Original Article

Effect of Strong CYP3A4 Inhibition, CYP3A4 Induction, and OATP1B1/3 Inhibition on the Pharmacokinetics of a Single Oral Dose of Sotorasib

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Abstract

Sotorasib is a small molecule that irreversibly inhibits the Kirsten rat sarcoma viral oncogene homolog (KRAS) protein with a G12C amino acid substitution mutant protein. The impact of cytochrome P450 (CYP) 3A4 inhibition and induction on sotorasib pharmacokinetics (PKs) was evaluated in 2 separate studies in healthy volunteers (N = 14/study). The impact of CYP3A4 inhibition was interrogated utilizing repeat doses of 200 mg of itraconazole, a strong CYP3A4 inhibitor, on 360 mg of sotorasib PKs. The impact of CYP3A4 induction was interrogated utilizing multiple doses of 600 mg of rifampin, a strong CYP3A4 inducer. Additionally, the impact of organic anion transporting polypeptide (OATP) 1B1/3 inhibition on 960 mg of sotorasib PKs was interrogated after a single dose of 600 mg of rifampin. CYP3A4 inhibition did not significantly impact sotorasib C_{max} but did lead to a 26% increase in sotorasib AUC_{inf}. CYP3A4 induction decreased sotorasib C_{max} by 35% and AUC_{inf} by 51%. OATP1B1/3 inhibition decreased sotorasib C_{max} and AUC_{inf} by 16% and 23%, respectively. These results support that sotorasib can be given together with strong CYP3A4 and OATP1B1/3 inhibitors but the co-administration of sotorasib and strong CYP3A4 inducers should be avoided.

Keywords

CYP3A4, drug interaction, KRAS inhibitor, oncology, sotorasib

The role of Kirsten rat sarcoma viral oncogene homolog (KRAS) gene mutations in human cancers has been known for decades[1]; only limited anticancer therapies targeting KRAS mutations have been successfully developed. KRAS p.G12C mutation is found in approximately 13% of lung adenocarcinoma (non-squamous, non-small-cell lung carcinoma), 3% of colorectal cancer, and 1%-2% of numerous other solid tumors.[2,3] Sotorasib is a first-in-class small molecule that inhibits the protein product of a mutant KRAS gene which results in a G12C mutation at the protein level (KRAS p.G12C). It forms a specific covalent bond with the mutant cysteine of $KRAS^{G12C}$, thereby irreversibly locking the protein in an inactive conformation that cripples oncogenic signaling. In the primary efficacy population (n = 124) from the registrational study CodeBreaK 100, sotorasib demonstrated substantial evidence of efficacy with an overall response rate of 36% (95% confidence interval [CI] 28, 45) and a median duration of response of 10 months (range 1.3-11.1). On May 28, 2021, the Food and Drug Administration (FDA) granted sotorasib accelerated approval for the treatment of patients with previously treated KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) taken as 960 mg orally once daily.

The pharmacokinetics (PKs) of sotorasib have been characterized in healthy subjects and in subjects with KRAS pG12C-mutated solid tumors, including NSCLC. Sotorasib is absorbed rapidly after single and multiple daily doses in healthy subjects and patients with advanced solid tumors across the tested dose range of 180-960 mg once daily.[4] Median sotorasib t_{max} is 1 hour and mean terminal elimination half-life after multiple daily doses was 5 hours in subjects with advanced NSCLC.[4] Sotorasib is metabolized mainly via

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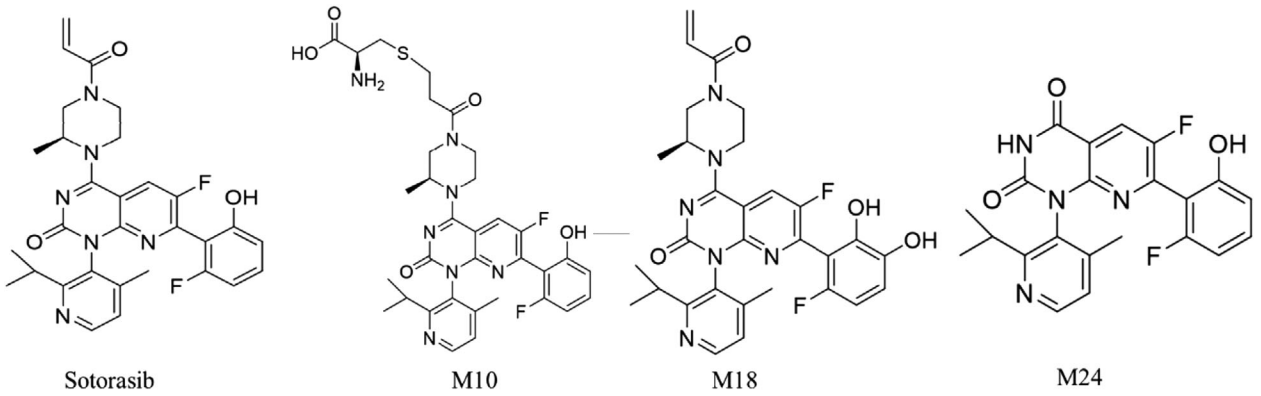

