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ORIGINAL ARTICLE

Lack of food effect on single-dose pharmacokinetics of brivanib, and safety and efficacy following multiple doses in subjects with advanced or metastatic solid tumors

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Abstract
Purpose Brivanib alaninate, an orally available prodrug of brivanib, is currently under evaluation for the treatment of several malignancies. This study aimed to (1) investigate effects of a high-fat meal on single-dose pharmacokinetics of brivanib in subjects with advanced/metastatic solid tumors and (2) assess the safety and preliminary efficacy of single and multiple doses of brivanib alaninate in this population.
Methods A two-part study was conducted consisting of a single-dose phase (Part A) and a multiple-dose phase (Part B). In Part A, subjects received a single dose of brivanib alaninate (800 mg) either in a fasting state or following ingestion of a high-fat meal (approximately 951 kcal [15% protein, 33% carbohydrate, 52% fat]); serial blood samples were collected for pharmacokinetic analysis up to 48 h post-dosing. In Part B, subjects received brivanib alaninate (800 mg) once daily until discontinuation. Throughout both phases, subjects were evaluated for adverse events (AEs) and best clinical response.
Results No clinically significant differences in brivanib exposure were observed between fed and fasting subjects in Part A; C_{max} was unchanged and AUC_{INF} decreased marginally when administered in a fed versus fasted state. In Part A, the incidence of treatment-emergent AEs was broadly similar in a fed or fasted state. Brivanib alaninate was generally well tolerated throughout the study and showed preliminary evidence of antitumor activity.
Conclusions Consumption of a high-fat meal had no significant effect on brivanib pharmacokinetics. The study further demonstrates the acceptable safety/tolerability profile and antitumor potential of brivanib in patients with advanced malignancies.

Keywords Pharmacokinetics · Exposure · Food · Safety · Brivanib alaninate · Solid tumors

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Introduction

Angiogenesis, the process by which new blood vessels are formed, is critical for tumor growth and metastasis and is mediated by several proangiogenic factors, such as vascular endothelial growth factor A (VEGF-A) and fibroblast growth factors 1 (FGF-1) and 2 (FGF-2) [1]. A number of antiangiogenic drugs that specifically inhibit VEGF receptor (VEGFR) signaling pathways have demonstrated survival benefits, either as monotherapy or when co-administered with other chemotherapy agents, in subjects with various advanced-stage malignancies, including renal cell carcinoma (RCC), non-small-cell lung cancer, hepatocellular carcinoma (HCC), and colorectal cancer [2–8]. Although the use of these VEGF inhibitors represents a breakthrough in the treatment of tumor angiogenesis, responses to date have been modest and transient, and treatment with these agents has varyingly been associated with significant toxicities [9, 10].

Brivanib alaninate, an alanine ester prodrug of the active moiety brivanib, is an orally bioavailable selective inhibitor of FGF and VEGF signaling pathways that has shown potent antitumor activity and no overt toxicity in preclinical cancer models, including colon, breast, liver, and lung [11–13]. Furthermore, administration of brivanib alaninate has been shown to be generally well tolerated at multiple doses up to 800 mg in subjects with various advanced cancers [14]. This dose has shown promising efficacy and safety in a recent phase II study in subjects with advanced or metastatic, nonresectable HCC [15], such that brivanib alaninate is currently under evaluation as monotherapy in a phase III HCC clinical program. In addition, combinations of brivanib and other anticancer agents are under investigation for the treatment of several malignancies, including colorectal cancer.

It is well established that the presence of food can alter gastric pH, gastric emptying, gastrointestinal motility, and bile secretion and may also affect the biotransformation of drugs in the gastrointestinal tract wall and/or liver. The aim of this study was to investigate the effect of food on single-dose pharmacokinetics of brivanib in subjects with various advanced or metastatic tumors. The study also included an extended treatment period, with the aim of providing further data on the safety and efficacy of multiple oral doses of brivanib alaninate in subjects with advanced malignancies.

