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ORIGINAL ARTICLE

Posaconazole-ibrutinib interaction cannot be avoided by staggered dosing: How to optimize ibrutinib dose during posaconazole treatment

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Aims: Ibrutinib is used in the treatment of certain B-cell malignancies. Due to its CYP3A4-mediated metabolism and highly variable pharmacokinetics, it is prone to potentially harmful drug-drug interactions.

Methods: In a randomized, placebo-controlled, three-phase crossover study, we examined the effect of the CYP3A4-inhibiting antifungal posaconazole on ibrutinib pharmacokinetics. Eleven healthy participants ingested repeated doses of 300 mg of posaconazole either in the morning or in the evening, or placebo. A single dose of ibrutinib (30, 70 or 140 mg, respectively) was administered at 9 AM, 1 or 12 h after the preceding posaconazole/placebo dose.

Results: On average, morning posaconazole increased the dose-adjusted geometric mean area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-}\infty}$) and peak plasma concentration (C_{max}) of ibrutinib 9.5-fold (90% confidence interval [CI] 6.3-14.3, $P < 0.001$) and 8.5-fold (90% CI 5.7-12.8, $P < 0.001$), respectively, while evening posaconazole increased those 10.3-fold (90% CI 6.7-16.0, $P < 0.001$) and 8.2-fold (90% CI 5.2-13.2, $P < 0.001$), respectively. Posaconazole had no significant effect on the half-life of ibrutinib, but substantially reduced the metabolite PCI-45227 to ibrutinib $AUC_{0\text{-}\infty}$ ratio. There were no significant differences in ibrutinib pharmacokinetics between morning and evening posaconazole phases.

Conclusions: Posaconazole increases ibrutinib exposure substantially, by about 10-fold. This interaction cannot be avoided by dosing the drugs 12 h apart. In general, a 70-mg daily dose of ibrutinib should not be exceeded during posaconazole treatment to avoid potentially toxic systemic ibrutinib concentrations.

KEYWORDS
antifungal, CYP3A4, drug-drug interaction, ibrutinib, posaconazole

† Deceased.

The authors confirm that the Principal Investigator for this paper is Janne Backman and that he had direct clinical responsibility for the subjects.

1 | INTRODUCTION

Ibrutinib is a covalent irreversible small-molecule inhibitor of Bruton's tyrosine kinase (BTK), an essential molecule in the B-cell receptor-signalling pathway.[1] It has proven to be effective in many B-cell malignancies, especially in chronic lymphocytic leukaemia (CLL),[1–5] and is also indicated for the treatment of chronic graft-*vs*-host disease.[1] In CLL, ibrutinib can be used as a time-limited therapy in combination with venetoclax, but in most cases, it is initiated for indefinite treatment until disease progression or unacceptable toxicity. Based on real-world studies, about one-third to half of CLL patients discontinue ibrutinib treatment, mostly because of adverse effects, such as infections and bleeding, and cardiac adverse effects, including atrial fibrillation.[6–8]

As the elimination of ibrutinib occurs by extensive metabolism via cytochrome P450 (CYP) 3A4 in the intestine and liver,[9] CYP3A4-mediated drug-drug interactions may lead to substantial changes in ibrutinib concentrations. The strong CYP3A4 inhibitor ketoconazole increased the area under the plasma concentration-time curve (AUC) of ibrutinib 24-fold under fasted conditions[10] and itraconazole increased the AUC 10-fold in a non-fasted state in healthy volunteers.[11] Furthermore, voriconazole increased the exposure to ibrutinib almost sixfold in a non-fasted state in patients with B-cell malignancy.[12] Of note, ibrutinib's interactions are dependent on fasting status, as food enhances the bioavailability of ibrutinib about twofold, most likely due to reduced hepatic first-pass extraction caused by increased hepatic blood flow.[13]

CLL patients treated with ibrutinib are at an increased risk of developing infections, including invasive aspergillosis and other fungal infections, either due to the disease itself or due to its treatment.[14–17] Posaconazole is recommended as a first-line choice for the prevention of fungal infections in high-risk hematologic patients.[18–20] While the European Medicines Agency (EMA) prescribing information of ibrutinib recommends caution and the smallest available tablet of 140 mg ibrutinib once daily, when it is used concomitantly with posaconazole, the US Food and Drug Administration (FDA) label recommends a daily dose of 70 or 140 mg and 140 or 280 mg ibrutinib in B-cell malignancies and chronic graft-*vs*-host disease, respectively. This equals a four- to eightfold and two- to fourfold reduction in ibrutinib dose to counteract the CYP3A4-mediated interaction as the standard dosage in most of these indications is 420 mg daily and in mantle cell lymphoma is 560 mg daily. These dose reductions seem to be small because strong CYP3A4 inhibitors have increased ibrutinib exposure by at least 10-fold.

Currently no clinical studies on the effect of posaconazole on ibrutinib exposure exist. Our randomized placebo-controlled three-phase crossover study with healthy volunteers sought to define the extent of the drug-drug interaction between posaconazole and ibrutinib when they are dosed 1 or 12 h apart to allow proper evidence-based dose adjustments during concomitant treatment.

What is already known about this subject

- Patients requiring ibrutinib are susceptible to fungal infections.
- Azole antifungals, such as posaconazole, are problematic due to pharmacokinetic interactions affecting ibrutinib's extensive metabolism by CYP3A4.
- No studies exist on the effect of posaconazole on ibrutinib exposure.

What this study adds

- Treatment with 300 mg of posaconazole daily increases ibrutinib exposure by about 10-fold and decreases interindividual variability in exposure regardless of the interval between posaconazole and ibrutinib intake.
- A daily dose of 70 mg of ibrutinib should not be exceeded when used concomitantly with posaconazole to avoid concentration-dependent toxicity.

2 | METHODS

2.1 | Study participants

Eleven healthy male volunteers (age range 20-36 years, body mass index range 19.7-31.4 kg m^{-2}) participated in the study after giving written informed consent. Their health was verified by medical history, clinical examination, laboratory tests and electrocardiogram before entering the study. All participants were nonsmoking and none of them had any continuous medication.

