Original Article

Impact of Acid-Reducing Agents on Sotorasib Pharmacokinetics and Potential Mitigation of the Impact by Coadministration With an Acidic Beverage

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Abstract

Sotorasib exhibits pH-dependent solubility, making it susceptible to altered exposures when coadministered with acid-reducing agents (ARAs). Several clinical studies were conducted to investigate the impact of ARAs on sotorasib pharmacokinetics under different clinically relevant scenarios and to identify potential mitigation strategies. Upon coadministration of 960 mg of sotorasib and 40 mg of omeprazole under fasted conditions, sotorasib area under the concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) decreased approximately 42% and 57%, respectively. Following coadministration with 40 mg of famotidine under fed conditions, sotorasib AUC and C_{max} decreased approximately 38% and 35%, respectively. The coadministration of sotorasib and 40 mg of omeprazole under fed conditions led to a 57% and 65% decrease in sotorasib AUC and C_{max}, respectively. When sotorasib was coadministered with omeprazole and an acidic beverage compared to sotorasib alone, AUC and C_{max} decreased approximately 23% and 32%, respectively, leading to a 19.0 percentage-point increase in AUC and a 24.6 percentage-point increase in C_{max} for sotorasib when compared to coadministration of sotorasib with omeprazole under fasted conditions. Sotorasib exposure decreased when coadministered with proton pump inhibitors and H_2 receptor antagonists. Coadministration with an acidic beverage increased sotorasib exposure upon concomitant administration with omeprazole, which may represent a clinically attractive method to allow ARA use with sotorasib.

Keywords

acid-reducing agents, drug-interaction, sotorasib

Sotorasib is a small-molecule inhibitor that covalently binds to the Kirsten rat sarcoma virus (KRAS) protein with a G12C mutation at the protein level. Sotorasib specifically binds and irreversibly inhibits the *KRAS* p.G12C mutant protein, thus representing an important advancement for the treatment of subjects with *KRAS* p.G12C mutated tumors. Inactivation of KRAS by small-molecule inhibition has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts that have *KRAS* mutations, including the *KRAS* p.G12C mutation.[1–5] Studies with sotorasib have confirmed these in vitro findings and have likewise demonstrated selective inhibition of cell growth and regression of tumors with *KRAS* p.G12C mutations.[6] A 2-year analysis of the registrational study CodeBreaK 100 demonstrated the long-term benefit of sotorasib in subjects with pretreated *KRAS* G12C-mutated non-small cell lung cancer. Sotorasib produced an overall response rate of 41%, median duration of response of 12.3 months, progression-free survival of 6.3 months, overall survival of 12.5 months, and 2-year overall survival rate of 33%.[7] In the refractory colorectal cancer patient population with

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the *KRAS* G12C mutation, sotorasib in combination with panitumumab yielded a median progression-free survival of 5.6 months (960 mg sotorasib arm) and 3.9 months (240 mg sotorasib arm) as compared with 2.2 months in the standard-care group.[8]

Sotorasib is absorbed rapidly after single and multiple daily doses in healthy subjects and patients with advanced solid tumors with a median time to maximum concentration (t_{max}) of 1 hour. The mean terminal elimination half-life is 5 hours in the dose range of 180-960 mg once daily.[9] At a dose of 960 mg once daily, the sotorasib steady-state mean volume of distribution at steady state is 211 L and the apparent clearance is 26.2 L/h. Sotorasib is primarily metabolized by nonenzymatic conjugation and oxidation via cytochrome P450 (CYP) 3As with 3 circulating metabolites.[10,11] Sotorasib exposure decreased when administered with a strong CYP3A4 inducer (rifampin), and therefore such combinations should be avoided. [12]

Acid-reducing agents (ARAs) are a class of pharmaceutical compounds that increases gastric pH. They are widely prescribed for the treatment of conditions associated with gastric acid overproduction, such as heartburn, gastroesophageal reflux disease, and ulcer. Approximately 20%-30% of patients with cancer are taking ARAs, among which proton pump inhibitors (PPIs) were the most prescribed agent, comprising 60%-80% of patients cancer receiving a prescription for an ARA.[13] Due to their mechanism of actions, ARAs may alter the absorption of some drugs with pH-dependent solubility and cause safety and efficacy concerns. Sotorasib has pKa values of 8.06 and 4.56. Sotorasib shows a pH-dependent solubility at 37°C, with highest solubility of 1.3 mg/mL observed at pH 1.2 hydrochloric acid media with subsequent reduction to its solubility at higher pH 0.07 mg/mL at pH 4.5-0.03 mg/mL at pH 6.8-7.4. In situations in which the pharmacokinetics (PK) of a compound are altered by the coadministration of an ARA, temporarily lowering the intragastric pH with an acidic beverage can mitigate the impact of ARAs on the absorption of those compounds. Several research articles reported that the coadministration of cola (pH 2.37-3.10) improved the absorption of weakly basic drugs such as erlotinib, velpatasvir/sofosbuvir, itraconazole, and ketoconazole.[14–19] Given that following a high-calorie, high-fat meal, sotorasib area under the concentration-time curve (AUC) from time 0 to infinity (AUC_{inf}) was increased by 38% in healthy volunteers and AUC from time 0 to 24 hours was increased by 25% in patients with cancer, coadministration of food was also assessed as a potential mitigation strategy.[20]