Methods

Study design

This was a two-part study involving subjects with advanced or metastatic solid tumors enrolled at 3 sites in the United States. The trial design consisted of an open-label, randomized, single-dose, two-treatment, two-period crossover phase (Part A) followed by a multiple-dose, open-label treatment phase (Part B). On day 1 of Part A of the study, subjects were randomly assigned to receive a single oral dose of brivanib alaninate 800 mg either following a 10-h fast (Treatment A) or after the ingestion of a high-fat meal within 30 min prior to dosing (Treatment B; approximately 951 kcal [15% protein, 33% carbohydrate, 52% fat]). On day 8 of Part A (after a 7-day washout period), subjects received oral brivanib alaninate 800 mg after the reverse fasting/meal instructions given on day 1 (Fig. 1). For Treatment A, subjects were required to fast for at least 4 h after study drug administration. Single oral doses of brivanib alaninate 800 mg were administered as 4 × 200 mg tablets, taken with 240 ml of water; no other fluid was allowed for 1 h before or after dosing with Treatment A or for 1 h after dosing with Treatment B.

Upon completion of Part A, subjects were entered into Part B of the study. In Part B, beginning on day 10, subjects received oral doses of brivanib alaninate 800 mg once daily (QD; Treatment C). Missed doses were not rescheduled; up to 2 dose reductions were allowed in the event of unacceptable toxicity. Subjects remained on treatment in Part B until they discontinued brivanib alaninate therapy due to disease progression or unacceptable toxicity (Fig. 1).

Informed consent was obtained from each subject prior to study participation, and the study was conducted in accordance with the Declaration of Helsinki and locally applicable guidelines on Good Clinical Practice. The protocol, amendments, and subject informed consent received appropriate approval by the institutional review board/independent ethics committee prior to study initiation at each site.

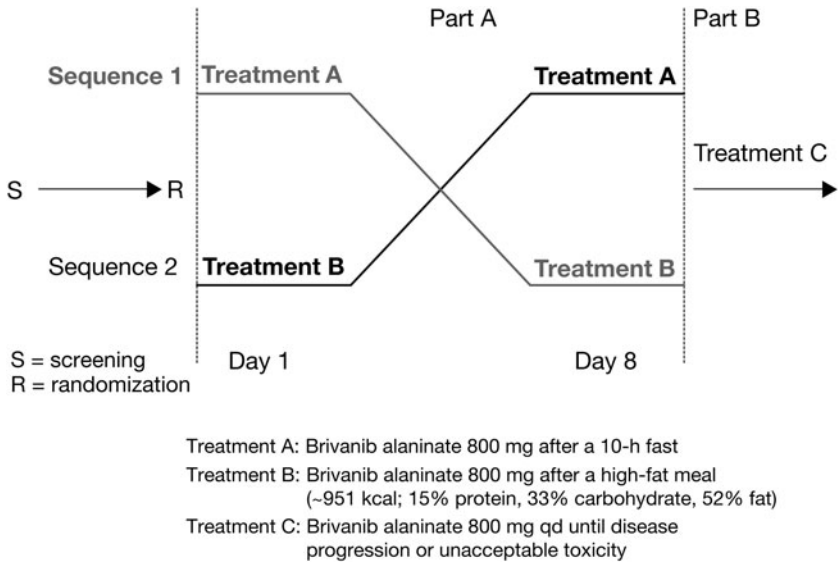

Fig. 1 Study design

Subject eligibility

Men and women aged at least 18 years were required to have the following characteristics for inclusion: a life expectancy of at least 3 months; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2; a histologic or cytologic diagnosis of advanced or metastatic solid tumors; and adequate hematologic, hepatic, and renal function. In addition, at least 4 weeks had to have passed since the subject last received chemotherapy, immunotherapy, radiotherapy, anticancer hormonal therapy, or targeted therapy; at least 6 weeks had to have passed since last therapy with nitrosoureas, mitomycin C, and/or liposomal doxorubicin; and any toxicity related to prior therapy had to have resolved, returned to baseline or been deemed irreversible, and been documented in the subject's medical history.

