

Title: The Effects of Liver Impairment on the Pharmacokinetics of Brivanib, a Dual Inhibitor of Fibroblast Growth Factor Receptor and Vascular Endothelial Growth Factor Receptor Tyrosine Kinases

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ABSTRACT

Background: Many patients with hepatocellular carcinoma (HCC) have liver impairment as a result of tumor burden and cirrhosis. Brivanib, which is administered orally as the prodrug brivanib alaninate, is a selective, dual inhibitor of fibroblast growth factor receptor and vascular endothelial growth factor receptor tyrosine kinases that is currently in phase III studies for HCC.

Methods: This phase I study compared the pharmacokinetic profile of brivanib in patients with HCC and varying levels of hepatic impairment with that of patients with advanced solid non-HCC malignancies and normal hepatic function. Patients were assigned to 1 of 4 study groups: Group A, HCC plus Child-Pugh (CP) A status (mild hepatic impairment); Group B, HCC plus CP B (moderate hepatic impairment); Group C, HCC plus CP C (severe hepatic impairment); and Group D, non-HCC malignancy and normal hepatic function. Plasma brivanib concentrations were determined on Days 1 and 28. Brivanib alaninate doses were 400 mg/day in Groups A, B, and D, and 200 mg/day in Group C.

Results: Of the 52 enrolled patients, 24 were assigned to 1 of the 4 groups (6 patients/group). After a single brivanib alaninate dose, the brivanib maximum observed plasma concentration and the area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}) in patients with HCC and mild or moderate hepatic impairment (Groups A and B) were comparable with those in patients with normal hepatic function (Group D). Brivanib AUC_{inf} was approximately 50% higher in patients with HCC and severe hepatic impairment (Group C) compared with patients with normal hepatic function (Group D). Brivanib alaninate 400 mg/day was tolerated in Groups A, B, and D. Tolerability could not be assessed in Group C because of dose interruptions and discontinuations. Based on modified World Health Organization criteria, stable disease was achieved in 8 of 18 patients (44.4%) with HCC and 1 of 6 patients (17%) with non-HCC tumors.

Conclusions: Brivanib exposure in patients with HCC and mild or moderate hepatic impairment was similar to that in patients with non-HCC malignancies and normal hepatic function, suggesting that dose adjustment is not necessary in HCC patients with CP A and B status. Experience in patients with HCC and CP C status is insufficient to recommend brivanib use in this population.

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1) **INTRODUCTION**

- a) Tumors depend on vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) signalling for their growth in terms of cellular proliferation, differentiation, invasiveness, motility, and survival, as well as angiogenesis [Korc 2009; Toner 2010].
 - i) As such, both VEGF and FGF signalling pathways are rationale therapeutic targets in oncology [Bergers 2008; Turner 2010].
 - ii) However, the benefits of anti-VEGF therapy are transitory and typically followed by a restoration of tumor growth and progression [Bergers 2008].
 - iii) Emerging evidence suggests that FGF may be involved in evasive resistance to VEGF pathway inhibitors [Bergers 2008; Turner 2010].
 - iv) FGF and VEGF have been found to act synergistically, with their coexpression being associated with more aggressive growth of tumor xenografts [Giavazzi 2003].
 - v) Moreover, aberrant FGF signalling plays an oncogenic role in several human cancers [Korc 2009; Toner 2010].
 - vi) Increased serum levels of FGF have been detected in patients just prior to or at the time of progression following anti-VEGF therapy [Batchelor 2007; Kopetz 2009].
 - vii) Given these clinical and laboratory findings, dual blockade of FGF and VEGF signalling may represent a strategy that overcomes evasive reinduction of tumor growth that characteristically occurs after anti-VEGF therapy.
- b) Brivanib (BMS-540215) is an orally administered, selective, dual inhibitor of FGF receptor and VEGF receptor tyrosine kinases [Marathe 2009].
 - i) Brivanib is administered as brivanib alaninate (BMS-582664), an L-alanine ester prodrug that is rapidly and completely converted to the active moiety brivanib presystemically through enzymatic hydrolysis [Marathe 2009].
 - ii) In preclinical studies, brivanib has demonstrated potent antiangiogenic effects as well as direct antitumor effects across a range of tumor types, including liver, colon, breast, and lung [Bhide 2006; Bhide 2010; Huynh 2008].
 - iii) In a recent phase II trial with patients with advanced/metastatic HCC, brivanib exhibited promising clinical activity, both as first- and second-line therapy, with an acceptable safety profile [Park 2011; Finn in press].
 - iv) Brivanib is currently in phase III trials for HCC [Park 2011].
- c) Since the liver represents the major site of elimination for many drugs, disease states that alter hepatic metabolic processes have the potential to alter the pharmacokinetics of drugs and their subsequent removal from the body.
 - i) Many patients with HCC have liver impairment as a result of tumor burden within the liver as well as associated degrees of fibrosis and cirrhosis that are associated with risk factors for HCC (eg, chronic hepatitis B virus [HBV] and hepatitis C virus [HCV] infection, alcohol-induced cirrhosis) [Sangiovanni 2004; Fattovich 2004].
 - ii) HCC commonly develops in a setting of chronic liver cell injury, which eventually leads to cirrhosis [Thomas 2005].
 - iii) Cirrhosis is present in 80% to 90% of patients with HCC [Fattovich 2004].
 - iv) Because brivanib is mainly eliminated through liver metabolism (primarily by the cytochrome P-450 enzyme CYP3A4) [Ganapathi 2009; Marathe 2009], it is hypothesized that administration of brivanib alaninate in the setting of decreased liver function could result in increased exposure to brivanib and excess toxicity.

- v) This study was designed to determine if the pharmacokinetic profile of brivanib is affected by varying degrees of hepatic impairment in patients with liver cirrhosis and HCC.

1) **METHODS**

a) **Study objectives**

- i) The primary objective of this study was to assess the pharmacokinetics of brivanib in patients with HCC and defined levels of hepatic impairment (as assessed using Child-Pugh [CP] classification) compared with the pharmacokinetics of brivanib in patients with advanced solid non-HCC malignancies and normal hepatic function.
- ii) Secondary objectives included the following: (1) assessment of the relationship between exposure to brivanib and other measures of hepatic impairment or function including Cancer of the Liver Italian Program (CLIP) score [Greico 2005] and monoethylglycinexylidide (MEGX) elimination test; (2) assessment of safety and tolerability of brivanib alaninate in patients with HCC with mild, moderate, and severe hepatic impairment and in patients with other advanced malignancies with normal hepatic function; and (3) preliminary assessment of efficacy of brivanib alaninate in patients with HCC and advanced solid non-HCC tumors.

