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**PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Sutent®/Sunitinib Malate**

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI.

**NCT NO.: NCT00247676**

**PROTOCOL NO.**: A6181055

**PROTOCOL TITLE**: An Open Label International Multi-Center Phase 2 Activity and Safety Study of SU011248 in Patients with Unresectable Hepatocellular Carcinoma

**Study Centers**: France (3 centers), Republic of Korea (4 centers), Taiwan (1 center)

**Study Initiation and Completion Dates:** 03 February 2006 to 03 February 2009

**Phase of Development**: Phase 2

**Study Objectives:**

**Primary:** To determine the antitumor efficacy of single-agent sunitinib malate at a dose of 50 mg orally once daily for 4 consecutive weeks repeated every 6 weeks (Schedule 4/2) in subjects with unresectable hepatocellular carcinoma (HCC).

**Secondary:** To assess measures of clinical benefit and duration of tumor control, to evaluate the safety and tolerability of sunitinib malate, to evaluate sunitinib malate and SU012662 trough concentration ($C_{trough}$) and to correlate these plasma concentrations with efficacy and safety parameters, and to explore the correlations of cancer biomarkers with cancer- and treatment-related outcomes.

**METHODS**

**Study Design:** This was an open-label, uncontrolled, multicenter, 2-stage, clinical study in subjects with unresectable HCC.

All subjects received repeated cycles of sunitinib malate until disease progression, occurrence of unacceptable toxicity, withdrawal of subject consent, or other withdrawal criteria were met. After discontinuation of treatment and the mandated 28-day follow up, subjects were followed only in order to collect information on further antineoplastic therapy and survival. In subjects discontinuing treatment for reasons other than disease progression,

tumor assessments continued until disease progression, or initiation of other antineoplastic therapies.

**Number of Subjects (Planned and Analyzed):** Sixty-three subjects were planned to be enrolled in the study as follows: 38 subjects were planned for enrollment in Stage 1; and if ≥2 of the subjects exhibited responses (PR or CR), the study would proceed to Stage 2 and another 25 eligible subjects were planned for enrollment.

Thirty-seven subjects were enrolled and received study treatment. All 37 subjects treated were analyzed for pharmacokinetics (PK), efficacy, and adverse event (AE) safety; 36 were analyzed for laboratory data.

**Diagnosis and Main Criteria for Inclusion:** Male or female subjects aged 18 years or older with a histologically confirmed diagnosis of HCC, resolution of all acute toxic effects of any prior local treatment to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 3.0) Grade, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), no cirrhosis or cirrhotic status up to Child Pugh Class B, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, were enrolled into the study.

**Study Treatment:** Subjects received open-label sunitinib malate at a starting dose of 50 mg once daily for 4 consecutive weeks followed by a 2-week off-treatment period to form a complete cycle of 6 weeks; the dose could have been reduced to 37.5 mg or 25 mg based on tolerability.

**Efficacy Evaluations:** The primary evaluation was the objective response rate (ORR) defined as the percent of subjects with confirmed CR or confirmed PR according to RECIST, relative to the total population of subjects enrolled who received at least 1 dose of study drug, had a baseline disease assessment, and the correct histological cancer type.

The following measurements defined the secondary efficacy endpoints: clinical benefit response (CBR) rate defined as the percent of subjects with confirmed CR, PR, or stable disease (SD) ≥12 weeks on study according to RECIST, relative to the total analysis population, duration of response (DR) defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of disease progression or to death due to any cause, progression-free survival (PFS) defined as the time from start of study treatment to first documentation of objective tumor progression, or to death due to any cause, whichever occurred first, time to tumor progression (TTP) defined as the time from the start of study treatment to the first documentation of objective tumor progression, overall survival (OS) defined as the time from the date of first dose of study treatment to the date of death due to any cause, and the 1-year survival rate defined as the probability of subjects who were alive 1 year after their first dose of study treatment.

**Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:** Blood samples for determination of $C_{trough}$ for sunitinib malate and its active metabolite (SU012662) were obtained pre-dose and analyzed using a validated method. Plasma for assessment of soluble

proteins was collected pre-dose. Blood samples were collected for the assessment of circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs) to complete the angiogenic profile of unresectable HCC, in addition to the soluble protein evaluation. Tumor paraffin blocks could be optionally provided for analyses of markers that may be associated with tumor proliferation or angiogenesis.

