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Shariq Syed, PhD, Pamela L. Clemens, PhD, Deanne Lathers, PhD, Georgia Kollia, PhD, Arindam Dhar, MD, PhD, Ian Walters, MD, and Eric Masson, PharmD

Brivanib alaninate is the orally available prodrug of brivanib, a dual inhibitor of fibroblast growth factor and vascular endothelial growth factor signaling pathways that is under therapeutic investigation for various malignancies. Brivanib alaninate inhibits CYP3A4 in vitro, and thus there is potential for drug-drug interaction with CYP3A4 substrates, such as midazolam. The present study evaluated pharmacokinetic parameters and safety/tolerability upon coadministration of brivanib alaninate and midazolam. Healthy participants received intravenous (IV) or oral midazolam with and without oral brivanib alaninate. Blood samples for pharmacokinetic analysis were collected up to 12 hours after midazolam and up to 48 hours after brivanib alaninate. Twenty-four participants were administered study drugs; 21 completed the trial. No clinically relevant effect of brivanib alaninate on the overall exposure to midazolam following IV or oral administration was observed. Orally administered brivanib alaninate was generally well tolerated in the presence of IV or oral midazolam. The lack of a pharmacokinetic interaction between brivanib and midazolam indicates that brivanib alaninate does not influence either intestinal or hepatic CYP3A4 and confirms that brivanib alaninate may be safely coadministered with midazolam and other CYP3A4 substrates.

Keywords: *brivanib; midazolam; pharmacokinetics; VEGF inhibitor; FGF inhibitor*

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Angiogenesis is a key component of tumorigenesis. As critical mediators of this process, vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are rational targets for therapeutic intervention.[1,2] Although antiangiogenic treatment delivered by VEGF receptor blockade alone is able to produce an initial antitumor response and is associated with a survival advantage for patients with advanced cancer,[3-5] responses to monotherapy are modest. In addition, associated increases in the selective pressure of the tumor microenvironment can lead to vascular remodeling, tumor escape, and resistance to therapy.[6] As a result, the use of alternative antiangiogenic strategies, including the dual inhibition of VEGF and FGF, is currently under investigation.

VEGF and FGF are known to act synergistically, and their simultaneous coexpression has been shown to result in fast-growing xenografts with high vessel density, patency, and permeability.[7] Because of its association with cellular proliferation, differentiation, and migration, aberrant FGF signaling has an oncogenic role in several human cancers, including hepatocellular carcinoma (HCC).[6,8-10] In a clinical setting, increased FGF levels have also been demonstrated prior to, or at the time of, progression following anti-VEGF therapy.[11,12] The dual blockade of FGF and VEGF in vitro produces a significant inhibition

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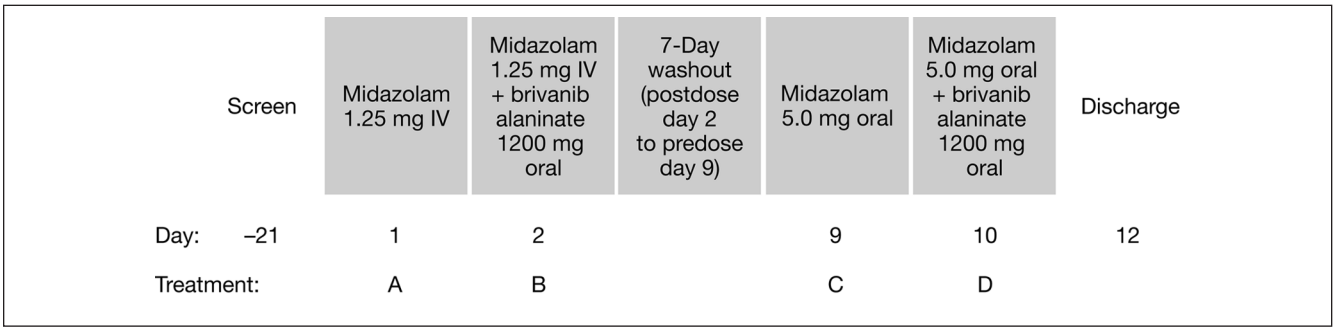

Figure 1. Study design. IV, intravenous.

of angiogenesis and tumor growth.[6,8,9] As such, concomitant blockade of FGF and VEGF signaling represents an opportunity to limit evasive reinduction of angiogenesis and consequent tumor regrowth that typifies the response to anti-VEGF therapy alone.