This article reports the results from 3 clinical studies. The primary objectives of the first 2 clinical studies were to assess the impact of omeprazole (PPI) and famotidine (H_2 receptor antagonist) on the PK of sotorasib in healthy subjects under fasted and fed conditions. The primary objective of the third clinical study was to evaluate the effects of omeprazole and an acidic beverage on sotorasib PK when administered orally in healthy volunteers.

Methods

All 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, and the International Conference on Harmonisation Good Clinical Practice Guidelines. Prior to the start of the studies, the study protocols, informed consent forms, investigator's brochures, and other relevant documents (eg, advertisements) were reviewed and approved by an independent ethics committee or institutional review board at each participating center. The studies were conducted at Fortrea Clinical Research Unit in Daytona Beach, Florida (Study I) and Dallas, Texas (Studies II and III). The study-related documents were reviewed and approved by Salus Institutional Review Board (Austin, TX).

Clinical Study Design

The 3 study schemas are presented in Figure 1.

Study I was a Phase 1, open-label, fixed-sequence study to investigate the PK of sotorasib when administered alone and in combination with omeprazole in healthy subjects. Enrolled subjects received a single oral dose of 960 mg of sotorasib on Day 1, 40 mg of omeprazole delayed-release tablet once daily from Days 4 to 8, and the combination of 40 mg of omeprazole with 960 mg of sotorasib on Day 9. The doses were administered after an overnight fast of at least 10 hours.

Study II was a Phase I, open-label, fixed-sequence study to evaluate the PK of sotorasib administered alone and in combination with either famotidine or omeprazole in healthy volunteers under fed conditions. Enrolled subjects received 960 mg of sotorasib (after a meal) on Day 1, 40 mg of famotidine on Day 3 given 10 hours prior to the next scheduled sotorasib dose, 960 mg of sotorasib (after a meal) followed by 40 mg of famotidine 2 hours later on Day 4, and 40 mg of omeprazole delayed-release capsule once daily from Days 6 to 10 and 40 mg of omeprazole followed by a meal and then 960 mg of sotorasib 30 minutes after the start of the meal on Day 11. Subjects consumed standard-calorie moderate-fat meals on dosing days.

Study III was a Phase 1, open-label, fixed-sequence study to assess the effect of coadministration of omeprazole with an acidic beverage on the PK of sotorasib in healthy volunteers. Enrolled subjects received

