Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: brivanib alaninate (BMS-582664)		
Name of Active Ingredient: brivanib		

SYNOPSIS

Final Clinical Study Report for Study CA182006

TITLE OF STUDY: A Phase 2 Open Label Study of Brivanib (BMS-582664), Administered Orally at a Dose of 800 mg Daily in Subjects with Unresectable, Locally Advanced or Metastatic Hepatocellular Carcinoma Who Have Received Either No Prior Systemic Therapy or One Prior Regimen of Angiogenesis Inhibitor Therapy.

INVESTIGATORS/STUDY CENTERS: There were 249 subjects enrolled at 34 investigational sites in the United States (16 sites), Asia (14 sites), and France (4 sites).

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 21-Dec-2006 **CLINICAL PHASE:** 2

Study Completion Date: 16-Apr-2010

OBJECTIVES:

Primary Objective:

- To estimate the 6-month progression free survival (PFS) rate in subjects with unresectable locally advanced or metastatic hepatocellular carcinoma (HCC) with no prior systemic therapy for HCC (first-line) treated with 800-mg brivanib alaninate once daily (QD).

Secondary Objectives:

- To estimate tumor response rate, time to response, duration of response, PFS, overall survival, and disease control rate for subjects with no prior systemic therapy and for subjects with 1 prior regimen of angiogenesis inhibitor therapy.
- To assess the safety and tolerability of brivanib alaninate for subjects with no prior systemic therapy, for subjects with 1 prior regimen of angiogenesis inhibitor therapy, and for all subjects on the study.
- To assess the effects of brivanib alaninate on pharmacodynamic markers in subjects with HCC.
- To obtain blood, paraffin embedded biopsy (if available), and (optional) fresh tumor samples to identify potential predictive markers of biological response utilizing enzyme-linked immunosorbent assays (ELISA), ribonucleic acid (RNA) profiling, protein profiling, single nucleotide polymorphism (SNP) analysis, and other techniques.

- To estimate differences in and to assess the impact of brivanib alaninate on subject symptoms using Functional Assessment of Cancer Therapy, Hepatobiliary, Symptom Index (FHSI-8) for subjects with no prior systemic therapy and for subjects with 1 prior regimen of angiogenesis inhibitor therapy.
- To obtain samples for population pharmacokinetics (PPK) of BMS-540215 (chemical parent and active moiety of brivanib) in subjects with HCC treated with BMS-582664 (addressed in a separate PPK report).

Other Objectives:

In addition to the protocol-specified objectives, the statistical analysis plan [SAP], written and approved before database lock (01-Jun-2010), allowed for time-to-progression (TTP) to be estimated for subjects with no prior systemic therapy and for subjects with 1 prior regimen of angiogenesis inhibitor therapy. Furthermore, an exploratory objective was added to assess the safety and tolerability of brivanib alaninate in second-line subjects who had 1 prior anti-angiogenesis therapy and received 400-mg brivanib alaninate as a twice daily (BID) regimen for a total of daily dose of 800 mg.

METHODOLOGY:

This study was originally designed as an open-label, controlled study of brivanib alaninate versus doxorubicin in first-line subjects with HCC. Protocol Amendments made the following significant changes to the study design:

- Based on a successful Phase 3 study of sorafenib showing an overall survival advantage over placebo control, this study protocol was amended to discontinue the doxorubicin arm, since doxorubicin was now considered an obsolete standard of care. Since fibroblast growth factor (FGF) levels have been implicated in vascular endothelial growth factor (VEGF) failures, the protocol was amended to allow entry of a second cohort of subjects who had been treated with 1 prior regimen of angiogenesis inhibitor therapy.
- Due to preliminary data indicating that BID dosing may be beneficial in lessening the severity and frequency of certain AEs (e.g., abnormal bilirubin), the protocol was amended to add a third cohort of up to 25 second-line subjects receiving 400-mg brivanib alaninate BID for a total daily dose of 800 mg. The analyses for this cohort are considered exploratory.