Figure 1. Chemical structures for sotorasib and its metabolites M10, M18, and M24.

non-enzymatic conjugation and oxidative metabolism by cytochrome P450 (CYP) 3As (CYP3As) with limited renal elimination. Sotorasib has 3 circulating metabolites (M10, M18, and M24) in humans.[5] Among them, only M18 maintains primary pharmacology effects; however, the effect is markedly reduced.[5] The chemical structures of Sotorasib and its 3 metabolites are presented in Figure 1.

Pooled human liver microsomes with CYP-selective chemical inhibitors, recombinant enzymes, human liver S9 fractions, or human kidney S9 fractions were used to determine the enzymes responsible for sotorasib metabolism in vitro.[5] Sotorasib depletion occurs in incubations with recombinant CYP2C8, CYP3A4, and CYP3A5. The M24 metabolite was formed primarily in incubations with recombinant CYP3A4 and CYP3A5.[5] These results suggested that CYP3A enzymes were primarily responsible for the depletion of sotorasib and M24 formation, indicating that sotorasib is a CYP3A substrate.[5] The evaluation of the PK of sotorasib in combination with itraconazole, a known inhibitor of CYP3A4, and rifampin, a known inducer of CYP3A4 (after multiple doses) and inhibitor of organic anion transporting polypeptide (OATP)1B1/3 (after a single dose), served to characterize the potential for drug-drug interactions to occur between sotorasib and concomitantly administered CYP3A4 modulators as well as OATP1B1/3 inhibitors.

This paper reports the results of 2 drug interaction studies that investigated the PKs of sotorasib administered alone and in combination with a CYP3A4 inhibitor, a CYP3A4 inducer, and an OATP1B1/3 inhibitor in healthy volunteers.

Methods

Study Design

Both studies were phase 1, single-center (United States), open-label, fixed-sequence design conducted in healthy male and female subjects. Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index of 18-30 kg/m^2 (inclusive) and no clinically significant findings from medical history, physical examination, 12-lead electrocardiography, vital signs measurements, and clinical laboratory evaluations were enrolled. Female subjects were of nonchild-bearing potential defined as permanently sterile or postmenopausal. Key exclusion criteria included evidence or history of clinically significant gastrointestinal, cardiovascular, hepatic, renal, or allergic disease; any condition possibly affecting drug absorption; history of alcohol or drug/chemical abuse; treatment with an investigational drug within 90 days or 5 half-lives before enrollment; use of over-the-counter or prescription medications within 30 days or 5 half-lives before enrollment; and use of vitamins, dietary, or herbal supplements therapy within 30 days prior to enrollment.

For each study, subjects were screened to assess their eligibility within 28 days before the first dose administration. Subjects (N = 14 for each study) provided written informed consent, were admitted into the clinical research unit on day −1, and were confined until discharge/end of study (EOS) on day 8 for the itraconazole study and day 20 for the rifampin study. Subjects in both studies were dosed in a gated fashion with 4 subjects dosed first followed by a period of at least 2 days before dosing the remaining 10 subjects. All dose administrations were implemented and monitored by clinical staff at the clinical research unit to ensure compliance.

The studies were conducted at the Covance Clinical Research Unit in Dallas, TX, USA (itraconazole study) and Madison, WI, USA (rifampin study). Both studies were conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Conference on Harmonization (ICH) Good Clinical Practice Guidelines, and applicable laws and regulations. Prior to the start of