Brivanib alaninate is the orally available prodrug of brivanib, a dual inhibitor of FGF and VEGF signaling pathways.[13-15] In preclinical studies, tumor growth inhibition by brivanib was associated with inhibition of vascular branching,[13] reduced microvessel density, and inhibition of cellular proliferation,[14] indicating antiangiogenic and antitumor activity. Furthermore, brivanib has demonstrated efficacy in xenograft models resistant to bevacizumab.[14] In addition, brivanib has shown evidence of preliminary efficacy and tolerability in clinical trials of patients with unresectable locally advanced or metastatic HCC and other metastatic solid tumors, including colorectal cancer.[15,16]

It has been estimated that more than a third of all drugs are metabolized, at least in part, by CYP3A4/5 enzymes.[17] CYP3A4 is expressed in both the intestine and liver and is a major determinant of the first-pass metabolism of oral drugs.[17] In vitro studies have indicated that brivanib alaninate is a potent inhibitor of CYP3A4, with a half-maximal inhibitory concentration (IC_{50}) of 0.51 μM when 7-benzyloxy-4-trifluoromethylcoumarin was used as a substrate. However, its primary active circulating metabolite in humans, brivanib, exhibited only moderate inhibitory activity against CYP3A4 (IC_{50} 18 μM) using the same substrate. Following oral administration, brivanib alaninate is rapidly converted to brivanib presystemically. As such, it was considered that the inhibition characteristics may differ for intestinal and hepatic CYP3A4 after brivanib alaninate treatment.

Because brivanib alaninate is intended for administration to cancer patients who, by the nature of their disease, require concomitant medications, it is important to assess the clinical impact of coadministering brivanib alaninate with CYP3A4 substrates. One such drug is the benzodiazepine midazolam, which is exclusively metabolized by CYP3A4 and is not a P-glycoprotein substrate, making it a sensitive probe to assess CYP3A4 activity.[18] Intravenous (IV) midazolam is used to phenotype hepatic CYP3A4 activity, whereas orally administered midazolam is used to phenotype intestinal and hepatic CYP3A4 activity.[18]

The present study was designed to evaluate pharmacokinetic interactions between oral brivanib alaninate and IV or oral midazolam and thereby assess the activity of brivanib against intestinal and hepatic CYP3A4. In addition, the safety and tolerability of coadministering brivanib alaninate with midazolam was investigated.

METHODS

Study Design

This was an open-label, single-sequence, 4-treatment, crossover study in healthy adult participants designed to evaluate the potential drug interaction of oral brivanib alaninate with IV or oral midazolam. The study design is shown in Figure 1. Eligible participants were admitted to the clinical facility on the day prior to dosing and remained confined until discharge from the study on day 12. All participants received 4 sequential treatments. On day 1, all participants received a single dose of midazolam 1.25 mg IV (treatment A), and on day 2, all participants were administered oral brivanib alaninate 1200 mg followed 2 hours later by a single dose of midazolam 1.25 mg IV (treatment B). Following a washout of 7 days, all participants received a single oral dose of midazolam 5.0 mg on day 9 (treatment C); on day 10, they were given oral brivanib alaninate 1200 mg

followed 2 hours later by a single oral dose of midazolam 5.0 mg (treatment D). All treatments were administered after a fast of at least 10 hours, and the oral doses were administered with 240 mL of water.

