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An Open-Label Study to Assess the Effect of Itraconazole and Rifampin on Parsaclisib Pharmacokinetics When Administered Orally in Healthy Participants

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Abstract

Parsaclisib, a selective, potent phosphatidylinositol 3-kinase delta inhibitor being developed for the treatment of cancer and autoimmune diseases, is primarily metabolized by cytochrome P450 (CYP) 3A4. This study assessed the pharmacokinetics (PK) and safety of parsaclisib alone or combined with itraconazole (potent CYP3A inhibitor) or rifampin (potent CYP3A4 inducer) in healthy participants. In this open-label, fixed-sequence study, cohort 1 received oral parsaclisib 10 mg once daily on days 1 and 8 and oral itraconazole 200 mg once daily on days 4-11; cohort 2 received oral parsaclisib 20 mg once daily on days 1 and 11 and oral rifampin 600 mg once daily on days 4-12. Parsaclisib plasma concentration was tested and PK parameters calculated by noncompartmental analysis. Geometric mean ratios (GMRs) and 2-sided 90% confidence intervals (CIs) were estimated by 2-factor analysis of variance. Thirty-six healthy participants were enrolled (18 per cohort). Parsaclisib maximum plasma drug concentration (C_{max}) and area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) were increased by 21% and 107% with concomitant itraconazole versus parsaclisib alone (GMR, 1.21; 90%CI, 1.14-1.29; and 2.07; 90%CI, 1.97-2.17, respectively). Parsaclisib C_{max} and AUC were reduced by 43% and 77%, respectively, with concomitant rifampin versus parsaclisib alone (GMR, 0.57; 90%CI, 0.53-0.60; and 0.23; 90%CI, 0.21-0.24, respectively). Headache was the most common adverse event, reported by 13.9% of participants (all in cohort 2). Single-dose parsaclisib alone or combined with itraconazole or rifampin appeared safe and well tolerated in healthy participants. Parsaclisib dose adjustment may be necessary with concomitant administration of strong CYP3A4 inhibitors or inducers.

Keywords

drug-drug interaction, pharmacokinetics, INCB050465, parsaclisib, PI3Kδ inhibitor

Dysregulation of phosphatidylinositol 3-kinase delta (PI3Kδ) is implicated in malignant B-cell activation, proliferation, and survival.[1,2] Parsaclisib (INCB050465) is a next-generation, potent inhibitor of the human PI3Kδ kinase enzyme (whole-blood half-maximal inhibitory concentration [IC_{50}] = 10 nM), with approximately 20 000-fold selectivity relative to other PI3K isoforms.[3,4] Preclinical models demonstrate the efficacy of parsaclisib,[3,5] and clinical studies support the benefit of parsaclisib in relapsed or refractory B-cell malignancies.[4,6] Parsaclisib is currently under investigation as monotherapy or in combination in a number of clinical trials in patients with B-cell malignancies, solid tumors, and autoimmune disorders.

Human pharmacokinetic (PK) studies with parsaclisib showed a time to maximum plasma drug concentration (t_{max}) of 0.5 to 1 hour and apparent plasma terminal phase disposition half-life ($t_{\frac{1}{2},\beta}$) of 8.6 to 11.5 hours.[6] Doses of up to 45 mg once daily have been evaluated in cancer patients, with doses > 5 mg once daily achieving exposure levels exceeding 90% of maximal inhibitory concentration throughout the dosing interval.[6] No time-dependent PK or sex differences in exposure were observed in humans. Although higher exposure was observed in Japanese patients because of low body weight, body weight-normalized clearance was comparable in white and Japanese patients. In addition to the PK profile allowing a favorable dosing regimen, the molecular structure of parsaclisib was designed to limit off-target

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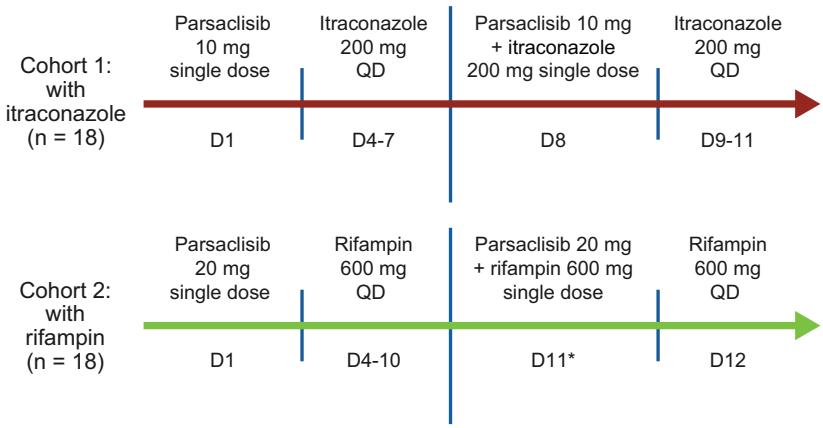