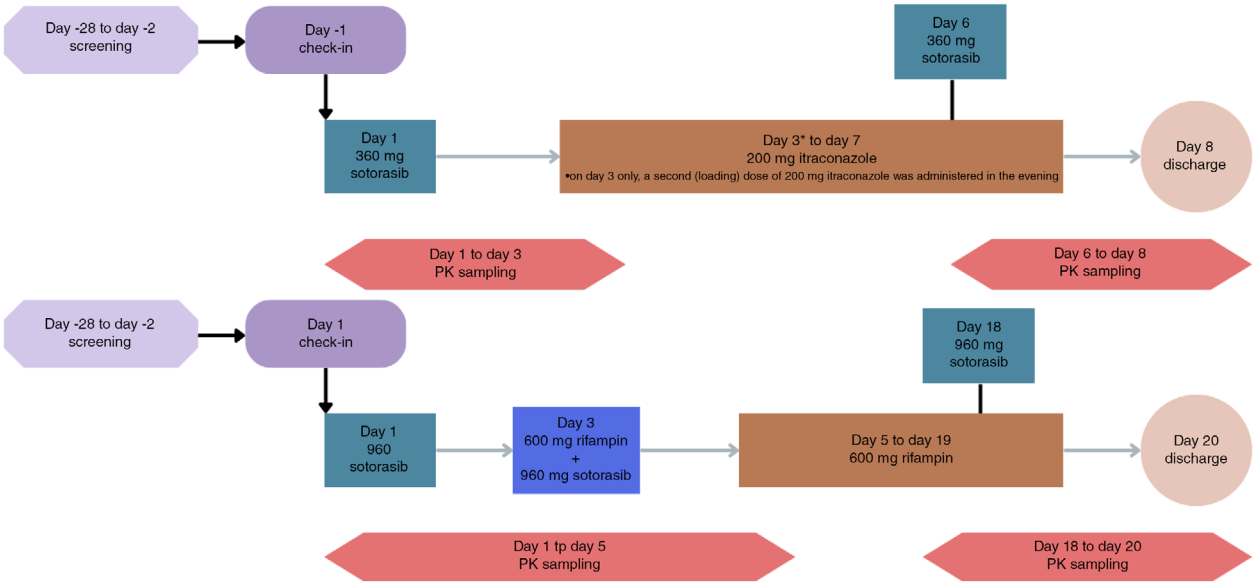

Figure 2. Itraconazole and rifampin study schema.

each study, the study protocol, protocol amendment, informed consent form, investigator's brochure, and other relevant documents (eg, advertisements) were reviewed and approved by Salus Institutional Review Board in Austin, TX, USA.

CYP3A4 Inhibitor (Itraconazole) Study. Eligible subjects received 360 mg of sotorasib alone orally after an overnight fast of at least 10 hours on day 1, 200 mg of itraconazole alone orally twice after a meal on day 3, and 200 mg of itraconazole alone once daily after a meal on days 4 and 5. On day 6, eligible subjects received 200 mg of itraconazole followed by 360 mg of sotorasib after an overnight fast of at least 10 hours (Figure 2).

CYP3A4 Inducer and OATP1B1/3 Inhibitor (Rifampin) Study. Eligible subjects received 960 mg of sotorasib alone orally after an overnight fast of at least 10 hours on day 1, 600 mg of rifampin followed by 960 mg of sotorasib orally after an overnight fast of at least 10 hours on day 3, and 600 mg of rifampin orally once daily after an overnight fast of at least 10 hours from days 5 to 19. On day 18, eligible subjects received 600 mg of rifampin followed by 960 mg of sotorasib orally after an overnight fast of at least 10 hours (Figure 2).

Dose and Design Rationale

Sotorasib is primarily metabolized by the CYP3A4/5 enzyme to form major metabolite M24 in vitro[5] and an increase in sotorasib exposure was expected with the co-administration of a strong CYP3A4 inhibitor. The safety of sotorasib at doses greater than the well-tolerated 960 mg was not established in any clinical trials. A lower dose was appropriate for this study to ensure the safety of healthy volunteers. Classically, ketoconazole was the index CYP3A4 inhibitor. Current regulatory agency guidance does not recommend the use of ketoconazole in healthy volunteer studies, but this position is contentious.[6–10] Consistent with ICH and FDA guidelines, itraconazole was selected for this study. Itraconazole is an antifungal agent used as an index perpetrator for the evaluation of drug interaction potential via CYP3A4 inhibition. Although the highest recommended daily dose of itraconazole is 400 mg, it has been shown to have a limited increase in inhibition of CYP3A4 compared with 200 mg.[11] Likewise, although it takes approximately 14 days to reach steady state, multiple drug interactions studies using 100-200 mg/day of itraconazole with a 3-day lead-in have shown adequately strong CYP3A inhibition and dosing with 200 mg of itraconazole for more than 3 days did not demonstrate an additional inhibitory effect.[12–15] In this study, a loading dose of 200 mg of itraconazole was administered on the evening of day 3 to ensure steady state was achieved before day 6. The attainment of steady-state exposure of itraconazole is important because it provides a greater magnitude of CYP3A4 inhibition when co-administered with the victim drug. To maintain sufficient inhibition throughout the study, itraconazole was continued on day 7, which is approximately 4 half-lives of sotorasib after co-administration.[16]