2.2 | Study design

The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (record number HUS/1208/2019) and the Finnish Medicines Agency Fimea (EudraCT number 2018-004814-16). The study was a randomized, placebo-controlled, three-phase crossover study with a washout period of 3 weeks. In phases 1 (morning posaconazole) and 3 (placebo) of the study, the participants ingested either 300 mg posaconazole (Noxafil 100 mg delayed-release tablet; Merck Sharp & Dohme Ltd.) or placebo capsules containing microcrystallized cellulose at 8 AM and 8 PM on day 1 (loading dose), and at 8 AM on days 2-6 (Figure 1). On day 5, following an overnight fast, the participants arrived in the

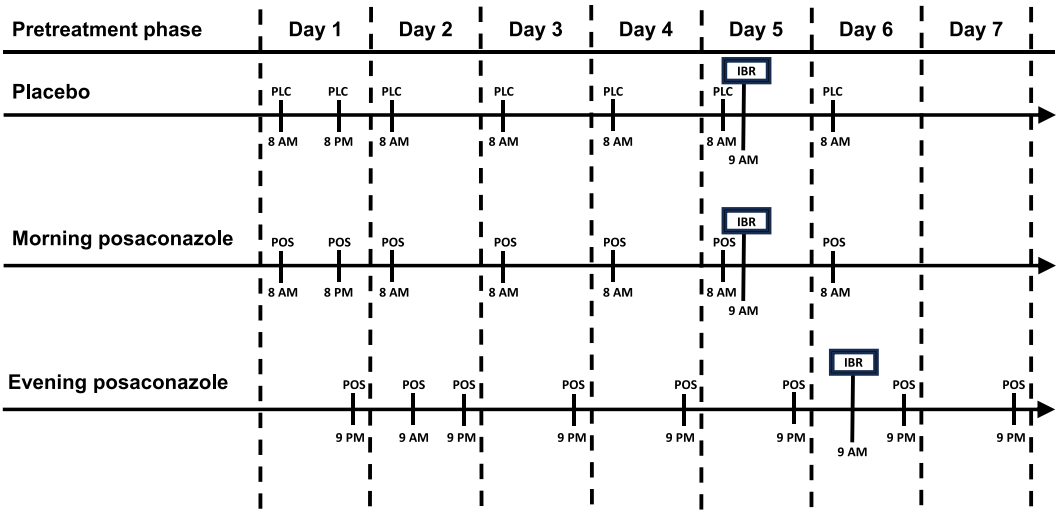

FIGURE 1 Study design. Eleven healthy individuals ingested as pretreatment either placebo (PLC) or 300 mg of posaconazole (POS) at 8 AM and 8 PM on day 1, and at 8 AM on days 2-6, or 300 mg of posaconazole at 9 PM on day 1, and at 9 AM and 9 PM on day 2, and at 9 PM on days 3-7. The study participants were administered an ibrutinib dose of 140 mg on day 5 (placebo phase) or 30 mg on day 5 (morning posaconazole phase) or 70 mg on day 6 (evening posaconazole phase). All ibrutinib doses (IBR) were administered at 9 AM.

laboratory in the morning and were given the posaconazole and placebo doses at 8 AM with 150 mL of water, followed by a standardized breakfast. Thereafter, a single oral dose of ibrutinib (30-mg dose in phase 1 and 140-mg dose in phase 3) was administered at 9 AM with 150 mL of water. In phase 2 (evening posaconazole) of the study, the participants ingested 300 mg of posaconazole at 9 PM on day 1, at 9 AM and 9 PM on day 2, and at 9 PM on days 3-7 (Figure 1). On day 6, following an overnight fast, the participants arrived in the laboratory in the morning and were given a standardized breakfast at 8 AM. Thereafter, a single 70-mg oral dose of ibrutinib was administered at 9 AM with 150 mL of water. The 30- and 70-mg ibrutinib capsules were prepared from the contents of the 140-mg ibrutinib capsules (Imbruvica 140 mg capsule; Janssen-Cilag) by mixing them with microcrystallized cellulose by HUS Pharmacy (Helsinki University Hospital, Hospital District of Helsinki and Uusimaa [HUS]). As described above, a standardized breakfast was served 1 h before ibrutinib administration. In addition, a warm meal was served 3 h and snacks 7 and 10 h after ibrutinib ingestion. The use of other drugs was prohibited from 1 week before to 1 week after each of the three study periods. The use of grapefruit was prohibited from 3 days before to the end of each study period and the use of alcohol was prohibited during each study period. Compliance with the study protocol was confirmed with a structured pretreatment diary and posaconazole concentration measurements.

Blood samples were collected at 8 AM (prior to the administration of the morning pretreatment), and 5 min before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 23 and 47 h after ibrutinib ingestion into tubes containing ethylenediaminetetraacetic acid. The samples were placed on ice immediately after they were drawn, and plasma was separated within 30 min. After separating the plasma, white blood cells were gathered from the first blood sample and stored at −20°C for DNA extraction. The separated plasma was stored at −70°C until analysis.

2.3 | Determination of drug concentrations

The plasma samples were prepared by use of a Phree phospholipid removal plate in 96-well format (Phenomenex) according to manufacturer's recommendations. In short, an aliquot of 100 µL of plasma was mixed with 400 µL of acetonitrile containing 1% formic acid and the deuterium-labelled internal standards ibrutinib-D5, PCI-45227-D4 and posaconazole-D4. The mixture was then drawn through the cartridge, evaporated to dryness in a centrifugal evaporator (GeneVac, Thermo Fisher Scientific) and reconstituted in 20% acetonitrile.