Figure 1. Study treatment schedule. D, day; QD, once daily. *PK parameter results for 1 participant on day 11 of cohort 2 were excluded from the statistical analysis based on the rifampin analysis results, which indicated the participant had not taken rifampin as scheduled.

hepatotoxicity seen with first-generation PI3Kδ inhibitors (eg, idelalisib and duvelisib).[7,8]

In vitro experiments demonstrated that parsaclisib is not likely a substrate of human OATP1B and OATP1B3, and at clinically relevant exposure, the potential of drug-drug interaction (DDI) via inhibition of human uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2K is low (data on file, Incyte Corporation). Parsaclisib is a P-glycoprotein (P-gp) substrate (efflux transport saturated at >100 μM) and a P-gp inhibitor, with IC_{50} = 18.1 μM (data on file, Incyte Corporation). However, the potential for a DDI is low with P-gp substrates or inhibitors based on the therapeutic clinical dose, the expected plasma concentrations of parsaclisib at that dose, its inhibitory potency for P-gp, and the decision tree in the U.S. Food and Drug Administration (FDA) guidance.[9] In vitro studies with recombinant human cytochrome P450 (CYP) isozymes have determined that parsaclisib is primarily metabolized by CYP3A4, is not an inhibitor of major CYPs tested, and is not a CYP3A4 inducer. In experiments using human liver microsomes and selective CYP chemical inhibitors, ketoconazole (a potent CYP3A4 inhibitor) inhibited parsaclisib metabolism (data on file, Incyte Corporation). In an in vitro study, parsaclisib metabolism was similar across tested species (rat, dog, and human), with no human-specific metabolite identified. Phase 1 metabolites identified from in vitro preparations were primarily oxidative, and no major metabolites were detected in clinical plasma samples (data on file, Incyte Corporation).

Itraconazole is a potent inhibitor of CYP3A, whereas rifampin is a potent inducer of CYP3A4.[9-11] Therefore, inhibition of parsaclisib metabolism by itraconazole has the potential to increase exposure of parsaclisib, whereas induction of parsaclisib metabolism by rifampin has the potential for reduced exposure. We conducted a clinical trial in healthy participants to evaluate the effects of CYP3A4 inhibition and induction on parsaclisib metabolism via CYP3A enzymes. The primary objective of this study was to assess the effect of itraconazole and rifampin on parsaclisib PK. The secondary objective was to evaluate the safety and tolerability of parsaclisib when administered alone or in combination with itraconazole or rifampin.

Methods

Study Design and Drug Treatment

The protocol for this study was reviewed and approved by a qualified institutional review board (IRB), Chesapeake IRB (now Advarra, Columbia, Maryland). The study was performed in accordance with the International Council for Harmonisation guideline for Good Clinical Practice, including the Declaration of Helsinki and local ethical and legal requirements. Participants signed an institutional review board/independent ethics committee–approved informed consent form prior to study entry. This study was conducted at 1 study center (Celerion, Tempe, Arizona).

This was an open-label, fixed-sequence DDI study to assess the effect of multiple doses of itraconazole or rifampin on the single-dose PK of parsaclisib. The study consisted of a screening period (up to 28 days), a treatment period (11 days for cohort 1, 12 days for cohort 2), and a posttreatment follow-up period (at least 30 [+6] days after the last dose of parsaclisib). During the treatment period (Figure 1), in cohort 1, parsaclisib 10 mg (5 mg × 2) was administered as a single dose in the fasted state (8 hours before and 4 hours after parsaclisib administration) on day 1, followed by itraconazole 200 mg (100 mg × 2) once daily in the fed state on days 4 to 7. On day 8, both parsaclisib and itraconazole were administered in the fasted state, followed by itraconazole in the fed state on days 9 to 11. In cohort 2, parsaclisib 20 mg was

administered as a single dose in the fasted state (8 hours before and 4 hours after parsaclisib administration) on day 1, followed by rifampin 600 mg (300 mg × 2) once daily in the fasted state (8 hours before and 1 hour after rifampin administration) on days 4 to 10. On day 11, both parsaclisib and rifampin were administered in the fasted state (according to parsaclisib fasting criteria), followed by rifampin in the fasted state on day 12. All drugs were administered orally with approximately 240 mL of water.