Available in vitro and clinical data suggested that sotorasib is susceptible to CYP3A induction. Evaluation of OATP1B1/3 inhibition impact on sotorasib was also included after a single dose of rifampin. Rifampin is a known index CYP3A4 inducer if given repeatedly and

OATP1B1/3 inhibitor if given as a single dose.[17] Rifampin induction is mediated by the activation of PXR, which regulates several genes, including those encoding CYP enzymes and glutathione-S-transferases (GST).[18] Its full induction effect on both intestinal and hepatic CYP3A4 induction is typically achieved with 11-14 days of repeated administration despite its short half-life.[19] The selected rifampin dose of 600 mg is the highest proposed clinical dose used for patients who are in need of antibacterial therapy and allows for the assessment of the "worst case" scenario.

Sample Collection

Itraconazole Study. Blood samples for determination of sotorasib and its metabolites' plasma concentrations and PK parameters were collected into K_2EDTA spray-coated tubes at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours postdose following administration of sotorasib on days 1 and 6.

Rifampin Study. Blood samples for determination of sotorasib and its metabolites' plasma concentrations and PK parameters were collected into K_2EDTA spray-coated tubes at predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours postdose following administration of sotorasib on days 1, 3, and 18.

For both studies, within 30 minutes of collection, samples were centrifuged under refrigeration (2-8°C) at 1500 × *g* for 15 minutes and subsequently stored in freezers set to approximately −70°C or colder until shipment.

Bioanalytical Method

The detailed method for the determination of sotorasib in human plasma is published elsewhere.[20] Bioanalysis was conducted by PPD (Richmond, VA) within the demonstrated long-term stability in human plasma containing K_2EDTA at −80°C. A 25.0-μL matrix aliquot was fortified with 125 μL of 40.0 ng/mL internal standard working solution (40.0 ng/mL sotorasib-^{13}C, d_3) in methanol. Analytes were isolated through protein precipitation on a Phenomenex Kinetex C8, 3.0 × 50 mm, 2.6-m column with 100:0.1 water/formic acid v/v as mobile phase A and 100:0.1 methanol/formic acid v/v as mobile phase B. A 40.0-μL aliquot of the resulting supernatant was diluted with 200 μL of 60:40 water/methanol v/v. The mass-to-charge ratio was monitored via 561.1 → 134.1 in multiple reaction monitoring mode. The final extract was analyzed via high-performance liquid chromatography and tandem mass spectrometry detection using positive ion electrospray. The intraday accuracy and precision of sotorasib quality control samples %CV ranged from 1.4% to 10.3%. The interday accuracy and precision %CV ranged from 2.3% to 8.3%. A linear, 1/concentration^2 weighted, least-squares regression algorithm was used to quantitate unknown samples. The nominal sotorasib concentration range of 10.0-10,000 ng/mL was chosen to quantitate samples.

Pharmacokinetic and Statistical Analysis

The PK parameters were determined using non-compartmental methods performed using Phoenix WinNonlin Version 8.1. The PK population included all subjects who received at least 1 dose of sotorasib and had evaluable PK data. Samples below the lower limit of quantification for sotorasib (10.0 ng/mL) were set to 0 ng/mL, and actual sample collection times were used in the data analyses. Evaluated PK parameters included area under the concentration-time curve (AUC) from time 0 to the time of last quantifiable concentration (AUC_{last}), AUC from time 0 extrapolated to infinity (AUC_{inf}), maximum observed plasma concentration (C_{max}), time of C_{max} (t_{max}), and apparent terminal elimination half-life ($t_{1/2}$). AUCs were calculated using the linear trapezoidal linear interpolation rule. All values below the limit of quantification were set as 0 and included as such in the calculation of descriptive statistics.

Data analysis was performed using the SAS statistical software package version 9.4 (or higher if up-versioned during the study). The natural log (ln)-transformed PK parameters were analyzed using a mixed model. The model included treatment as a fixed effect and subject as a random effect. For each PK parameter, the least squares mean (LSM) for each treatment, difference in LSMs between the test and fasted treatments, and corresponding 90% CIs were estimated; these values were then back-transformed to give the geometric least square mean (GLSM), ratio of GLSMs, and corresponding 90% CI.