Subjects were excluded from the study if they had any of the following characteristics: brain metastasis or signs and symptoms suggestive of brain metastasis; concomitant second malignancies except nonmelanoma skin cancer, early-stage prostate cancer, or carcinoma in situ of the cervix; proteinuria $\geq$1+ at study entry; uncontrolled or significant cardiovascular disease, including uncontrolled hypertension (systolic blood pressure $\geq$150 mm Hg and diastolic blood pressure $\geq$100 mm Hg); a serious uncontrolled medical disorder or active infection that would impair the ability to receive study medication; a psychiatric disorder that would impair the ability to provide informed consent; thromboembolic disease requiring full anticoagulation within 6 months of study entry; gastrointestinal disease that could impact brivanib absorption; or a history of allergy to VEGF/FGF receptor inhibitors or related compounds. Pregnant or breast-feeding women, or women of child-bearing potential who were unwilling or unable to use an acceptable method of contraception to avoid pregnancy for the entire study period and for at least 3 months after the study, were not permitted to participate.

Concurrent use of hormonal replacement therapy, or luteinizing hormone–releasing hormone agonist therapy in subjects with prostate cancer, was allowed. However, subjects were excluded if they were receiving other concomitant standard or investigational chemotherapy, hormonal therapy, immunotherapy, or radiotherapy regimens. Additional treatment-related exclusion criteria included any prior exposure to brivanib, exposure to any investigational drug within 4 weeks prior to study drug administration, exposure to drugs generally accepted to have a risk of causing torsade de pointes within 5 days (or at least 5 half-lives of the drug) prior to first dose of study drug, and exposure to prescription or over-the-counter acid controllers (proton pump inhibitors, antacids, or H_2 blockers) within 1 week prior to drug administration in Part A of the study.

Study objectives

In Part A, the primary objective was to assess the effect of a high-fat meal on the pharmacokinetics of brivanib in subjects with advanced or metastatic solid tumors. A secondary objective was to evaluate the safety/tolerability of oral brivanib alaninate administration among these subjects under fasted and fed (i.e., after a high-fat meal) conditions. In Part B, the primary objective was to assess the safety/tolerability and therapeutic efficacy of multiple doses of oral brivanib alaninate in subjects with advanced or metastatic solid tumors.

Assessments

Pharmacokinetics

In Part A, plasma samples were collected up to 48 h postdose after each treatment and brivanib assayed using a validated liquid chromatography–tandem mass spectrometry method. Single-dose pharmacokinetic parameters for brivanib, including maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration–time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{0-T}), AUC from time zero extrapolated to infinite time (AUC_{INF}), and terminal half-life ($T_{1/2}$), were derived from plasma concentration versus time under fasted and fed conditions. Pharmacokinetic assessments were not performed in Part B of the study.

Safety/tolerability

Subjects were closely monitored for adverse events (AEs) throughout the duration of the study. The incidence of observed AEs was tabulated and reviewed for potential significance and clinical importance. All AEs were coded using the Medical Dictionary for Regulatory Activities version 12.1. Physical examinations, vital signs, clinical laboratory tests, electrocardiograms, echocardiograms, and assessment of signs and symptoms were also performed at selected times throughout the study.

Efficacy

Responses to treatment were assessed, as deemed appropriate by the institution's or investigator's standard of care. Best overall clinical response outcomes were listed and summarized by frequency distribution.

Statistical methods

In Part A, a sample size of 22 subjects was calculated to provide 89% power to conclude an absence of food effect if there was no effect of a high-fat meal on brivanib AUC_{INF}

and 79% power to conclude a lack of food effect if the high-fat meal reduced the brivanib AUC_{INF} geometric mean by 5%. In addition, 22 subjects would provide 98% confidence that the estimate of the fed/fasted ratio of C_{max} geometric means would be within 20% of its true value.

To evaluate the effect of food on brivanib pharmacokinetics in Part A, analyses of variance were performed on log C_{max} and log AUC_{INF}. The factors in the analysis model were sequence, subjects within sequence, period, and treatment (A or B, i.e., fasted or fed, respectively). Point estimates and 90% confidence intervals (CIs) for treatment differences were exponentiated to obtain estimates for the fed/fasted ratios of geometric means on the original scale. Absence of food effect was concluded on AUC_{INF} if the corresponding 90% CI for the ratio of population geometric means of fed/fasted treatments was contained within an equivalence interval of 80–125% (i.e., 0.80–1.25).