The plasma ibrutinib, the active metabolite PCI-45227 and posaconazole were quantified using a Qtrap5500 liquid chromatography-tandem mass spectrometer (AB Sciex). The mobile phase consisted of 0.1% formic acid and acetonitrile, and the analytical column was a Luna C18 (2.1 × 100 mm inner diameter, 1.6 µm particle size; Phenomenex). The separation was achieved in 6 min using a linear gradient from 20% to 77% of acetonitrile at constant 300 µL min^{-1} flow rate and 35°C column temperature. The mass spectrometer was operated in positive multiple reaction-monitoring mode utilizing electrospray ionization. Ibrutinib, PCI-45227 and posaconazole were monitored using mass-to-charge ratios (m/z) 441 to 138, 475 to 84, and 701 to 683, and the lower limits of quantification were 0.2, 0.2 and 100 ng mL^{-1}, respectively. The between-day ($n = 6$) precisions for ibrutinib and PCI-45227 were 7.1% and 3.7% (quality control

4.0 ng ml^{-1}), and 9.1% and 6.8% (quality control 100 ng mL^{-1}). For posaconazole, the between-day precisions were 3.9% (330 ng mL^{-1}) and 7.1 (2000 ng mL^{-1}). The between-day accuracies were within ±15% for all analytes.

2.4 | Pharmacokinetics

For comparisons between study phases, ibrutinib and its active metabolite, PCI-45227, concentrations were adjusted to a single 140-mg ibrutinib dose, assuming dose-linearity (dose-adjusted AUC = measured AUC × [140/administered ibrutinib dose in mg]), as shown previously.[21] Pharmacokinetic calculations were performed for these concentrations using standard noncompartmental methods in Phoenix WinNonlin, Version 6.4 (Certara) to determine the peak plasma concentration (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{½}$), $AUC_{0\text{-}23h}$ and $AUC_{0\text{-}\infty}$. For comparisons between clinically recommended doses of ibrutinib alone and with posaconazole, ibrutinib concentrations and AUC values were also adjusted to 420- and 70-mg doses for individual plasma concentration-time curves. For posaconazole, the C_{max}, $AUC_{0\text{-}5h}$ and $AUC_{0\text{-}13h}$ were determined based on concentrations observed in the study days (from 8 AM sample onwards).

2.5 | Genotyping

Genomic DNA was extracted from buffy coats using the Maxwell® 16 LEV Blood DNA Kit (Promega). Study participants were genotyped for the decreased function allele *CYP3A4*22* (rs35599367) and the no function *CYP3A5*3* allele (6986A > G; rs776746) using TaqMan® Genotyping assays on a QuantStudio 12 K Flex Real-Time PCR system (Thermo Fisher Scientific). Samples with confirmed wild-type, *22 or *3 alleles were used as controls. Alleles containing the reference nucleotide were designated as *1.

2.6 | Statistical analyses

Based on previous data,[11] a sample size of 10 participants was estimated to be sufficient to detect a 40% difference in the AUC of ibrutinib between placebo and posaconazole phases with a power of at least 80% (α level 5%). To allow potential dropouts, final sample size was set to 12. Statistical analyses were performed using IBM SPSS Statistics for Macintosh Version 26.0 (IBM Corporation). Prior to analysis, the pharmacokinetic variables, except t_{max}, were logarithmically transformed. These pharmacokinetic variables were compared between the different study phases by repeated-measures analysis of variance with treatment phase as a within-subjects factor. The Wilcoxon signed rank test was used in comparing the t_{max} data. *P* values below 0.05 were considered statistically significant. All results are expressed as geometric means and geometric mean ratios with geometric coefficient of variation (CV) or 90% confidence intervals (CI) unless stated otherwise. Correlations between pharmacokinetic variables were examined using Pearson's correlation coefficients.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[22]

3 | RESULTS

One out of 12 participants dropped out before initiation of pretreatment. All remaining 11 participants completed the study. No adverse effects were reported or observed. The original unadjusted ibrutinib and ibrutinib metabolite PCI-45227 concentration-time profiles are shown in Figure S1. After adjusting the concentrations to a 140-mg dose of ibrutinib, both morning and evening posaconazole greatly increased the exposure to ibrutinib, but had only minor effects on exposure to the ibrutinib metabolite PCI-45227 (Table 1 and Figure 2).

3.1 | Effects of posaconazole on ibrutinib pharmacokinetic variables

In the morning posaconazole phase, with a 1-h interval between posaconazole and ibrutinib intake, posaconazole increased the 140-mg dose-adjusted geometric mean $AUC_{0\text{-}\infty}$ and C_{max} of ibrutinib 9.5-fold (90% CI 6.3-14.3, $P < 0.001$) and 8.5-fold (90% CI 5.7-12.8, $P < 0.001$), respectively (Table 1 and Figure 2). It also increased the $AUC_{0\text{-}\infty}$ of the sum of active compounds (ibrutinib +1/15 of PCI-45227) 7.5-fold (90% CI 5.6-9.9, $P < 0.001$).

In the evening posaconazole phase, with a 12-h interval between posaconazole and ibrutinib intake, posaconazole increased the dose-adjusted geometric mean $AUC_{0\text{-}\infty}$ and C_{max} of ibrutinib 10.3-fold (90% CI 6.7-16.0, $P < 0.001$) and 8.2-fold (90% CI 5.2-13.2, $P < 0.001$), respectively (Table 1 and Figure 2). The $AUC_{0\text{-}\infty}$ of active compounds was increased 8.1-fold (90% CI 5.7-11.5, $P < 0.001$). Posaconazole had no significant effect on the half-life of ibrutinib in either phase. No significant differences were found in the ibrutinib pharmacokinetic variables between the posaconazole phases.

