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

PROTOCOL NO.: A6181170

PROTOCOL TITLE: A Multinational, Randomized, Open-Label, Phase 3 Study of Sunitinib Malate Versus Sorafenib in Patients With Advanced Hepatocellular Carcinoma

Study Centers: A total of 137 centers took part in the study and enrolled subjects; 3 in Australia, 3 in Belgium, 5 in Canada, 17 in China, 13 in France, 3 in Germany, 4 in Hong Kong, 6 in Italy, 20 in Japan, 12 in Korea, 3 in Malaysia, 7 in Philippines, 2 in Poland, 3 in Russian Federation, 2 in Singapore, 1 in South Africa, 5 in Spain, 1 in Sweden, 11 in Taiwan, 3 in Thailand, 2 in Turkey, 2 in the United Kingdom and 9 in the United States.

Study Initiation Date and Final Completion Dates: 11 July 2008 to 08 December 2011. The study was terminated prematurely due to potential safety issues.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To demonstrate that overall survival (OS) on sunitinib is superior or equivalent to overall survival on sorafenib in subjects with advanced hepatocellular carcinoma (HCC).

Secondary Objectives:

- To compare progression-free survival (PFS) and time to tumor progression (TTP) between both treatment arms.
- To evaluate the safety and tolerability of sunitinib in this subject population.
- To compare subject's health status between both treatment arms.

METHODS

Study Design: The A6181170 study was a multicenter, randomized (1:1), open-label, parallel-arm, Phase 3 clinical study to evaluate the efficacy and safety of sunitinib compared to sorafenib in subjects with advanced HCC. Subjects were randomized to receive either sunitinib (Treatment A) or sorafenib (Treatment B).

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The study treatment may have been permanently discontinued upon progression of disease, occurrence of unacceptable toxicity, withdrawal of subject consent, or another withdrawal criterion was met, unless there was sufficient evidence of clinical benefit to justify continuation of study treatment at the discretion of the Investigator. However, subjects who required different cancer treatment from what they were assigned at randomization had to be withdrawn from the study and followed as described below.

After discontinuation of study treatment and the mandated 28-day follow-up period, subjects were followed in order to collect information on further antitumor therapy and survival. Subjects discontinuing study treatment without documented evidence of disease progression should have continued tumor imaging assessments at the same frequency until disease progression, or initiation of another anticancer treatment, whichever was earlier.

A schedule of activities is presented in Table 1.

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Table 1. Schedule Of Activities

Protocol Activities and Forms to be Completed	Screening (Day)	Treatment (4-Week Cycles)[a]						Post-Treatment		
	≤21	Cycle 1			Beyond Cycle 1			End of Treatment/ Withdrawal[b]	28 Days Post-Treatment	Survival Follow-Up
		Day 1[c] –3/+0	Day 14 –/+3	Day 28 –3/+3	Day 1[d] –3/+0	Day 14 –7/+7	Day 28 –3/+3			Approximately Every 2 Months
Baseline documentation										
Informed consent[e]	X									
Medical/Oncologic history and demographics[f]	X									
Baseline signs and symptoms[g]		X								
Physical examination[h]	X	(X)			X			X	(X)	
Laboratory studies[i]										
Hematology[j]	X	(X)	X	X	X[j]		X	X	(X)	
Blood chemistry[k]	X	(X)	X	X	X[k]		X	X	(X)	
Coagulation[l]	X	(X)	X	X	X[l]		X	X	(X)	
Pregnancy test[m]	X									
Urinalysis (dipstick) [n]	X	(X)		X	X		X	X	(X)	
12-lead electrocardiogram (ECG) [o]	X		(X)	X	(X)	(X)	(X)	X	(X)	
Left ventricular ejection fraction (LVEF) [p]	X									
Thyroid-stimulating hormone (TSH)[q]	X									
Endoscopy[r]	X									
Randomization[s]	X									
Study drug[t]		→	→	→	→		→			
Tumor assessments										
Tumor imaging[u]	X					X, first 24 wks[u]	X, after 24 wks[u]	X		
Brain scan[v]	(X)					(X)	(X)	(X)		
Bone scan[w]	(X)					(X)	(X)	(X)		
Sample banking for exploratory research[x]	(X)	(X)	(X)	(X)			(X) Cycle 2 only			
Other clinical assessments										