Taking into account the protocol amendments, a total of 125 subjects were planned to be treated with a daily dose of 800-mg brivanib alaninate and were enrolled into the following 3 groups:

- **First-line QD Cohort** = Subjects with no prior systemic therapy treated with 800 mg brivanib alaninate QD.
- **Second-line QD Cohort** = Subjects with 1 prior regimen of angiogenesis inhibitor therapy treated with 800 mg brivanib alaninate QD.
- **Second-line BID Cohort** = Subjects with 1 prior regimen of angiogenesis inhibitor therapy treated with 400 mg brivanib alaninate BID.

The primary endpoint, 6-month PFS rate for subjects in the first-line QD cohort, was to be analyzed when all subjects were treated and followed for 6 months. All secondary endpoints were analyzed when the majority of subjects were off study.

NUMBER OF SUBJECTS (Planned and Analyzed):

A total of 125 subjects were planned: 50 subjects in the first-line QD cohort, 50 subjects in the second-line QD cohort, and 25 subjects in the second-line BID cohort.

A total of 123 subjects were treated with brivanib alaninate and analyzed: 55 subjects in the first-line QD cohort, 46 subjects in the second-line QD cohort, and 22 subjects in the second-line BID cohort.

In addition, 14 subjects were treated with doxorubicin from the original protocol; however, the data from the 123 brivanib-alaninate-treated subjects are the focus of this report.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The study included male and female subjects aged 18 or greater with unresectable locally advanced or metastatic HCC having received no prior systemic therapy for HCC or 1 prior regimen of angiogenesis inhibitor therapy (including sorafenib, sunitinib, thalidomide, or bevacizumab).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Brivanib alaninate (200-mg tablets) was administered orally (PO) on a continuous daily schedule at a dose of 800 mg, until disease progression or unacceptable toxicity. Batch numbers for brivanib alaninate were: 6B16980, 6H10715, and 7B28235.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Before the doxorubicin arm was discontinued, 14 subjects were administered doxorubicin with the following batch numbers: 6B16980 and 6H10715.

CRITERIA FOR EVALUATION:

Efficacy Endpoints: The primary endpoint of this study is the 6 month PFS rate as assessed by an Independent Response Review Committee (IRRC), using modified World Health Organization (mWHO) criteria, for first-line subjects with HCC.

The following secondary efficacy endpoints were assessed for subjects in the first-line and second-line cohorts: PFS, tumor response rate, disease control rate, time to response, duration of response, duration of disease control, TTP, overall survival, and the change in serum alpha fetoprotein (AFP). The second-line BID cohort was added primarily to assess the safety benefit of BID dosing; therefore, the limited efficacy analyses for this cohort are considered exploratory.

Safety Endpoints: The safety and tolerability assessments of brivanib alaninate were secondary safety endpoints assessed for subjects in the first-line and second-line QD and BID cohorts. Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, electrocardiograms (ECGs), echocardiograms, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated and reviewed for potential significance and clinical importance.

Pharmacodynamic Endpoints: Changes from baseline in Collagen IV (Col IV) were explored at Week 3, Week 6, and at the end of treatment.

Other Endpoints: Changes from baseline in FHSI-8 total score over time were evaluated.

STATISTICAL CONSIDERATIONS:

Discrete variables were summarized with the number and proportion of subjects falling into each category. Continuous variables were summarized with univariate statistics median, minimum and maximum values. Medians for time-to-event variables were computed using Kaplan-Meier (K-M) method. Corresponding confidence intervals were computed using the method of BrookMeyer and Crowley.

Efficacy: Analyses of tumor response were assessed by both IRRC and investigator according to the modified World Heath Organization (mWHO) criteria for tumor response. The 6-month PFS rate for the first-line QD cohort was tabulated based on progression determined by IRRC (primary analysis), and by investigator (sensitivity analysis). An exact binomial two-sided 95% confidence interval for the PFS rate was computed. The 6-month PFS rate was also estimated using the K-M method. The 95% CI of the PFS rate at 6 month was calculated using the Greenwood formula. PFS was the time from the day of first dose

until the time disease progression was first documented or death from any cause. Response rate was the proportion of evaluable subjects whose confirmed response was partial response (PR) or complete response (CR); disease control rate was the proportion of evaluable subjects whose best response was PR, CR, or stable disease (SD). An exact two-sided 95% Clopper-Pearson CI was computed for response and disease control rate.