The primary statistical pharmacokinetic analysis was based on subjects who had evaluable data for both Treatments A and B, and who had consumed at least 800 kcal of the high-fat meal, of which at least 50% were fat calories. In Parts A and B, all subjects who received at least 1 dose of study medication were included in the efficacy and safety data sets.

Results

Subject disposition and demographics

Thirty-five subjects were enrolled, 29 of whom received at least 1 dose of brivanib alaninate in Part A and 27 of whom received brivanib alaninate in Part B (Table 1). Of the 29 subjects who received brivanib alaninate in Part A, 25 received both Treatments A and B; the other 4 subjects each received only 1 dose of brivanib alaninate with a high-fat meal. Two of these 4 subjects discontinued treatment due to an AE, and the other 2 were discontinued from Part A because they ingested substantially fewer calories from the high-fat meal than required for the primary pharmacokinetic analysis; these latter 2 subjects received subsequent treatment in Part B of the study. Among the 25 subjects who completed both treatment periods in Part A, 6 were excluded from the primary pharmacokinetic analysis either because the plasma samples for one treatment were severely hemolyzed (2 subjects) or because they only ingested between 500 and 780 kcal of the high-fat meal (4 subjects). In light of these exclusions from the primary pharmacokinetic analysis, a secondary analysis was performed based on 23 subjects with evaluable data from both treatments in Part A; these subjects received at least 500 kcal of the high-fat meal.

Table 1 Subject disposition and baseline demographics and characteristics

Subjects	Subjects, *n*		
	Part A	Part B	Total
Enrolled	35	35	35
Treated	29	27	29
Available for primary pharmacokinetic analysis[a]	19	NA	19
Available for safety analysis	29	27	29
Available for efficacy analysis	29	27	29
Demographic			***N* = 29**
Age, years			
Mean (SD)			64 (11)
Range			42–82
Gender, *n* (%)			
Male			16 (55)
Female			13 (45)
Race, *n* (%)			
White			24 (83)
Black			3 (10)
Asian			1 (3)
Other			1 (3)
ECOG, *n* (%)			
0			12 (41)
1			13 (45)
2			4 (14)
Site of primary tumor, *n* (%)			
Colon			8 (28)
Lung			6 (21)
Ovary			3 (10)
Thyroid			2 (7)
Pancreas			2 (7)
Esophagus			2 (7)
Other sites			6 (21)
Prior therapy, *n* (%)			
Surgery			26 (90)
Hormonal, immunologic, or biologic therapy			15 (52)
Radiotherapy			9 (31)
Chemotherapy[b]			29 (100)
No. of chemotherapy regimens			
1			1 (3)
2			5 (17)
≥3			23 (79)

[a] Ten subjects were ineligible for inclusion in the primary pharmacokinetic analysis in Part A: 2 discontinued therapy, 2 had severely hemolyzed plasma samples for 1 treatment, and 6 had consumed too few calories of the high-fat meal

[b] Included prior systemic anticancer agents

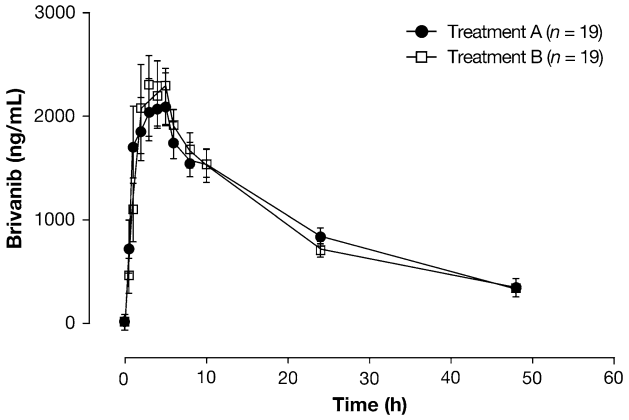

Fig. 2 Mean (+SE) plasma concentration–time profiles of brivanib following administration of brivanib alaninate with and without a high-fat meal