b) **Study design**

- i) This was a phase I, multi-institutional, open-label, multi-dose study of brivanib alaninate in patients with HCC and varying levels of hepatic impairment or other advanced solid malignancies and normal hepatic function.
 - (1) Patients were assigned to 1 of 4 study groups based on tumor type and level of hepatic impairment, as follows: Group A, HCC plus CP A (mild hepatic impairment); Group B, HCC plus CP B (moderate hepatic impairment); Group C, HCC plus CP C (severe hepatic impairment); and Group D, advanced solid non-HCC malignancies and normal hepatic function.
 - (2) Patients had screening evaluations to determine eligibility within 28 days prior to the first dose of brivanib alaninate.

c) **Patients**

- i) Eligible patients were males or females at least 18 years of age with HCC and hepatic impairment or with an advanced solid malignancies and normal hepatic function who met the following disease criteria: (1) in Group D, patients with proven biopsy for advanced solid tumor or (2) in Groups A, B and C, patients with biopsy-proven HCC or patients without biopsy-proven HCC having bi-dimensionally measurable disease with lesion >2cm (as seen on enhanced spiral CT or MRI), positive serology for HBV or HCV infection, and alpha fetoprotein level >400 mg/dL.
 - (1) Additional inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status score 0 to 3, adequate bone marrow and renal function, and adequate hepatic function for Group D (total bilirubin \leq institutional upper limit of normal [IULN], except for known Gilbert's syndrome), aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 1.5 \times$ IULN, serum albumin >3.5 g/dL, international normalization ratio (INR) $\leq 1.8 \times$ IULN.
 - (2) Key exclusion criteria were portal-systemic encephalopathy with a clinical grade ≥ 2 ; evidence of portal hypertension (>10 mm Hg) resulting in variceal bleeding or intractable ascites; other primary malignancies; brain metastasis; uncontrolled or significant cardiovascular disease; and a history of allergy to brivanib alaninate or related compounds.

d) **Brivanib alaninate doses**

- i) Patients from Groups A and D (normal and mild hepatic impairment, respectively) were enrolled to the study first. The initial dose for patients in Groups A and D was chosen at 400 mg of brivanib alaninate administered orally (PO) each day (QD), which represented the minimal active biologic dose based on phase I study results and is 50% lower than the maximum tolerated dose (MTD) of 800 mg PO QD. After single-dose pharmacokinetic results were obtained from Day 1, patients were allowed to continue treatment beginning on Day 15 with the 400 mg QD starting dose, or a reduced dose based on the individual patient's exposure (**Figure 1**). If the area under the concentration-time curve from time zero to 24 hours post-dose (Day 1 only) (AUC_{0-24}) was $>200 \mu M \cdot hr$, but $<300 \mu M \cdot hr$, the daily dose would be 200 mg of brivanib alaninate. If the brivanib AUC_{0-24} was $>300 \mu M \cdot hr$, the daily dose would be 100 mg. The cutoff of $200 \mu M \cdot hr$ was chosen as it represents an exposure two standard deviations above the mean single-dose exposure in patients treated with brivanib alaninate at the MTD (800 mg PO QD). Patients who experienced dose limiting toxicities would be dose reduced.
- ii) In Groups B and C (moderate and severe hepatic impairment, respectively), a point estimate representing the ratio of geometric means (Group A/Group D) was calculated from the Day 1 brivanib AUC_{0-24} after single dose pharmacokinetic analysis had been completed for at least 6 evaluable patients from each group. The starting dose in Groups B and C were determined based on the ratio of Day 1 exposures in Groups A and D as follows: (1) point estimate <1.5 : Group B dose would be 400 mg and Group C dose would be 200 mg; (2) point estimate ≥ 1.5 and <3 : Group B dose would be 200 mg and Group C dose would be 100 mg; (3) point estimate ≥ 3 and <6 : Group B dose would be 100 mg and Group C would receive no treatment; point estimate >6 : Groups B and C would receive no treatment. Dose modification could have also occurred in Groups B and C based on their Day 1 pharmacokinetic exposure.
- iii) After sufficient pharmacokinetic information had been obtained from Cycle 1 Day 1, and patients had tolerated ≥ 28 days of continuous daily dosing with brivanib alaninate (through study Day 42), consideration for dose escalation was considered. For patients in Groups A and D, if 400 mg QD was tolerable up to Day 42, then the investigator could have considered increasing the brivanib dose up to 800 mg QD beginning after Day 42. In the event the starting dose for Group B was 400 mg QD, then for patients who tolerated brivanib up to Day 42, the investigator could have considered increasing the brivanib alaninate dose to 600 mg OD beginning after Day 42. Dose escalation was not allowed in Group C.
- iv) Patients were not allowed to take the strong cytochrome P450 enzyme inhibitors ketoconazole, itraconazole, erythromycin, and clarithromycin within 7 days prior to first treatment administration until the end of study therapy. Calcium channel blockers, which are often CYP3A4 substrates, were not to be used for study-emergent hypertension. Since brivanib is a CYP2C8 inhibitor, exposure to CYP2C8 substrates (loperamide, paclitaxel, pioglitazone, repaglinide, and rosiglitazone) might be increased in the presence of brivanib.

e) Hepatic function assessment

- i) Hepatic function was assessed using the CP classification system [Pugh 1973], a clinical staging system for liver impairment that is widely used in the setting of HCC [Forner 2010]. CP A corresponds with mild hepatic impairment, CP B with moderate impairment, and CP C with severe impairment.
- ii) Hepatic function was also assessed using the CLIP scoring system, a prognostic system specific for HCC [Greico 2005]. A CLIP score of 0 corresponds to the early stage of hepatic impairment, a score of 1 to 3 to the intermediate stage, and a score of 4 to 6 to the advanced stage of impairment.
- iii) The MEGX test is a rapid, sensitive indicator of liver metabolic function that is recommended by the US Food and Drug Administration (FDA). MEGX is a primary metabolite of lidocaine, which is mainly metabolized by the liver. As such, MEGX concentrations are decreased with hepatic impairment. A MEGX test was performed as a secondary test to assess hepatic function at one time point during the 28-day screening period. Groups A and D received

lidocaine 1 mg/kg dose (infused at a constant rate over the defined 2 minute period by a controlled infusion device). Groups B and C received lidocaine 0.5 mg/kg. The maximum dose of lidocaine for testing was not to exceed 100 mg.

