2035.32 (46.97)	520.78 (39.18)	2.03 (1.0, 4.0)	2.15 (1.4, 4.5)
		Zanubrutinib 80 mg BID + fluconazole	1911.93 (46.97)	235.72 (42.53)	2.93 (1.0, 4.0)	2.10 (1.7, 3.3)
		Zanubrutinib 80 mg BID + diltiazem	1653.07 (44.88)	211.06 (36.59)	2.05 (1.0, 4.2)	2.14 (1.4, 4.0)
Arm B	13	Zanubrutinib 320 mg QD alone[a]	1578.12 (49.53)	428.88 (43.56)	3.00 (1.0, 4.0)	1.79 (1.2, 2.5)
		Zanubrutinib 80 mg QD + voriconazole	1376.02 (25.09)	353.11 (30.23)	2.05 (1.0, 3.9)	2.38 (1.6, 2.8)
		Zanubrutinib 80 mg QD + clarithromycin[b]	766.71 (60.44)	215.15 (51.79)	2.08 (0.5, 7.9)	2.08 (1.4, 2.9)

Notes: AUC_{0-24h}: AUC from 0 to 24 h (extrapolated to 24 h postdose for the QD regimen; for the BD regimen, the AUC_{0-24h} was estimated as twice that of AUC_{0-12h}); BID, twice a day; C_{max}: maximum concentration; CV: coefficient of variation; $t_{1/2}$: half-life; T_{max}: time of maximum concentration; QD: once a day. Values are presented as geometric mean (geometric CV %) for AUC_{0-24h}, and C_{max}, median (minimum, maximum) for T_{max}, and geometric mean (minimum, maximum) for $t_{1/2}$.

[a]AUC_{0-24h} and $t_{1/2}$ are only available for 12 patients.

[b]AUC_{0-24h} and $t_{1/2}$ are only available for 11 patients.

Table 3. Analysis of zanubrutinib steady-state pharmacokinetic parameters.

Arm	Parameter	Treatment	*N*	Ratio of GLSMs (90% CI)	Within patient CV (%)
Arm A	AUC_{0-24h} (h*ng/mL)	320 mg QD zanubrutinib	13		
		80 mg BID zanubrutinib + 400 mg QD fluconazole	13	0.94 (0.82–1.08)	20.5
		80 mg BID zanubrutinib + 180 mg QD diltiazem	13	0.81 (0.66–0.99)	29.3
	C_{max} (ng/mL)	320 mg QD zanubrutinib	13		
		80 mg BID zanubrutinib + 400 mg QD fluconazole	13	0.45 (0.35–0.58)	36.9
		80 mg BID zanubrutinib + 180 mg QD diltiazem	13	0.41 (0.32–0.51)	34.8
Arm B	AUC_{0-24h} (h*ng/mL)	320 mg QD zanubrutinib	11		
		80 mg QD zanubrutinib + 200 mg BID voriconazole	11	0.83 (0.65–1.06)	32.5
		80 mg QD zanubrutinib + 250 mg BID clarithromycin	11	0.48 (0.40–0.58)	24.5
	C_{max} (ng/mL)	320 mg QD zanubrutinib	13		
		80 mg QD zanubrutinib + 200 mg BID voriconazole	13	0.82 (0.68–1.00)	28.9
		80 mg QD zanubrutinib + 250 mg BID clarithromycin	13	0.50 (0.39–0.64)	36.5

Notes: AUC_{0-24}: AUC from 0 to 24 h (extrapolated to 24 h postdose for the QD regimen; for the BID regimen, AUC_{0-24h} was estimated as twice that of AUC_{0-12h}); BID: twice a day; CI: confidence interval; C_{max}: maximum concentration; CV: coefficient of variation; GLSM: geometric least squares mean; QD: once a day.

Table 4. Analysis of dose-normalized zanubrutinib steady-state pharmacokinetic parameters.