*Other Evaluation – Post-Hoc Efficacy Evaluation*

Changes in tumor density on CT-scans observed in subjects with SD were often associated with sustained clinical benefit.

To more objectively quantify the changes in tumor density in the whole tumor, a computerized tomographic assessment centralized review was performed to evaluate the anti-tumor activity of sunitinib malate using tumor density and volumetric measurement of percent tumor necrosis (VMTN). A tridimensional measurement of intratumoral density by comparing the overall volume of hypodensity was performed prior to and after treatment with sunitinib malate. For the centralized review, the radiological studies were collected from study sites and a radiological review was performed at one site by the same radiologist.

To further explore the modifications of perfusion parameters induced by sunitinib malate, a subset of subjects treated at one site (same as above) had an additional specific assessment of blood flow and volume using perfusion CT scans. The perfusion CT technique was incorporated into the CT protocol at the site for therapeutic monitoring of sunitinib malate activity and was applied to calculate the liver hemodynamic parameters including intra-tumor blood perfusion.

**Safety Evaluations:** AEs, laboratory assessments (hematology, chemistry, coagulation), physical examination, ECOG performance status, vital signs, and 12-lead ECG.

**Statistical Methods:** The study followed a 2-stage Simon design. It was planned that if ≤1 objective response (OR) (complete response [CR] or partial response [PR]) was observed in the first 38 eligible subjects, the study would end. If ≥2 of these subjects exhibited CR or PR, then the study proceeded to Stage 2 by enrolling 25 additional subjects. The intention-to-treat population (ITT; subjects who received at least one study drug dose) was used for the efficacy and safety analyses.

The primary endpoint, ORR, was calculated and a 2-sided 95% exact confidence interval (CI) was provided. The secondary endpoints were analyzed as follows: CBR was calculated and a 2-sided 95% exact CI was provided. PFS, TTP, DR, and OS were analyzed using Kaplan-Meier methods. DR was summarized for the subgroup of subjects who achieved confirmed objective response and had the correct histological cancer type. PFS and TTP were summarized for the ITT population with the correct histological cancer type and a baseline assessment of disease. OS was summarized for the ITT population overall.

Descriptive statistics were used to summarize all subject characteristics, diagnoses, treatment administration, efficacy endpoints, safety parameters, pharmacokinetic variables and cancer biomarkers.

For sunitinib malate, SU012662, and total drug (sunitinib malate + SU012662), individual values and descriptive statistics (n, mean, standard deviation, coefficient of variation [CV], median, minimum and maximum) for $C_{trough}$ were presented by study day and cycle.

The results of biomarker studies were reported descriptively and in relation to clinical response and PK endpoints.

Safety data were summarized for all subjects receiving at least 1 dose of study drug (ITT population). Safety data analyses were descriptive and included summaries of AEs, serious AEs (SAEs), deaths, discontinuations due to AEs, and clinical laboratory, ECG, and vital sign results. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 12.0) and graded according to the NCI CTCAE (Version 3.0).

**RESULTS**

**Subject Disposition and Demography:** Enrollment of this study, designed using a Simon 2-stage, was halted after the first stage because the minimum number of responders needed to continue into Stage 2 was not reached. Thirty-seven subjects were enrolled and received study treatment. Thirty-six subjects discontinued from the study (16 due to an AE, in 8 a treatment-related AE and in 8 a treatment-unrelated AE, 15 due to lack of drug efficacy; 3 due to other reasons; and 2 due to the subject no longer willing to participate), and 1 subject had completed the study, but died 3 days following end of study treatment due to an AE that was considered treatment related.

Among the 37 subjects treated in this study, 34 (91.9%) were male and 3 (8.1%) were female. Sixteen subjects (43.2%) were from Asia and 21 subjects (56.8%) were from Europe. The median age was 61 years, with a range from 29 to 82 years. The median weight was 73 kg, with a range from 51 to 120 kg. Fifteen subjects (40.5%) had received locoregional treatment prior to study entry. At baseline, 19 subjects (51.4%) had ECOG performance status of 0, and 18 subjects (48.7%) had ECOG performance status of 1. There were 31 subjects (83.8%) who were classified as Child Pugh Class A, and 6 subjects (16.2%) classified as Child Pugh Class B. The most common conditions related to the primary diagnosis were alcohol abuse (11 subjects, 29.7%), hepatic cirrhosis (12 subjects, 32.4%), hepatitis B (17 subjects, 45.9%), and partial portal vein thrombosis (17 subjects, 45.9%).