3.2 | Effects of posaconazole on PCI-45227 pharmacokinetic variables

Posaconazole postponed the C_{max} of PCI-45227 from 3 to 4 h ($P = 0.024$) in the morning phase and tended to decrease the

TABLE 1 Pharmacokinetic variables of ibrutinib and its metabolite PCI-45227 adjusted to a single 140-mg ibrutinib dose in 11 healthy subjects following a single 140-mg (with placebo), 30-mg (with morning posaconazole) or 70-mg (with evening posaconazole) oral dose of ibrutinib during a 7-day pretreatment with once-daily placebo in the morning or 300 mg of posaconazole in the morning or evening

Variable	Placebo	Morning posaconazole	Evening posaconazole	Geometric mean ratio (90% CI) Morning posaconazole *vs* placebo	Geometric mean ratio (90% CI) Evening posaconazole *vs* placebo	Geometric mean ratio (90% CI) Morning *vs* evening posaconazole
Ibrutinib						
C_{max} (ng mL^{-1})	21.2 (1.24)	180.1 (0.56)	175.4 (0.64)	8.52 (5.66, 12.8) $P < 0.001$	8.23 (5.20, 13.2) $P < 0.001$	1.03 (0.79, 1.34) $P = 0.146$
t_{max} (h)	3 (1.5, 4)	4 (2, 4)	3 (1, 4)	$P > 0.999$	$P = 0.643$	$P = 0.161$
$t_{½}$ (h)	4.8 (0.25)	5.0 (0.40)	5.1 (0.32)	1.05 (0.86, 1.28) $P = 0.678$	1.06 (0.85, 1.33) $P = 0.638$	0.99 (0.78, 1.25) $P = 0.919$
AUC_{0-23h} (ng·h mL^{-1})	74.7 (1.27)	704.9 (0.53)	770.7 (0.58)	9.43 (6.28, 14.2) $P < 0.001$	10.3 (6.61, 16.1) $P < 0.001$	0.91 (0.71, 1.18) $P = 0.544$
$AUC_{0-\infty}$ (ng·h mL^{-1})	76.9 (1.26)	732.3 (0.53)	794.3 (0.58)	9.52 (6.34, 14.3) $P < 0.001$	10.3 (6.65, 16.0) $P < 0.001$	0.92 (0.71, 1.19) $P = 0.577$
PCI-45227						
C_{max} (ng mL^{-1})	33.7 (0.40)	26.3 (0.39)	27.9 (0.35)	0.78 (0.63, 0.96) $P = 0.056$	0.83 (0.66, 1.03) $P = 0.156$	0.94 (0.82, 1.08) $P = 0.439$
t_{max} (h)	3 (1.5, 4)	4 (3, 6)	3 (3, 6)	$P = 0.024$	$P = 0.167$	$P = 0.066$
$t_{½}$ (h)	7.3 (0.21)	10.8 (0.25)	12.9 (0.21)	1.47 (1.31, 1.65) $P < 0.001$	1.76 (1.48, 2.09) $P < 0.001$	0.83 (0.69, 1.01) $P = 0.108$
AUC_{0-23h} (ng·h mL^{-1})	253.1 (0.40)	269.5 (0.40)	300.1 (0.38)	1.06 (0.85, 1.33) $P = 0.616$	1.19 (0.93, 1.51) $P = 0.234$	0.90 (0.77, 1.05) $P = 0.228$
$AUC_{0-\infty}$ (ng·h mL^{-1})	287.3 (0.41)	364.4 (0.41)	431.6 (0.43)	1.27 (1.01, 1.60) $P = 0.092$	1.50 (1.14, 1.98) $P = 0.024$	0.84 (0.71, 1.01) $P = 0.109$
PCI-45227/Ibrutinib $AUC_{0-\infty}$ ratio	3.7 (1.01)	0.50 (0.51)	0.54 (0.56)	0.13 (0.10, 0.18) $P < 0.001$	0.15 (0.10, 0.20) $P < 0.001$	0.92 (0.76, 1.10) $P = 0.398$
Ibrutinib + active metabolite[a]						
$AUC_{0-\infty}$ (ng·h mL^{-1})	101.9 (0.90)	759.1 (0.52)	826.6 (0.57)	7.45 (5.59, 9.93) $P < 0.001$	8.12 (5.74, 11.5) $P < 0.001$	0.92 (0.71, 1.18) $P = 0.552$

Note: Data are given as geometric mean with geometric coefficient of variation, t_{max} as median with range. The geometric mean ratios between the phases are given with 90% confidence interval.
Abbreviations: $AUC_{0\text{-}23h}$, area under the plasma concentration-time curve from time 0 to 23 h; $AUC_{0\text{-}\infty}$, area under the plasma concentration-time curve from time from zero to infinity; CI, confidence interval; C_{max}, peak plasma concentration; t_{max}, time to C_{max}; $t_{1/2}$, elimination half-life.
[a]Active metabolite is defined as 1/15 of PCI-45227 $AUC_{0\text{-}\infty}$.