Parsaclisib (INCB050465) 5- and 20-mg tablets were manufactured by Xcelience (Tampa, Florida). Itraconazole 100-mg capsules were manufactured by Mylan Pharmaceuticals Inc. (Canonsburg, Pennsylvania). Rifampin capsules, USP 300 mg, were distributed by Lannett Company, Inc. (Philadelphia, Pennsylvania).

Participants

Eligible participants were healthy adults between 18 and 55 years of age at the time of screening, with a body mass index between 18 and 32 kg/m^2 inclusive. Exclusion criteria included current or history of a clinically significant disorder, such as renal (estimated glomerular filtration rate $\leq$ 80 mL/min/1.73 m^2), hepatic, or metabolic impairment. Use of medication within 7 days before study entry, including CYP and P-gp inhibitors and inducers, was not allowed. Conditions present at the time of informed consent were recorded on the Medical History Form in the electronic Case Report Form.

Bioanalytical Methods

Blood samples were collected at scheduled times in the treatment period after each parsaclisib administration, with or without itraconazole (cohort 1) or rifampin (cohort 2) coadministration, to determine plasma concentrations of parsaclisib. For cohort 1, PK samples were collected on study visit day 1 (predose, then 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose), day 2 (24 hours postdose), day 3 (48 hours postdose), day 4 (72 hours postdose), day 8 (predose, then 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose), day 9 (24 hours postdose), day 10 (48 hours postdose), day 11 (72 hours postdose), and day 12 (96 hours postdose). For cohort 2, PK samples were collected on study visit day 1 (predose, then 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose), day 2 (24 hours postdose), day 3 (48 hours postdose), day 4 (72 hours postdose), day 11 (predose, then 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose), day 12 (24 hours postdose), and day 13 (48 hours postdose).

Plasma samples were shipped to Incyte Corporation (Wilmington, Delaware) for assessment of parsaclisib plasma concentrations using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. A 50-μL aliquot plasma sample was placed into respective tubes in a 96-well format. After the addition of the internal standard (INCB050904, a structural analogue of parsaclisib [Incyte Research Institute]), an aliquot of 100 μL of 0.1 M $NaHCO_3$ was added. Then, 800 μL of methyl tert-butyl ether (MTBE) was added, and the samples were vortexed. After centrifugation, 150 μL of MTBE layer was transferred to clean tubes in a 96-well format by a Tomtec liquid handler (Hamden, Connecticut). The samples were then dried under nitrogen and reconstituted with 250 μL of reconstitution solution (acetonitrile:water, 50:50, v/v) and rigorously mixed. The plates were placed in the autosampler tray, and 1 μL of the sample was injected into an LC-MS/MS system, which was composed of binary high-performance liquid chromatography pumps and an autosampler coupled to a SCIEX 6500 QTRAP tandem mass spectrometer (Framingham, Massachusetts). The mass spectrometer was operated in positive electrospray ionization mode, and the multiple reaction monitoring was *m/z* 433.2 → 150.2 for parsaclisib and *m/z* 440.3 → 150.2 for the internal standard.

The assay range was 5 to 5000 nM with a 10-fold dilution factor verified. Calibration standards (including 10 concentrations ranging from 5 to 5000 nM) were prepared in control blank human K2-ethylenediaminetetraacetic acid (EDTA) plasma by spiking with stock solutions of parsaclisib (Incyte Research Institute) prepared in acetonitrile:water (50:50, v/v). Quality control samples were also prepared in control blank human K2-EDTA plasma at 15, 250, and 4000 nM. The assay was confirmed for lack of interference from rifampin and itraconazole prior to sample analysis. An exploratory analysis to quantify the other study drugs was performed using residual plasma samples.

Safety Assessments

New or worsening adverse events (AEs) were recorded, and participants were monitored for new AEs during the posttreatment follow-up period. A new or worsening AE occurring after the first dose of study drug was considered a treatment-emergent adverse event (TEAE). AEs were tabulated by the Medical Dictionary for Regulatory Activities preferred term and system organ class. Severity of AEs was described and graded using a FDA toxicity grading scale.[12]

Study End Points

The primary study end points were parsaclisib maximum plasma drug concentration (C_{max}) and area under the concentration-time curve (AUC) extrapolated to infinity ($AUC_{0-\infty}$). Secondary PK end points were parsaclisib t_{max}, $t_{\frac{1}{2},\beta}$, AUC up to the last measurable