f) Pharmacokinetic assessment

- i) Pharmacokinetic parameters for brivanib included the maximum observed plasma concentration (C_{max}), time of maximum observed plasma concentration (T_{max}), terminal plasma half-life (T-half), area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-t}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), AUC_{0-24} , and apparent total body clearance (assessed for Day 1 only) (CLT).
- ii) Brivanib in human stabilized EDTA plasma was assayed using a validated liquid chromatography-tandem mass spectrometry method during the period of known analyte stability.
- iii) Plasma samples for determination of brivanib concentrations were collected on Day 1 before study drug administration and at 0.5, 1, 2, 4, 6, 8, 24, 48 and 72 hours after study drug administration, and on Day 28 before study drug administration and at 0.5, 1, 2, 4, 6, 8 and 24 hours after study drug administration.
 - (1) Patients were fasting for Day 1 and Day 28 pre-dose pharmacokinetic sample collections.
 - (2) Individual patient pharmacokinetic parameter values were derived by non-compartmental methods.
 - (3) To assess the effects of hepatic impairment by CP classification (Groups A, B, and C) in patients with HCC on the pharmacokinetics of brivanib, versus the pharmacokinetics in patients with normal hepatic function and non-HCC malignancies (Group D), analyses of variances were performed on log-transformed AUC ($AUC_{TAU} = AUC_{0-24}$ on Day 1) and the C_{max} of brivanib. The factors in the analysis were hepatic function group (CP class), day (1 or 28), and group-by-day interaction. The C_{max} and AUC values for patients in Group C were dose-normalized to the 400 mg dose prior to analysis, assuming approximate dose proportionality. For comparisons of each group with hepatic dysfunction (Groups A, B, or C) to the group with normal hepatic function (Group D), point estimates and the corresponding two-sided 90% confidence intervals for means and differences between means on the log scale were exponentiated to express the results as geometric means and ratios of geometric means on the original scale. No adjustments were made for multiplicity.

g) Safety assessments

- i) Safety was assessed based on adverse event reports and the results of vital sign measurements, electrocardiograms, echocardiograms, physical examinations, and clinical laboratory tests.

h) Efficacy assessments

- i) Tumor response was assessed using the modified World Health Organization (mWHO) tumor response criteria. Tumor measurements by CT/MRI were obtained at pretreatment/baseline (within 28 days prior to the start of treatment) and every 6 weeks after Day 15 and at end of treatment. Patients meeting the criteria for a complete response or partial response had confirmatory tumor measurements obtained at least 4 weeks (but within 8 weeks) of initially demonstrating a response.

i) Statistical considerations

- i) The number of patients in this study was not based on statistical power considerations. Data from 6, 10, or 12 patients in Group A (CP A) and Group D (normal hepatic function), provided 90% confidence that the estimated impaired:normal (Group A:D) ratio of the AUC_{0-t} and of C_{max} geometric means were each within 44%, 33%, and 30% of the true population ratios,

respectively. These calculations assumed that the between-patient coefficient of variation (CV) of both C_{\max} and AUC_{0-t} was approximately 40%. If the observed CV for patients in Groups A and D in this study was 30%, then the precision of the above estimates would be 32%, 24%, and 22%, respectively for 6, 10, and 12 patients. It was anticipated that up to 12 evaluable patients would have to be enrolled in each treatment group to adequately assess the pharmacokinetic parameters leading to an enrollment of between 24 and 72 patients.

3) **RESULTS**

a) **Patients**

- i) Fifty-two patients were enrolled in this study, 24 of whom received at least one dose of brivanib alaninate. These 24 patients were assigned to 1 of 4 groups, based on tumor type and level of hepatic impairment and were treated at 4 sites in the United States and at 1 site in Spain.
 - (1) Demographic characteristics for treated patients (n=24) are shown in **Table 1**, and the patient population according to CP class is shown in **Table 2**.
 - (2) Most patients (58.3%) had an ECOG performance of 1; the remaining patients had an ECOG performance of 0 (25%) or 2 (16.7%).
 - (3) In Groups A, B, and C, tumor types were HCC. In Group D, tumor types were colon (n=4), rectal (n=1), and anal (n=1).
 - (4) Pharmacokinetic data were obtained from 24 patients (6 patients per group).
 - (5) Fifteen of the 24 patients had received prior chemotherapy (including systemic chemotherapy or chemoembolization in 9 of 18 patients with HCC), with 9 (38%) patients having ≥ 3 regimens of prior chemotherapy. Two patients had received prior chemoembolization for HCC. A total of 13 (54%) had undergone prior surgery and 3 patients (13%) had received prior radiotherapy.

b) **Brivanib alaninate doses**

- i) The initial dose of brivanib alaninate for patients in Group D (normal hepatic function) and Group A (mild hepatic impairment) was 400 mg PO QD. After single-dose pharmacokinetic results were obtained from Day 1, patients were allowed to continue treatment on Day 15 with the 400 mg QD starting dose, or a reduced dose based on the individual patient's exposure.
 - (1) The starting dose in Group B (moderate hepatic impairment) and Group C (severe hepatic impairment) was 400 mg and 200 mg, respectively; this was based on the ratio of Day 1 exposures in Groups A and D. However, to account for potential inter-individual pharmacokinetic variability, dose modification could have also occurred in Groups B and C based on the patient's own Day 1 pharmacokinetic exposure. Dosing in Groups B and C continued on Day 15.
 - (2) No patients in any group met the criteria of $AUC_{0-24} > 200 \mu\text{M}\cdot\text{hr}$, and none were administered a reduced dose beginning on Day 15. Although dose increase after Day 42 was permitted at the investigator's discretion in Groups A, B, and D, no patients had a dose increase.
- ii) Overall, the median duration of study drug therapy (ie, total time period from the first day of dosing regardless of dose interruptions/modifications) was 14.5 weeks for Group A, 10 weeks for Group B, 3.5 weeks for Group C, and 9.5 weeks for Group D. Time on treatment was shorter in Group C (200 mg) than in Groups A, B, and D, with frequent liver-related events and rapid clinical deterioration consistent with the natural history of disease in the CP class C patient population.

- (1) All 24 patients discontinued therapy at the end of the study. Reasons for treatment discontinuation were disease progression (17 patients, 71%), adverse events unrelated to study drug (4 patients, 17%), study drug toxicity (2 patients, 8%), and patients who withdrew consent (1 patient, 4%).
- (2) A total of 13 patients had at least 1 dose modification or interruption of brivanib alaninate, including 3 patients in Group A, 4 patients in Group B, 4 patients in Group C, and 2 patients in Group D.