Baseline demographics are also shown in Table 1. Most subjects were white (82.7%), the mean age was 64 years, mean body mass index was 27.1 kg/m^2, and 55% were male. A majority of subjects had baseline ECOG status scores of 0 or 1. Subjects presented with various primary tumor types, including cancer of the colon (8 subjects), lung (6 subjects), ovary (3 subjects), thyroid (2 subjects), pancreas (2 subjects), esophagus (2 subjects), or kidney, breast, unspecified gland tissue, prostate, endometrium, or mesothelium (1 subject each). All 29 treated subjects had received prior chemotherapy, 79% of whom had received 3 or more regimens (Table 1). Fifteen subjects (51.7%) had previously received 1 or more targeted, immunologic or hormonal anticancer therapies, including sorafenib, sunitinib, bevacizumab, cetuximab, and tamoxifen, and 9 (31.0%) had received 1 or more cycles of radiotherapy.

Pharmacokinetics

Based on the primary pharmacokinetic analysis of 19 subjects with evaluable data for both Treatment A and Treatment B and who consumed at least 800 kcal of the high-fat meal (of which at least 50% were fat calories), there was no marked difference in the mean plasma concentration–time profiles of brivanib among fasting subjects and subjects who had recently ingested a high-fat meal (Fig. 2). Administration of brivanib alaninate with a high-fat meal did not change plasma brivanib C_{max} and reduced brivanib AUC_{INF} and AUC_{0-T} by only 9 and 11%, respectively (Table 2). The 90% CIs for both C_{max} and AUC_{INF} were entirely contained within the equivalence interval of 0.80–1.25; the lower limit of the 90% CI for AUC_{0-T} was 0.79. Median T_{max} occurred at 3.1 h following administration of brivanib alaninate with a high-fat meal, and approximately 0.9 h earlier versus administration of brivanib alaninate to fasting subjects; however, the range of T_{max} values was similar for both treatments (Table 3). $T_{1/2}$ was similar for both treatments and averaged about 18 h. Overall, the pharmacokinetic variability of brivanib was approximately the same with or without food (Table 3).

In the secondary pharmacokinetic analysis, based on 23 subjects with evaluable data from both Treatments A and B and who received at least 500 kcal of the high-fat meal, statistical analysis results were similar to those of the primary analysis with 90% CIs for ratios of geometric means of 0.82–1.02 for AUC_{INF}, 0.84–1.08 for C_{max}, and 0.79–1.00 for AUC_{0-T}.

Safety

Overall, brivanib AEs were manageable in both Part A and Part B of this study. In Part A, the incidence of treatment-emergent AEs was generally similar and of grade 1 or 2 in severity regardless of whether brivanib alaninate was administered under fasted or fed conditions (Table 4). Approximately half of the AEs reported in Part A were considered treatment related (14 of 30 events [47%] under fasted conditions and 24 of 52 events [46%] under fed conditions); fatigue was the most common treatment-related AE, reported in 2 subjects (7%) under fasted conditions and 6 subjects (21%) under fed conditions. In Part A, grade 3 nonserious, treatment-related hypertension was reported in 1 subject. Two serious AEs (SAEs), grade 3 intestinal obstruction and grade 3 pneumonia, both of which were considered unrelated to treatment, were reported in another subject following administration of brivanib alaninate with a high-fat meal on day 1. In Part A, 2 of the 29 treated subjects discontinued due to AEs: 1 subject discontinued due to intestinal obstruction and 1 withdrew consent coincident with an AE of fatigue.