**Efficacy Results:** Among the 37 subjects, 1 subject (2.7%) achieved a RECIST-defined confirmed PR lasting 32.4 weeks as determined by the investigator (95% CI of 0.1% to 14.2%), and 15 subjects (40.5%) had a best RECIST-defined response of SD as determined by the investigator. In total, 14 subjects (37.8%) had a PR or SD lasting ≥12 weeks (CBR) (95% CI of 22.5% to 55.2%), with a median CBR duration of 29.7 weeks.

Overall, the median TTP for the ITT population was 23.0 weeks (95% CI of 11.7 to 34.1 weeks) and the median PFS was 16.1 weeks (95% CI of 8.0 to 28.0 weeks). The median OS for the ITT population was 34.6 weeks (95% CI of 19.0 to 57.0 weeks). The 1-year survival rate was 32.4% (95% CI of 16.8% to 47.9%).

Overall, in the ITT Child-Pugh A population (31 subjects), the median TTP was 23.0 weeks (95% CI of 16.1 to 34.1 weeks), the median PFS was 21.0 weeks (95% CI of 8.1 to 32.4 weeks), and the median OS was 40.4 weeks (95% CI of 23.4 to 65.1 weeks).

**Pharmacokinetic, Pharmacodynamic, and/or Other Results:** Following intermittent daily dosing of sunitinib malate (Schedule 4/2; 4 weeks on and 2 weeks off), mean $C_{trough}$ at steady state (Day 28 of Cycles 1, 2, 3 and 5) for sunitinib malate, SU012662, and sunitinib malate + SU012662 ranged from 31.99 ng/mL to 64.19 ng/mL, 11.19 ng/mL to 20.77 ng/mL, and 47.11 ng/mL to 87.99 ng/mL, respectively. Dose-corrected (reference dose: 50 mg) mean $C_{trough}$ of sunitinib malate, SU012662, and sunitinib malate + SU012662 at steady state (Day 28 of Cycles 1, 2, 3 and 5) ranged from 58.50 ng/mL to 78.20 ng/mL, 18.38 ng/mL to 24.67 ng/mL , and 76.87 ng/mL to 102.40 ng/mL, respectively.

Plasma levels of the sunitinib malate mechanism-related soluble proteins changed markedly in response to treatment. Plasma VEGF was elevated above baseline levels at the end of the first dosing period, returning towards baseline during the first 2-week off-dose period. Similar dosing-related changes in plasma VEGF levels occurred in the subsequent cycle. In contrast, plasma levels of VEGF-C declined progressively throughout the first 2 cycles, with no return towards baseline during the off-dosing period. Plasma levels of sVEGFR-2 and sVEGFR-3 declined during the first dosing period and showed a partial return towards baseline during the 2-week off-dosing period, after which levels declined to a similar extent during the second dosing cycle. In contrast to these reversible pharmacodynamic changes in soluble VEGF receptors levels, there was a progressive decline in plasma sKIT during the first 2 cycles, with no return towards baseline during the off-dosing period.

Correlative analysis of baseline levels of soluble proteins and of changes from baseline at each time point revealed a significant association between high baseline levels of VEGF-C and improved clinical outcome, as assessed by best response, time to tumor progression or overall survival. There was also a trend towards higher baseline VEGF-C levels in subjects with a greater reduction in tumor density. High baseline levels of VEGF were positively associated with best response, but not with TTP or OS. Reduction from baseline in plasma sKIT levels on Cycle 1 Day 14 was associated with improved TTP and with greater tumor density reduction. For sVEGFR-2, longer OS was associated with greater reduction from baseline at the end of the first dosing cycle, and for sVEGFR-3, longer TTP was associated with greater reduction from baseline at the same time point. Greater reductions in plasma VEGF-C from baseline were associated with prolonged TTP and with prolonged OS at 2 time points, while there was a trend towards an association between reduction in VEGF-C from baseline levels and decrease in tumor density.

Analyses of gene expression profiling data and similar methods applied to soluble protein data planned for in the protocol have not yet been performed. Blood samples for CECs and CEP cells were collected during the study, but evaluations of these samples have not yet been performed.