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Eastern Cooperative Oncology Group (ECOG)[h], body weight, and vital	X	X			X			X	X	
Adverse events signs and symptoms[y]	X	X	X	X	X		X	X	X	
Study drug compliance[z]				X			X	X		
Concomitant medications and treatments [aa]	X	X	X	X	X		X	X	X	
EuroQol 5D (EQ-5D) Questionnaire[bb]		X			X			X		
Poststudy anticancer treatment[cc]										X
Poststudy survival status[cc]										X

a. During treatment with study drug: All assessments were performed prior to dosing with study drug unless otherwise indicated. Acceptable time windows for performing each assessment are described below each scheduled treatment day. For subjects randomized to Arm B, additional safety evaluations may have been performed as clinically indicated according to sorafenib package insert or equivalent documentation.

b. End of study drug/withdrawal: These assessments were obtained if not completed during the last week on study (during the last 6 or 8 weeks, on study for radiological tumor assessments).

c. Cycle 1 Day 1: Hematology and blood chemistry assessments were not required if acceptable screening assessment was performed within 7 days prior to the start of treatment with study drug.

d. Day 1 assessments of new cycle did not need to be repeated if they coincided with Day 28 assessments of the previous cycle.

e. Informed consent: had to be obtained prior to undergoing any study procedure and may have occurred prior to the 21-day screening period.

f. Medical/oncology history and demographics: Included age, race, sex, hepatitis virus exposure, Child-Pugh score, Cancer Liver Italian Program (CLIP) score, histological diagnosis of hepatocellular carcinoma by previous or recent biopsy, and information on prior cancer treatments.

g. Baseline signs and symptoms: Subjects were asked about any signs or symptoms experienced within the previous 14 days.

h. Physical examination: During Screening and on Day 1 of each cycle: Examination of major body systems, height (at screening visit only), Eastern Cooperative Oncology Group (ECOG) performance status, body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate). Physical examination was not required if acceptable screening assessment was performed within 7 days prior to the start of study drug. During the 28-day post-treatment visit: Examination of major body systems, body weight, and vital signs only.

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		Day 1[c] –3/+0	Day 14 –/+3	Day 28 –3/+3	Day 1[d] –3/+0	Day 14 –7/+7	Day 28 –3/+3			Approximately Every 2 Months

i. Laboratory studies: Samples were analyzed using local laboratories.

j. Hematology: White blood cell (WBC) with differential count, hemoglobin, and platelet count. Hematology screening assessment was required within 7 days prior to the start of study treatment. From Cycle 2, Day 1 assessment was not required if interval from prior cycle Day 28 assessment ≤3 days, and as clinically indicated.

k. Blood chemistry: Total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl transferase (GGT), total protein, , albumin, sodium, potassium, calcium, phosphorus, magnesium, blood urea nitrogen (BUN), creatinine, uric acid, ammonia, glucose, alfa-fetoprotein (AFP). Blood chemistry screening assessment was required within 7 days prior to the start of study treatment. From Cycle 2, Day 1 assessment was not required if interval from prior cycle Day 28 assessment ≤3 days, and as clinically indicated.

l. Coagulation: International Normalized Ratio (INR), prothrombin time (PT). Coagulation screening assessment was required within 7 days prior to the start of study treatment. From Cycle 2, Day 1 assessment was not required if interval from prior cycle Day 28 assessment ≤3 days, and as clinically indicated.

m. Pregnancy test (Serum or Urine): Women of reproductive potential had to be tested within 7 days prior to the start of study treatment.

n. Urinalysis (by dipstick): Screening assessment was required within 7 days prior to the start of study treatment. From Cycle 2, Day 1 assessment was not required if interval from prior cycle Day 28 assessment ≤3 days, and as clinically indicated.

o. ECG: Three consecutive 12-lead ECGs approximately 2 minutes apart were performed to determine the mean corrected QT interval (QTc) interval. If the mean QTc interval was prolonged (>500 msec), the ECG was repeated and if still prolonged, it was re-read by a specialist at the site for confirmation. Additional ECGs may have been performed as clinically indicated to include 2 weeks following intra-subject dose adjustments.

p. LVEF was evaluated at baseline. Additional determinations were done as clinically indicated, with same method used at baseline.