Three subjects had measurable concentrations of sotorasib prior to dose administration on day 3. The concentrations were low (<1% of respective C_{max}) and were included in summary statistics and GLSM ratio calculations. While there were 2 sample time deviations greater than ±10%, they were included in summary statistics.

Safety and Tolerability Assessments

The safety population included all subjects who received at least 1 dose of sotorasib and had at least 1 postdose safety assessment. All adverse events were coded using the Medical Dictionary for Regulatory Activities version 22.0. Adverse events, clinical laboratory values, vital signs, and 12-lead electrocardiograms were monitored and/or collected from check-in to EOS.

Table 1. Summary of the Pharmacokinetic Parameters for Sotorasib in Healthy Volunteers in Itraconazole Study

Pharmacokinetic parameter	360 mg of sotorasib alone on day 1	360 mg of sotorasib + 200 mg of itraconazole on day 6
N	14	13
Arithmetic mean (SD)		
C_{max} (ng/mL)	6380 (1710)	6540 (1500)
AUC_{last} (ng•h/mL)	25,300 (10,600)	31,600 (10,100)
AUC_{inf} (ng•h/mL)	26,900 (9550)[a]	32,000 (10,000)
$t_{1/2}$ (hour)	7.16 (3.01)[a]	8.00 (3.00)
Geometric mean (geometric CV%)		
C_{max} (ng/mL)	6130 (31.3)	6380 (23.4)
AUC_{last} (ng•h/mL)	22,700 (56.5)	30,100 (34.6)
AUC_{inf} (ng•h/mL)	25,000 (44.7)[a]	30,500 (33.8)
$t_{1/2}$ (hour)	6.65 (40.9)	7.61 (31.4)
Median (range)		
t_{max} (hour)	0.508 (0.500-1.55)	1.00 (0.500-2.00)

Values are reported to 3 significant figures. N, number of subjects; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last measurable concentration; C_{max}, maximum observed drug concentration; CV%, coefficient of variation; N, number of subjects; SD, standard deviation; t_{max}, time to reach C_{max}; $t_{1/2}$, half-life.
[a] N = 13.

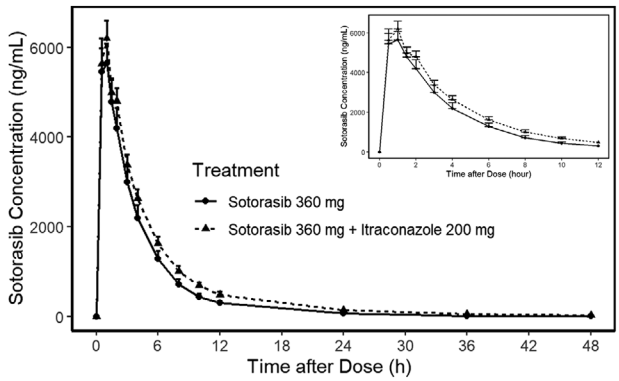

Figure 3. Mean (+standard error) plasma sotorasib concentration-time profile following a single oral administration of 360 mg of sotorasib alone or 360 mg of sotorasib in combination with 200 mg of itraconazole in healthy subjects.

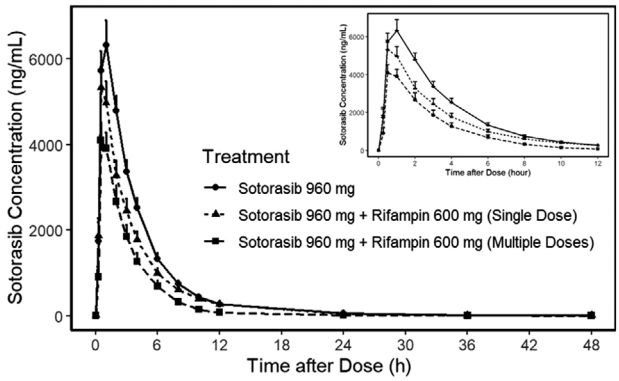

Figure 4. Mean (+standard error) plasma sotorasib concentration-time profile following a single oral administration of 960 mg of sotorasib alone, 960 mg of sotorasib in combination with a single administration of 600 mg of rifampin, or 960 mg of sotorasib in combination with 600 mg of rifampin following multiple administrations of 600 mg of rifampin in healthy subjects.

Results

Study Population

For each study, 14 subjects were enrolled and completed the studies. The demographic characteristics of the study populations are summarized in Table S1.