c) Brivanib pharmacokinetics and hepatic function by CP classification

- i) The mean plasma concentration-time profiles of brivanib, normalized to a dose of 400 mg brivanib alaninate, on Day 1 and Day 28 are shown in **Figures 2A and 2B**, respectively.
 - (1) Summary statistics for brivanib pharmacokinetic parameters by study group are listed in **Table 3**. The C_{max} , AUC_{inf} , and AUC_{TAU} parameters in Group C were dose-normalized to the 400-mg dose prior to the summary, by multiplying by the dose proportionality factor (400:200), assuming approximate dose proportionality. After a single dose of brivanib alaninate, median T_{max} was similar for Groups A and D, while it was delayed by 2 hours in Group B and by 1 hour in Group C, as compared to Group D. However, the range of T_{max} values was similar across all groups. Mean half-lives were on average longer by 2.15 hours, 3.83 hours, and 5.77 hours in Groups A, B, and C, respectively, compared with Group D. Geometric mean CLT (Day 1 only) was lowest in Group C and 32.5% lower than in Group D than in Group C (13.2 L/h vs 8.9 L/h). CLT was 5% to 9% lower in Groups A and B, respectively, compared with Group D.
 - (2) A scatter plot of brivanib CLT vs CP score is shown in **Figure 3**. Scores of 5 or 6 correspond to Group A, scores of 7 to 9 to Group B, and scores of 10 to 15 to Group C. In Group C, only patients with scores of 10 (n=5) and 11 (n=1) were enrolled. Geometric means (SE) for brivanib CLT were calculated by group and overlaid on the scatter plot of individual CLT values vs CP score.
- ii) Statistical analyses results are summarized for C_{max} and AUC_{inf} on Day 1 in **Table 4**. Geometric mean C_{max} and AUC_{inf} in Groups A and B of hepatic impairment were comparable with those with Group D, following single doses of brivanib alaninate, as indicated by the similarity in confidence intervals for geometric mean ratios. A nearly 50% increase in AUC_{inf} exposure was observed in Group C compared with Group D, while C_{max} was reduced approximately 26%.
- iii) Following 14 days of dosing, geometric mean C_{max} and AUC_{TAU} were higher in Group B than in Group D by 48% and 32%, respectively. However, the confidence intervals indicate comparable pharmacokinetics at steady state among these two groups. The small number of patients with evaluable pharmacokinetics after 14 days of dosing, and the occurrence of dose reductions in Group C, does not allow for meaningful comparisons of Groups A or C with Group D at steady state. Only patients in Group C had pharmacokinetic assessments on Day 28, and their exposure were 1.34 and 4.53 higher compared with Group D.

d) Brivanib pharmacokinetics and hepatic function by CLIP score

- i) A scatter plot of individual CLT values overlaid with geometric mean CLT calculated for patients within each CLIP stage is presented in **Figure 4**. A score of 0 corresponds to early stage impairment, scores of 1 to 3 to intermediate impairment, and scores of 4 to 6 to advanced impairment. The geometric mean (SE) brivanib CLT was 17.5 (0) in early stage, 11.64 (1.12) in intermediate stage, and 9.97 (1.19) in advanced stage. It is difficult to compare the early stage impairment by CLIP, since only one patient was enrolled in that stage; however, brivanib CLT was similar in the intermediate and advanced stages by CLIP.

e) Brivanib pharmacokinetics and hepatic function by MEGX

- i) As some patients were administered a 0.5 mg/kg lidocaine dose (mainly Groups B and C), the MEGX concentrations were dose-adjusted for those patients to 1 mg/kg prior to graphical

presentations. There were 23 patients with MEGX concentration data. To investigate a potential linear association of low MEGX concentration with low brivanib clearance, a linear regression was estimated and overlaid with the scatter plot of individual CLT, as shown in **Figure 5**. There was no apparent overall (across the CP groups) statistically significant linear association of brivanib CLT with MEGX concentration, although the 2 patients with the lowest clearance within Group C had some of the lowest MEGX concentrations.

f) Safety results

- i) Brivanib alaninate 400 mg/day was tolerated in Groups A, B, and D; the safety profile in these patients was consistent with the natural history of their diseases (HCC in Groups A and B, non-HCC solid tumors in Group D). In Group C, interruption or discontinuation occurred in all patients early in dosing, consistent with the natural history of disease in the CP class C patient population. As a result, no patient received more than 3 weeks of continuous dosing at 200 mg, and tolerability in this population could not be established.
- ii) The most frequently reported treatment-related adverse events ($\geq 10\%$ of patients) were fatigue (54.2%), decreased appetite (41.7%), AST increased (25%), blood bilirubin increased (20.8%), ALT increased (16.7%), nausea (16.7%), dizziness (16.7%), hyperbilirubinemia (16.7%), hyperkalemia (12.5%), platelet count decreased (12.5%), diarrhea (12.5%) and dysgeusia (12.5%).
 - (1) The majority of treatment-related adverse events were Grade 1 to 3 in severity; 8 patients (33.3%) had treatment-related Grade 3 adverse events and 3 patients (12.5%) had treatment-related Grade 4 adverse events.
 - (2) The most common treatment-related Grade 3/4 adverse events were Grade 3 AST elevations (16.7%), Grade 4 hyperbilirubinemia (12.5%), Grade 3 bilirubin elevations (8.3%), and Grade 3 decreases in platelet count (8.3%).
- iii) Liver-related adverse events were common in Groups A, B, and C (CP status A, B, and C, respectively), and were a common cause of discontinuation in Group C. Most liver-related events were considered not related to study drug.
 - (1) In Groups A and B, 2 patients discontinued for liver adverse events (1 each in Group A [Grade 4 hyperbilirubinemia] and Group B [Grade 5 liver failure], both not related to treatment.
 - (2) In Group C, 4 patients discontinued for liver adverse events (Grade 4 hyperbilirubinemia [n=2, possibly related and not likely related to study drug]; Grade 4 esophageal hemorrhage [n=1, not likely related to study drug]; Grade 4 ALT increased [n=1, not related to study drug]). The remaining 2 patients in Group C interrupted treatment for liver adverse events (Grade 3 hepatic encephalopathy [not related to study drug]; Grade 3 upper gastrointestinal hemorrhage [not likely related to study drug]), followed by discontinuation less than 1 month later for progression of HCC.
- iv) Overall, there were 16 deaths in the study. Of these, a total of 9 deaths were reported during treatment or within 30 days of last dose: 8 of these 9 deaths were reported as due to disease, and all were considered unrelated (n=7) or unlikely (n=1) related to study drug or unknown (n=1). One death was reported of unknown cause as the patient was lost to follow-up. Seven of the deaths were due to malignant disease progression, 1 death was due to progression of hepatic cirrhosis, and 1 death was reported of unknown cause as the patient was lost to follow-up.

g) Efficacy results

- i) Stable disease (SD) was noted in 9 patients, including 8 of 18 patients (44.4%) with HCC. In Group A, 4 patients (67%) had SD. In Group B, 3 patients (50%) had SD.
 - (1) One patient (17%) in each in Groups A and B could not be assessed, and the remainder had progressive disease (PD).

- (2) In Group C, 1 patient (17%) had SD, 4 patients (67%) could not be assessed, and 1 patient (17%) had PD.
- (3) In Group D, 5 patients (83%) had PD and 1 patient (17%) had SD.