q. TSH test: Collected at screening, then as clinically indicated thereafter; test was performed at the local laboratory.

r. Endoscopy (screening): To exclude subjects with esophageal varices and/or ulcers at risk of bleeding.

s. Randomization: Subject number, study arm assignments were obtained via a centralized system.

t. Study drug: Treatment started on Cycle 1 Day 1 after completing all predose assessments. Subjects received sunitinib capsules at a starting dose of 37.5 mg daily (QD) on continuous daily dosing schedule (Arm A), or sorafenib at 400 mg twice daily (BID; 800 mg total dose daily) (Arm B). The study drug dose may have been interrupted and/or adjusted according to individual subject tolerance.

u. Tumor imaging: CT or MRI scans of the chest, abdomen, and pelvis, and other applicable sites of disease, were to be performed at screening and at fixed intervals during the study. The schedule of assessments was fixed according to the calendar, regardless of treatment delays. Allowable time windows for on study tumor assessment were ±7 days. Tumor imaging assessments should have been performed:

- At 6 weeks after the start of treatment and every 6 weeks for the first 24 weeks, thereafter every 8 weeks,
- Whenever disease progression was suspected,
- To confirm a partial or complete response (at least 4 weeks after initial documentation of response; these confirmatory scans should not have altered the fixed,

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6-week or 8-week timing),

- At the time of withdrawal from the study, if not done in the previous 6 weeks (for the first 24 weeks on study) or 8 weeks (after 24 weeks on study),
- If subject discontinued without documented evidence of tumor progression, then tumor imaging assessments continued at the same frequency until tumor progression, or initiation of another anticancer treatment, whichever was earlier.

v. Brain CT or MRI scan required only in case of clinical suspicion of central nervous system metastases at screening or subsequently.

w. Bone scan required at screening only in case of clinical suspicion of bone metastases, and repeated at 12-week intervals if bone metastases were present or whenever new disease was suspected.

x. Molecular Profiling: Archival tumor was to be collected at screening or at any time during the study. Whole blood for germline deoxyribonucleic acid (DNA) was collected once at screening or at any time subsequently. Whole blood for ribonucleic acid (RNA) was to be collected on predose on Cycle 1 Day 1 and Cycle 1 Day 28. Plasma for biomarkers (soluble proteins) was to be collected predose on Cycle 1 Day 1, Cycle 1 Day 14, and Cycle 2 Day 28.

y. Adverse events (AEs): Subjects were followed for AEs from the first day of study drug until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities resolved or were determined to be "chronic" or "stable," whichever was later. Serious adverse events were monitored and reported as described in the protocol.
Tumor-Related Signs and Symptoms: Baseline tumor-related signs and symptoms were recorded as AEs during the trial if they worsened in severity or increased in frequency.

z. Adverse events (AEs): Subjects were followed for AEs from the first day of study drug until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities resolved or were determined to be "chronic" or "stable," whichever was later. Serious adverse events were monitored and reported as described in the protocol.
Tumor-Related Signs and Symptoms: Baseline tumor-related signs and symptoms were recorded as AEs during the trial if they worsened in severity or increased in frequency.

aa. Concomitant medications and treatments: Concomitant medications and treatments were recorded from 30 days prior to the start of study treatment, at study entry, and during the study. Once the subject withdrawn from the study, concomitant medications and treatments were recorded for 28 days or until all study drug-related toxicities resolved, whichever was later.

bb. Patient Reported Outcomes (EuroQol 5D [EQ-5D]): Day 1 of each cycle, and at the end of treatment/withdrawal.

cc. Poststudy survival status: After discontinuation of study drug as assigned at randomization, any new poststudy anticancer treatments were recorded and poststudy survival status was collected by clinic visit or telephone contact approximately every 2 months until death.

Number of Subjects (Planned and Analyzed): It was planned to enroll 1200 subjects to be randomly assigned in a ratio of 1:1 to Arm A: sunitinib (600 subjects) and Arm B: sorafenib (600 subjects). A total of 1074 subjects were assigned to study treatment. No subjects received a treatment different from the assigned one. A total of 1068 (99.4%) subjects were treated (526 received sunitinib and 542 received sorafenib). Six subjects were assigned to study treatment (4 to sunitinib and 2 to sorafenib, respectively), but were not treated.