Pharmacokinetic Analysis

The arithmetic mean (+SE) plasma concentration-time profiles for sotorasib following a single dose of 360 mg sotorasib alone and when co-administered with a strong CYP3A4 inhibitor are presented in Figure 3. The PK parameters of sotorasib in plasma are summarized in Table 1. A summary of the statistical analysis of plasma PK data is presented in Table 2. Data from 1 subject were excluded from descriptive statistics for sotorasib on day 6 due to missing samples around the expected sotorasib t_{max} on that day.

The arithmetic mean (+SE) plasma concentration-time profiles for sotorasib following a single dose of 960 mg sotorasib alone and when co-administered with a strong CYP3A4 inducer and OATP1B1/3 inhibitor are presented in Figure 4. The PK parameters of sotorasib are summarized in Table 3. A summary of the statistical analysis of PK data is presented in Table 2.

Impact of CYP3A4 Inhibition on Sotorasib PKs. Exposure (AUC values) of sotorasib increased when co-administered with a strong CYP3A4 inhibitor. However, C_{max} values were similar (Table 1). Geometric

Table 2. Summary of the Statistical Analysis

Pharmacokinetic parameter	360 mg of sotorasib alone on day 1 (reference) N = 14 Geometric LSM	360 mg of sotorasib + 200 mg of itraconazole on day 6 (test) N = 13 Geometric LSM	Geometric LSM ratio Day 6/Day 1 (90% CI)
AUC_{last} (ng•h/mL)	22,700	30,700	1.350 (1.141, 1.598)
AUC_{inf} (ng•h/mL)	24,600[a]	31,000	1.261 (1.119, 1.420)
C_{max} (ng/mL)	6130	6370	1.040 (0.929, 1.164)
	960 mg of sotorasib alone on day 1 (reference) N = 14 Geometric LSM	960 mg of sotorasib + 600 mg of rifampin on day 3 (test) N = 14 Geometric LSM	Geometric LSM ratio Day 3/Day 1 (90% CI)
AUC_{last} (ng•h/mL)	25,400	19,400	0.765 (0.659, 0.889)
AUC_{inf} (ng•h/mL)	25,600	19,600	0.766 (0.661, 0.887)
C_{max} (ng/mL)	6350	5340	0.840 (0.763, 0.925)
	960 mg of sotorasib alone on day 1 (reference) N = 14 Geometric LSM	960 mg of sotorasib + 600 mg of rifampin on day 18 (test) N = 14 Geometric LSM	Geometric LSM ratio Day 18/Day 1 (90% CI)
AUC_{last} (ng•h/mL)	25,400	12,300	0.484 (0.417, 0.562)
AUC_{inf} (ng•h/mL)	25,600	12,400	0.487 (0.420, 0.563)
C_{max} (ng/mL)	6350	4110	0.647 (0.588, 0.713)

Model: ln(parameters) = treatment + random error. The ratios and CIs were obtained by taking the exponential of the corresponding differences and CIs on the natural-log (ln) scale. AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last measurable concentration; C_{max}, maximum observed drug concentration; CI, confidence interval; LSM, least square mean; N, number of subjects with valid observations.
[a] N = 13.

mean exposure AUC_{inf} increased to 1.26-fold when sotorasib was co-administered with a strong CYP3A4 inhibitor (Table 2). The median t_{max} was delayed by 0.5 hours (from 0.508 to 1.00 hours) (Table 1). Exposures of M10 and M18 increased whereas M24 exposure decreased (Figure 5).

Impact of CYP3A4 Induction on Sotorasib PKs. Exposures, based on both C_{max} and AUC_{inf}, of sotorasib were decreased when co-administered with a strong CYP3A4 inducer (Figure 4 and Table 3). Geometric mean exposures (AUC_{inf} and C_{max}) decreased to 0.487- and 0.647-fold, respectively (Table 2). Median t_{max} was 0.5 hours shorter after co-administration (Table 3). Exposures of M10, M18, and M24 decreased (Figure 6).

Impact of OATP1B1/3 Inhibitor on Sotorasib PKs. Exposures, based on both C_{max} and AUC_{inf}, of sotorasib decreased when co-administered with an OATP1B1/3 inhibitor (Figure 4 and Table 3). Geometric mean AUC_{inf} and C_{max} decreased to 0.766- and 0.840-fold, respectively (Table 2). Median t_{max} was numerically shorter after co-administration (Table 3). Exposures of M10 and M18 increased whereas M24 exposure decreased (Figure 6).

Safety and Tolerability

CYP3A4 Inhibitor (Itraconazole) Study. No treatment-emergent adverse events (TEAEs) were reported following co-administration of sotorasib with itraconazole. All events were considered mild in severity and resolved prior to the end of the study. No serious adverse events or TEAEs led to discontinuation from the study. There were no other safety findings.