Table 2 Summary of primary statistical analysis results on the effect of a high-fat meal on brivanib pharmacokinetics

Treatment (n = 19)	AUC_{INF} (ng h/ml) Geo. mean (adj) (90% CI)	AUC_{0-T} (ng h/ml) Geo. mean (adj) (90% CI)	C_{max} (ng/ml) Geo. mean (adj) (90% CI)
Brivanib alaninate 800 mg fasted	53,930 (46,150–63,018)	44,854 (38,728–51,949)	2,870 (2,411–3,417)
Brivanib alaninate 800 mg fed	49,234 (42,133–57,532)	39,853 (34,410–46,157)	2,888 (2,426–3,437)
Treatment comparison	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
Brivanib alaninate 800 mg fed/fasted	0.92 (0.82–1.02)	0.89 (0.79–1.00)	1.00 (0.86–1.18)

Geo. mean (adj) geometric mean adjusted for factors in the model, *GMR* ratios (fed/fasted) of adjusted geometric means

Table 3 Summary statistics for brivanib pharmacokinetic parameters

Treatment (n = 19)	C_{max} (ng/ml) Geo. mean (% CV)	AUC_{INF} (ng h/ml) Geo. mean (% CV)	AUC_{0-T} (ng h/ml) Geo. mean (% CV)	T_{max} (h) Median (min–max)	$T_{1/2}$ (h) Mean (SD)
Brivanib alaninate 800 mg fasted	2,847 (40)	53,685 (36)	44,610 (32)	4.0 (1.0–9.8)	18.3 (6.4)
Brivanib alaninate 800 mg fed	2,877 (46)	48,823 (40)	39,503 (39)	3.1 (1.0–10.0)	17.7 (5.8)

Geo. mean geometric mean, *CV* coefficient of variation

The most frequently reported treatment-emergent AEs in Part B are shown in Table 4. The most frequent treatment-related AEs were fatigue (15 subjects, 56%), diarrhea (12 subjects, 44%), hypertension and nausea (8 subjects each, 30%), and decreased appetite (7 subjects, 26%). As in Part A, most were judged as grade 1 or 2 in severity. The most frequently reported grade 3 AE was fatigue (5 subjects, 17%); other grade 3 AEs occurring in more than 1 subject were hypertension (4 subjects, 14%), increased alkaline phosphatase (3 subjects, 10%), and abdominal pain, diarrhea, dyspnea, hyponatremia, intestinal obstruction, pneumonia, and small intestinal obstruction (2 subjects each, 7%). Twenty-one SAEs were reported for 12 subjects during treatment in Part B, most commonly small intestinal obstruction or intestinal obstruction (4 events in 3 subjects), dyspnea (2 subjects), and progression of malignant neoplasm (2 subjects). Four subjects experienced life-threatening (grade 4) SAEs; 2 thromboembolic events (pulmonary embolism and ischemic stroke) were considered possibly related to treatment. The 2 remaining grade 4 SAEs were considered unrelated to treatment and included increased blood bilirubin and arrhythmia in 1 subject each.

Grade 3 elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or total bilirubin occurred in a total of 4 subjects. Three of these elevations were associated with malignant progression. The fourth, with concurrent elevations in ALT, AST, alkaline phosphatase, and bilirubin, was associated with obstructive jaundice requiring stenting. No subject met Hy's Law criteria for severe drug-induced liver injury.

Three subjects died due to disease progression that was unrelated to treatment; this included progression of malignant neoplasm in 2 subjects and acute dyspnea related to disease progression in 1 subject. In Part B, 26 subjects discontinued treatment. Reasons for discontinuation were disease progression in 14 subjects (54%) and AEs in 12 subjects (46%). The majority of discontinuations due to AEs (7 of 12 subjects) were considered unrelated/not likely related to treatment. For the remaining 5 subjects, treatment-related discontinuations included fatigue (2 subjects)

Table 4 Treatment-emergent AEs occurring in >20% of subjects treated with brivanib alaninate in the overall study population