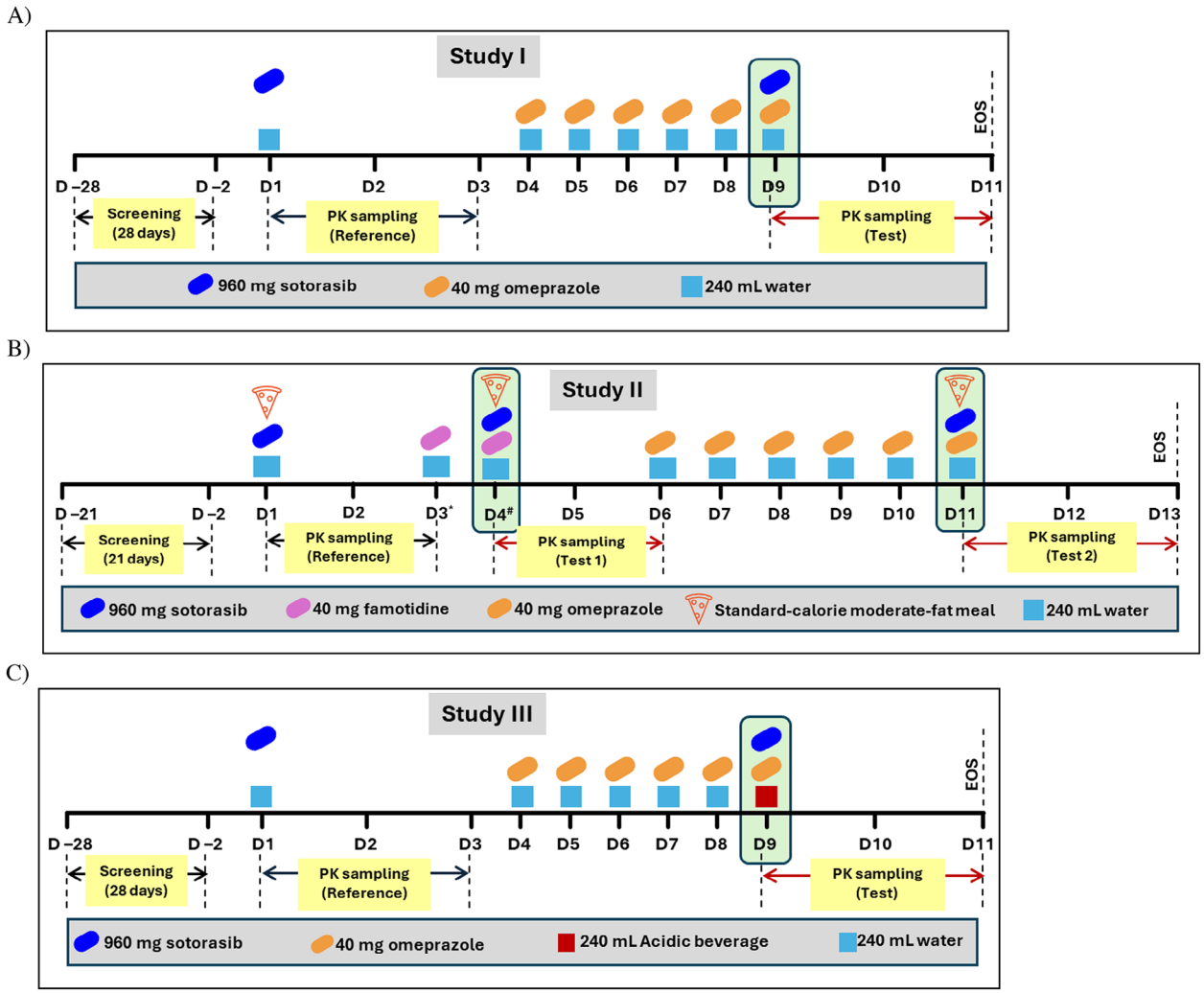

Figure 1. Study schemas. EOS, end of study; PK, pharmacokinetic.

960 mg sotorasib by mouth with a glass of water on Day 1, 40 mg of omeprazole once daily with a glass of water from Days 4 to 8, and the combination of 40 mg of omeprazole and 960 mg of sotorasib with a glass of Coca-Cola on Day 9. The doses were administered under fasted conditions (after an overnight fast of at least 10 hours).

Eligibility criteria included 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 non-childbearing 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 or dietary or herbal supplements therapy within 30 days prior to enrollment.

Sample Collection

Blood samples were collected into dipotassum ethylenediaminetetraacetic acid spray-coated tubes before dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours after dosing following administration of sotorasib alone or in combination with an ARA. Blood samples were centrifuged at 1500 × *g* and 2° to 8°C for 15 minutes within 30 minutes of collection and kept in freezers at −70°C or lower until shipment.

Bioanalytical Method

Bioanalyses were conducted by PPD Laboratories in Richmond, Virginia, for Study I; PPD Laboratories in Middleton, Wisconsin, for Study II; and Altasciences Company Inc. in Laval, Quebec, Canada, for Study III. All samples were analyzed within the demonstrated long-term stability in human plasma containing dipotassum ethylenediaminetetraacetic acid at −80°C.

Quantification of sotorasib concentrations in human plasma followed the same method as previously published.[21] In short, a 25.0-µL matrix aliquot is 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 mm × 50 mm, 2.6 µm 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 coefficient of variation ranged from 1.4% to 10.3%. The interday accuracy and precision coefficient of variation 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

PK parameters of interest included AUC from time 0 to the time of last quantifiable concentration (AUC_{last}), AUC_{inf}, AUC from time 0 to 24-hour after dosing, maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), and apparent terminal elimination half-life. The analysis data set included all subjects who received at least 1 dose of sotorasib and had evaluable PK data. Noncompartmental analysis was performed using Phoenix WinNonlin Version 8.1 to calculate the PK parameters. AUCs were calculated using the linear trapezoidal interpolation rule. Actual sample collection times were used in the data analyses. All values below the limit of quantification were set as 0 and included as such in the calculation of descriptive statistics.

A mixed model was used to analyze the natural log-transformed PK parameters. The model included treatment as a fixed effect and subject as a random effect. The least-square mean (LSM) for each treatment, difference in LSMs between test and reference treatments, and corresponding 90% confidence interval were calculated for each PK parameter. These values were then back-transformed to give the geometric LSM (GLSM), ratio of GLSMs, and corresponding 90% confidence interval.

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 (MedDRA) Version 22.0 and higher at the time of the study. Adverse events, clinical laboratory values, vital signs, and 12-lead electrocardiograms were monitored from check-in to end of study.