Table 1. Summary of Demographic and Baseline Characteristics

Characteristic	Cohort 1: Parsaclisib + Itraconazole (n = 18)	Cohort 2: Parsaclisib + Rifampin (n = 18)	Total (n = 36)
Age, years			
Mean (SD)	34.8 (9.7)	35.9 (10.0)	35.4 (9.7)
Median (range)	33.0 (19-52)	33.0 (21-55)	33.0 (19-55)
Sex, n (%)			
Male	18 (100)	16 (88.9)	34 (94.4)
Female	0	2 (11.1)	2 (5.6)
Race, n (%)			
White	14 (77.8)	16 (88.9)	30 (83.3)
Black/African American	4 (22.2)	2 (11.1)	6 (16.7)
Weight, kg			
Mean (SD)	79.2 (12.3)	82.3 (11.6)	80.8 (11.9)
Median (range)	80.9 (59.3-106.0)	80.6 (55.3-99.7)	80.6 (55.3-106.0)

SD, standard deviation.

concentration ($AUC_{0\text{-}t}$), oral dose clearance (CL/F), and apparent oral dose volume of distribution (V_z/F). Additional secondary end points included monitoring AEs and vital signs, physical examinations, 12-lead electrocardiograms (ECGs), and clinical laboratory blood and urine sample assessments.

Statistical Methods and Planned Analyses

The sample size of 18 participants per cohort was chosen to enable evaluation of the magnitude of any changes in parsaclisib PK when administered with a potent CYP3A4 inhibitor or inducer. A 0.05 (2-sided) significance level and 90% confidence interval (CI) were used to test all hypotheses for PK.

The PK-evaluable population included participants who received at least 1 dose of study drug and provided at least 1 sample for PK analysis. The PK data were described by descriptive statistics for continuous and categorical variables. Parsaclisib plasma concentration data were analyzed using standard noncompartmental PK methods with Phoenix WinNonlin v8.0 software (Certara, Princeton, New Jersey). Comparison of the log-transformed PK parameters among the treatments was performed using a 1-way, 2-factor analysis of variance (ANOVA) with treatment as the fixed factor and participant as the random factor. Parsaclisib geometric mean ratios (GMRs) and 90%CIs of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were calculated based on the least-squares means from the ANOVA. The statistical significance of median treatment difference in t_{max} was assessed by the Wilcoxon signed rank test. The statistical analyses were performed using SAS v9.4 software (SAS Institute, Inc, Cary, North Carolina).

Safety data from the safety-evaluable population (participants who received the study drug) were summarized using descriptive statistics (SAS software).

Results

Demographics and Baseline Clinical Characteristics

Thirty-six healthy adults were enrolled in the study with 18 participants each in cohorts 1 and 2. Baseline demographics and clinical characteristics were similar in cohorts (Table 1). Mean ± standard deviation (SD) age was 34.8 ± 9.7 years in cohort 1 and 35.9 ± 10.0 years in cohort 2. The mean ± SD body weight was 79.2 ± 12.3 kg in cohort 1 and 82.3 ± 11.6 kg in cohort 2. All 18 participants in cohort 1 and 16 of 18 participants in cohort 2 were men.

Participant Disposition

Study drugs were administered at the assigned times under the supervision of clinic personnel. All participants were included in the PK analysis with the exception of a single participant in cohort 2. A preliminary analysis of parsaclisib PK profiles showed that 1 participant had similar PK profiles on day 1 and day 11. Exploratory measurement of plasma rifampin concentrations for this participant confirmed levels were below the limit of quantitation at all times, suggesting that the participant may not have taken rifampin as documented by the clinical site (data on file, Incyte Corporation). This participant was excluded from all DDI analyses involving rifampin. All participants were included in the safety analysis population.

Effect of Itraconazole on Pharmacokinetics of Parsaclisib (Cohort 1)

Parsaclisib was absorbed quickly following oral administration and achieved peak plasma concentrations within 1 hour, either alone or with concomitant itraconazole (Figure 2); parsaclisib plasma concentration declined in a biphasic manner. Concomitant administration of itraconazole increased the parsaclisib

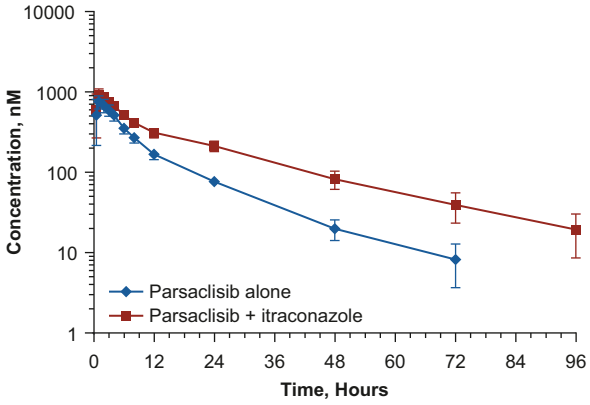

Figure 2. Mean plasma concentrations of parsaclisib following administration of parsaclisib (10 mg) with or without concomitant itraconazole (200 mg) in healthy participants. Error bars represent standard deviation.