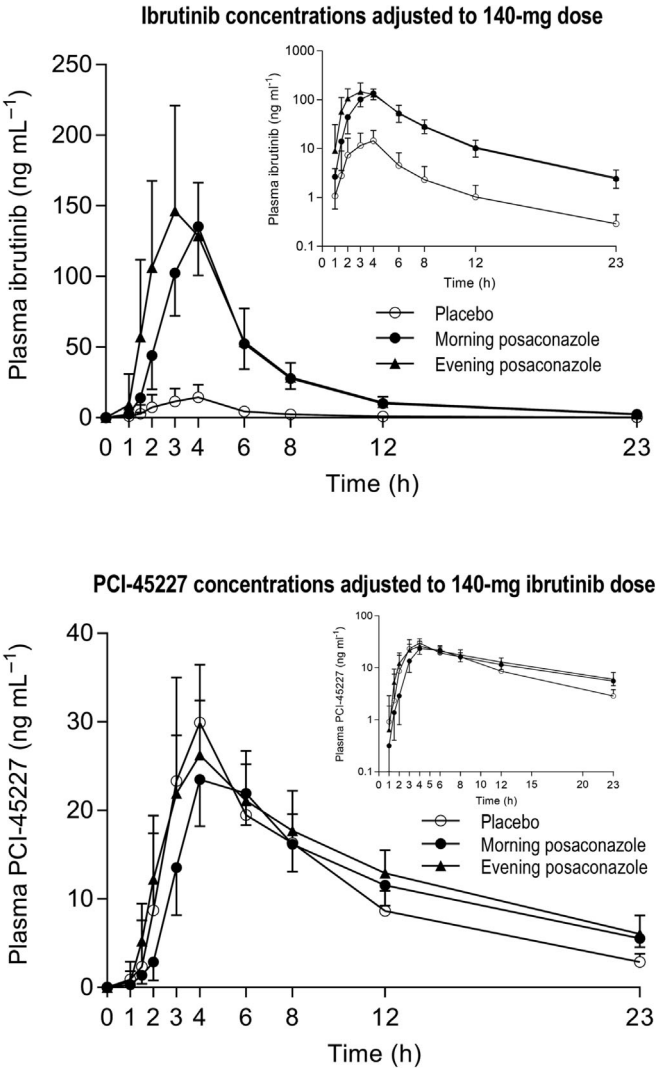

FIGURE 2 The plasma concentrations of ibrutinib and its metabolite PCI-45227 in a randomized crossover study in 11 healthy subjects after a single 140-mg (placebo phase) or 30-mg (morning posaconazole phase) or 70-mg (evening posaconazole phase) oral dose of ibrutinib following pretreatment with either posaconazole or placebo. Ibrutinib and PCI-45227 concentrations for both posaconazole phases were adjusted to a 140-mg dose. Data are presented as geometric means with 90% confidence intervals. Insets depict the same data on a semilogarithmic scale.

dose-adjusted C_{max} slightly in both phases (Table 1). On the other hand, it prolonged the $t_{½}$ of PCI-45227 by 47% and 76% in the morning and evening phases, respectively ($P < 0.001$), resulting in a 1.50-fold (90% CI 1.14-1.98, $P = 0.024$) increase in the dose-adjusted $AUC_{0-\infty}$ of PCI-45227 in the evening phase. The metabolite PCI-45227/ibrutinib $AUC_{0-\infty}$ ratio was decreased by posaconazole to 13% (90% CI 10-18%, $P < 0.001$) and 15% (90% CI 10-20%, $P < 0.001$) of control in the morning and evening phases, respectively.

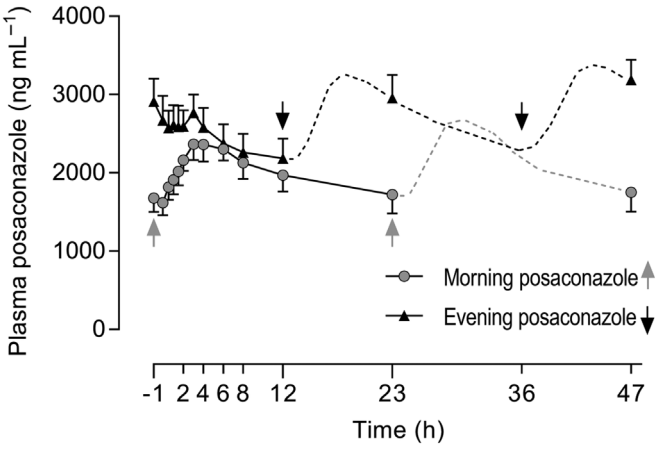

FIGURE 3 The plasma concentrations of posaconazole in a randomized crossover study in 11 healthy subjects on days 5-7 (morning posaconazole phase) and days 6-8 (evening posaconazole phase). In the morning posaconazole phase, the study participants ingested 300 mg of posaconazole at 8 AM and 8 PM on day 1, and at 8 AM on days 2-6. In the evening posaconazole phase, the study participants ingested 300 mg of posaconazole at 9 AM on day 1, and at 9 AM and 9 PM on day 2, and at 9 PM on days 3-7. Data are presented as geometric means with 90% confidence intervals. Arrows depict the time of posaconazole administration. Time frame is relative to ibrutinib administration.

3.3 | Posaconazole pharmacokinetics

On the day of ibrutinib administration, the concentrations of posaconazole were higher in the evening posaconazole phase than in the morning phase (Figure 3). In the evening phase, the C_{max} of posaconazole was 29% higher (90% CI 19-39%, $P < 0.001$) than that in the morning phase (data not shown). The AUC_{0-5h} and AUC_{0-13h} of posaconazole in the evening phase were 32% (90% CI 21-44%, $P < 0.001$) and 16% (90% CI 6.7-26%, $P = 0.010$) greater than those in the morning phase, respectively.

3.4 | Variability in ibrutinib pharmacokinetics and extent of interaction

The variability in ibrutinib pharmacokinetics in the placebo phase was substantial, with more than 20-fold interindividual differences in ibrutinib C_{max} and $AUC_{0-\infty}$, resulting in geometric CV values above 120% (Table 1 and Figure 4). Posaconazole reduced the variability in $AUC_{0-\infty}$ to 53-58%. The effect of posaconazole on ibrutinib $AUC_{0-\infty}$ varied substantially from 3.6- to 55.4-fold and 3.2- to 52.0-fold in the morning and evening phases, respectively. The greatest increases were observed in individuals with the lowest $AUC_{0-\infty}$ and highest PCI-45227/ibrutinib $AUC_{0-\infty}$ ratio, an index of individual CYP3A4-metabolizer status, in the control phase (Figure 5). Accordingly, significant correlations (Pearson 2-tailed, $r^2 = 0.97$ (morning) and $r^2 = 0.86$ (evening), $P < 0.001$) were seen between the fold-