Results

Fourteen healthy volunteers completed Study I and Study II, and 16 healthy volunteers completed Study III. The demographic characteristics are summarized in Table S1.

Pharmacokinetic Analysis

The arithmetic mean (±standard error) plasma concentration-time profiles for sotorasib following a single dose of 960 mg of sotorasib alone and when coadministered with an ARA are presented in Figures 2–4. The PK parameters of sotorasib are summarized in Tables 1–3. A summary of the statistical analysis of PK data is presented in Table 4.

The plasma concentration-time profiles for sotorasib alone (reference) and sotorasib coadministered with omeprazole under fasted conditions (test) were characterized by a relatively rapid absorption phase, although median t_{max} increased slightly, by 0.75 hours after dosing, with coadministration. Geometric mean AUCs and C_{max} decreased approximately 42% and 57%, respectively, when sotorasib was coadministered with omeprazole. The ratios (test/reference) of the GLSM for sotorasib AUC_{inf}, AUC_{last}, and C_{max} were 0.582, 0.576, and 0.431, respectively, when coadministered with omeprazole compared to sotorasib alone.

Following fed-state administration of sotorasib alone (reference) or with 40 mg of famotidine (alone), median t_{max} of each was similar. Geometric mean exposures of sotorasib, based on AUCs and C_{max}, decreased approximately 38% and 35%, respectively, following coadministration with 40 mg of famotidine under fed conditions. The ratios (test/reference) of the GLSM of sotorasib coadministered with famotidine compared to sotorasib alone were 0.619, 0.622, and 0.654 for AUC_{last}, AUC_{inf}, and C_{max}, respectively. Median t_{max}

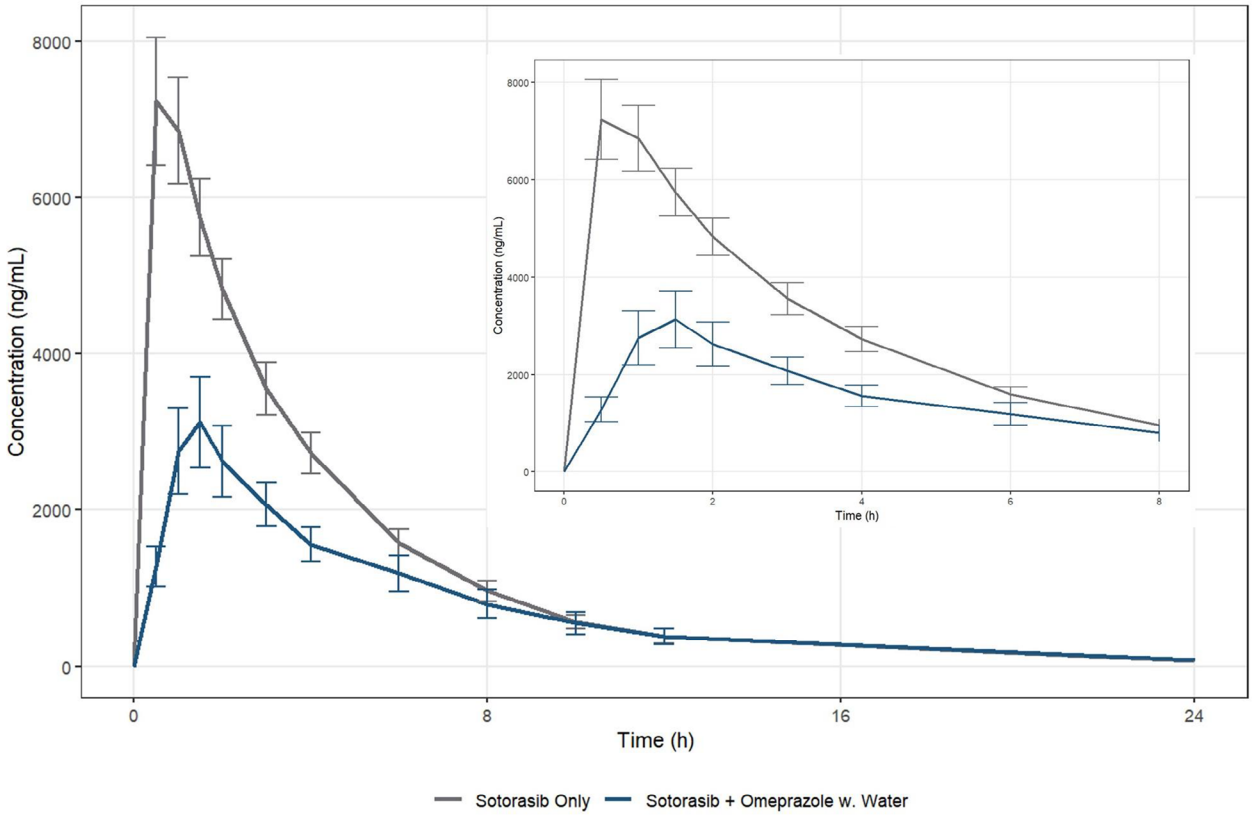

Figure 2. Arithmetic mean (±standard error) plasma concentration-time profiles of sotorasib alone and following coadministration of omeprazole with water under fasted conditions.