Time to response was the time from the day of first dose until the first day criteria were met for CR or PR, whichever occurred first (computed only for subjects whose best response was PR or CR). Duration of response was the time from the first day all criteria were met for CR or PR, whichever occurred first, to the date progressive disease (PD) was first documented or date of death (computed only for subjects whose best response was PR or CR). Duration of disease control was measured from the date of the best response (whichever occurred first) until the date of documented PD or death (computed only for subjects whose best response was a PR, CR, or SD). Time to progression was the time (in months) from first dosing date to the date of progression. Overall survival was the time (in months) from first dosing until the date of death. The change in serum AFP was a best on-study decrease from baseline ≥ 50% summarized for subjects who had a baseline and at least 1 on-study AFP measurement.

Safety: Incidence of AEs, drug-related AEs, serious AEs (SAEs), drug-related SAEs, AEs of special interest (AEOSI), and AEs leading to discontinuation of therapy were tabulated. Drug-related AEs were those events with a relationship to study therapy of certain, probable, possible, or missing. All on-study AEs were summarized for the entire treatment period from the first dosing date to the last dosing date plus 14 days for AEs and from the first dosing date to the last dosing date plus 30 days for SAEs. On-study laboratory tests were defined as laboratory tests that were conducted after the start of treatment and no more than 30 days after the last dose of study treatment. The analysis population for each test was restricted to treated subjects who had taken the test.

Other: Summary statistics for change from baseline in Col IV were tabulated by study day. The FHSI-8 included 8 items representing HCC-related symptoms; each symptom was rated by subjects on a scale of from 0 to 4.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics/Exposure:

A total of 249 subjects were enrolled in this study and 123 were treated with brivanib alaninate in the first-line QD, second-line QD, and second-line BID cohorts (Table 1). Additionally, 14 subjects were treated with doxorubicin in Cohort D. Of the 112 subjects who were never treated, most subjects (94) were not treated because they no longer met study criteria. The data from the 123 brivanib-alaninate-treated subjects are the focus of this report. Of the 123 subjects treated with brivanib alaninate in the first-line and second-line cohorts, 122 subjects were off study by database lock for this report and 1 subject remained on therapy. Most of the 122 subjects left the study because of disease progression (72.4%) and the remaining subjects discontinued the study because of study drug toxicities (18.7%), withdrawal of consent (4.1%), AEs unrelated to study drug (3.3%), and death (0.8%) (Table 1).

Subjects who entered into the first-line QD, second-line QD, and second-line BID cohorts generally reflected the known demographics of an advanced HCC population (Table 2). The majority of subjects were male (71.7% to 89.1% across cohorts), with a median age of between 55 to 61 years old. Approximately 26% of subjects were ≥ 65 years of age in the QD cohorts and 40.9% were ≥ 65 years in the BID cohort. Most of the patients were Korean (32.7%, 50.0%, and 68.2% in the first-line QD, second-line QD, and second-line BID cohorts, respectively). The next largest populations were white (32.7%, 26.1%, and 18.2%) and Chinese (20.0%, 10.9%, and 0%), in the first-line QD, second-line QD, and second-line BID cohorts, respectively (Table 2).

Risk factors for HCC were consistent with the geographical distribution of subjects entered into the study. Since many of the subjects came from Asia, the predominant risk factor in over half the subjects was hepatitis B (56.9%), with about one fifth of the population each with hepatitis C (22.0%) and alcoholic liver disease (20.3%). Most subjects (77.2% per IRRC) had extra hepatic spread, 72.4% had metastatic disease, and 20.3% had portal vein invasion and/or thrombosis. Most subjects (65%) had an ECOG performance of 1 (Table 2).

The area under the curve (AUC) duration (95% CI) of study therapy was 3.9 (2.4 - 5.4) months, 3.2 (2.3 - 4.0) months, and 3.1 (2.1 - 4.1) months for subjects in the first-line QD, second-line QD, and second-line BID cohorts, respectively.