The number of subjects enrolled was lower than planned in the protocol because the study was terminated prematurely. During the periodic review held in April 2010, the independent Data Monitoring Committee (DMC) members concluded that the data showed superiority in terms of OS for the sunitinib arm was very unlikely to be shown at the end of the study, with a higher toxicity profile, and that in their opinion the study should be stopped. The sponsor agreed with the DMC recommendation to terminate the study.

Diagnosis and Main Criteria for Inclusion: Eligible subjects had a histologically-confirmed diagnosis of hepatocellular carcinoma, presence of measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST]) by radiographic imaging, Child-Pugh class A, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and adequate organ function. Subjects with prior treatment with any systemic treatment for HCC, prior local treatment within 4 weeks from study entry, presence of clinically relevant ascites, severe hemorrhage <4 weeks of starting study treatment, known human immunodeficiency virus (HIV) or serious acute or chronic illness, current treatment on another clinical trial or who were pregnant or breastfeeding were excluded from the study.

Study Treatment:

Sunitinib (Treatment A): Sunitinib was administered orally at a starting dose of 37.5 mg (3 x 12.5 mg capsules) daily on a continuous daily dosing (CDD) schedule to subjects randomized to sunitinib. Self-administration of sunitinib capsules took place on an outpatient basis. Capsules should have been taken once daily in the morning without regard to meals. Subjects experiencing dose-limiting toxicity attributed to study medication had at least 1-week treatment breaks inserted into the CDD schedule as needed and/or treatment was interrupted or reduced, depending on individual tolerability. Dose interruptions and/or reductions were dependent on the severity (based on National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v3.0 grade), manageability, and relatedness of toxicity to the study drug. Recovery to acceptable levels of toxicity was required to allow continuation in the study. Intra-subject dose reductions in 12.5 mg decrements were allowed depending on the type and severity of toxicity encountered (based on NCI CTCAE v3.0 grade), provided that criteria for subject withdrawal from study treatment had not been met. Doses reduced for drug toxicity were generally not escalated. However, intrasubject re-escalation back to the previous dose level was permitted in the absence of Grade ≥3 hematologic or Grade ≥2 non-hematologic treatment-related toxicity in the previous 4-week cycle.

Sorafenib (Treatment B): Sorafenib was administered orally at the starting dose of 400 mg (2 x 200 mg film-coated tablets) twice daily (BID; 800 mg total daily dose) on a CDD

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schedule to subjects randomized to sorafenib. Self-administration of sorafenib tablets took place on an outpatient basis. Tablets should have been taken without food or with a low or moderate fat meal. If the subject intended to have a high-fat meal, sorafenib tablets were taken at least 1 hour before or 2 hours after the meal. The tablets were swallowed with a glass of water. Subjects experiencing dose-limiting toxicities attributed to sorafenib had treatment breaks inserted into the daily dosing period as needed and/or treatment was interrupted or reduced depending on individual tolerability. Intrasubject dose adjustments and/or interruptions were applied depending on the type and severity of toxicity encountered (based on NCI CTCAE v3.0 grade), provided that criteria for subject withdrawal from study treatment had not been met. When dose reductions were necessary, sorafenib dose was reduced to 2 tablets of 200 mg once daily (400 mg total once daily). If additional dose reductions were required, sorafenib was reduced to 2 tablets of 200 mg every other day (400 mg total every other day). Sorafenib package insert or equivalent documentation was to be used as reference for dose reduction guidelines.

Sorafenib was commercially available for the HCC indication and locally sourced. Sunitinib was supplied by the Sponsor as 12.5 mg and 25 mg hard-gelatin capsules.

Efficacy Endpoints:

Primary Endpoint:

- Overall survival (OS).

Secondary Endpoints:

- Progression free survival (PFS).
- Time to tumor progression (TTP).
- Type, incidence, severity (graded by NCI CTCAE), timing, seriousness, and relatedness of adverse events and laboratory abnormalities.
- Health status measured by the EuroQol-EQ-5D Self Report Questionnaire (EQ-5D).

Safety Evaluations: Safety evaluations included clinical monitoring for adverse events (AEs), clinical laboratory evaluations, physical examinations, ECOG performance status, vital signs, 12-lead electrocardiograms (ECGs), and left ventricular ejection fraction (LVEF).