was approximately 1 hour later for sotorasib following fed-state coadministration with omeprazole (test) compared to sotorasib alone (reference). Geometric mean exposures of sotorasib, based on AUCs and C_{max}, decreased approximately 57% and 65%, respectively, following coadministration with 40 mg of omeprazole under fed conditions. The ratios (test/reference) of the GLSM of sotorasib coadministered with omeprazole compared to sotorasib alone under fed conditions were 0.414, 0.430, and 0.349 for AUC_{last}, AUC_{inf}, and C_{max}, respectively.

The median t_{max} of a single oral dose of sotorasib alone (reference) and following coadministration with a single oral dose of omeprazole and an acidic beverage under fasted conditions (test) was similar (1 and 1.25 hours after dosing, respectively). Geometric mean AUCs and C_{max} decreased approximately 23% and 32%, respectively, when sotorasib was coadministered with omeprazole and an acidic beverage under fasted conditions. The ratios (test/reference) of the GLSM for AUC_{last}, AUC_{inf}, and C_{max} were 0.766, 0.771, and 0.677, respectively, when sotorasib is coadministered with omeprazole and an acidic beverage compared to sotorasib administered alone.

Safety and Tolerability

No sotorasib-related treatment-emergent adverse events was reported in the studies. There were otherwise no clinically significant changes, related to sotorasib, in laboratory tests, vital signs, or 12-lead electrocardiograms observed during the studies. All doses of sotorasib were well tolerated in healthy volunteers.

Discussion

The solubility of sotorasib peaks at pH 1.3 in aqueous media and decreases as the pH increases, making it liable to potential drug interactions when administered with ARAs. These studies evaluated the effect of ARAs on sotorasib PK in various clinically relevant scenarios. Study I was designed to assess such impact under fasted conditions. A PPI was chosen because PPIs' inhibitory effect on acid secretion is in general the greatest among other ARAs such as H_2 receptor antagonists and local antacids.[22,23] To evaluate the maximum impact conditions, omeprazole 40 mg was given for 5 days prior to the coadministration of 960 mg of sotorasib so that maximal gastric acid suppression had reached a plateau.[24–26] From a metabolic drug interaction