Table 1: Subject Disposition: First- and Second-Line Subjects Treated with Brivanib Alaninate

	Number of Subjects (%)			
	First-line QD Cohort N = 55	**Second-line QD Cohort N = 46**	**Second-line BID Cohort N = 22**	**Total N =123**
No. of Subjects Treated	55	46	22	123
Still on Study	1 (1.8) [a]	0	0	1 (0.8)
Off-Study	54 (98.2)	46 (100.0)	22 (100.0)	122 (99.2)
Reason Off Study [b]				
Adverse Event Unrelated to Study Drug	2 (3.6)	2 (4.3)	0	4 (3.3)
Death	1 (1.8)	0	0	1 (0.8)
Disease Progression	37 (67.3)	36 (78.3)	16 (72.7)	89 (72.4)
Study Drug Toxicity [c]	11 (20.0)	7 (15.2)	5 (22.7)	23 (18.7)
Subject Withdrew Consent	3 (5.5)	1 (2.2)	1 (4.5)	5 (4.1)

[a] Subject was still on study as of database cutoff date of 01-Jun-2010.

[b] Reason for not continuing brivanib alaninate treatment.

[c] Subjects discontinued due to study drug toxicity for any reason other than confirmed tumor progression.

Table 2: Demographics and Baseline Disease Characteristics: First- and Second-Line Subjects Treated with Brivanib Alaninate

	Number of Subjects (%)			
	First-line QD Cohort N = 55	**Second-line QD Cohort N = 46**	**Second-line BID Cohort N = 22**	**Total N =123**
Age (years)				
Mean	59.1	55.6	61.0	-
Median	60.0	55.0	61.0	-
Min-Max	27.0 - 80.0	21.0 - 81.0	36.0 - 83.0	-
Gender (%)				
Female	6 (10.9)	13 (28.3)	3 (13.6)	22 (17.9)
Male	49 (89.1)	33 (71.7)	19 (86.4)	101 (82.1)

Table 2: Demographics and Baseline Disease Characteristics: First- and Second-Line Subjects Treated with Brivanib Alaninate

	Number of Subjects (%)			
	First-line QD Cohort N = 55	**Second-line QD Cohort N = 46**	**Second-line BID Cohort N = 22**	**Total N =123**
Race (%)				
Korean	18 (32.7)	23 (50.0)	15 (68.2)	56 (45.5)
White	18 (32.7)	12 (26.1)	4 (18.2)	34 (27.6)
Chinese	11 (20.0)	5 (10.9)	0	16 (13.0)
Asian Other	5 (9.1)	3 (6.5)	2 (9.1)	10 (8.1)
Other[a]	3 (5.5)	3 (6.5)	1 (4.5)	7 (5.7)
ECOG Performance Status				
0	25 (45.5)	12 (26.1)	2 (9.1)	39 (31.7)
1	27 (49.1)	33 (71.7)	20 (90.9)	80 (65.0)
2	3 (5.5)	1 (2.2)	0	4 (3.3)
CLIP Score				
0	7 (12.7)	4 (8.7)	2 (9.1)	13 (10.6)
1	18 (32.7)	14 (30.4)	6 (27.3)	38 (30.9)
2	16 (29.1)	18 (39.1)	10 (45.5)	44 (35.8)
3	14 (25.5)	10 (21.7)	4 (18.2)	28 (22.8)
BCLC Stage				
A	0	0	0	0
B	6 (10.9)	2 (4.3)	0	8 (6.5)
C	49 (89.1)	44 (95.7)	22 (100.0)	115 (93.5)
Child-Pugh Status				
A	50 (90.9)	42 (91.3)	21 (95.5)	113 (91.9)
B	5 (9.1)	4 (8.7)	1 (4.5)	10 (8.1)
HCC Risk Factor				
Subjects with Identified Risk[b]	46 (83.6)	40 (87.0)	22 (100.0)	108 (87.8)
Alcoholic Liver Disease	14 (25.5)	6 (13.0)	5 (22.7)	25 (20.3)
Hepatitis B	29 (52.7)	30 (65.2)	11 (50.0)	70 (56.9)
Hepatitis C	12 (21.8)	8 (17.4)	7 (31.8)	27 (22.0)
Non-alcoholic Fatty Liver Disease/ Steatohepatitis	1 (1.8)	2 (4.3)	4 (18.2)	7 (5.7)
Other	9 (16.4)	3 (6.5)	2 (9.1)	14 (11.4)

[a] Includes Black/African American (4.1%), Malaysian (0.8%), and Native Hawaiian/Other Pacific Islander (0.8%).

[b] Subjects may have more than 1 HCC risk factor.