4) **DISCUSSION**

- a) Patients with HCC may have liver function abnormalities due to tumor burden and associated liver cirrhosis.
- i) Cirrhosis of the liver is a major risk factor for HCC, and most patients with HCC have underlying cirrhosis [Shariff 2009].
 - ii) Brivanib, an orally administered, selective, dual inhibitor of FGF receptor and VEGF receptor tyrosine kinases, is currently being investigated in phase III trials for HCC [Park 2011].
 - iii) Brivanib is the active moiety of the prodrug brivanib alaninate and is primarily metabolized by the liver [Ganapathi 2009; Marathe 2009].
 - iv) Therefore, administration of brivanib alaninate in patients with decreased liver function could result in increased exposure to brivanib and excess toxicity.
 - v) The primary objective of this phase I, multi-institutional, open-label, multi-dose study was to assess the pharmacokinetics of brivanib after administration of brivanib alaninate in patients with HCC diagnosed with mild, moderate, or severe hepatic impairment (as classified by CP status) compared with patients with other advanced solid malignancies and normal hepatic function.
- b) After a single dose of 400 mg of brivanib alaninate, exposures to brivanib (C_{max} , AUC) were comparable in patients with HCC and mild or moderate hepatic impairment (CP class A or B) and those with non-HCC solid malignancies and normal hepatic function.
- i) However, in patients with HCC and severe hepatic impairment (CP class D), dose-normalized brivanib C_{max} was reduced, and an approximate 50% increase in AUC_{inf} was observed after a single dose of 200 mg of brivanib alaninate.
 - ii) The higher AUC observed in patients with severe hepatic impairment correlated with the reduced clearance observed in this group relative to patients with normal hepatic function (8.9 L/h vs 13.2 L/h, respectively).
 - iii) The reduced clearance observed is suggestive of reduced metabolic function in patients with severe hepatic impairment.
 - iv) These results suggest that HCC patients with CP A and B status can be treated with the same dose of brivanib alaninate used in patients without hepatic impairment.
 - v) Currently, there is insufficient data to recommend a dose adjustment for HCC patients with CP D status.
- c) Exposures to brivanib were also assessed on Day 28 of the study after daily dosing of brivanib alaninate.
- i) However, data were limited on Day 28 due to reduced sampling and reduced number of patients with available data.
 - ii) Nevertheless, patients with mild hepatic impairment had no increase in systemic exposure on Day 28 compared with patients with normal hepatic function.
 - iii) For patients with moderate hepatic impairment, brivanib exposures appeared higher (48% and 32% for C_{max} and AUC_{TAU} , respectively) relative to patients with normal hepatic function; however, the confidence intervals were wide and exposures between patients with moderate hepatic impairment and normal hepatic function largely overlapped. Only 2 patients with

severe hepatic impairment had pharmacokinetic assessments on Day 28, and their exposure were 1.34 and 4.53 higher compared with patients with normal hepatic function.

- d) A secondary objective of this study was to assess the relationship between exposure to brivanib and other measures of hepatic function, such as CLIP score.
 - i) The CLIP scoring system utilizes several factors, including CP score, to determine a score for mild, moderate, or severe HCC. In this study, CLIP score largely correlated with CP classification, with all CP C patients given CLIP scores of 4 to 6 points (advanced stage HCC) and most CP B patients given CLIP scores of 1 to 3 (intermediate stage HCC). Brivanib clearance was similar across patients with intermediate and advanced stages of hepatic impairment. Consequently, there was no apparent association between brivanib clearance and CLIP scores.
- e) The MEGX test was also performed prior to dosing as a secondary assessment of hepatic function, as recommended by the FDA Guidance for Industry on studies in patients with hepatic impairment [U.S. Department of Health and Human Services 2003].
 - i) The formation of MEGX, a metabolite of lidocaine catalyzed by CYP3A, has been shown to be a simple method to distinguish differences in metabolic capacity between patients with mild, moderate, and severe hepatic impairment. Similar to CLIP scores in this study, the MEGX concentrations in general correlated with CP classification. However, there was no apparent association between brivanib clearance and MEGX concentrations, suggesting that brivanib clearance is not sensitive to changes in hepatic impairment as measured by MEGX concentrations, as the formation of MEGX is more dependent on liver blood flow than on oxidative clearance.
- f) Safety and efficacy were also evaluated as secondary endpoints in this study.
 - i) Brivanib alaninate 400 mg/day was tolerated in Groups A, B, and D; the safety profile in Groups A and B was consistent with the natural history of disease in the populations studied and was similar to the larger safety database of brivanib monotherapy in cancer patients. Experience in HCC patients with severe hepatic impairment (CP C status) is insufficient to recommend use of brivanib in this population.
 - ii) Based on mWHO criteria, no complete or partial responses were observed in this study. SD was observed in 8 of 18 patients (44%) with HCC and 1 of 6 patients (17%) with non-HCC tumors.
- g) In summary, exposures to brivanib were comparable in patients with HCC and with mild and moderate hepatic impairment compared with patients with advanced solid non-HCC malignancies and normal hepatic function, while a 50% increase in exposure was observed in patients with HCC and severe hepatic impairment.
 - i) These results suggest that dose adjustment is not necessary in HCC patients with CP A and B hepatic impairment.
 - ii) Data from this study were insufficient to recommend dose adjustment for HCC patients with CP C hepatic impairment, and experience in CP class C is insufficient to recommend use of brivanib in this population.

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TABLES

Table 1. Demographic Characteristics for Treated Patients

	Study Group^b				Overall (n=24)
	Group A (n=6)	Group B (n=6)	Group C (n=6)	Group D (n=6)	
Age, y (SD)	71.0 (13.4)	62.8 (10.4)	58.0 (6.4)	57.2 (9.0)	62.3 (11.0)
Gender, n (%)					
Male	5 (83.3)	5 (83.3)	5 (83.3)	2 (33.3)	17 (70.8)
Female	1 (16.7)	1 (16.7)	1 (16.7)	4 (66.7)	7 (29.2)
Race, n (%)					
White	2 (33.3)	5 (83.3)	3 (50.0)	4 (66.7)	14 (58.3)
Black/African American	1 (16.7)	0	1 (16.7)	0	2 (8.3)
Asian	2 (33.3)	1 (16.7)	2 (33.3)	0	5 (20.8)
Other	1 (16.7)	0	0	2 (33.3)	3 (12.5)

^aECOG PS scores range from 0 to 5, with higher scores indicating greater symptomatic impairment (5 indicates death).

^bGroup A, HCC plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C; Group D, advanced solid non-HCC malignancy and normal hepatic function.

Abbreviations: CP, Child-Pugh; CLIP, Cancer of the Liver Italian Program; ECOG PS, Eastern Cooperative Oncology Group performance status HCC, hepatocellular carcinoma; SD, standard deviation.

Table 2. Patient Population According to Child-Pugh Class

Study Group^a	CP Class	CP core	Patients, n (%)	Diagnosis
A (n=6)	A	5	1 (20)	HCC
		6	5 (80)	HCC
B (n=6)	B	7	3 (50)	HCC
		9	3 (50)	HCC
C (n=6)	C	10	5 (80)	HCC
		11	1 (20)	HCC
D (n=6)	N/A	N/A	6 (100)	Non-HCC malignancy ^b

^aGroup A, HCC plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C; Group D, advanced solid non-HCC malignancy and normal hepatic function.