The 1200-mg dose of brivanib alaninate was selected for the current study based on data from a prior multiple-ascending dose trial,[15] in which the geometric mean area under the plasma concentration-time curve (AUC) of brivanib increased approximately 1.5-fold from day 1 to day 26 following continuous administration of brivanib alaninate 800 mg. Thus, a single dose of 1200 mg brivanib alaninate was used in the current study to reflect steady-state brivanib plasma concentrations achieved with an 800-mg daily dose. The purpose of the 2-hour separation of doses between brivanib alaninate and midazolam was to administer midazolam near the previously reported median time to maximum observed plasma concentration (t_{max}) for brivanib, which was 2 hours following a 26-day continuous administration of oral brivanib alaninate 800 mg.[15] In addition, the mean plasma half-life ($t_{1/2}$) of brivanib was 12.3 hours in that previous trial,[15] justifying the use of a 7-day washout period in the current study design.

Participants

Healthy, nonsmoking male or female adult participants aged 18 to 55 years and with a body mass index of 18 to 32 kg/m^2, who were not on any concomitant medications, were eligible for enrollment into the study. Female participants who were nursing, pregnant, or of childbearing potential were excluded, as were any participants with clinically significant findings by medical history, physical examination, 12-lead electrocardiogram, or clinical laboratory testing; history of alcohol or drug abuse within the past 6 months; history of medication intolerance; or allergy to benzodiazepines. All participants were required to refrain from consuming any food or drink containing grapefruit or Seville oranges for at least 1 week prior to study entry and during the study. The study protocol was approved by an institutional review board, and written informed consent was obtained from each participant prior to study enrollment.

Blood Sample Collection and Assessments

Blood samples for the determination of midazolam pharmacokinetics were collected at predose and at 0.25 (IV only), 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, and 12 hours after each midazolam dose. Blood samples for brivanib pharmacokinetics (upon coadministration with oral midazolam only) were collected at predose and at 0.5, 1, 2, 3, 4, 6, 8, 24, and 48 hours post dosing. Physical examinations, vital sign measurements, and clinical laboratory evaluations were performed at selected times throughout the study, and participants were continuously monitored for adverse events (AEs).

Pharmacokinetic Analysis

Midazolam concentrations were measured in EDTA plasma after liquid-liquid extraction followed by a liquid chromatography/tandem mass spectrometry method using a deuterated internal standard (midazolam-D_4 maleate). Concentrations of brivanib were measured in EDTA plasma after solid-phase extraction followed by a liquid chromatography/tandem mass spectrometry method using a stable-labeled internal standard of brivanib ([$^{13}C_3$,$^{15}N_2$] brivanib). The high-performance liquid chromatography system consisted of a Shimadzu high-performance liquid chromatography (HPLC) pump (Shimadzu Corporation, Columbia, Maryland), an Alcott (Hamilton Square, New Jersey) or PerkinElmer (Waltham, Massachusetts) Autosampler, and either a Gemini C6-Phenyl column, 5 µm 2.0 × 50 mm (for midazolam), or a Phenomenex (Torrance, California) Luna Silica column, 3 µm 4.6 × 50 mm (for brivanib). The HPLC system was interfaced to a Sciex API 4000 mass spectrometer (Applied Biosystems, Foster City, California) operated in the positive ion electrospray ionization mode. Measurement of midazolam or brivanib concentrations was performed during the period of known analyte stability.

Single-dose pharmacokinetics for midazolam were derived from plasma concentration versus time data following coadministration of oral brivanib and IV or oral midazolam. Single-dose pharmacokinetics for brivanib were assessed following coadministration of oral brivanib and oral midazolam to confirm that brivanib exposures were consistent with previous reported values. The pharmacokinetic parameters assessed included maximum observed plasma concentration (C_{max}), t_{max}, AUC from time zero to time of last quantifiable concentration (AUC_{0-t}), AUC from time zero extrapolated to infinite time (AUC_{∞}), and $t_{1/2}$. Individual subject pharmacokinetic parameter values for brivanib and midazolam were derived by a noncompartmental method via a validated pharmacokinetics program (Kinetica 4.4.1 within the eToolbox version 2.6.1 [Thermo Scientific,