Statistical Methods: The full analysis population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from which they were randomized to. The full analysis population was the primary population for evaluating all efficacy endpoints and subject characteristics. The per protocol (PP) population included all subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The PP population was the primary population for evaluating safety and treatment

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compliance/administration. Efficacy and clinical benefit endpoints were assessed in this population as well.

Efficacy: For the analysis of OS data, the primary analysis was based on data censored at the date of last contact at which the subject was known to be alive. For the analysis of primary efficacy endpoint OS, the results were summarized in the full analysis population using Kaplan-Meier methods and displayed graphically. The median event time and corresponding 2-sided 95% confidence interval (CI) for the median were provided for OS. The hazard ratio and its 95% CI were estimated.

Safety: Safety results were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject disposition and datasets analyzed is provided in Table 2.

A total of 1074 subjects were assigned to study treatment. No subjects received a treatment different from the assigned one. A total of 1068 (99.4%) subjects were treated (526 received sunitinib and 542 received sorafenib). Six subjects were assigned to study treatment (4 subjects to sunitinib and 2 subjects to sorafenib) but were not treated. Overall, subject disposition was generally similar between treatment arms.

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Table 2. Subject Disposition and Datasets Analyzed

Number (%) of Subjects	Sunitinib	Sorafenib	Total
Assigned to study treatment[a]	530	544	1074
Treated	526 (99.2)	542 (99.6)	1068 (99.4)
Discontinued	526 (99.2)	542 (99.6)	1068 (99.4)
Primary reason for withdrawal from study			
Subject died	93 (17.7)	83 (15.3)	176 (16.5)
Adverse event	70 (13.3)	67 (12.4)	137 (12.8)
Global deterioration of health status	7 (1.3)	8 (1.5)	15 (1.4)
Lost to follow-up	3 (0.6)	5 (0.9)	8 (0.7)
No longer willing to participate in study	34 (6.5)	44 (8.1)	78 (7.3)
Objective progression or relapse	281 (53.4)	277 (51.1)	558 (52.2)
Other	18 (3.4)	15 (2.8)	33 (3.1)
Protocol violation	2 (0.4)	6 (1.1)	8 (0.7)
Study terminated by sponsor	13 (2.5)	28 (5.2)	41 (3.8)
Full analysis population	530	544	1074
Per protocol population	526	542	1068
Analyzed for Safety[b]			
Adverse events	525 (99.8)	540 (99.6)	1065 (99.7)
Laboratory data	521 (99.0)	537 (99.1)	1058 (99.1)

Since there was no case report form page for discontinuation from study, the reasons for discontinuation were attained from the following (in order): Notice of Death (deaths on study only), Subject Summary-End of Treatment page, or from the adverse events Permanently Discontinued or Action - Withdrawn from Study. For 'Subject Died', only deaths on study (within 28 days after last dose of study medication) were shown on this table.
Three subjects (1 sunitinib and 2 sorafenib) died, but were never treated. Therefore, these subjects were not part of the per protocol population.
Three subjects (1 sunitinib, 'lost to follow up', 1 sunitinib, 'no longer willing to participate in study', and 1 sunitinib, 'other') were randomized, but never treated. Therefore, they were not part of the per protocol population.
Five sunitinib subjects and 9 sorafenib subjects died after 28 days of last dose. These subjects were not counted on this table because they did not die on study. The full analysis population was defined as all subjects randomized to treatment.
The Per protocol population was defined as all subjects who received at least 1 dose of study treatment.

a. Percentages based on the number of subjects assigned to study treatment within each treatment group.
b. Percentages based on the number of subjects treated within each treatment group.

A summary of demographic characteristics is provided in Table 3.

Most subjects were male (83.3%). The mean age of subjects was 58.3 years (range, 18 to 85 years). Most subjects were Asian (77.2%), followed by white (20.8%).

Overall, demographic characteristics were similar between treatment arms. There were no differences between treatment arms in demographics including age, sex, race, weight, or height.