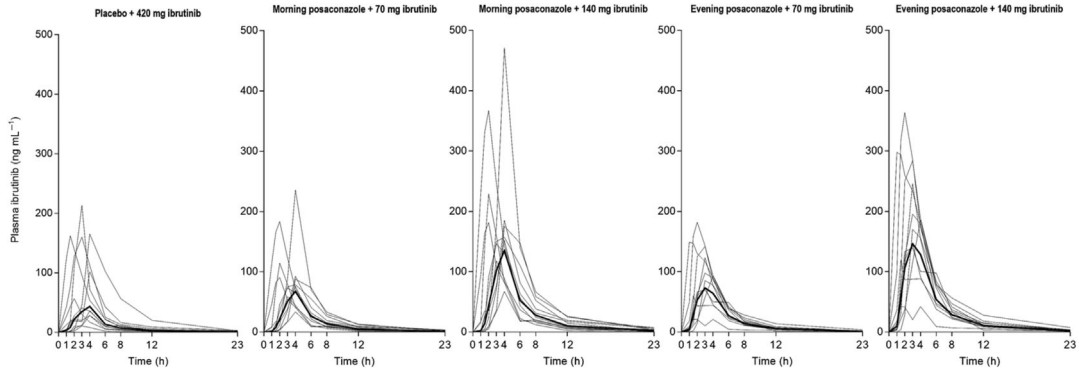

FIGURE 4 The individual plasma concentration-time curves of ibrutinib in placebo and posaconazole phases. For the placebo phase, the ibrutinib concentrations are adjusted to a 420-mg oral dose of ibrutinib. For the posaconazole phases, the ibrutinib concentrations were adjusted to either a 70- or 140-mg oral dose of ibrutinib. The bold lines represent the geometric means.

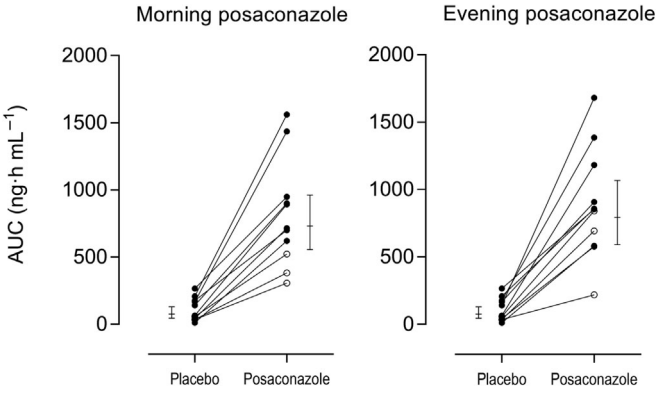

FIGURE 5 The individual areas under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) of ibrutinib in the placebo phase and both posaconazole phases with 90% confidence intervals following a single 140-mg oral dose of ibrutinib. White symbols depict CYP3A5 expressors.

change in ibrutinib $AUC_{0-\infty}$ and the control PCI-45227/ibrutinib $AUC_{0-\infty}$ ratio (Figure 6).

Three of the subjects had the CYP3A5 expressor genotype (*CYP3A5*1/*3*), while the other eight subjects were CYP3A5 non-expressors. Compared to CYP3A5 non-expressors, the expressors seemed to have a lower ibrutinib AUC with and without posaconazole, but there were no other apparent differences between the genotypes in ibrutinib pharmacokinetic variables or extent of interaction (Figures 5 and 6). There was no correlation between fold increase in ibrutinib AUC and the C_{max}, $AUC_{0\text{-}5h}$ or $AUC_{0\text{-}13h}$ of posaconazole (data not shown).

3.5 | Evaluation of clinically recommended dose adjustments of ibrutinib during posaconazole coadministration

To evaluate the appropriateness of the recommended 70- and 140-mg daily doses of ibrutinib during posaconazole treatment, we adjusted the concentrations and $AUC_{0-\infty}$ of ibrutinib during the posaconazole phases to these doses and during the placebo phase to the typical 420 mg (daily) dose of ibrutinib in absence of interactions (Figures 4 and 7). Based on these adjustments, a 70- or 140-mg ibrutinib dose with posaconazole in the morning would result in a geometric mean $AUC_{0-\infty}$ of ibrutinib that is 59% and 217% larger than that after 420 mg ibrutinib without posaconazole, respectively (Figure 7). With posaconazole in the evening, the respective geometric mean $AUC_{0-\infty}$ of ibrutinib would be 72% and 244% larger than that after 420 mg of ibrutinib without posaconazole (Figure 7). On the other hand, due to reduced variability, the highest individual exposure and $AUC_{0-\infty}$ values of ibrutinib with the 70-mg dose during posaconazole treatment remained in the same range as with 420 mg ibrutinib without posaconazole.

4 | DISCUSSION

Our results showed that treatment with typical posaconazole doses increased the exposure to ibrutinib by about 10-fold, simultaneously decreasing interindividual variation in ibrutinib concentrations. The extent of the interaction varied greatly, from a threefold to a 55-fold increase in ibrutinib AUC. This is likely due to high variability in the rate of CYP3A4-mediated ibrutinib metabolism; individuals with the lowest exposures to ibrutinib and the highest metabolite to ibrutinib ratios in the placebo phase had the highest fold-changes in ibrutinib AUC (Figures 5 and 6). Of note, individuals with a CYP3A5 expressor genotype had neither a particularly high PCI-45227/ibrutinib ratio nor large AUC increases and remained in the lower range of AUC values during posaconazole treatment. Nevertheless, the reduced interindividual variability in ibrutinib exposure indicates that a strong CYP3A4 inhibitor, such as posaconazole, reduces variability due to differences in CYP3A4 activity, thereby resulting in more predictable ibrutinib pharmacokinetics.