Waltham, Massachusetts]). C_{max} and t_{max} were recorded directly from experimental observations, whereas AUC_{0-t} was calculated by mixed log- and linear-trapezoidal summation. Without using a weighting factor, the slopes of the terminal phases of the plasma concentration-time profiles, λ, were determined by log-linear regression of at least 3 data points, which yielded a minimum mean square error. The absolute values of λ were used to estimate plasma $t_{1/2}$, with $t_{1/2} = \ln 2/\lambda$. AUC_{∞} was estimated by summing AUC_{0-t} and the extrapolated area, computed by the quotient of the last observable concentration λ.

Statistical Analysis

To assess the effect of concomitant administration of brivanib alaninate on the pharmacokinetic profile of midazolam (IV or oral), analyses of variance were performed on IV (treatment A, day 1; treatment B, day 2) and oral (treatment C, day 9; treatment D, day 10) midazolam $\log(C_{max})$, $\log(AUC_{\infty})$, and $\log(AUC_{0-t})$ values. Point estimates and 90% confidence intervals (CIs) for treatment differences on the log scale were exponentiated to obtain estimates for ratios B/A and D/C of geometric means on the original scale. As per US Food and Drug Administration (FDA) guidance on drug interaction studies, absence of a clinically meaningful effect of brivanib on the pharmacokinetics of IV midazolam was to be concluded if the 90% CIs for the geometric mean ratios (GMRs) of C_{max} and AUC_{∞} were entirely contained within the range of 0.80 to 1.25.[19] Similarly, based on FDA guidance, a weak effect of brivanib on the pharmacokinetics of oral midazolam was to be concluded if the point estimate for the ratio of the geometric means with and without brivanib was below 2. No adjustments were made for multiplicity.

RESULTS

Baseline Demographics and Patient Disposition

Twenty-four participants were enrolled and received study drug, with 21 participants completing the study as planned. Participant demographics and baseline characteristics are summarized in Table I.

The majority of participants were men (83%), and all were white, with a median age of 46 years and a median body mass index of 27.4 kg/m^2. All 24 participants completed both IV treatments (treatments A and B), with 23 of these participants being evaluable for IV midazolam pharmacokinetic analyses.

Table I Participant Demographics and Baseline Characteristics

	Participants (N = 24)
Median age, y (range)	46 (25-53)
Gender, No. (%)	
Male	20 (83)
Female	4 (17)
Race, No. (%)	
White	24 (100)
Ethnicity, No. (%)	
Hispanic/Latino	6 (25)
Not Hispanic/Latino	18 (75)
Median weight, kg (range)	75.4 (58.1-90.8)
Median height, cm (range)	167.0 (149.5-182.5)
Median body mass index, kg/m^2 (range)	27.4 (22.9-30.1)

Table II Statistical Analysis Results for IV and Oral Midazolam Pharmacokinetics

Pharmacokinetic Parameter	IV Midazolam + Brivanib Alaninate/IV Midazolam GMR (90% CI)	Oral Midazolam + Brivanib Alaninate/Oral Midazolam GMR (90% CI)
C_{max}	1.12 (1.06-1.19)	0.90 (0.82-0.99)
AUC_{∞}	1.05 (1.02-1.09)	0.87 (0.82-0.92)
AUC_{0-t}	1.04 (1.01-1.08)	0.86 (0.81-0.92)

CI, confidence interval; GMR, geometric mean ratio; IV, intravenous.

One participant was not evaluable for IV midazolam pharmacokinetics because of a sample collection error. Twenty-one participants completed both oral treatments (treatments C and D) and were evaluable for oral midazolam pharmacokinetic analyses. Three participants discontinued treatment: 1 because of an AE of elevated alanine aminotransferase (ALT), 1 because of withdrawn consent, and 1 because of personal reasons.