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Table 3 Summary of Demographic Characteristics (Full Analysis Population)

	Sunitinib (N=530)	Sorafenib (N=544)	Total (N=1074)
Age (years)			
<18	0	0	0
18-44	85 (16.0)	79 (14.5)	164 (15.3)
45-64	261 (49.2)	270 (49.6)	531 (49.4)
≥65	184 (34.7)	195 (35.8)	379 (35.3)
Mean (SD)	58.1 (12.9)	58.5 (12.9)	58.3 (12.9)
Median	59.0	59.0	59.0
Range	18, 85	18, 84	18, 85
Sex			
Male	436 (82.3)	459 (84.4)	895 (83.3)
Female	94 (17.7)	85 (15.6)	179 (16.7)
Race			
White	111 (20.9)	112 (20.6)	223 (20.8)
Black	6 (1.1)	10 (1.8)	16 (1.5)
Asian	411 (77.5)	418 (76.8)	829 (77.2)
Other	2 (0.4)	4 (0.7)	6 (0.6)
Weight (kg)			
N	529	544	1073
Mean (SD)	65.8 (13.2)	66.2 (13.0)	66.0(13.1)
Median	64.0	64.0	64.0
Range	33.1, 132.0	38.5, 120.0	33.1, 132.0
Height (cm)			
N	530	544	1074
Mean (SD)	166.3 (8.2)	166.0 (8.2)	166.1 (8.2)
Median	167.0	166.2	167.0
Range	125.4, 196.0	130.0, 194.0	125.4, 196.0

SD = standard deviation; N = number of subjects.

Efficacy Results:

Primary:

Kaplan-Meier curves of OS are provided in Figure 1. For all subjects, the median survival time was longer for sorafenib than sunitinib. The median time to death was 34.3 weeks for sunitinib, with a 95% CI of (31.9, 39.9). The median time to death was 43.9 weeks for sorafenib, with a 95% CI of (38.1, 48.7).

The hazard ratio was 1.3 (sunitinib vs. sorafenib), with a 95% CI of (1.1, 1.5). The p-value testing that median survival for the sunitinib group was superior to the median survival for the sorafenib group was 0.9993. The hazard ratio was 1.3 (sunitinib vs sorafenib) with a 80% CI of (1.2, 1.4), which has a lower limit greater than the prespecified non-inferiority margin of 1.1263 for the HR of OS. Therefore, the study did not achieve non-inferiority after failing to show superiority.

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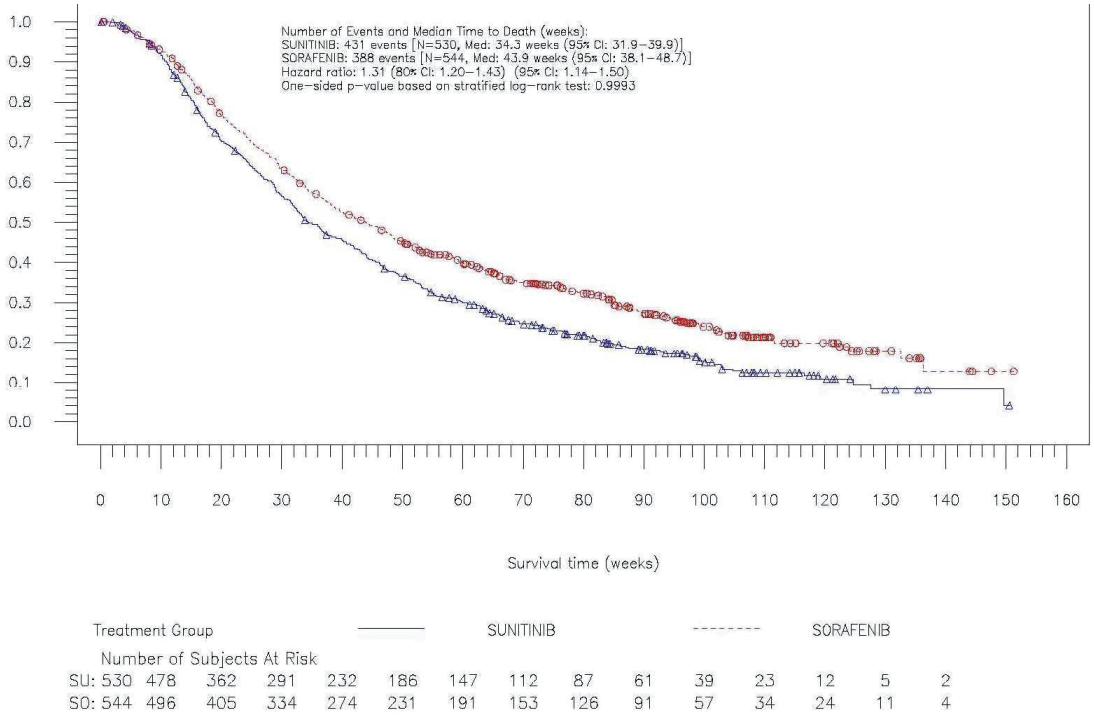
Figure 1. Kaplan-Meier Curves of Overall Survival by Treatment (Full Analysis Population)