CYP3A4 Inducer and OATP1B1/3 Inhibitor (Rifampin) Study. Three TEAEs were reported by 2 subjects (14.3%) following administration of sotorasib alone on day 1, 19 TEAEs were reported by 14 subjects (100%) following co-administration of sotorasib and rifampin on day 3, 5 TEAEs were reported by 3 subjects (21.4%) following administration of rifampin alone on days 5 through 17, and 2 TEAEs were reported by 1 subject (7.1%) following co-administration of sotorasib and rifampin on day 18. No concomitant medication was administered for sotorasib-related TEAEs. No serious adverse events

Table 3. Summary of the Pharmacokinetic Parameters for Sotorasib in Healthy Volunteers in Rifampin Study

Pharmacokinetic parameter	960 mg of sotorasib alone on day 1	960 mg of sotorasib + 600 mg of rifampin on day 3	960 mg of sotorasib + 600 mg of rifampin on day 18
N	14	14	14
Arithmetic mean (SD)			
C_{max} (ng/mL)	6660 (2090)	5620 (1850)	4400 (1580)
AUC_{last} (ng•h/mL)	26,900 (9130)	20,900 (8330)	14,000 (6620)
AUC_{inf} (ng•h/mL)	27,000 (9130)	21,100 (8340)	14,100 (6600)
$t_{1/2}$ (hour)	6.41 (2.76)	6.19 (2.22)	4.88 (3.62)
Geometric mean (geometric CV%)			
C_{max} (ng/mL)	6350 (32.9)	5340 (34.7)	4110 (41.2)
AUC_{last} (ng•h/mL)	25,400 (36.8)	19,400 (42.2)	12,300 (60.2)
AUC_{inf} (ng•h/mL)	25,600 (36.4)	19,600 (41.7)	12,400 (59.2)
$t_{1/2}$ (hour)	6.00 (36.7)	5.89 (32.5)	4.07 (65.3)
Median (range)			
t_{max} (hour)	1.00 (0.500-1.07)	0.500 (0.500-1.00)	0.750 (0.500-2.00)

Values are reported to 3 significant figures. AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last measurable concentration; C_{max}, maximum observed drug concentration; N, number of subjects; t_{max}, time to reach C_{max}; $t_{1/2}$, half-life.

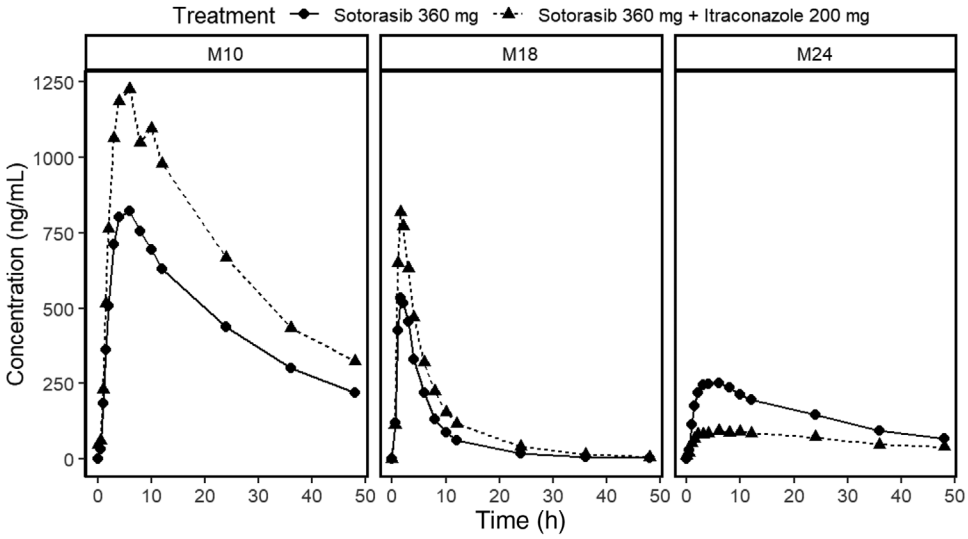

Figure 5. Sotorasib metabolite M10, M18, and M24 concentrations following oral administration of 360 mg of sotorasib alone and following oral administration of 360 mg of sotorasib with 200 mg of itraconazole.

or TEAEs led to discontinuation from the study. There were no other safety findings.