NA = not available; BCLC = Barcelona Clinic Liver Cancer; CLIP: Cancer for the Liver Italian Program Score; ECOG = Eastern Cooperative Oncology Group

Efficacy Results:

The primary efficacy objective, to estimate the 6-month PFS rate in first-line subjects with HCC, showed a 20.0% (95% CI: 10.4, 33.0) 6-month PFS rate using the exact binomial estimate and a 22.4% (95% CI: 10.9, 33.9) 6-month PFS rate using the Kaplan-Meier estimate (per IRRC, using mWHO Criteria) (Table 3).

Tumor response and disease control rate were measured by the IRRC using mWHO criteria. Tumor response rates (CR or PR) were 7.3% and 4.3% in the first-line and second-line QD cohorts, respectively, and about half the subjects (50.9% and 45.7% in the first-line and second-line QD cohorts, respectively) had disease control (SD, CR, or PR). For the 4 subjects in the first-line cohort with best overall tumor response of PR or CR (per IRRC using mWHO criteria), time to response ranged from 1.4 months to 20.7 months and duration of response ranged from 1.4 months to 20.7 months. For the 2 subjects in the second-line cohort, the time to response was 1.4 months for both subjects and duration of response was 2.8 months and 5.5 months.

The overall survival was 10.0 and 9.8 months in first- and second-line QD subjects, respectively. Table 3 displays a summary of PFS, TTP, overall survival, tumor response rate, and disease control rate as measure by mWHO criteria.

Approximately half of the subjects in the first-line and second-line QD cohorts had AFP response which was defined as a decrease > 50% from baseline level. Among subjects with baseline AFP > 200ng/ml, approximately half of the subjects in the first-line and second-line QD cohorts had AFP response (> 50% decrease).

Table 3: Overall Efficacy Summary

Efficacy Endpoint	First-line QD Cohort N = 55	Second-line QD Cohort N = 46
	% (95% CI)[a]	
Six-month PFS Rate by IRRC (Primary endpoint)		
Using the Exact Binomial Estimate	20.0 (10.4, 33.0)	-
Using the K-M Estimate	22.4 (10.9, 33.9)	-
Tumor Response Rate[b] by IRRC	7.3 (2.0, 17.6)	4.3 (0.5, 14.8)
Disease Control Rate[c] by IRRC	50.9 (37.1, 64.6)	45.7 (30.9, 61.0)
	Median Months (95% CI)	
Time to Progression		
IRRC	2.8 (1.5 - 3.5)	1.8 (1.4 - 4.0)
Investigator	2.6 (1.5 - 2.8)	2.7 (1.4 - 4.1)
Overall Survival	10.0 (6.8 -15.2)	9.8 (5.5 - 13.2)
PFS		
IRRC	2.7 (1.5 - 3.0)	2.0 (1.4 - 3.9)
Investigator	2.6 (1.5 - 2.8)	2.7 (1.5 - 4.0)

[a] Exact (Clopper-Pearson) Confidence Interval.

[b] Complete response + partial response.

[c] Complete response + partial response + stable disease.

Safety Results:

In general, subjects who received brivanib alaninate had a manageable safety profile when administered QD or BID at 800 mg. Twelve deaths (9.8%) were reported during treatment or within 30 days of the last dose; no deaths were considered related to study drug. No SAEs were reported for more than 5% of subjects; the most common SAEs (> 3%) were vomiting, encephalopathy, malignant neoplasm progression, abdominal pain, diarrhea, and pleural effusion. The most common AEs leading to discontinuation were hypertension (4.1%) and fatigue (3.3%). The most common Grade 3/4 AEs (> 5%) were fatigue (13.0%), hypertension (12.2%), hyponatremia (10.6%), alanine aminotransferase (ALT) increased (6.5%), diarrhea, and abdominal pain (5.7% each). Table 4 summarizes all AEs > 5% in brivanib alaninate treated subjects.