Note 1: The p–value is from the stratified log–rank test controlling the effects of Geographic Region, Prior TACE and Tumor Invasion Condition.

n = number of subjects; CI = confidence interval; Med = median; TACE = transarterial chemoembolization; SU = sunitinib; SO = sorafenib.

Secondary:

Kaplan-Meier curves of PFS are provided in Figure 2. For all subjects, the median PFS was longer for sunitinib than sorafenib. The median PFS was 15.3 weeks for sunitinib, with a 95% CI of (12.1, 17.7). The median PFS was 12.6 weeks for sorafenib, with a 95% CI of (12.1, 17.3). The hazard ratio was 1.1 (sunitinib vs. sorafenib), with a 95% CI of (1.0, 1.3). Sunitinib failed to demonstrate superiority over sorafenib (p=0.8857).

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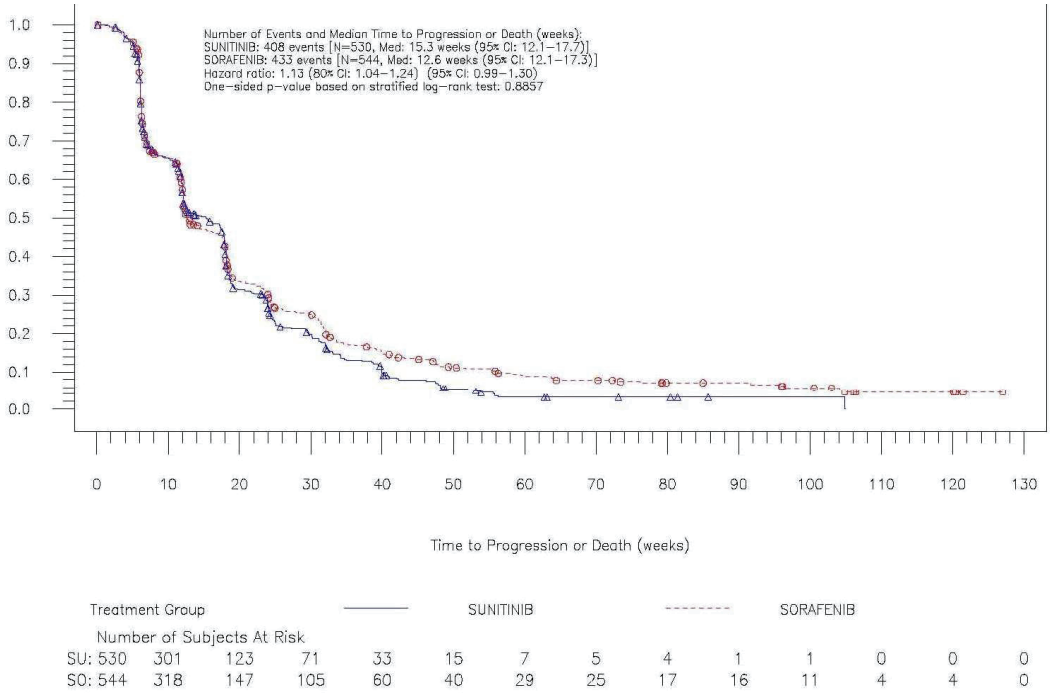
Figure 2. Kaplan-Meier Curves of Progression-Free Survival by Treatment (Full Analysis Population)



Note 1: We allowed 28 days after the date of discontinuation of treatment or the final cycle period to consider a PFS event.
Note 2: Any gap between 2 assessments of more than 12 weeks will be censored to the previous assessment.
Note 3: The p–value is from the stratified log–rank test controlling the effects of Geographic Region, Prior TACE and Tumor Invasion Condition.

n = number of subjects; CI = confidence interval; Med = median; TACE = transarterial chemoembolization; PFS = progression-free survival; SU = sunitinib; SO = sorafenib.