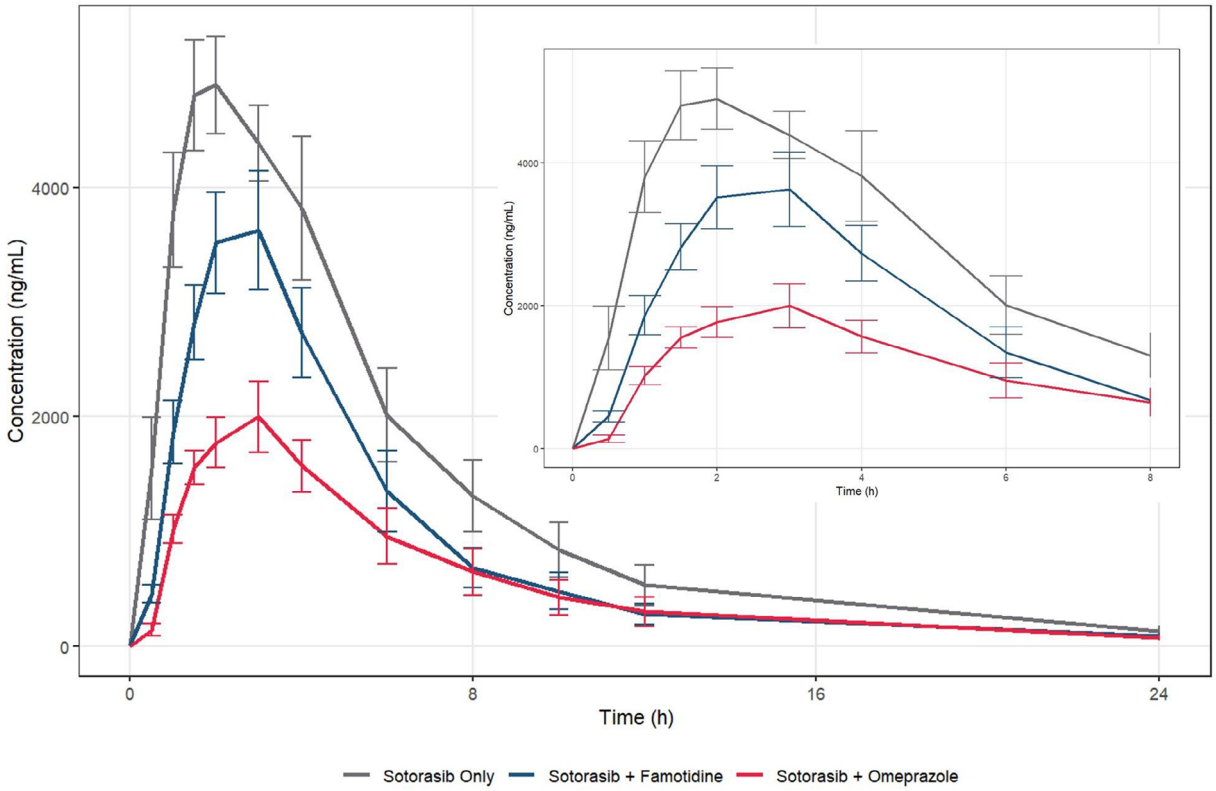

Figure 3. Arithmetic mean (±standard error) plasma concentration-time profiles of sotorasib alone and following coadministration of famotidine and omeprazole with water under fed conditions.

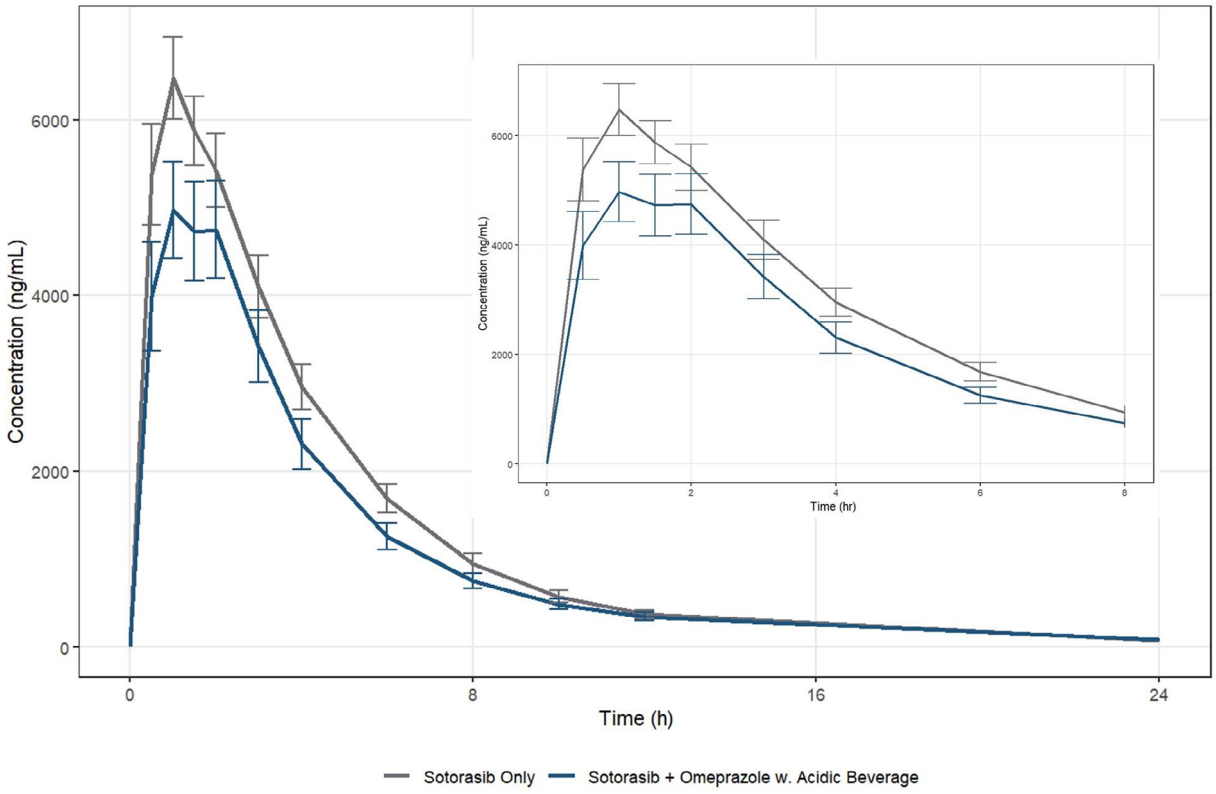

Figure 4. Arithmetic mean (±standard error) plasma concentration-time profiles of sotorasib alone and following coadministration of omeprazole with an acidic beverage under fasted conditions.