^bPatients in Group D had non-HCC solid malignancies (colon [n=4], rectal [n=1], and anal [n=1]).

Abbreviations: CP, Child-Pugh; HCC, hepatocellular carcinoma; N/A, not applicable.

Table 3. Selected Summary Statistics for Brivanib Pharmacokinetic Parameters

Study Group ^a	Day	C _{max} (ng/mL) GMean [n] (CV)	T _{max} (h) median [n] (Min-Max)	AUC _{0-t} (ng*h/mL) GMean [n] (CV)	AUC _{inf} (ng*h/mL) GMean [n] (CV)	AUC ₀₋₂₄ ^b (ng*h/mL) GMean [n] (CV)	T-half (h) Mean [n] (SD)	CLT (L/h) GMean [n] (CV)
A	1	1928 [6] (34.45)	3.03 [6] (1.00-6.00)	24828 [6] (47.93)	26817 [6] (45.03)	18434 [6] (40.85)	14.45 [6] (1.609)	12.53 [6] (37.32)
	28	3176 [4] (56.64)	1.00 [4] (1.00-2.00)			23897 [2] (10.91)	14.08 [3] (1.420)	
B	1	1666 [6] (40.52)	5.00 [6] (2.02-7.13)	26149 [6] (29.53)	27869 [6] (30.89)	18074 [6] (32.98)	16.13 [6] (7.386)	12.06 [6] (33.58)
	28	3128 [5] (28.95)	4.00 [5] (1.00-6.00)			34672 [4] (33.02)	11.58 [3] (5.407)	
C ^c	1	1467 [6] (36.89)	4.00 [6] (1.00-8.00)	31154 [6] (40.66)	37688 [5] (39.22)	21439 [6] (36.03)	18.07 [5] (11.769)	8.92 [5] (44.80)
	28	3586 [2] (75.44)	2.29 [2] (0.50-4.08)			64407 [2] (78.39)	48.66 [1]	
D	1	1983 [6] (45.47)	3.00 [6] (0.50-8.00)	24761 [6] (33.91)	25414 [6] (33.66)	18658 [6] (40.34)	12.30 [6] (4.536)	13.22 [6] (37.96)
	28	2107 [6] (51.30)	4.00 [6] (1.00-6.00)			26200 [5] (47.23)	12.71 [4] (5.127)	

^aGroup A, HCC plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C; Group D, advanced solid non-HCC malignancy and normal hepatic function.

^bAUC₀₋₂₄ = AUC_{TAU} on Day 28.

^cIn Group C, C_{max}, AUC_{0-t}, AUC_{inf} and AUC₀₋₂₄ were normalized to a brivanib alaninate dose of 400 mg.

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve from time zero to 24 hours post-dose; AUC_{0-t}, area under the concentration-time curve from time zero to the last quantifiable concentration; AUC_{inf}, area under the concentration-time curve from time zero extrapolated to infinity; CLT, apparent total body clearance; C_{max}, maximum observed plasma concentration; CP, Child-Pugh; CV, coefficient of variation; GMean, geometric mean; HCC, hepatocellular carcinoma; SD, standard deviation; T-half, terminal plasma half-life; T_{max}, time of maximum observed plasma concentration.

Table 4. Statistical Analysis Results of Effect of Hepatic Impairment by Child-Pugh Status on Brivanib Pharmacokinetics on Day 1

Study Group^a	C_{max} (ng/mL) GMean (90% CI)	C_{max} Gmean Ratio A, B, C vs D (90% CI)	AUC_{inf} (ng*h/mL) GMean (90% CI)	AUC_{inf} Gmean Ratio A, B, C vs D (90% CI)
A (n=6)	1928 (1374, 2707)	0.97 (0.60, 1.57)	26817 (20185, 35629)	1.06 (0.71, 1.58)
B (n=6)	1666 (1187, 2339)	0.84 (0.52, 1.36)	27869 (20977, 37026)	1.10 (0.73, 1.64)
C (n=6) ^b	1467 (1045, 2059)	0.74 (0.46, 1.19)	37688 ^c (27609, 51448)	1.48 (0.97, 2.26)
D (n=6)	1983 (1413, 2785)	–	25414 (19129, 33765)	–

^aGroup A, HCC plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C; Group D, advanced solid non-HCC malignancy and normal hepatic function.

^bIn Group C, C_{max} and AUC_{inf} values are dose-adjusted to a brivanib alaninate dose of 400 mg.

^cn=5 for AUC_{inf}

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero extrapolated to infinity; C_{max}, maximum observed plasma concentration; CI, confidence interval; CP, Child-Pugh; GMean, geometric mean; HCC, hepatocellular carcinoma.

FIGURES

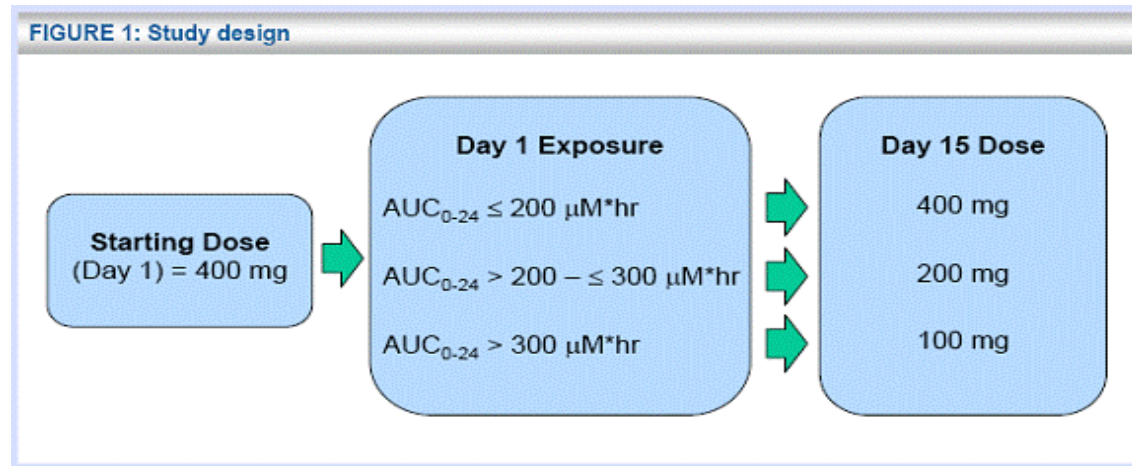


Figure 2A. Mean (SD) Plasma Concentration Versus Time Profiles for Brivanib After Administration of a Single Dose of Brivanib Alaninate to Subjects with Hepatic Impairment and Normal Hepatic Function on Day 1 (Normalized to a Brivanib Alaninate Dose of 400 mg)