*Other Evaluation – Post-Hoc Efficacy Evaluation:* Centralized review of CT scans confirmed the only PR, as assessed by the study investigator. Among the 26 subjects assessable for tumor density, 21 (80.7%) and 16 (61.5%) subjects had a ≥15% and a ≥30%

decrease in tumor density, respectively. Twenty-two subjects (84.6%) could be classified as responders according to Choi criteria (either ≥15% decrease in density or ≥10% decrease in tumor size). Among the 21 subjects assessable for VMTN, 13 (62%) and 10 (48%) had ≥15% and ≥30% of tumor volume decreasing in density, respectively, when compared to baseline. Among the 4 subjects assessable for the hemodynamic perfusion parameters, median decrease in blood flow was 56.3% and the median decrease in blood volume was of 59.3%, following sunitinib malate administration. An attempt to correlate TTP and OS with extent of tumor density reduction on CT scan (tumor density decrease by <15% and ≥15%) was also performed, but no significant differences were observed between the 2 groups for both endpoints.

**Safety Results:** Thirty-seven subjects experienced at least 1 treatment-emergent AE; of those, 36 subjects experienced at least 1 treatment-related AE. A summary of all-causality AEs reported in >15% of the study population by preferred term and CTCAE Grade is presented in Table S1 and a summary of treatment-related AEs reported in >15% of the study population by preferred term and CTCAE Grade is presented in Table S2.

**Table S1. Incidence of All-Causality Treatment-Emergent Adverse Events (>15%) in the Overall As-Treated Population**

| Adverse Events | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Grade 5 n (%) | Total n (%) |
|---|---|---|---|---|---|---|
| Thrombocytopenia | 1 (2.7) | 5 (13.5) | 9 (24.3) | 5 (13.5) | 0 (0.0) | 20 (54.1) |
| Anorexia | 13 (35.1) | 3 (8.1) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 17 (45.9) |
| Asthenia | 3 (8.1) | 7 (18.9) | 5 (13.5) | 1 (2.7) | 1 (2.7) | 17 (45.9) |
| Nausea | 12 (32.4) | 3 (8.1) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 17 (45.9) |
| Diarrhea | 12 (32.4) | 4 (10.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 16 (43.2) |
| Epistaxis | 9 (24.3) | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 11 (29.7) |
| Palmar-plantar erythrodysaesthesia syndrome | 4 (10.8) | 3 (8.1) | 4 (10.8) | 0 (0.0) | 0 (0.0) | 11 (29.7) |
| Anemia | 0 (0.0) | 2 (5.4) | 6 (16.2) | 2 (5.4) | 0 (0.0) | 10 (27.0) |
| Neutropenia | 0 (0.0) | 1 (2.7) | 9 (24.3) | 0 (0.0) | 0 (0.0) | 10 (27.0) |
| Vomiting | 5 (13.5) | 5 (13.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 10 (27.0) |
| Ascites | 1 (2.7) | 2 (5.4) | 5 (13.5) | 0 (0.0) | 1 (2.7) | 9 (24.3) |
| Abdominal pain | 6 (16.2) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Headache | 5 (13.5) | 3 (8.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Leukopenia | 1 (2.7) | 2 (5.4) | 5 (13.5) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Pyrexia | 6 (16.2) | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Stomatitis | 6 (16.2) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Upper abdominal pain | 5 (13.5) | 3 (8.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Constipation | 5 (13.5) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Dry skin | 6 (16.2) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Dyspepsia | 4 (10.8) | 3 (8.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Dyspnea | 4 (10.8) | 1 (2.7) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Elevated AST | 2 (5.4) | 2 (5.4) | 3 (8.1) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Mucosal inflammation | 5 (13.5) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Cough | 4 (10.8) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Elevated ALT | 1 (2.7) | 3 (8.1) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Hair color changes | 5 (13.5) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Hyperbilirubinemia | 0 (0.0) | 4 (10.8) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Insomnia | 4 (10.8) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Musculoskeletal pain | 5 (13.5) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Peripheral edema | 3 (8.1) | 2 (5.4) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Skin discoloration | 5 (13.5) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Decreased weight | 5 (13.5) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |

n = subset of the number of subjects used in the analysis; AST = aspartate transaminase, ALT = alanine transaminase