Table 1. Summary of PK Parameters for Sotorasib—Study I

PK parameters	960 mg of sotorasib	960 mg of sotorasib + 40 mg of omeprazole with water
N	14	14
Arithmetic mean (SD)		
C_{max} (ng/mL)	7880 (2780)	3590 (2200)
AUC_{last} (ng•h/mL)	31,300 (12,000)	19,200 (11,500)
AUC_{inf} (ng•h/mL)	31,500 (12,100)	19,500 (11,700)
$t_{1/2}$ (hour)	7.71 (3.14)	8.44 (2.11)
Geometric mean (geometric CV%)		
C_{max} (ng/mL)	7200 (54.6)	3100 (57.7)
AUC_{last} (ng•h/mL)	29,000 (44.9)	16,700 (56.1)
AUC_{inf} (ng•h/mL)	29,300 (44.5)	17,000 (55.6)
$t_{1/2}$ (hour)	7.11 (44.4)	8.17 (27.1)
t_{max} (hour), median (range)	0.75 (0.50-1.50)	1.50 (0.50-6.00)

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 plasma concentration; CV, coefficient of variation (%); PK, pharmacokinetic; t_{max}, time to reach maximum plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life.

Table 2. Summary of PK Parameters for Sotorasib—Study II

PK parameters	960 mg of sotorasib	960 mg of sotorasib + 40 mg of famotidine	960 mg of sotorasib + 40 mg of omeprazole
N	14	14	13
Arithmetic mean (SD)			
C_{max} (ng/mL)	5970 (2000)	4060 (1860)	2150 (1110)
AUC_{last} (ng•h/mL)	33,000 (17,800)	21,100 (13,800)	15,000 (11,800)
AUC_{inf} (ng•h/mL)	33,200 (18,000)	21,400 (14,000)	15,800 (12,200)
$t_{1/2}$ (hour)	6.72 (2.42)	7.57 (3.65)	11.5 (5.30)
Geometric mean (geometric CV%)			
C_{max} (ng/mL)	5700 (30.9)	3730 (43.9)	1950 (46.8)
AUC_{last} (ng•h/mL)	29,900 (45.2)	18,500 (52.0)	12,200 (66.9)
AUC_{inf} (ng•h/mL)	30,100 (45.2)	18,800 (51.4)	12,900 (68.9)
$t_{1/2}$ (hour)	6.35 (34.9)	6.90 (45.6)	10.5 (47.5)
t_{max} (hour), median (range)	1.78 (1.504.05)	2.02 (1.00-4.00)	3.01 (1.03-4.00)

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 plasma concentration; CV, coefficient of variation (%); PK, pharmacokinetic; t_{max}, time to reach maximum plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life.

perspective, omeprazole is not expected to interact with sotorasib in a clinically significant manner. Sotorasib is mainly metabolized via CYP3A enzymes and can induce CYP3A. Although omeprazole is a CYP3A substrate, 2 single doses of sotorasib with adequate washout in between are unlikely to elicit the induction effect. Study I results showed 42% and 57% reduction in sotorasib AUCs and C_{max}, which is congruent with the physicochemical characteristics of sotorasib.

It is crucial to identify alternative options for patients who cannot avoid ARAs considering that 37% of the patient population in the CodeBreaK 100 trial were taking ARAs. Research indicates that administering an H_2 receptor antagonist in a staggered manner, 10 hours before and 2 hours after, does not alter the absorption of drugs whose exposures decrease upon coadministrations of ARAs.[27–30] Additionally, in the food-effect study, following consumption of a high-calorie, high-fat meal, sotorasib exposure increased by 25% and 38% in patients with cancer and healthy volunteers, respectively.[20] Therefore, Study II investigated the impact of famotidine (staggered dosing) and omeprazole on sotorasib PK under fed conditions. In this study, standard-calorie moderate-fat meals were consumed to reflect real-world situations. Under fed conditions, coadministration of omeprazole decreased sotorasib AUC and C_{max} by 57% and 65%, respectively, which are numerically greater reductions in sotorasib exposure than those observed in Study I under fasted conditions. This difference could be explained by inter-study difference or by the presence of food. Although sotorasib exposure increased in the food-effect study

Table 3. Summary of PK Parameters for Sotorasib—Study III

PK parameters	960 mg of sotorasib	960 mg of sotorasib + 40 mg of omeprazole with an acidic beverage
N	16	14
Arithmetic mean (SD)		
C_{max} (ng/mL)	7330 (1620)	5450 (2190)
AUC_{last} (ng•h/mL)	31,600 (10,500)	26,000 (10,400)
AUC_{inf} (ng•h/mL)	31,800 (10,500)	26,200 (10,400)
$t_{1/2}$ (hour)	6.42 (2.02)	7.72 (3.19)
Geometric mean (geometric CV%)		
C_{max} (ng/mL)	7160 (22.9)	4850 (65.6)
AUC_{last} (ng•h/mL)	30,000 (33.3)	23,200 (62.2)
AUC_{inf} (ng•h/mL)	30,200 (33.3)	23,500 (60.4)
$t_{1/2}$ (hour)	6.14 (31.6)	7.16 (41.1)
t_{max} (hour), median (range)	1.00 (0.50-2.00)	1.25 (0.50-2.00)

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 plasma concentration; CV, coefficient of variation (%); PK, pharmacokinetic; t_{max}, time to reach maximum plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life.