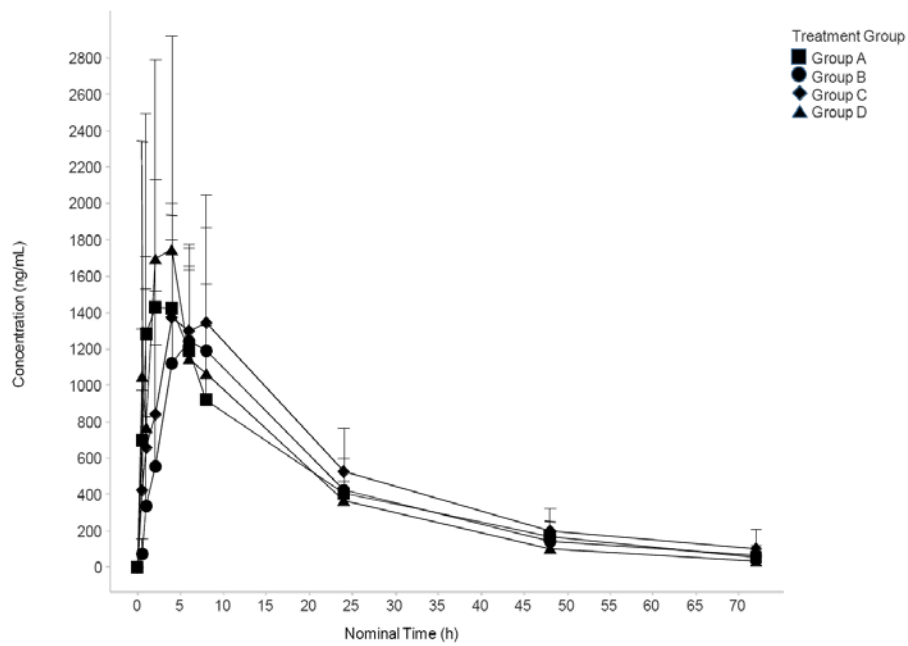
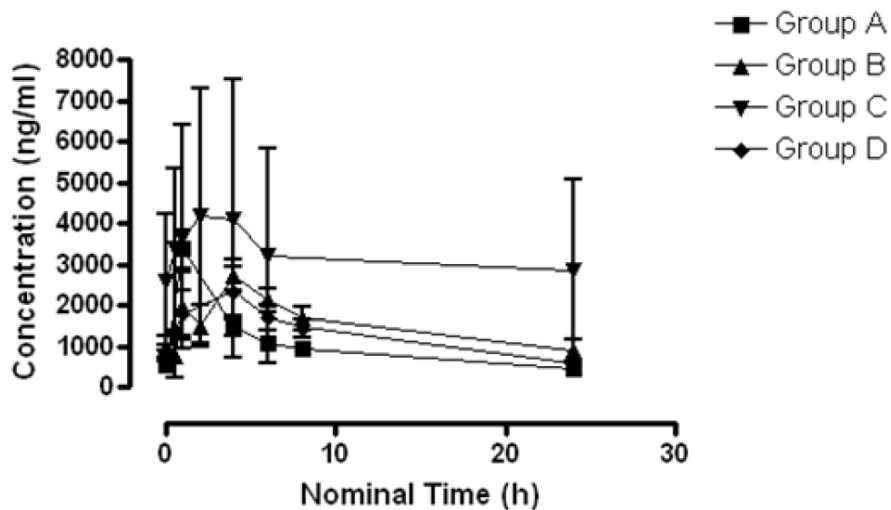


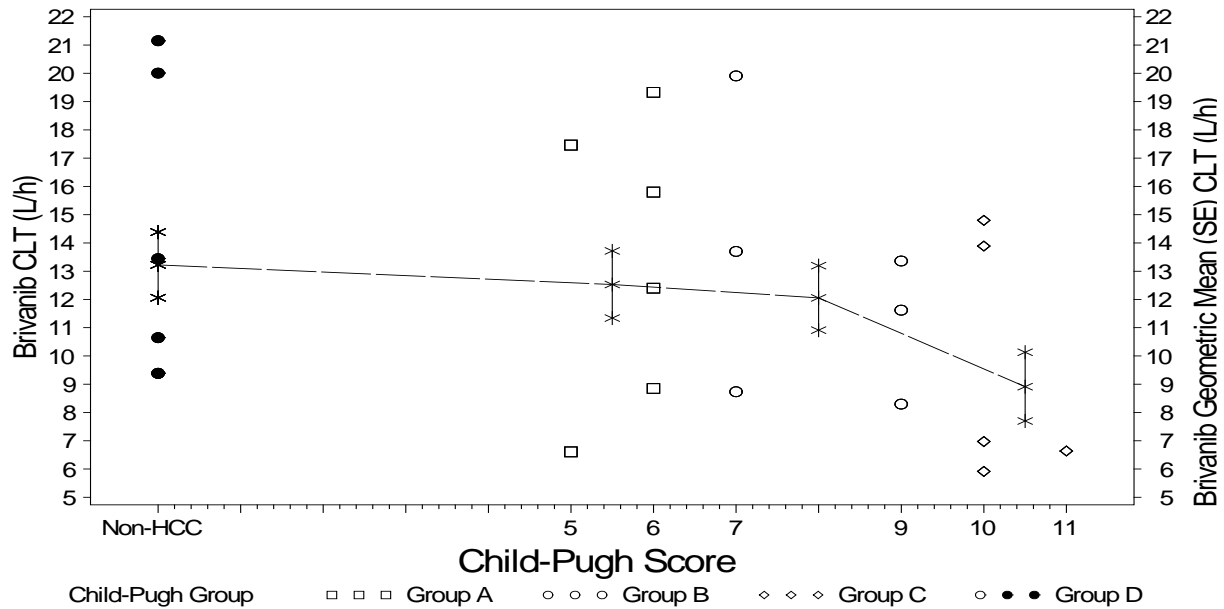
Figure 2B. Mean (SD) Plasma Concentration Versus Time Profiles for Brivanib After Administration of Brivanib Alaninate to Subjects with Hepatic Impairment and Normal Hepatic Function on Day 28 (Normalized to a Brivanib Alaninate Dose of 400 mg)



Group A, hepatocellular carcinoma plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C; Group D, advanced solid non-HCC malignancy and normal hepatic function.

Abbreviations: CP, Child-Pugh; HCC, hepatocellular carcinoma.