geometric mean C_{max} by 21% (90%CI, 14%-29%) and increased the parsaclisib geometric mean $AUC_{0-\infty}$ by 107% (90%CI, 97%-117%); see Table 2. Comparisons of parsaclisib C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} values for individual participants with and without concomitant treatment with itraconazole are presented in Figure 3. Itraconazole prolonged the parsaclisib mean $t_{\frac{1}{2},\beta}$ by 59% (21.1 hours with itraconazole versus 13.2 hours for parsaclisib alone; $P < .0001$; Table 2). Itraconazole decreased parsaclisib geometric mean CL/F by approximately 51% (1.4 L/h with itraconazole and 2.9 L/h with parsaclisib alone; $P < .0001$). Coadministration of itraconazole reduced the mean ± SD V_z/F by approximately 24% (41.7 ± 9.1 L) compared with parsaclisib alone (54.7 ± 13.9 L); $P < .0001$).

Effect of Rifampin on Pharmacokinetics of Parsaclisib (Cohort 2)

Parsaclisib was absorbed quickly following oral administration, either alone or with concomitant rifampin, and reached peak plasma concentrations within 1 hour followed by biphasic decline (Figure 4). Concomitant administration of rifampin reduced the parsaclisib C_{max} by 43% (90%CI, 40%-47%; 1650 ± 272 nM for parsaclisib alone versus 934 ± 184 nM with rifampin) and decreased the parsaclisib $AUC_{0-\infty}$ by 77% (90%CI, 76%-79%; 14 800 ± 2440 nM·h with parsaclisib alone versus 3340 ± 478 nM·h with rifampin); see Table 3. Comparisons of parsaclisib C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} values for individual participants with and without concomitant rifampin administration are presented in Figure 5. Rifampin shortened the parsaclisib mean $t_{\frac{1}{2},\beta}$ by 71% (4.15 hours with rifampin versus 14.7 hours for parsaclisib alone; $P < .0001$; Table 3). Rifampin increased the parsaclisib geometric mean CL/F by approximately 4.4-fold (12.9 L/h with rifampin and 2.9 L/h for parsaclisib alone; $P < .0001$). Mean ± SD V_z/F was similar for the 2 treatments, 77.6 ± 15.2 L with rifampin and 63.0 ± 20.7 L for parsaclisib alone ($P = .0070$).

Safety and Tolerability (All Participants)

No dose interruptions or reductions, participant discontinuations, serious AEs, or deaths due to TEAEs occurred in the study. Five participants (27.8%) in cohort 1 and 8 participants (44.4%) in cohort 2 experienced TEAEs. Headache was the most common TEAE, reported by 5 participants (13.9%, all in cohort 2), followed by generalized pruritus and maculopapular rash, both reported by 2 participants (5.6%, all in cohort 2).

TEAEs reported by only 1 participant (2.8% overall) were mucosal edema, ear abrasion, arthralgia, somnolence, and oropharyngeal pain in cohort 1 and palpitations, constipation, geographic tongue, feeling hot, noncardiac chest pain, increased blood creatine phosphokinase, myalgia, dizziness, dry throat, dyspnea,

Table 2. Comparison of Parsaclisib Pharmacokinetic Parameters Following Administration of Parsaclisib (10 mg) With and Without Concomitant Itraconazole (200 mg)

	Parsaclisib Alone (n = 18)		Parsaclisib + Itraconazole (n = 18)		*P* Values From a Crossover ANOVA of Log-Transformed Data	Geometric Mean Ratio (90%CI)[b]
PK Parameter	Mean ± SD	Geometric Mean	Mean ± SD	Geometric Mean		
C_{max}, nM	793 ± 169	777	954 ± 161	941	–	1.2 (1.1-1.3)
t_{max}, h[a]	1.00 (0.5-2.0)	–	1.0 (0.50-3.0)	–	.0049	–
$t_{\frac{1}{2},\beta}$, h	13.2 ± 3.1	12.8	21.1 ± 5.6	20.4	< .0001	–
AUC_{0-t}, nM·h	7310 ± 792	7270	14 900 ± 1970	14 800	–	2.0 (2.0-2.1)
$AUC_{0-\infty}$, nM·h	7500 ± 787	7460	15 600 ± 2290	15 400	–	2.1 (2.0-2.2)
CL/F, L/h	2.9 ± 0.3	2.9	1.4 ± 0.2	1.4	< .0001	–
Vz/F, L	54.7 ± 13.9	52.9	41.7 ± 9.1	40.8	< .0001	–

AUC, area under the plasma concentration-time curve; CI, confidence interval; CL/F, oral dose clearance; C_{max}, maximum plasma drug concentration; PK, pharmacokinetic; SD, standard deviation; $t_{\frac{1}{2},\beta}$, terminal half-life; t_{max}, time to maximum plasma drug concentration; V_z/F, apparent oral dose volume of distribution.