Table 4. GLSM of Sotorasib PK Parameters

	GLSM ratio (90% CI) (test/reference)			
	Study I[a]	Study II–Famotidine[b]	Study II–Omeprazole[c]	Study III[d]
AUC_{last} (ng•h/mL)	0.576 (0.472-0.703)	0.619 (0.536-0.714)	0.414 (0.356-0.482)	0.766 (0.619-0.948)
AUC_{inf} (ng•h/mL)	0.582 (0.478-0.708)	0.622 (0.539-0.719)	0.430 (0.3673-0.503)	0.771 (0s.628-0.948)
C_{max} (ng/mL)	0.431 (0.333-0.559)	0.654 (0.561-0.764)	0.349 (0.296-0.411)	0.677 (0.547-0.839)

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; CI, confidence interval; C_{max}, maximum observed plasma concentration; GLSM, geometric least-square mean; PK, pharmacokinetic.

[a]Test treatment: sotorasib + omeprazole with water (fasted); reference treatment: sotorasib with water (fasted).

[b]Test treatment: sotorasib + famotidine with food; reference treatment: sotorasib with food.

[c]Test treatment: sotorasib + omeprazole with food; reference treatment: sotorasib with food

[d]Test treatment: sotorasib + omeprazole with an acidic beverage (fasted); reference treatment: sotorasib with water (fasted).

and food intake has been shown to mitigate ARAs' impact on small-molecule drug exposure, food effects are multifactorial and can be intricate.[31] The fat content in the meals used in Study II is lower than that in the food-effect study of sotorasib. Additionally, physiological changes induced by food can result in delayed gastric emptying, stimulation of bile flow, changes in gastrointestinal pH, and increase in splanchnic blood flow.[32,33] As a result, the net impact of food intake on the mitigation of decreased intragastric pH caused by ARAs can be difficult to predict.

Giving famotidine in a staggered manner can be an effective mitigation strategy while maintaining gastric acid suppression. Unlike omeprazole, there was no cumulative effect with repeated doses of famotidine. Maximum inhibitory effect is achieved by the 40-mg dose, which also resulted in the greatest uniformity of response over time.[34] A single evening oral dose of 40 mg of famotidine inhibited basal and nocturnal acid secretion, and the effect lasts for a period of at least 10 hours.[34] The same dose given in the morning after breakfast resulted in inhibition of the meal-stimulated acid secretion.[34] Coadministration of staggered dose famotidine under fed conditions resulted in improved sotorasib exposure when compared to coadministration with omeprazole (GLSM ratio 0.619 versus 0.571 for AUC_{last}). However, the impact of famotidine coadministration can potentially be diminished under fasted conditions, given the observation of the food effect in the omeprazole period.

Finally, Study III, which evaluated sotorasib exposure when coadministered with an acidic beverage and omeprazole to mitigate the negative effects of PPIs, had the highest GLSM ratios across all 3 studies. In clinical practice, many prescribers hesitate to switch patients from PPIs to weaker ARAs (ie, H_2 receptor antagonist and local antacids) either because patient medical conditions require PPIs or due to patient preferences. In those cases, a viable solution for managing this drug interaction is to temporarily lower the

gastric pH by administering an acidic beverage. The result from Study III showed that taking sotorasib and a PPI with an acidic beverage can negate a portion of the impact from PPIs (Figure S1). Upon coadministration of sotorasib and omeprazole with an acidic beverage, sotorasib AUCs and C_{max} decreased approximately 23% and 32%, respectively. This was an improvement over staggered famotidine under fed conditions. Compared to the GLSM ratios of sotorasib and omeprazole taken with water (Study I), sotorasib and omeprazole with an acidic beverage resulted in a 24.6 percentage-point increase in C_{max} and 19.0 percentage-point increase in AUC for sotorasib. Consideration of the overall acidity of a beverage would be important, as this range can be quite large.[14]

Conclusion

Sotorasib exposure decreased when coadministered with PPIs and H_2 receptor antagonists. Coadministration with an acidic beverage increased sotorasib exposure upon concomitant administration with omeprazole, which may represent a clinically attractive method to allow ARA use with sotorasib.

Conflicts of Interest

All authors are employees of Amgen, Inc.

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