Arm	Parameter	Treatment	*N*	Ratio of GLSMs (90% CI)	Within patient CV (%)
Arm A	AUC_{0-24h} normalized by dose (h*ng/mL/mg)	320 mg QD zanubrutinib	13		
		80 mg BID zanubrutinib + 400 mg QD fluconazole	13	1.88 (1.63–2.16)	20.5
		80 mg BID zanubrutinib + 180 mg QD diltiazem	13	1.62 (1.33–1.98)	29.3
	AUC_{0-t} normalized by dose (h*ng/mL/mg)	320 mg QD zanubrutinib	13		
		80 mg BID zanubrutinib + 400 mg QD fluconazole	13	1.94 (1.67–2.25)	21.6
		80 mg BID zanubrutinib + 180 mg QD diltiazem	13	1.68 (1.37–2.06)	29.7
	C_{max} normalized by dose (ng/mL/mg)	320 mg QD zanubrutinib	13		
		80 mg BID zanubrutinib + 400 mg QD fluconazole	13	1.81 (1.41–2.32)	36.9
		80 mg BID zanubrutinib + 180 mg QD diltiazem	13	1.62 (1.28–2.05)	34.8
Arm B	AUC_{0-24h} normalized by dose (h*ng/mL/mg)	320 mg QD zanubrutinib	11		
		80 mg QD zanubrutinib + 200 mg BID voriconazole	11	3.30 (2.58–4.22)	32.5
		80 mg QD zanubrutinib + 250 mg BID clarithromycin	11	1.92 (1.60–2.32)	24.5
	AUC_{0-t} normalized by dose (h*ng/mL/mg)	320 mg QD zanubrutinib	13		
		80 mg QD zanubrutinib + 200 mg BID voriconazole	13	3.24 (2.64–3.96)	29.6
		80 mg QD zanubrutinib + 250 mg BID clarithromycin	13	1.97 (1.66–2.33)	24.8
	C_{max} normalized by dose (ng/mL/mg)	320 mg QD zanubrutinib	13		
		80 mg QD zanubrutinib + 200 mg BID voriconazole	13	3.29 (2.70–4.01)	28.9
		80 mg QD zanubrutinib + 250 mg BID clarithromycin	13	2.01 (1.57–2.57)	36.5

Notes: AUC_{0-24}: AUC from 0 to 24 h (extrapolated to 24 h postdose for the QD regimen; for the BID regimen, AUC_{0-24h} was estimated as twice that of AUC_{0-12h}); AUC_{0-t} (0–10 h postdose): AUC to last nonzero concentration; BID, twice daily; CI: confidence interval; C_{max}: maximum concentration; CV: coefficient of variation; GLSM: geometric least squares mean; QD: once a day.

Efficacy

The ORR was 69.2% (18/26 patients) with a median follow-up of 5.65 months. One patient with MCL had a CR. The most common best response was PR (13/26 [50.0%] patients). By disease indication, the ORR was 100.0% (3/3 patients) in CLL, 81.3% (13/16 patients) in WM, 50.0% (1/2 patients) in MCL, and 20.0% (1/5 patients) in MZL. The VGPR or better rate in patients with WM was 12.5% (2/16 patients). The median TTR was 2.83 months across all patients.

Safety

Zanubrutinib monotherapy and at lower doses in combination with moderate/strong CYP3A inhibitors demonstrated a favorable safety and tolerability profile. Overall, 24/26 (92.3%) patients experienced ≥1 TEAE, and the incidence of TEAEs was similar between arms (Table 5). The most frequently reported TEAEs were contusion (7 [26.9%] patients), back pain (5 [19.2%] patients), constipation and neutropenia (4 [15.4%] patients each), and rash, diarrhea, and fall (3 [11.5%] patients each).

In Cycle 1, 9 (69.2%) and 12 (92.3%) patients in Arms A and B, respectively, experienced ≥1 AE. Six (46.2%) patients in both arms experienced ≥1 AE attributed to zanubrutinib alone. In Arm A, 4 (30.8%) and 6 (46.2%) patients experienced ≥1 AE attributed to zanubrutinib plus fluconazole or zanubrutinib plus diltiazem, respectively. In Arm B, nine (69.2%) and eight (61.5%) patients experienced ≥1 AE attributed to zanubrutinib plus voriconazole or zanubrutinib plus clarithromycin, respectively. The most frequently reported AEs in Arm A were contusion and neck pain (two [15.4%] patients each); in Arm B were contusion, constipation, and diarrhea (three [23.1%] patients each) and fatigue (two [15.4%] patients).