Adverse event, n (%)	Part A		Part B	Overall (n = 29)
	800 mg, SD fasted (n = 25)	800 mg, SD fed (n = 29)	800 mg QD[a] (n = 27)	
Any AE	17 (68)	20 (69)	27 (100)	29 (100)
Fatigue	2 (8)	8 (28)	22 (81)	25 (86)
Diarrhea	2 (8)	2 (7)	16 (59)	16 (55)
Nausea	2 (8)	1 (3)	13 (48)	15 (52)
Decreased appetite	0 (0)	3 (10)	13 (48)	15 (52)
Hypertension	2 (8)	2 (7)	11 (41)	13 (45)
Constipation	2 (8)	2 (7)	8 (30)	11 (38)
Vomiting	0 (0)	0 (0)	10 (37)	10 (34)
Cough	1 (4)	1 (3)	9 (33)	9 (31)
Dyspnea	1 (4)	2 (7)	6 (22)	8 (28)
Dizziness	1 (4)	2 (7)	6 (22)	8 (28)
Dysphonia	0 (0)	1 (3)	6 (22)	7 (24)
Peripheral edema	1 (4)	1 (3)	7 (26)	7 (24)
Dehydration	0 (0)	0 (0)	7 (26)	7 (24)
Increased ALT	0 (0)	0 (0)	7 (26)	7 (24)
Increased AST	0 (0)	1 (3)	6 (22)	6 (21)
Decreased weight	0 (0)	0 (0)	6 (22)	6 (21)
Hypothyroidism	0 (0)	0 (0)	6 (22)	6 (21)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *SD* single dose

[a] Thirteen subjects had a dose reduction to either 600 or 400 mg QD during Part B

and pulmonary embolism, ischemic stroke, and hemoptysis (1 subject each). At the time of writing, 1 subject, with mesothelioma, has continued treatment with brivanib alaninate treatment for more than 3 years.

Of the 29 subjects treated in the study, 14 (48%) had at least 1 dose reduction and 16 (55%) had at least 1 dose interruption; reasons for the first dose modification were AEs (22 subjects, 76%), other reasons (7 subjects, 24%), and dosing error (1 subject, 3%). Of the 14 subjects who had at least 1 dose reduction, 10 had a single dose reduction from 800 to 600 mg QD, 1 had a single reduction from 800 to 400 mg QD, and 2 had 2 reductions from 800 to 600 mg QD to 400 mg QD. The other subject had an unintentional dose reduction due to a dosing error, but resumed treatment with 800 mg QD. Among the 16 subjects who had at least 1 dose interruption during treatment, the most common reasons for the dose interruption were fatigue, diarrhea, hypertension, and dizziness. Most subjects were able to resume treatment, often at a reduced dose, with no recurrence of intolerable AEs.

Efficacy

At the time of writing, 28 of the 29 treated subjects have discontinued brivanib therapy; 1 subject with mesothelioma remains on treatment for more than 3 years with stable disease. Best overall clinical response data were available for 22 of the 28 discontinued subjects; response was nondeterminable in 6 subjects, 5 of whom discontinued brivanib treatment prior to response assessments. Of these 22 subjects, 13 (59%) had a best overall response of stable disease and 9 (41%) had progressive disease. The 13 subjects with stable disease had primary tumors of the colon (5 subjects), ovary (3 subjects), lung (2 subjects), thyroid (1 subject), kidney (1 subject), and endometrium (1 subject); 1 of the subjects with primary ovarian cancer and a best overall response of stable disease received brivanib therapy for more than 1 year.

Discussion

This study reports the effect of food on single-dose pharmacokinetics of brivanib in subjects with advanced or metastatic solid tumors. Following administration of oral brivanib alaninate with a high-fat meal, no clinically significant changes in brivanib exposure were observed; C_{max} was unchanged and AUC_{INF} decreased only marginally (9%) when brivanib alaninate was taken under fed versus fasted conditions. Crucially, 90% CIs for both C_{max} and AUC_{INF} were within the bioequivalence range of 0.8–1.25 (80–125%), demonstrating a lack of food effect.

During Part A of the study, 7 of the 29 treated subjects were unable to ingest at least 780 kcal of the high-fat meal (includes 1 subject who discontinued therapy in Part A due to an AE). This illustrates a difficulty in performing food effect studies in subjects with advanced cancer. Indeed, due to the inability of some subjects to consume the required calories, the overall number of subjects eligible for the initial primary pharmacokinetic analysis ($n = 19$) was marginally lower than was planned based on the protocol sample size calculations ($n = 22$). However, based on the outcomes of this primary pharmacokinetic analysis, enrollment into the study was stopped as it was determined that enough subjects had completed both treatment periods in Part A and had consumed enough calories to sufficiently demonstrate a lack of food effect for brivanib.