The effect of posaconazole on ibrutinib pharmacokinetics was approximately as strong as that of the strong CYP3A4 inhibitor itraconazole.[11] The effect was even stronger than what was expected

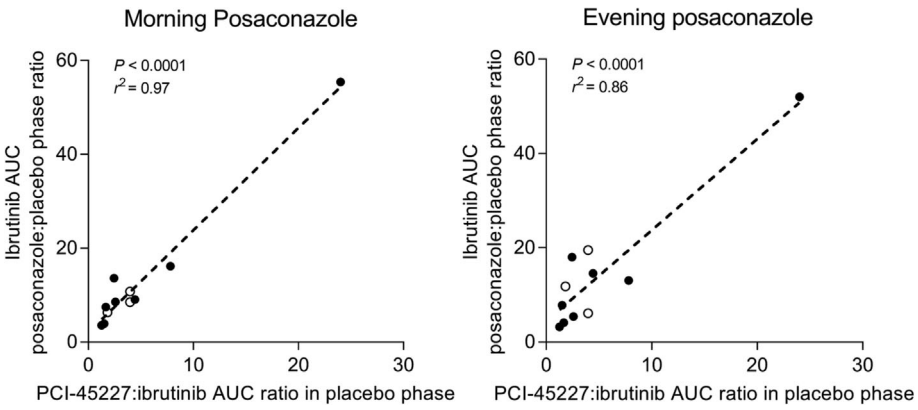

FIGURE 6 The correlation of the PCI-45227:ibrutinib area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) ratio in the placebo phase with the ibrutinib $AUC_{0-\infty}$ posaconazole to control ratio for both morning and evening posaconazole phases. White symbols depict CYP3A5 expressors.

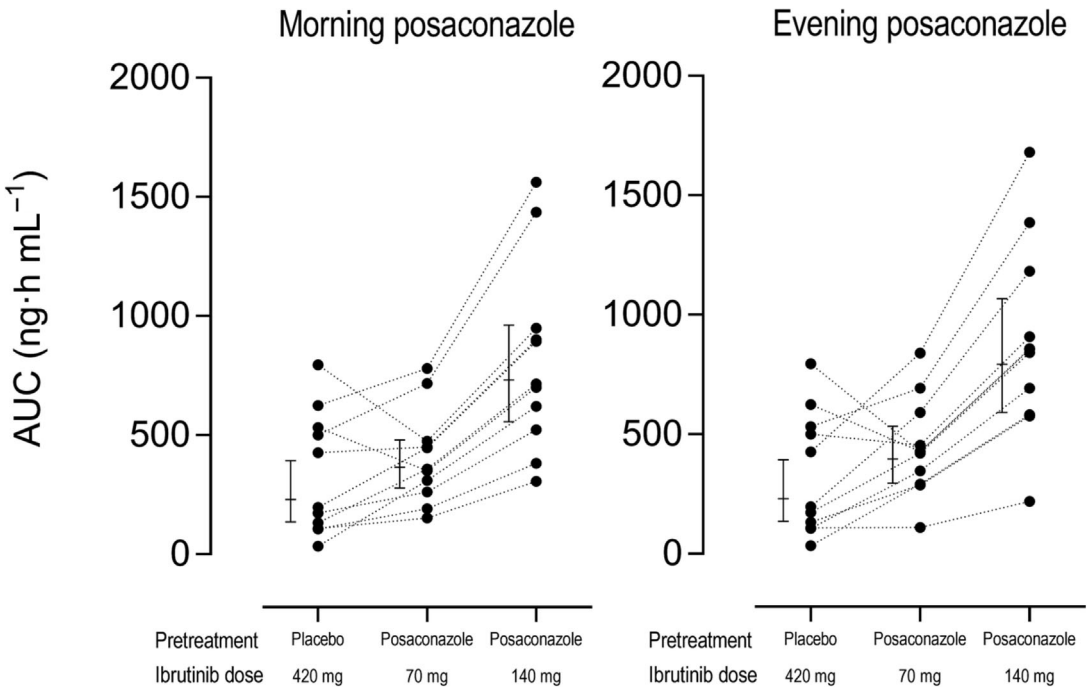

FIGURE 7 The individual (black circles) and geometric mean (horizontal lines with error bars indicating ± 90% confidence interval) areas under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) of ibrutinib in the placebo phase and both posaconazole phases adjusted to either a single 420-mg (placebo phase) or 70-mg (both posaconazole phases) or 140-mg (both posaconazole phases) oral dose of ibrutinib.

based on earlier studies on posaconazole and CYP3A4 substrates. Posaconazole in 200-800 mg daily doses previously increased the AUC of midazolam, a gold-standard CYP3A4-index substrate, 4.6-6.2-fold,[23,24] while itraconazole has increased the exposure to midazolam more than 10-fold.[25,26] Similarly, the effect of posaconazole on the pharmacokinetics of simvastatin, a statin with very extensive presystemic CYP3A4-mediated metabolism, seems to have been smaller than that of itraconazole.[24,27] A possible explanation is that posaconazole has a relatively stronger effect at the hepatic level than at the intestinal level; much of the first-pass metabolism of ibrutinib seems to occur at the hepatic level, as it is not particularly sensitive to interaction caused by grapefruit juice,[10] and the effect of posaconazole on ibrutinib AUC was strong even when it was given 12 h before ibrutinib.

Administering ibrutinib 12 h after the preceding posaconazole dose led to an equally strong effect on ibrutinib AUC as administering ibrutinib 1 h after posaconazole. This is likely due to posaconazole's long half-life (up to 31 h in healthy volunteers following oral dosing[28]) resulting in high predose (trough) concentrations in plasma and tissues during once-daily dosing. In our study, posaconazole concentrations seemed to be approximately 30% higher in the evening phase than in the morning phase, suggesting a circadian pharmacokinetic variation, eg, due to dietary influence on absorption of posaconazole. The morning dose was taken after an overnight fast with breakfast, while the evening dose was taken with no preceding long fasting. Food intake can increase the exposure to posaconazole up to 50% when using delayed-release tablets.[29] Nevertheless, it can be argued that the inhibition of presystemic metabolism of ibrutinib was at a near-maximal

level in both posaconazole phases, explaining the lack of differences in ibrutinib concentrations between the morning and evening phases. Of note, posaconazole had no significant effect on ibrutinib's half-life, which indicates that the interaction is caused by inhibition of CYP3A4 during the first pass of ibrutinib.