Table 5. Treatment-emergent adverse events in ≥5% of overall patients by system organ class and preferred term.

System organ class Preferred term, n (%)	Arm A (*n* = 13)	Arm B (*n* = 13)	Overall (*n* = 26)
Patients with at least one TEAE	12 (92.3)	12 (92.3)	24 (92.3)
Skin and subcutaneous tissue disorders			
Rash	1 (7.7)	2 (15.4)	3 (11.5)
Petechiae	1 (7.7)	1 (7.7)	2 (7.7)
Gastrointestinal disorders			
Constipation	1 (7.7)	3 (23.1)	4 (15.4)
Diarrhea	0 (0.0)	3 (23.1)	3 (11.5)
Upper abdominal pain	0 (0.0)	2 (15.4)	2 (7.7)
Injury, poisoning and procedural complications			
Contusion	3 (23.1)	4 (30.8)	7 (26.9)
Fall	1 (7.7)	2 (15.4)	3 (11.5)
Musculoskeletal and connective tissue disorders			
Back pain	2 (15.4)	3 (23.1)	5 (19.2)
Musculoskeletal chest pain	0 (0.0)	2 (15.4)	2 (7.7)
Neck pain	2 (15.4)	0 (0.0)	2 (7.7)
Infections and infestations			
Upper respiratory tract infection	1 (7.7)	1 (7.7)	2 (7.7)
Blood and lymphatic system disorders			
Neutropenia	2 (15.4)	2 (15.4)	4 (15.4)
General disorders and administration site conditions			
Fatigue	0 (0.0)	2 (15.4)	2 (7.7)
Peripheral edema	1 (7.7)	1 (7.7)	2 (7.7)
Investigations			
Blood creatinine increased	0 (0.0)	2 (15.4)	2 (7.7)

Notes: TEAE: treatment-emergent adverse event; patients with multiple events for a given system organ class or preferred term are counted only once for each category. Events are sorted by decreasing frequency of system organ class and preferred term.

One patient died <30 days after the last dose of study treatment; the cause of death was disease under study. Four of 26 (15.4%) patients experienced ≥1 SAE, including single events of neck pain, *pneumonia cryptococcal*, radiculopathy, fall, traumatic hemorrhage, and refractory MCL. Treatment discontinuation due to TEAE occurred in one (3.8%) patient (*pneumonia cryptococcal*), and dose reduction due to TEAE occurred in one (3.8%) patient (neutrophil and platelet count decreased).

Fourteen instances occurred of hematology parameters with worsening shifts of ≥2 CTCAE toxicity grades; 11 of these instances were shifts to Grade ≥3 CTCAE postbaseline toxicity grades. The hematology parameters with worsening shifts of ≥2 CTCAE toxicity grades reported in ≥2 patients overall were neutrophils decreased (7 [26.9%] patients), leukocytes decreased (4 [15.4%] patients), and platelets decreased (2 [7.7%] patients).

Four instances occurred of serum chemistry parameters with worsening shifts of ≥2 CTCAE toxicity grades, one instance each in the parameters of alanine aminotransferase increased, albumin decreased, bilirubin increased, and sodium decreased. One of these instances (sodium decreased) was a shift to a Grade ≥3 CTCAE postbaseline toxicity grade. No patients had a Grade ≥3 CTCAE postbaseline QTcF value >500 ms or an increase from baseline of >60 ms.

Discussion

This was a multicenter, phase 1, open-label, randomized clinical study to evaluate the DDI potential of zanubrutinib when coadministered with moderate/strong CYP3A inhibitors in patients with B-cell malignancies per USPI dose recommendations.