Pharmacokinetics

The mean plasma concentration-time profiles of IV or oral midazolam with and without brivanib alaninate are shown in Figure 2. Midazolam pharmacokinetics after either IV or oral administration was unaffected by coadministration with brivanib alaninate. The 90% CIs for the midazolam GMR with and without brivanib alaninate were within the required 0.80 and 1.25 lower and upper limits for AUC_{∞}, AUC_{0-t}, and C_{max} (Table II). Summary statistics for IV

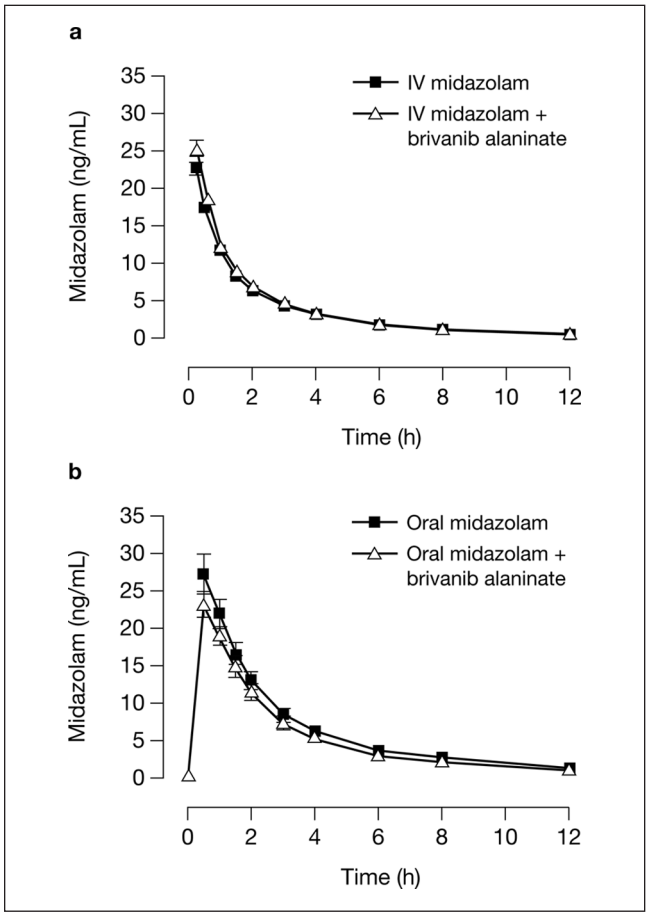

Figure 2. Mean (± standard error) plasma concentration-time profile of midazolam administered intravenously (A) or orally (B) with or without brivanib alaninate. IV, intravenous.

Table III Summary Statistics for IV and Oral Midazolam Pharmacokinetic Parameters

Pharmacokinetic Parameter, Units	IV Midazolam (n = 24)	IV Midazolam + Brivanib Alaninate (n = 23)
t_{max}, h, median (range)	0.25 (0.25-0.52)	0.25 (0.25-0.50)
C_{max}, ng/mL, geometric mean (%CV)	22.3 (17)	25.1 (19)
AUC_{0-t}, ng·h/mL, geometric mean (%CV)	43.0 (17)	45.4 (18)
AUC_{∞}, ng·h/mL, geometric mean (%CV)	46.3 (18)	48.3 (18)
$t_{1/2}$, h, mean (SD)	3.7 (1.4)	3.4 (0.9)
Pharmacokinetic Parameter, Units	**Oral Midazolam (n = 22)**	**Oral Midazolam + Brivanib Alaninate (n = 21)**
t_{max}, h, median (range)	0.5 (0.42-1.50)	0.5 (0.50-1.50)
C_{max}, ng/mL, geometric mean (%CV)	26.0 (43)	23.4 (27)
AUC_{0-t}, ng·h/mL, geometric mean (%CV)	72.0 (49)	62.4 (45)
AUC_{∞}, ng·h/mL, geometric mean (%CV)	78.9 (52)	68.0 (48)
$t_{1/2}$, h, mean (SD)	3.9 (1.1)	3.9 (0.9)

CV, coefficient of variation; IV, intravenous.

or oral midazolam pharmacokinetic parameters are tabulated by treatment in Table III. The data show a similar pharmacokinetic profile for midazolam irrespective of whether it is coadministered with brivanib alaninate. Individual subject AUC_{∞} parameters for midazolam are shown in Figure 3 and further suggest a lack of effect of brivanib on IV or oral midazolam pharmacokinetics.