Lab abnormalities were commonly observed during the study. In all cohorts, Grade 3 to 4 hepatic function test abnormalities of ALT, aspartate aminotransferase (AST), and bilirubin were reported for 10.6%, 11.4%, and 13.0%, of subjects, respectively. The incidence of Grade 3/4 hepatic function test abnormalities was higher in first-line subjects (ALT: 18.2%; AST: 20.0%; bilirubin: 25.5%) than second-line subjects (ALT: 4.4%; AST: 4.4%; bilirubin: 2.9%). In all cohorts, Grade 3/4 hematologic abnormalities (regardless of baseline values) of white blood cell (WBC) count, absolute neutrophil count (ANC), platelets, and hemoglobin were reported for 4.9%, 4.1%, 7.3%, and 4.1% of subjects, respectively. In all cohorts, Grade 3/4 low sodium was reported for 32.5% of subjects. Abnormalities in coagulation disorder markers (prothrombin time and international normalized ratio) were common (> 50%); however, most were mild to moderate in severity. On-study increases in thyroid stimulating hormone (TSH) levels were reported for 65.2%, 66.7%, and 90.0% of subjects (regardless of elevations at baseline) in the first-line QD, second-line QD, and second-line BID cohorts, respectively.

Table 4: Adverse Events > 5%: Brivanib Alaninate Treated Subjects in CA182006

SYSTEM ORGAN CLASS (%) PREFERRED TERM (%)	Worst CTC Grade Any Grade	 Severe (3-4)	 Grade 5
Subjects with Any Adverse Event	122 (99.2)	70 (56.9)	8 (6.5)
GASTROINTESTINAL DISORDERS	103 (83.7)	23 (18.7)	0
DIARRHOEA	50 (40.7)	7 (5.7)	0
NAUSEA	48 (39.0)	5 (4.1)	0
VOMITING	39 (31.7)	4 (3.3)	0
CONSTIPATION	24 (19.5)	0	0
ABDOMINAL PAIN UPPER	19 (15.4)	3 (2.4)	0
STOMATITIS	19 (15.4)	0	0
ABDOMINAL PAIN	17 (13.8)	7 (5.7)	0
DYSPEPSIA	12 (9.8)	0	0
ASCITES	11 (8.9)	3 (2.4)	0
DRY MOUTH	9 (7.3)	0	0
ABDOMINAL DISTENSION	7 (5.7)	0	0
DYSPHAGIA	7 (5.7)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	86 (69.9)	23 (18.7)	1 (0.8)
FATIGUE	67 (54.5)	16 (13.0)	0
OEDEMA PERIPHERAL	17 (13.8)	0	0
ASTHENIA	9 (7.3)	4 (3.3)	0
PYREXIA	7 (5.7)	0	0
METABOLISM AND NUTRITION DISORDERS	71 (57.7)	20 (16.3)	0
DECREASED APPETITE	55 (44.7)	3 (2.4)	0
HYPONATRAEMIA	16 (13.0)	13 (10.6)	0
HYPOALBUMINAEMIA	7 (5.7)	1 (0.8)	0

Table 4: Adverse Events > 5%: Brivanib Alaninate Treated Subjects in CA182006

SYSTEM ORGAN CLASS (%) PREFERRED TERM (%)	Any Grade	Worst CTC Grade Severe (3-4)	Grade 5
Subjects with Any Adverse Event	122 (99.2)	70 (56.9)	8 (6.5)
NERVOUS SYSTEM DISORDERS	62 (50.4)	18 (14.6)	0
HEADACHE	22 (17.9)	2 (1.6)	0
DIZZINESS	21 (17.1)	1 (0.8)	0
DYSGEUSIA	8 (6.5)	0	0
ENCEPHALOPATHY	7 (5.7)	5 (4.1)	0
INVESTIGATIONS	56 (45.5)	22 (17.9)	0
WEIGHT DECREASED	24 (19.5)	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	12 (9.8)	9 (7.3)	0
ALANINE AMINOTRANSFERASE INCREASED	11 (8.9)	8 (6.5)	0
PLATELET COUNT DECREASED	10 (8.1)	5 (4.1)	0
VASCULAR DISORDERS	56 (45.5)	15 (12.2)	0
HYPERTENSION	56 (45.5)	15 (12.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	50 (40.7)	7 (5.7)	1 (0.8)
DYSPHONIA	18 (14.6)	0	0
DYSPNOEA	15 (12.2)	4 (3.3)	0
COUGH	12 (9.8)	1 (0.8)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	44 (35.8)	4 (3.3)	0
BACK PAIN	16 (13.0)	1 (0.8)	0
MUSCULOSKELETAL PAIN	12 (9.8)	1 (0.8)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	39 (31.7)	1 (0.8)	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	10 (8.1)	1 (0.8)	0
RASH	10 (8.1)	0	0
DRY SKIN	8 (6.5)	0	0
PSYCHIATRIC DISORDERS	21 (17.1)	4 (3.3)	0
INSOMNIA	11 (8.9)	0	0
RENAL AND URINARY DISORDERS	20 (16.3)	7 (5.7)	2 (1.6)
PROTEINURIA	8 (6.5)	4 (3.3)	0
ENDOCRINE DISORDERS	17 (13.8)	1 (0.8)	0
HYPOTHYROIDISM	17 (13.8)	1 (0.8)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	16 (13.0)	7 (5.7)	0
THROMBOCYTOPENIA	10 (8.1)	4 (3.3)	0
HEPATOBILIARY DISORDERS	15 (12.2)	9 (7.3)	1 (0.8)
HYPERBILIRUBINAEMIA	7 (5.7)	5 (4.1)	0