Pharmacokinetic and absorption effects are known issues for many other oral agents that target VEGFR pathways, including sorafenib and pazopanib. Pharmacokinetic studies have shown a 29% reduction in sorafenib bioavailability when the drug is administered with a high-fat meal (900 kcal, 50% of calories from fat) [16, 17], and administration of pazopanib with food results in an approximate twofold increase in AUC and C_{max} [18]; both agents have labeling recommendations that they be administered without food. The differences in the effect of food on drug exposure between these agents are likely due to their differing physiochemical properties, such as drug solubilization and dissolution.

Brivanib alaninate, whether administered as single or repeated doses, was generally well tolerated, and the incidence of both treatment-emergent and treatment-related AEs was mostly similar in the presence or absence of food. In single doses, the only notable exception to this observation was fatigue, which was reported in a higher proportion of subjects receiving brivanib alaninate with a high-fat meal versus subjects under fasted conditions. Overall, the results of the pharmacokinetic and safety analyses support a schedule of once-daily dosing of brivanib alaninate 800 mg with or without food in subjects with cancer. With repeated doses, the most frequently reported drug-related AEs were fatigue, diarrhea, hypertension, nausea, and decreased appetite. Many of these AEs are common to the class of VEGFR inhibitors [2, 5–7, 19, 20], and they are consistent with those reported in previous studies of brivanib alaninate 800 mg in patients with advanced or metastatic solid tumors [14]. Of note, both the AEs reported here and those reported elsewhere with brivanib alaninate 800 mg [14] were mainly mild to moderate at grade 1 or 2.

Although this was a phase I study with a small number of patients, there were no reported cases of hand–foot syndrome, a dermatologic toxicity that is commonly observed following sunitinib or sorafenib treatment [6, 7, 9, 17, 19, 21]. This finding is consistent with the reported low rate of hand–foot syndrome in previous studies of brivanib in patients with various solid malignancies [14, 15].

In the current study, 2 subjects experienced a grade 4 thromboembolic event (pulmonary embolism and ischemic stroke) that was considered possibly related to treatment. They were discontinued from the study. This may be due to a class effect, as an increased risk of both arterial and/or venous thromboembolic events is observed with other anti-angiogenic agents, such as sorafenib, sunitinib, and bevacizumab [10, 22–24]. Other SAEs reported following brivanib alaninate administration in this study were generally consistent with underlying disease and were not considered related to treatment.

Therapeutic response to brivanib alaninate treatment was not a primary end point of the current study but was assessed for each subject, as deemed appropriate by the institutional or investigator's standard of care. A best overall clinical response of stable disease was reported in 13 of 28 subjects (46%) who discontinued therapy; notably, 5 of the 8 subjects with primary cancer of the colon achieved stable disease (data not shown). During the study, 2 patients were treated with brivanib alaninate for more than 1 year: 1 patient with ovarian cancer received therapy for just over 1 year and achieved a best overall response of stable disease; another patient with mesothelioma has continued to receive brivanib alaninate for more than 3 years, with stable disease. Although preliminary, these data provide further evidence of antitumor activity to support findings from previous small-scale studies of brivanib, as monotherapy or in combination with other anticancer therapy, for the treatment of advanced or metastatic solid tumors [14, 15, 25, 26]. Moreover, results of this study suggest that longer-term therapy with brivanib may have the potential to be both safe and effective.

In conclusion, a high-fat meal had no significant effect on brivanib pharmacokinetics, thus supporting once-daily and repeated dosing of brivanib alaninate with or without food in people with cancer. In addition, results from this study further demonstrate the tolerable safety profile and preliminary antitumor activity of brivanib in patients with advanced malignancies and support ongoing studies to determine the potential of brivanib to provide clinical benefit in the treatment of various cancers.

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