[a] t_{max} is reported as median (range).

[b] Reference is parsaclisib alone.

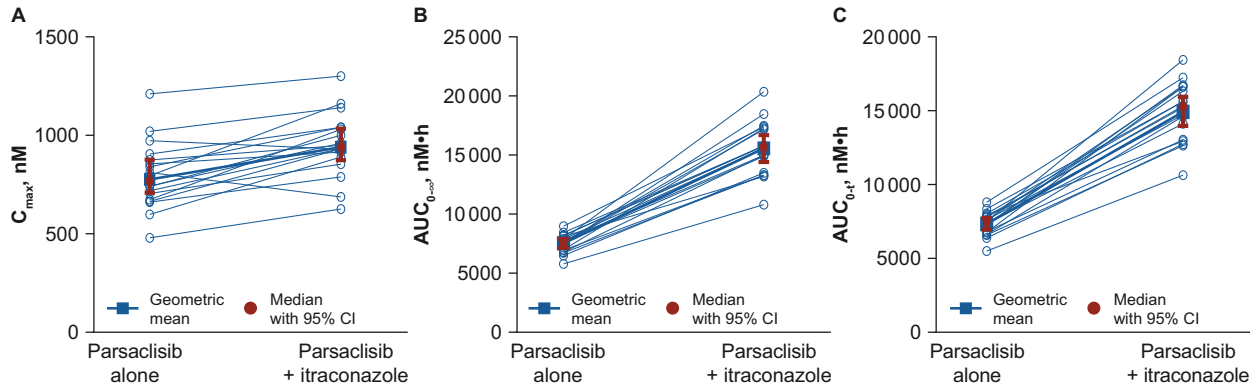

Figure 3. (A) C_{max}, (B) $AUC_{0-\infty}$, and (C) AUC_{0-t} values for parsaclisib for individual study participants, following administration of parsaclisib (10 mg) with and without concomitant itraconazole (200 mg). AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma drug concentration.

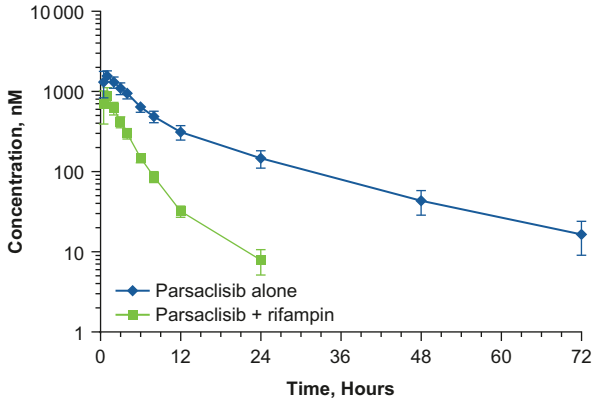

Figure 4. Mean plasma concentrations of parsaclisib following administration of parsaclisib (20 mg) with or without concomitant administration of rifampin (600 mg) in healthy participants. Error bars represent standard deviation.

and nasal congestion in cohort 2. No TEAE was considered related to itraconazole or parsaclisib. TEAEs considered related to rifampin alone were reported by 2 participants and included generalized pruritus and maculopapular rash. No vital sign or ECG-related TEAEs were reported in this study.

No grade 3 TEAE was reported in either cohort. One participant (5.6%) in cohort 2 experienced a grade 4 TEAE of increased creatine phosphokinase (CPK) accompanied by increased aspartate aminotransferase, at the follow-up visit on day 44 from the start of the study (32 days after the last dose of study treatment). By day 56 results for both laboratory parameters had returned to normal. This acute and transient elevation of CPK was likely because of physical activity. The AE of increased CPK was not considered by the investigator to be related to either parsaclisib or rifampin. The participant's CPK values from screening to day 12 (discharge from the unit) was in the normal range.

Discussion

This study investigated the impact of CYP3A4 inhibition or induction on the PK of parsaclisib, a potent and selective next-generation PI3Kδ inhibitor. Open-label and fixed-sequence study design was used because the primary end point, PK parameters, is an objective end point that would not be influenced by a sequence effect. Also, a 2-sequence design would have made it difficult to determine the length of washout period needed following both the induction of CYP3A4 and the inhibition of CYP3A, increasing the chance of carryover parsaclisib concentrations affecting the start of the next sequence.