Following coadministration of brivanib alaninate and oral midazolam, the geometric mean C_{max} for brivanib was 7.5 µg/mL (coefficient of variation [CV], 34%), geometric mean AUC_{0-t} was 88.7 µg·h/mL (CV, 38%), geometric mean AUC_{∞} was 101 µg·h/mL (CV, 40%), mean $t_{1/2}$ was 16.4 hours (standard deviation, 5.4), and median t_{max} was 2 hours (range, 1-6 hours).

Safety

Coadministration of brivanib alaninate with single doses of IV or oral midazolam was generally well tolerated by the healthy participants in this study. There were no deaths or serious toxicities. A single participant receiving IV midazolam with brivanib alaninate (treatment B) discontinued because of a grade 1 toxicity of increased ALT, which was considered by study investigators to be possibly related to treatment. Toxicities were reported more frequently following coadministration of brivanib alaninate with IV or oral midazolam (49 AEs in 20 participants; 83%) than with administration of IV or oral midazolam alone (16 AEs in 11 participants; 46%).

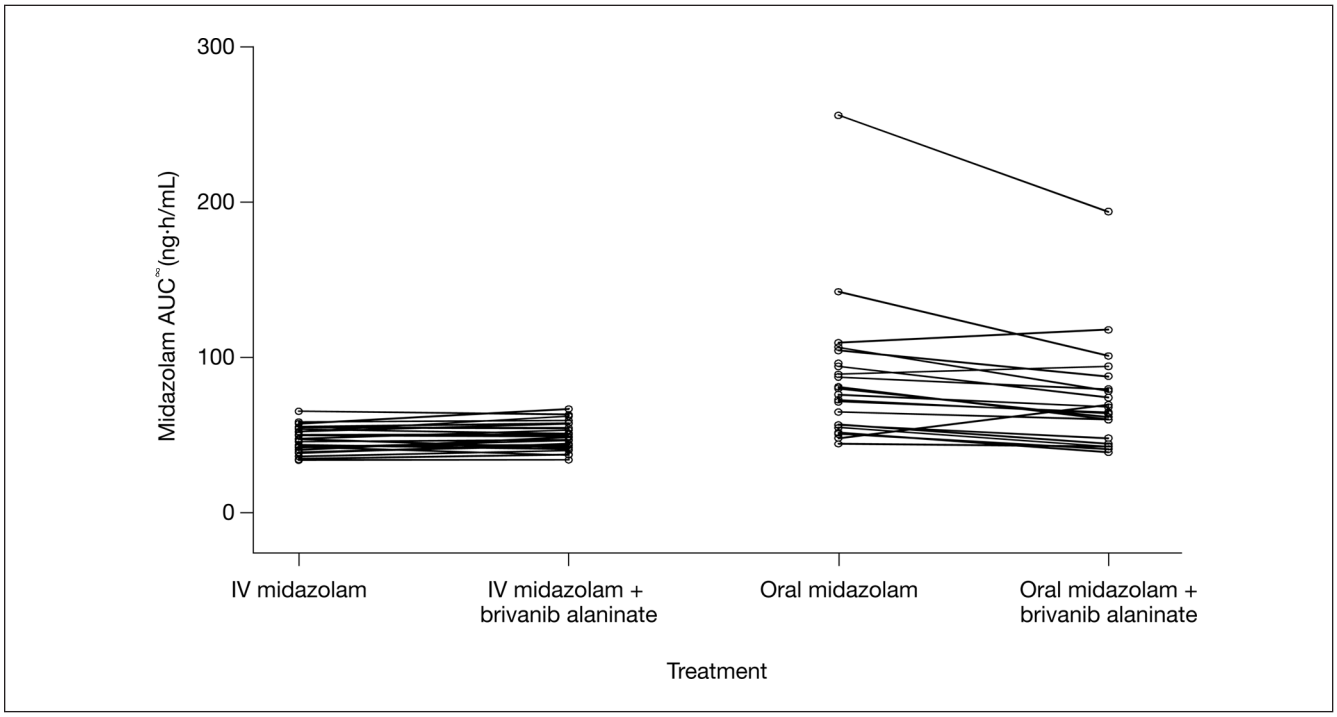

Figure 3. Individual subject AUC_{∞} profiles for midazolam before and after concomitant brivanib alaninate treatment. IV, intravenous.

Table IV Treatment-Emergent Toxicities

	Toxicity, No. (%)			
	IV Midazolam (n = 24)	**IV Midazolam + Brivanib Alaninate (n = 24)**	**Oral Midazolam (n = 22)**	**Oral Midazolam + Brivanib Alaninate (n = 21)**
Any AE	10 (42)	15 (63)	3 (14)	11 (52)
Dizziness	5 (21)	8 (33)	0	4 (19)
Somnolence	2 (8)	4 (17)	0	5 (24)
Thirst	0	6 (25)	0	0
Dry mouth	0	4 (17)	0	0
Headache	1 (4)	1 (4)	1 (5)	2 (10)
Decreased heart rate	0	4 (17)	0	0
Nausea	0	0	0	2 (10)
Vision blurred	0	1 (4)	0	1 (5)

AE, adverse event; IV, intravenous.

Treatment-emergent AEs occurring in more than 1 participant are listed in Table IV. All AEs were considered nonserious and grade 1 (mild) or grade 2 (moderate) in intensity. The most frequent toxicities across all participants were dizziness (42%) and somnolence (33%); a majority of these events were assessed as having a probable relationship to treatment. Somnolence was the most