Discussion

Co-administration of a strong CYP3A4 inhibitor with sotorasib demonstrated 4% and 26% increases in sotorasib C_{max} and AUC_{inf}, respectively, which is considered a weak drug interaction.[21] The small increases in sotorasib AUC_{inf} and $t_{1/2}$ may be due to compensatory mechanisms from other metabolic pathways such as nonenzymatic glutathione conjugation, gamma glutamyl-transferase (GGT)#x02010;mediated hydrolysis of glutathione adduct, and direct CYP2C8-mediated oxidation.[5] This was consistent with increases in exposures of M10 and M18, and a decrease in exposure of M24 on co-administration of itraconazole (Figure 5). The minimal increase in C_{max} and small delay in t_{max} are consistent with the increase in AUC_{inf} as C_{max} and t_{max} are functions of both absorption and elimination.

Co-administration of a strong CYP3A4 inducer with sotorasib led to a 35% decrease in C_{max} and a 51% decrease in AUC_{inf}. This along with a shorter half-life suggests that the induction impacted both intestinal and hepatic CYP3A4 enzymes. However, exposures

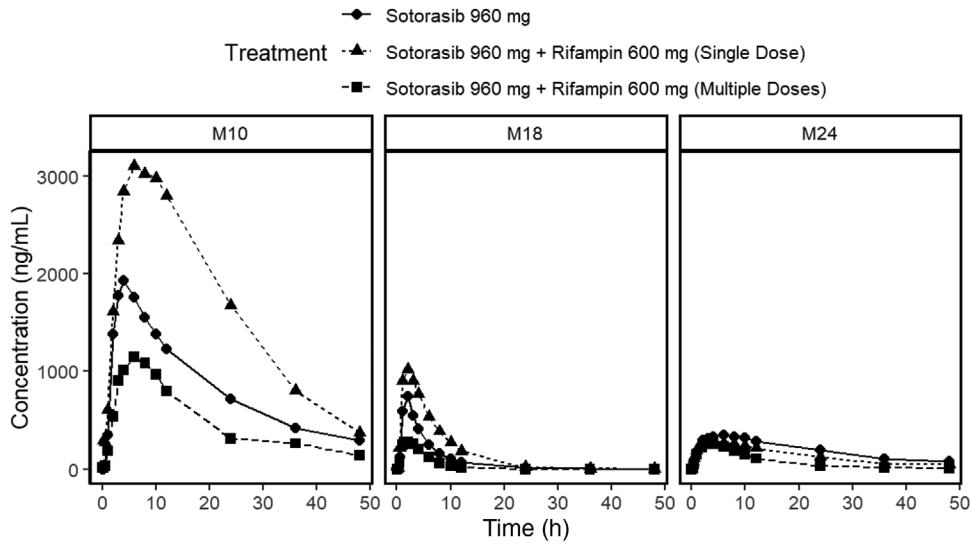

Figure 6. Sotorasib metabolite M10, M18, and M24 concentrations following oral administration of 960 mg of sotorasib alone, 960 mg of sotorasib with 600 mg of rifampin (single dose) and 960 mg of sotorasib with 600 mg of rifampin (multiple doses).

to all 3 circulating metabolites (M10, M18, and M24) decreased as opposed to expected increases in M10 (via GSTs induction), M18 (via CYP2C8 induction), and M24 exposures (Figure 6). This could potentially be explained by increased metabolism of the metabolites or a greater magnitude of intestinal CYP3A4 induction compared to that of the hepatocytes due to higher expression of CYP3A4 protein in intestine than in liver, which led to lower bioavailability of parent sotorasib overall.[19,22]

Co-administration of an OATP1B1/3 inhibitor did not increase sotorasib C_{max} and AUC_{inf}, and $t_{1/2}$ was similar to that on day 1. This suggests that OATP1B1/3 plays a limited role in the distribution and elimination of sotorasib. The paradoxical finding of a decrease in sotorasib C_{max} and AUC_{inf} along with the shift toward non-CYP3A4 mediated metabolite formation (Figure 6) on co-administration of rifampin may be due to transient CYP3A4 inhibition.[23,24]

Conclusion

Co-administration of sotorasib with a strong CYP3A4 inhibitor did not affect C_{max}, but increased AUC_{inf} by 26%. Sotorasib is not a substrate of OATP1B1. CYP3A4 induction decreased sotorasib AUC_{inf} by 51% and C_{max} by 35%, indicating sotorasib is a CYP3A4 substrate, consistent with in vitro data. Collectively, the results suggest that sotorasib can be given together with strong CYP3A4 and OATP1B1/3 inhibitors but the co-administration of sotorasib and strong CYP3A4 inducers should be avoided.

Conflicts of Interest

All authors are employees of Amgen, Inc.

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