In a recent phase 1/2 study with parsaclisib in relapsed or refractory B-cell malignancies, the dose-exposure relationship for parsaclisib at steady state was linear over the dose range from 5 to 45 mg, and 20 mg once daily was chosen as the phase 2 dose.[6] Therefore, the parsaclisib dose of 20 mg was selected for the CYP3A4 induction study. Because parsaclisib is primarily metabolized by CYP3A4 and coadministration with a potent CYP3A inhibitor such as itraconazole can potentially increase the drug exposure, a lower dose level of 10 mg was selected for the CYP3A4 inhibition study to avoid unexpected safety issues and was therefore considered acceptable. A PK interaction is anticipated with inhibitors or inducers of CYP3A4 based on in vitro data showing that parsaclisib is primarily metabolized by CYP3A4. This clinical study was therefore conducted to confirm the presence and determine the magnitude of a DDI with a potent CYP3A4 inhibitor and inducer and to help guide potential parsaclisib dosage adjustment recommendations.

Following administration of a single 10-mg dose of parsaclisib, concomitant administration with the potent inhibitor of CYP3A4 itraconazole resulted in an approximately 2-fold increase in the exposure of parsaclisib; the GMRs of C_{max} and $AUC_{0-\infty}$ of

Table 3. Comparison of Parsaclisib Pharmacokinetic Parameters Following Administration of Parsaclisib (20 mg) With and Without Concomitant Rifampin (600 mg)

	Parsaclisib Alone (n = 18)		Parsaclisib + Rifampin (n = 17)		*P* Values From a Crossover ANOVA of Log-Transformed Data	Geometric Mean Ratio (90%CI)[b]
PK Parameter	Mean ± SD	Geometric Mean	Mean ± SD	Geometric Mean		
C_{max}, nM	1650 ± 272	1630	934 ± 184	917	–	0.6 (0.5–0.6)
t_{max}, h[a]	1.0 (0.5-1.0)	–	1.0 (0.5-2.0)	–	.8423	–
$t_{\frac{1}{2},\beta}$, h	14.7 ± 3.6	14.2	4.15 ± 0.6	4.1	< .0001	–
$AUC_{0\text{-}t}$, nM·h	14 400 ± 2420	14 200	3280 ± 473	3250	–	0.23 (0.22–0.25)
$AUC_{0\text{-}\infty}$, nM·h	14 800 ± 2440	14 600	3340 ± 478	3310	–	0.23 (0.21–0.24)
CL/F, L/h	3.0 ± 0.5	2.9	13.0 ± 1.7	12.9	< .0001	–
Vz/F, L	63.0 ± 20.7	60.0	77.6 ± 15.2	76.2	.0070	–

AUC, area under the plasma concentration-time curve; CI, confidence interval; CL/F, oral dose clearance; C_{max}, maximum plasma drug concentration; PK, pharmacokinetic; SD, standard deviation; $t_{\frac{1}{2},\beta}$, terminal half-life; t_{max}, time to maximum plasma drug concentration; V_z/F, apparent oral dose volume of distribution.
[a]t_{max} is reported as median (range).
[b]Reference is parsaclisib alone.

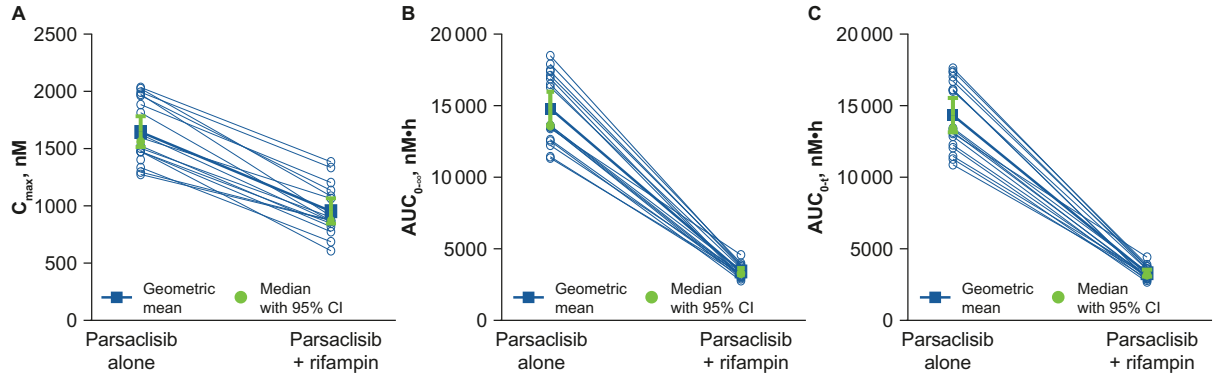

Figure 5. (A) C_{max}, (B) $AUC_{0\text{-}\infty}$, and (C) $AUC_{0\text{-}t}$ values for parsaclisib for individual study participants, following administration of parsaclisib (20 mg) with or without concomitant rifampin (600 mg). AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma drug concentration.