Subjects may have had more than one event within a class.
MedDRA Version: 13

Pharmacodynamic Results:

Collagen IV was measured at Day 1, at Week 3, Week 6, and at the end of treatment. For subjects in the first-and second-line QD cohorts, the mean Col IV change from baseline was -98.2 and -84.6 ng/mL at Week 3, -111.1 and -91.0 ng/mL at Week 6, and -55.5 and -38.6 ng/mL at the end of treatment, respectively.

Other Results:

The FHSI-8 analysis indicated that HCC symptoms appeared to stay constant over time and consistent within cohorts for subjects treated with brivanib alaninate in both the first- and second-line cohorts. Even though there was an initial increase in symptoms (decrease in score) between baseline and first assessment (Week 3) as might be expected (the drug may not begin to work immediately), the scores stabilized over time and in some cases, returned to near baseline levels for some subjects in both the second-line QD and second-line BID cohorts.

CONCLUSIONS:

- In first-line subjects, the 6-month PFS rate (per IRRC, using mWHO Criteria) was between 20.0% and 22.4%, depending on the estimate used for calculation.
- Brivanib alaninate monotherapy at 800 mg QD demonstrated antitumor activity in HCC subjects who were treatment-naive (first-line) and angiogenesis therapy failures (second-line):
  - The median TTP was 2.8 and 1.8 months for first- and second-line QD subjects, respectively, using mWHO criteria.
  - The median overall survival was 10.0 months for first-line subjects and 9.8 months for second-line QD subjects.
  - The median PFS was 2.7 and 2.0 months for first- and second-line QD subjects, respectively, using mWHO criteria.
  - Confirmed tumor response rates were 7.3% and 4.3% for first- and second-line QD subjects, respectively, using mWHO criteria.
  - Disease control rates were 50.9% and 45.7% for first- and second-line QD subjects, respectively, using mWHO criteria.
  - For first-line subjects with best overall tumor response of PR or CR (per IRRC using mWHO criteria), time to response ranged from 1.4 months to 20.7 months and duration of response ranged from 1.4 months to 20.7 months. For second-line QD subjects, the time to response was 1.4 months and duration of response ranged from 2.8 months to 5.5 months.
- In general, brivanib alaninate had a manageable safety profile at 800 mg. No deaths were considered related to study drug. No SAEs were reported for more than 5% of subjects; the most common SAEs (> 3%) were vomiting, encephalopathy, malignant neoplasm progression, abdominal pain, diarrhea, and pleural effusion. The most common Grade 3/4 AEs (in > 5% of subjects) were fatigue (13.0%), hypertension (12.2%), hyponatremia (10.6%), ALT increased (6.5%), diarrhea, and abdominal pain (5.7% each).
- Decreases in Col IV levels were reported at Week 3, at Week 6 (for subjects still on treatment), and at the end of the study treatment for subjects in the first- and second-line QD cohort.
- Approximately half of the subjects in the first-line and second-line QD cohorts had AFP response which was defined as a decrease > 50% from baseline level. A similar trend was observed in subset of subjects with elevated AFP at baseline.
- The FHSI-8 analysis indicated that HCC symptoms appeared to stay constant over time and consistent within cohorts for subjects treated with brivanib alaninate in both the first- and second-line QD cohorts.

DATE OF REPORT: 04-Apr-2011