An increased risk for early occurring invasive fungal infections (IFI), including invasive aspergillosis, has been described in patients receiving ibrutinib.[14,15,30,31] The 1-year incidence of IFI by ibrutinib has been reported to be 3%.[31] At the moment, there is no recommendation for routine antifungal prophylaxis for patients using single-agent ibrutinib. However, patients with other predisposing factors, such as prior chemotherapy, haematopoietic stem cell transplant, neutropenia and the use of corticosteroids and/or rituximab, are at high risk for life-threatening fungal infections and can benefit from prophylaxis.[14,15,30,31]

Posaconazole is recommended as the primary antifungal prophylaxis in patients at high risk for IFI.[19,20] Posaconazole regimen-specific guidelines exist for ibrutinib dosing when used concomitantly with posaconazole.[1,5] Instead of the generally used 420- or 560-mg daily ibrutinib dose in absence of interacting medications, the FDA label recommends a reduced 70-mg ibrutinib dose once daily in B-cell malignancies and a 140-mg dose in chronic graft-*vs*-host disease when used together with once-daily 300-mg posaconazole delayed-release tablets. On the other hand, the EMA summary of product characteristics recommends a 140-mg daily ibrutinib dose with any posaconazole regimen, but only if the benefit outweighs the risks. Of note, 140 mg is the smallest available tablet in Europe.

Our results show that during posaconazole treatment even the lowest commercially available dose of 70 mg of ibrutinib results in a mean exposure to ibrutinib that exceeds that obtained with the typical 420-mg daily doses in absence of CYP3A4 inhibitors. On the other hand, due to the reduced interindividual variability in ibrutinib pharmacokinetics, it seems that by using the 70-mg daily ibrutinib dose with posaconazole it is possible to avoid excessive ibrutinib exposures at individual level, at least those exceeding the exposure range with the standard 420-mg dose. However, using the 140-mg dose of ibrutinib with posaconazole, as recommended in the European prescribing information, will lead to exposures that markedly exceed those with standard daily doses in most individuals, likely leading to risk of concentration-dependent adverse effects. Similar to the above suggestions, both the average change in bioavailability or AUC and reduction in interindividual variability should be taken into account if CYP3A inhibitor drug-drug interactions are intentionally used to boost ibrutinib pharmacokinetics, as suggested previously.[11,32–34]

It has been suggested that CYP3A4 inhibitors can be intentionally used together with ibrutinib to reduce its cost.[11,34,35] The financial burden of standard-dose ibrutinib treatment is extensive. Based on emerging evidence from small case series, it seems that administration of low-dose ibrutinib concomitantly with the strong CYP3A4 inhibitor itraconazole can result in a very good treatment response with no excess adverse effects, simultaneously reducing drug costs by at least two thirds.[11,35] Especially in low-income countries, such a substantial reduction in costs could make the treatment available to a much larger number of patients than would otherwise be possible. Moreover, both itraconazole and posaconazole have been shown to reduce the individual variability in ibrutinib exposure by about 50%, which may even reduce adverse events due to decreased risk of reaching excessive or toxic ibrutinib concentrations in individual patients. Of note, posaconazole is a high-cost drug in itself, and thus its concomitant use with low-dose ibrutinib has a lesser effect on the financial burden of the treatment unless it is required as an antifungal agent in any case. In any event, azole antifungals can provide prophylaxis to fungal infections, which can sometimes be necessary in patients treated with ibrutinib.

Although ibrutinib has demonstrated marked efficacy in CLL, in the long term up to half of patients discontinue ibrutinib therapy, toxicity being the most common reason for discontinuation in clinical practice.[6–8] The most common adverse effects include atrial fibrillation, cytopenias, bleeding, arthralgias and rash.[36] Dose reductions due to adverse effects are also common, especially during the first year of treatment. Some of the adverse effects of ibrutinib are due to off-target inhibition of kinases other than BTK, for example the proarrhythmic effect of ibrutinib, causing atrial fibrillation, has been found to result from off-target inhibition of C-terminal Src kinase by ibrutinib.[37] Such effects are likely to be concentration-dependent, ie, high ibrutinib concentrations increase the risk for adverse effects. Our data suggest that to avoid excessive ibrutinib exposure and mitigate the risk of concentration-dependent adverse effects, the 70-mg daily dose of ibrutinib should not be exceeded during posaconazole treatment. Already this dose seems to ensure a sufficient ibrutinib exposure in all patients during concomitant posaconazole.

Due to ibrutinib's extensive CYP3A4-mediated metabolism and highly variable pharmacokinetics, its safe and efficient use can be challenging. The results of this study show that treatment with typical daily doses of posaconazole increases ibrutinib exposure substantially, by about 10-fold, and decreases interindividual variability in exposure regardless of the dosing interval between posaconazole and ibrutinib. Our results also suggest that the currently recommended relatively modest ibrutinib dose reductions can lead to excessive ibrutinib concentrations and increased risk for adverse effects. Our study can be viewed as a pilot study in determining an optimal safe and effective ibrutinib dose when used together with posaconazole. We believe that the results can be extrapolated to patients, since the pharmacokinetics of ibrutinib are similar between healthy volunteers and CLL patients.[13] We thus suggest that a 70-mg daily dose of ibrutinib should not be exceeded during posaconazole treatment to avoid ibrutinib concentrations exceeding the typical therapeutic range.

AUTHOR CONTRIBUTIONS

Aleksi M. Olkkola, Tuija Tapaninen, Aleksi Tornio, Pertti J. Neuvonen, Mikko Niemi and Janne T. Backman contributed to the study design. Aleksi M. Olkkola, Tuija Tapaninen, Aleksi Tornio, Milka Hauta-aho, Outi Lapatto-Reiniluoto, Mikko Neuvonen, Johanna I. Kiiski, Mikko Niemi and Janne T. Backman contributed to the research and acquisition of data and to analysis and interpretation of data. Aleksi

M. Olkkola, Tuija Tapaninen, Aleksi Tornio and Janne T. Backman drafted the manuscript. All authors reviewed and accepted the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

Individual-level data from this clinical study cannot be shared publicly because it includes confidential personal information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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