frequent grade 2 AE and was reported for 2, 4, and 5 participants in the IV midazolam, IV midazolam with brivanib alaninate, and oral midazolam with brivanib alaninate groups, respectively. Other grade 2 AEs were dizziness (3 participants, IV midazolam with brivanib alaninate), asthenia (1 participant, IV midazolam), and

gastrointestinal pain (1 participant, oral midazolam). All treatment-emergent AEs had resolved by the end of the study.

Overall, there were no clinically significant changes over time in any laboratory or vital sign parameters. Individual clinically significant abnormalities were reported in 4 participants, including a grade 1 toxicity of ALT increase, for which the participant discontinued, and 3 vital sign–related grade 1 toxicities of decreased heart rate.

DISCUSSION

Brivanib alaninate is an oral dual inhibitor of FGF and VEGF receptor kinases with potent antiangiogenic, as well as antitumor, activity.[13,14] It is one of a class of tyrosine kinase inhibitors, including imatinib, dasatinib, nilotinib, gefitinib, erlotinib, lapatinib, sunitinib, and sorafenib, that are metabolized by CYP3A4.[20] Drug-drug interactions are a consideration in the administration of tyrosine kinase inhibitors as a result of their metabolism by CYP3A4 and, in the case of imatinib, dasatinib, nilotinib, and lapatinib, the subsequent inhibition of CYP3A4. Because the coadministration of these drugs with other CYP3A4 substrates may result in greater drug exposure, their use must be carefully considered in clinical practice.[21] The reported geometric mean C_{max} for brivanib following daily 800-mg dosing is 6610 ng/mL (18 μM).[15] As a potent in vitro inhibitor of CYP3A4 with an IC_{50} of 0.51 μM, brivanib alaninate, together with its active moiety, brivanib (IC_{50} of 18 μM), has the potential for inhibiting CYP3A4 in vivo, which could lead to increased plasma concentrations of CYP3A4 substrates. The present study was therefore conducted to evaluate the potential inhibitory effect of oral brivanib alaninate and its active moiety, brivanib, on CYP3A4 enzymes in healthy participants.