Figure 3. Plot of Brivanib Individual and Group Geometric Mean Apparent Total Body Clearance (Day 1 only) vs Child-Pugh Score^a in All Groups^b



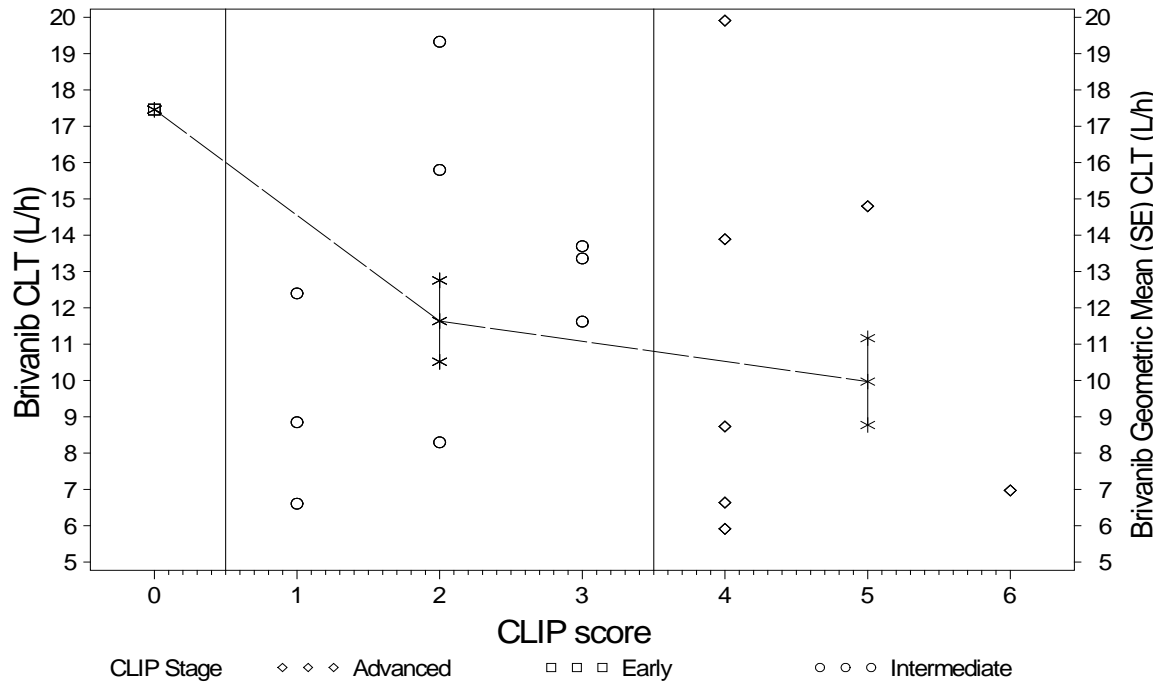
Geometric Mean CLT is estimated for each Child-Pugh Group, presenting a common statistic across Child-Pugh Scores in a Group
 PROGRAM SOURCE: /gbs/prod/din/programs/ca/182/015/csrstat/rpt/rg-pk-brdchp-v01.sas RUN DATE: 11APR11 12:49

^aCP scores of 5 or 6 correspond to Group A (CP status A), scores of 7 to 9 to Group B (CP status A), and scores of 10 to 15 to Group C (CP status A).

^bGroup A, hepatocellular carcinoma plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C; Group D, advanced solid non-HCC malignancy and normal hepatic function.

Abbreviations: CLT, apparent total body clearance; CP, Child-Pugh; HCC, hepatocellular carcinoma; SE, standard error.

Figure 4. Plot of Individual and Cancer of the Liver Italian Program (CLIP) Score^a Geometric Mean Brivanib Apparent Total Body Clearance (CLT) vs CLIP Score: Groups A, B, and C^b



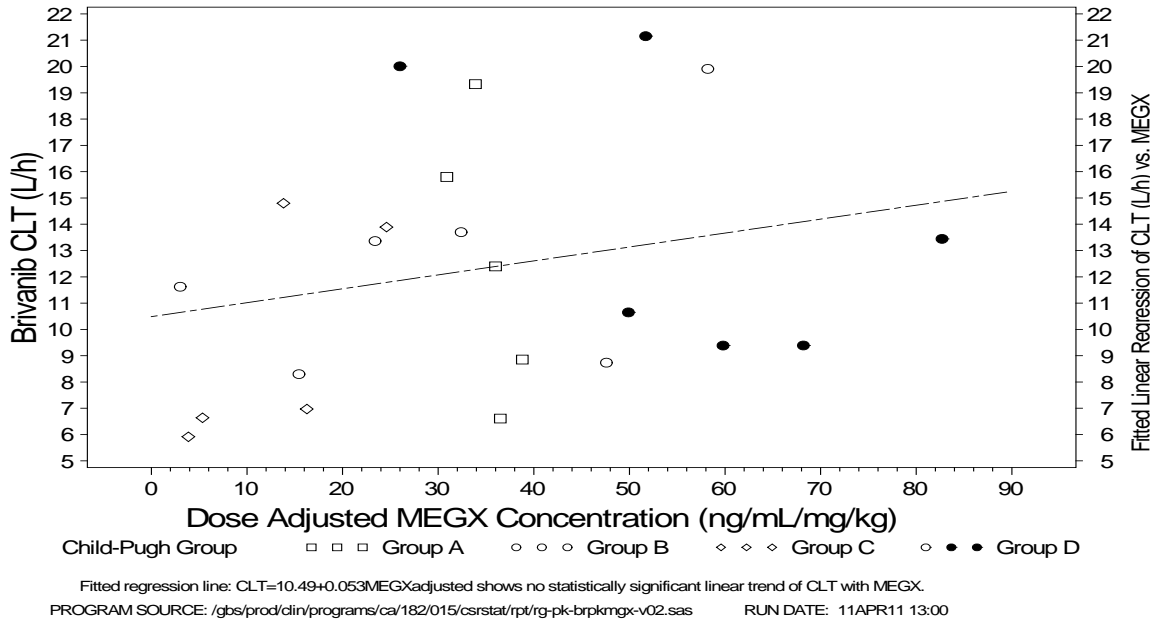
CLIP Scoring System for HCC: 0: Early Stage, 1 to 3: Intermediate Stage, 4 to 6: Advanced Stage.
 The geometric means (SE) are calculated across the CLIP Scores within each of the three CLIP Class.
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^aA CLIP score of 0 corresponds to early stage impairment, scores of 1 to 3 to intermediate impairment, and scores of 4 to 6 to advanced impairment.

^bGroup A, hepatocellular carcinoma plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C.

Abbreviations: CLIP, Cancer of the Liver Italian Program; CLT, apparent total body clearance; CP, Child-Pugh; HCC, hepatocellular carcinoma; SE, standard error.

Figure 5. Scatter Plot with Fitted Linear Regression of Brivanib Apparent Total Body Clearance (CLT) vs Monoethylglycinexylidide (MEGX) Concentration: All Groups^a



^aGroup A, hepatocellular carcinoma plus CP A; Group B, HCC plus CP B; Group C, HCC plus CP C; Group D, advanced solid non-HCC malignancy and normal hepatic function.

Abbreviations: CLT, apparent total body clearance; CP, Child-Pugh; HCC, hepatocellular carcinoma; MEGX, monoethylglycinexylidide.