parsaclisib were 1.2 (90%CI, 1.1-1.3) and 2.1 (90%CI, 2.0-2.2), respectively. Conversely, after administration of a single 20-mg dose of parsaclisib, concomitant administration with the potent inducer of CYP3A4 rifampin resulted in an approximately 4-fold decrease in the exposure of parsaclisib; the GMR of C_{max} and $AUC_{0\text{-}\infty}$ of parsaclisib were 0.6 (90%CI, 0.5-0.6) and 0.23 (90%CI, 0.21-0.24), respectively. Parsaclisib dose adjustment may therefore be warranted when administered with a strong CYP3A4 inhibitor (eg, boceprevir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, itraconazole, posaconazole, voriconazole),[13] and it may be appropriate to avoid coadministration with strong CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin),[13] owing to the potential for increased exposure or reduced efficacy of parsaclisib, respectively.

First-generation PI3Kδ inhibitors (eg, idelalisib and duvelisib) have been associated with toxicities including transaminitis (increased alanine and aspartate transaminase levels), colitis, diarrhea, and pneumonitis.[7,8,14] Parsaclisib demonstrated a favorable safety profile in a phase 1/2 study, with no dose-limiting toxicities identified.[6] In the current study, headache was the most common TEAE, reported by 13.9% of participants. Generalized pruritus and maculopapular rash (reported by 5.6% of participants) were considered related to rifampin.

Conclusions

Single doses of parsaclisib when administered to healthy participants alone or in combination with itraconazole or rifampin appeared to be safe and well tolerated in this study of healthy participants. These data will help inform parsaclisib dosage guidelines and DDI risk management.

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Conflicts of Interest

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Data-Sharing Statement

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Author Contributions

Xuejun Chen, Kevin Rockich, Naresh Punwani, Noam Epstein, and Swamy Yeleswaram were involved in the conception/design of the work. Brad Yuska acquired the data. Jia Li and Gongfu Zhou analyzed the data. All authors drafted the article or revised it critically for important intellectual content.

Informed Consent

Informed consent was obtained from all participants included in this study.

References

1. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. *Nat Rev Cancer*. 2015;15(1):7-24.
2. Puri KD, Gold MR. Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory diseases and B-cell malignancies. *Front Immunol*. 2012;3:256.
3. Shin N, Koblish H, Covington M, et al. INCB050465, a novel PI3Kδ inhibitor, synergizes with PIM protein kinase inhibition to cause tumor regression in a model of DLBCL [AACR abstract 2671]. *Cancer Res*. 2015;75(15 suppl):2671.
4. Forero-Torres A, Wertheim MS, Phillips TJ, et al. Preliminary safety, efficacy, and pharmacodynamics of a highly selective PI3Kδ inhibitor, INCB050465, in patients with previously treated B-cell malignancies [AACR abstract CT056]. *Cancer Res*. 2016;76(14 suppl):CT056.
5. Stubbs MC, Collins R, Hall L, et al. Preclinical studies on potential therapeutic combination partners for the potent and selective PI3Kδ inhibitor INCB050465 in DLBCL [AACR abstract 143]. *Cancer Res*. 2017;77(13 suppl):143.
6. Forero-Torres A, Ramchandren R, Yacoub A, et al. Parsaclisib, a potent and highly selective PI3Kδ inhibitor, in patients with relapsed or refractory B-cell malignancies. *Blood*. 2019;133(16):1742-1752.
7. Coutré SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymphoma*. 2015;56(10):2779-2786.
8. Flinn IW, O'Brien S, Kahl B, et al. Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. *Blood*. 2018;131(8):877-887.
9. U.S. Food and Drug Administration. Guidance for industry: clinical drug interaction studies – study design, data analysis, and clinical implications. 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-study-design-data-analysis-and-clinical-implications-guidance. Accessed July 26, 2019.
10. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet*. 2003;42(9):819-850.
11. Ke AB, Zamek-Gliszczynski MJ, Higgins JW, Hall SD. Itraconazole and clarithromycin as ketoconazole alternatives for clinical CYP3A inhibition studies. *Clin Pharmacol Ther*. 2014;95(5):473-476.
12. U.S. Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers. 2007. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical. Accessed July 26, 2019.
13. U.S. Food and Drug Administration. Drug development and drug interactions_ table of substrates, inhibitors and inducers. 2017. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed August 9, 2019.
14. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018.