Midazolam is recommended by the FDA as a probe substrate for CYP3A4 drug-drug interaction studies,[19] based on its selective metabolism by CYP3A4.[22,23] In this study, midazolam was selected to assess CYP3A4 drug-drug interactions with brivanib alaninate in healthy volunteers. In addition, the availability of midazolam in both IV and oral formulations allowed for an evaluation of hepatic and intestinal first-pass CYP3A4 metabolism.[18] A unique strength of this study was its single-sequence, 4-treatment design, which permitted the assessment of hepatic and combined hepatic and intestinal inhibition of CYP3A4, respectively, in the same participants.

Our findings demonstrate that brivanib alaninate and its active moiety did not affect the pharmacokinetics of either IV or oral midazolam, thus indicating that there was no inhibition of hepatic or intestinal CYP3A4. Using FDA guidance that establishes the upper and lower bounds for demonstrating the absence of any drug-drug interactions,[19] the 90% CIs for the GMR of midazolam C_{max} and AUC_{∞} either with or without brivanib were entirely contained within the 0.8 to 1.25 no-effect interval. In addition, coadministration of either IV or oral midazolam with oral brivanib alaninate was generally well tolerated by healthy volunteers in this study. Toxicities were all grade 1 or 2 in severity and resulted in study discontinuation in only 1 participant (with a grade 1 toxicity of increased ALT). There were no deaths or serious toxicities throughout the study. The incidence of some treatment-emergent AEs that are common to midazolam (eg, dizziness, somnolence, and nausea) were reported at a higher frequency with coadministration of midazolam and brivanib alaninate than historical information when midazolam is administered alone; however, many of these AEs are also common to brivanib.[15,16] Careful monitoring for these events should be implemented when these 2 agents are administered together.

The fact that brivanib alaninate is rapidly converted to brivanib in vivo suggests that the inhibitory effect of brivanib alaninate would primarily be on the intestinal system, whereas the liver would be primarily exposed to brivanib. The results, however, show no significant inhibitory effect on the intestinal or hepatic systems based on negligible changes in IV and oral midazolam exposure. Coadministration of brivanib alaninate with IV midazolam resulted in a less than 5% increase in midazolam C_{max} and AUC_{∞}, whereas coadministration of brivanib alaninate with oral midazolam resulted in a small decrease in midazolam exposure (10% and 14% decrease in C_{max} and AUC_{∞}, respectively).

A secondary objective of this study was to characterize the pharmacokinetics of brivanib following coadministration of brivanib alaninate with oral midazolam. A single dose of 1200 mg brivanib alaninate was used in this study to mimic the steady-state brivanib plasma concentrations achieved with an 800-mg daily dose currently being evaluated in phase III trials. Following a single oral dose of brivanib alaninate 1200 mg with oral midazolam, brivanib systemic exposure was comparable to that achieved at steady state, with the 800-mg once-daily dose currently being investigated in clinical trials of patients with advanced cancer,[15] and also to that achieved in other studies of single 1200-mg doses in normal healthy volunteers.[24] Moreover, median t_{max} for brivanib in the current study was 2 hours, a finding that further supports the selection of a 2-hour

dosing interval between brivanib alaninate and midazolam.

In conclusion, administration of brivanib alaninate had no effect on the pharmacokinetics of either IV or oral midazolam. These results indicate that brivanib alaninate and its active moiety, brivanib, do not affect intestinal or hepatic CYP3A4 in a clinically meaningful manner. Thus, in cancer patients, who are often prescribed multiple concomitant medications, brivanib alaninate may be coadministered with CYP3A4 substrates without dose adjustments and with acceptable tolerability.

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