**Table S2. Incidence of Treatment-Related Treatment-Emergent Adverse Events (>15%) in the Overall As-Treated Population**

| Adverse Events | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Grade 5 n (%) | Total n (%) |
|---|---|---|---|---|---|---|
| Thrombocytopenia | 1 (2.7) | 5 (13.5) | 9 (24.3) | 5 (13.5) | 0 (0.0) | 20 (54.1) |
| Asthenia | 3 (8.1) | 7 (18.9) | 4 (10.8) | 1 (2.7) | 1 (2.7) | 16 (43.2) |
| Anorexia | 12 (32.4) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 14 (37.8) |
| Diarrhea | 9 (24.3) | 4 (10.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 13 (35.1) |
| Nausea | 8 (21.6) | 3 (8.1) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 12 (32.4) |
| Epistaxis | 9 (24.3) | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 11 (29.7) |
| Palmar-plantar erythrodysaesthesia syndrome | 4 (10.8) | 3 (8.1) | 4 (10.8) | 0 (0.0) | 0 (0.0) | 11 (29.7) |
| Neutropenia | 0 (0.0) | 1 (2.7) | 9 (24.3) | 0 (0.0) | 0 (0.0) | 10 (27.0) |
| Stomatitis | 6 (16.2) | 3 (8.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9 (24.3) |
| Anemia | 0 (0.0) | 4 (10.8) | 2 (5.4) | 2 (5.4) | 0 (0.0) | 8 (21.6) |
| Leukopenia | 1 (2.7) | 2 (5.4) | 5 (13.5) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Vomiting | 4 (10.8) | 4 (10.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (21.6) |
| Headache | 4 (10.8) | 3 (8.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Mucosal inflammation | 5 (13.5) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (18.9) |
| Dry skin | 5 (13.5) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Hair color changes | 5 (13.5) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |
| Skin discoloration | 5 (13.5) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (16.2) |

n = subset of the number of subjects used in the analysis

A summary of Grade 5 events reported are detailed in Table S3.

**Table S3. Individual Subject Adverse Events with Grade 5 Severity (All Cycles)**

| | | Grade 5 [a] | |
|---|---|---|---|
| **Sex/Age (years)** | **Event** | **Cycle Start/Stop** | **Study Start Day/Stop Day** |
| M/61 | Esophageal varices hemorrhage[b] | 1/1 | 39/41 |
| M/51 | Ascites[c] | 2/2 | 53/>57 |
| | Hepatic cirrhosis[c] | 2/2 | 53/>57 |
| M/79 | Depressed level of consciousness[c] | 1/1 | 56/56 |
| M/71 | Myocardial infarction[d] | 4/4 | 190/190 |
| M/68 | Hepatic encephalopathy[b] | 1/1 | 20/>20 |
| | Somnolence[b] | 1/1 | 20/>20 |
| M/61 | Renal failure[b] | 7/7 | 283/>283 |
| M/82 | Asthenia[b] | 1/1 | 33/>38 |

[a] By definition, Grade 5 AEs were death related.
[b] Treatment related.
[c] Unrelated to treatment (causality was disease under study).
[d] Unrelated to treatment (causality was cardiac failure in postoperative period after partial right hepatectomy).

Discontinuations are shown in Table S4.

**Table S4. Permanent Discontinuations Due to Adverse Events**

| Sex/Age (years) | Event | Cycle Start/Stop | Study Start Day/ Stop Day | Grade | SAE (Y/N) |
|---|---|---|---|---|---|
| M/61[a] | Esophageal varices hemorrhage[b] | 1/1 | 39/41 | 5 | Y |
| | Hepatic encephalopathy[c] | 1/1 | 27/41 | 4 | Y |
| M/51[a] | Ascites[c] | 2/2 | 53/>57 | 5 | Y |
| | Hepatic cirrhosis[c] | 2/2 | 53/>57 | 5 | Y |
| M/79[a] | Fatigue[c] | 1/1 | 43/>56 | 3 | N |
| | Depressed level of consciousness[c] | 1/1 | 56/56 | 5 | Y |
| M/66 | Empyema[c] | 1/1 | 13/>15 | 3 | Y |
| | Dyspnea[c] | 1/1 | 13/>15 | 3 | N |
| M/62 | Leg pain[d] | 4/4 | 176/192 | 2 | Y |
| M/29 | Esophageal varices hemorrhage[c] | 2/2 | 52/>92 | 3 | Y |
| M/53 | Thrombocytopenia[b] | 1/1 | 16/>36 | 4 | N |
| | Esophageal varices[c] | 1/1 | 16/>36 | 3 | N |
| | Upper gastrointestinal hemorrhage[e] | 1/1 | 16/18 | 3 | Y |
| | Hepatic encephalopathy[c] | 1/1 | 16/18 | 4 | Y |
| F/68 | Pulmonary embolism[c] | 7/7 | 315/>322 | 3 | Y |
| M/74 | Asthenia[b] | 2/2 | 84/>84 | 3 | Y |
| M/68[a] | Hepatic encephalopathy[b] | 1/1 | 8/19 | 3 | Y |
| | Hepatic encephalopathy[b] | 1/1 | 20/>20 | 5 | Y |
| M/62 | Hepatic hematoma[b] | 8/8 | 322/>363 | 1 | N |
| M/70 | Cerebrovascular accident[b] | 1/Follow-up | 26/70 | 4 | Y |
| M/79 | Neurological deficit[c] | 7/7 | 249/>249 | 3 | Y |
| M/61[a] | Hypercreatinemia[b] | 7/7 | 282/>282 | 3 | Y |
| M/82[a] | Asthenia[b] | 1/1 | 33/>38 | 5 | Y |
| F/43 | Peritoneal hemorrhage[b] | 1/1 | 28/47 | 3 | Y |