Coadministration of zanubrutinib (80 mg BID) with the moderate CYP3A inhibitors fluconazole and diltiazem resulted in comparable exposures to zanubrutinib (320 mg QD) with AUC_{0-24h} GLSM ratios approaching 1 (0.94; 90% CI: 0.82–1.08 and 0.81; 90% CI: 0.66–0.99, for fluconazole and diltiazem, respectively). Analysis of dose-normalized PK parameters showed 1.88-fold and 1.81-fold increases of AUC_{0-24h} and C_{max}, respectively, after coadministration of zanubrutinib with fluconazole, whereas a 1.62-fold increase for both AUC_{0-24h} and C_{max} was observed with diltiazem. As such, the current 2-fold dose reduction recommendation for moderate CYP3A inhibitors ensures zanubrutinib exposures do not exceed those of a 320 mg QD dose. When coadministered with fluconazole and diltiazem, the zanubrutinib C_{max} GLSM ratios approached 0.5 as expected (0.45; 90% CI: 0.35–0.58 and 0.41; 90% CI: 0.32–0.51, for fluconazole and diltiazem, respectively). Lower C_{max} ratios are due to lower C_{max} values associated with coadministration of zanubrutinib (80 mg BID) with moderate inhibitors versus zanubrutinib alone (320 mg QD).

As for the strong CYP3A inhibitors, coadministration of zanubrutinib (80 mg QD) with the strong CYP3A inhibitor voriconazole resulted in comparable exposures to zanubrutinib (320 mg QD) with the AUC_{0-24h} GLSM ratio approaching 1 (0.83). The analysis of dose-normalized PK parameters showed a 3.30-fold and 3.29-fold increase of AUC_{0-24h} and C_{max}, respectively, after coadministration of zanubrutinib with voriconazole. Accordingly, the current 4-fold dose reduction recommendation for strong CYP3A inhibitors ensures zanubrutinib exposures do not exceed those of a 320 mg QD dose.

However, when administered with the strong CYP3A inhibitor, clarithromycin (250 mg BID), zanubrutinib exposures increased similarly as with moderate rather than strong inhibition. This was likely due to a reduced dose of clarithromycin chosen for this study to mitigate the potential concern for *Clostridium difficile*-associated diarrhea in the elderly [26]. Clarithromycin is a potent dose-dependent inhibitor of both intestinal and hepatic CYP3A4 activity [27,28]. Thus, the reduced dose of clarithromycin and the resultant increases of zanubrutinib exposures in this study align with modeling predictions of it behaving

more like a moderate inhibitor. The typical dose of clarithromycin in CYP3A DDI studies is 500 mg BID which may result in higher zanubrutinib exposures than those seen in the current study [29].

Additionally, the extent of DDI varies within the same category of moderate/strong CYP3A inhibitors; the proposed dose modification considers the overall extent of DDI within each inhibitor category and is intended to provide simplified dosing guidelines: 4-fold and 2-fold reduced doses with strong and moderate CYP3A inhibitors, respectively. The proposed dose reduction is supported by exposure-response analysis for zanubrutinib, which shows no exposure-response relationships for efficacy and safety endpoints over a wide range of zanubrutinib concentrations [30].

Based on prior PBPK simulations, we predicted an approximate 3.4-fold, 2.57-fold, and 2.83-fold increase in zanubrutinib AUC during coadministration of zanubrutinib with fluconazole (400 mg), diltiazem, and clarithromycin, respectively. In the current study, dose-normalized PK parameters showed an increased exposure of zanubrutinib when coadministered with moderate/strong CYP3A inhibitors compared with zanubrutinib alone. However, the magnitude of DDI with moderate/strong CYP3A inhibitors on observed zanubrutinib exposures was lower compared with PBPK modeling predictions; we observed 1.88-fold, 1.92-fold, and 1.92-fold increases for fluconazole (400 mg), diltiazem, and clarithromycin, respectively [31]. These results are not unexpected based on population PK analysis and may be attributed to the population differences (health status and age) of this study in comparison to the population (healthy volunteers) utilized for PBPK simulations. Cancer patients may have a lower expression of CYP3A enzymes due to disease-associated inflammation, possibly resulting in a lower clearance of various compounds metabolized by CYP3A [32,33]. In a population PK analysis of zanubrutinib, including data from healthy volunteers and patients with B-cell malignancies, the impact of health status was identified as a statistically significant but not clinically meaningful covariate [34]. PBPK simulations for coadministration of zanubrutinib with CYP3A inhibitors were previously constructed based upon a healthy volunteer population (aged 20–50 years), whereas the median age range in this study was for patients aged 72.5 years [31]. The reduced activity of CYP3A in cancer patients along with increased age could explain the difference in magnitude between predictions from PBPK simulations and the observed data.