[a] Subject died.
[b] Treatment related.
[c] Unrelated to treatment (causality was disease under study).
[d] Unrelated to treatment (causality was other illness – bone metastasis).
[e] Unrelated to treatment (causality was other illness – esophageal varices).

Twenty-four subjects (64.9%) were reported to have experienced at least 1 SAE during the study period; 15 of those subjects had treatment-related SAEs. The most common SAEs were hemorrhage (19 incidences), neurological (18 incidences), asthenia (8 incidences), anemia (6 incidences), and thrombocytopenia (6 incidences). Some subjects experienced more than 1 SAE at any time.

Overall, 4 subjects experienced a shift from Grade 0 or 1 to Grade 3 shift in hemoglobin level. Three subjects experienced a Grade 0 or 1 to Grade 3 shift in WBC count. Seven subjects experienced a Grade 0 to Grade 3 shift in neutrophil count. Seventeen subjects experienced a Grade 0-2 to Grade 3-4 shift in platelet count. In addition, 12 subjects experienced a Grade 0-2 to Grade 3-4 shift in lymphocyte count.

Overall, 6 subjects experienced a Grade 0 or 1 to Grade 3 shift in ALT level; 11 subjects experienced a Grade 0-2 to Grade 3 shift in AST level; 1 subject (2.8%) experienced a Grade 0 to Grade 3 shift in alkaline phosphatase; 7 subjects experienced a Grade 0-2 to Grade 3-4 shift in GGT level; 9 subjects experienced a Grade 0-2 to Grade 3

shift in total bilirubin level. Three subjects experienced a Grade 0 to Grade 3 or 4 shifts in hyperkalemia, and 1 subject experienced a shift from Grade 0 to Grade 3 in hypokalemia. Six subjects experienced a Grade 0 or 1 to Grade 3 shift in hyponatremia level. One subject experienced a Grade 1 to Grade 4 shift in hyperuricemia level; 3 subjects experienced a Grade 0 to Grade 3 shift in hypophosphatemia; and 1 subject experienced a shift from Grade 0 to Grade 4 in hypocalcemia.

Overall, SBP >150 mmHg or DBP >100 mmHg was experienced at least once during the study by 11 subjects (31.4%), 5 of these were already diagnosed as having hypertension at baseline, and SBP>200 mmHg or DBP >100 mmHg was experienced at least once during the study by 5 subjects (14.3%).

No changes of QTc interval from baseline observed on study were reported by the investigators as clinically significant.

**CONCLUSIONS:**

- Sunitinib malate 50 mg on Schedule 4/2 is an active therapy in subjects with unresectable HCC by VMTN but not by RECIST.

- The safety profile of sunitinib malate was acceptable and manageable, as AEs were generally similar to those reported in other studies of single-agent sunitinib malate and/or normally encountered by advanced HCC patients.

- Trough concentration values for sunitinib malate and its metabolite SU012662, following a 4/2 dosing schedule in HCC subjects, were consistent with the previously reported PK of sunitinib malate and SU012662 for the 4/2 dosing schedule and other schedules in Phase 1 and 2 studies of subjects with RCC, GIST and solid tumors. No unexpected accumulation of sunitinib malate and SU012662 was observed throughout the study.

- Elevated plasma levels of VEGF-C were associated with sunitinib malate antitumor activity in HCC.