Overall, safety findings were consistent with those observed in zanubrutinib studies [35]. Here, the coadministration of zanubrutinib at a reduced dose with moderate/strong CYP3A inhibitors resulted in decreased exposures compared with that of zanubrutinib (320 mg) alone and support the current USPI recommendations [3].

The small number of patients enrolled with CLL, MCL, and MZL limit the efficacy conclusions that can be drawn in patients with these indications. However, the major response rate (75%) and the TTR (2.83 months) for patients with WM are consistent with those observed in zanubrutinib studies in patients with WM. Although the CR and VGPR rates in the ASPEN trial (36%) were higher than this small cohort (12.5%), this may be due to minimal follow-up as responses can deepen over time [15,36].

Conclusion

Results demonstrate an increase in zanubrutinib dose-normalized steady-state exposures when coadministered with moderate/strong CYP3A inhibitors. Despite that increase, zanubrutinib exposures upon concurrent administration with moderate/strong CYP3A inhibitors (80 mg BID and 80 QD, respectively) did not exceed exposures with zanubrutinib (320 mg) alone. Response rates were comparable with rates in previous studies and demonstrate a favorable safety and tolerability profile in patients with B-cell malignancies. No new safety signals were identified. Results support the USPI dose modifications, which suggest coadministration of zanubrutinib (80 mg BID) with moderate CYP3A inhibitors and zanubrutinib (80 mg QD) with strong CYP3A inhibitors [3].

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Author contributions

Study design: BT, YCO, JCS, WN, SS; collection and assembly of data: BT, JCS, CL, WN; enrolled patients: NWD, PW, KLL, SO; data analysis and interpretation: BT, YCO, JCS, VM, CL, SS.

Disclosure statement

BT is employed by BeiGene and holds stock with BeiGene. YCO is employed by BeiGene, is in a leadership position at BeiGene, holds stock with BeiGene, and has received research funding from BeiGene. JCS is employed by BeiGene and holds stock with BeiGene. VM is employed by BeiGene and holds stock with BeiGene. NWD has nothing to disclose. PW has nothing to disclose. KLL has received honoraria from AstraZeneca, Janssen, Roche, served as a consultant for AstraZeneca, Roche, Loxo/Lilly, IQVIA, and received travel expenses and compensation from conference attendances from Novartis, Janssen, and Loxo/Lilly. CL is employed by BeiGene and holds stock with BeiGene. WN was employed by BeiGene at the time of the study and holds stock with BeiGene. SS is employed by BeiGene, is in a leadership position at BeiGene, holds stock with BeiGene, and has received research funding and travel expenses from BeiGene. SO has received honoraria from AbbVie, BeiGene, AstraZeneca, BMS, CSL Behring, Gilead, Janssen, Merck, Roche, Takeda, served as a consultant for AbbVie, BeiGene, AstraZeneca, BMS, CSL Behring, Gilead, Janssen, Merck, Roche, Takeda, and received research funding from AbbVie, AstraZeneca, BeiGene, CSL Behring, Gilead, Janssen, Merck, Pharmacyclics, Roche, and Takeda.

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Data availability statement

All authors had access to the original data for the analyses described here. On request and subject to certain criteria, conditions, and exceptions, BeiGene will provide access to individual deidentified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. Data requests may be submitted to DataDisclosure@beigene.com.

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