Kaplan-Meier curves of TTP are provided in Figure 3. The median TTP was 17.7 weeks for sunitinib, with a 95% CI of (13.6, 18.0). The median TTP was 15.4 weeks for sorafenib, with a 95% CI of (12.3, 18.1). The hazard ratio was 1.1 (sunitinib vs. sorafenib), with a 95% CI of (1.0, 1.3). Sunitinib failed to demonstrate superiority over sorafenib (p=0.8459).

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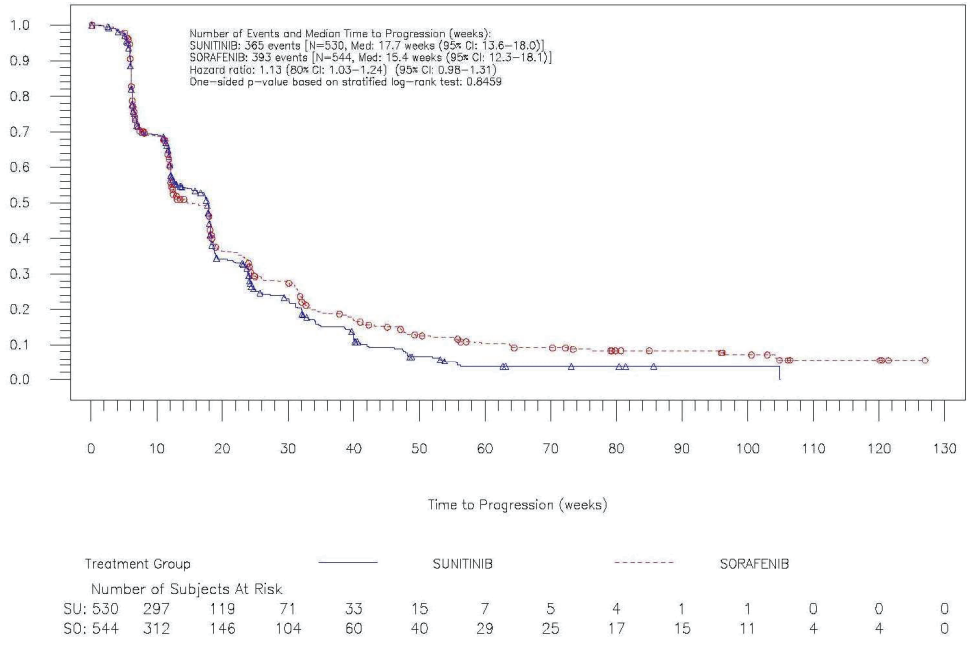
Figure 3. Kaplan-Meier Curves of Time to Tumor Progression by Treatment (Full Analysis Population)



Note 1: We allowed 28 days after the date of discontinuation of treatment or the final cycle period to consider a progression event.
Note 2: Any gap between 2 assessments of more than 12 weeks will be censored to the previous assessment.
Note 3: The p-value is from the stratified log-rank test controlling the effects of Geographic Region, Prior TACE and Tumor Invasion Condition.

n = number of subjects; CI = confidence interval; Med = median; TACE = transarterial chemoembolization; SU = sunitinib; SO = sorafenib.

Patient-reported outcomes (PROs) were not analyzed since this study was terminated prematurely.

Safety Results:

An overall summary of treatment-emergent AEs (all causalities) is provided in Table 4. Treatment-emergent non-serious AEs (all causalities) occurring in ≥5% of subjects in either treatment group are summarized in Table 5.

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Table 4 Overall Summary of Treatment-Emergent Adverse Events (All Causalities) (Per Protocol Population)

Number (%) of Subjects	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
With AEs	523 (99.4)	540 (99.6)	1063 (99.5)
With SAEs	240 (45.6)	204 (37.6)	444 (41.6)
With Grade 3 or 4 AEs	435 (82.7)	402 (74.2)	837 (78.4)
With Grade 5 AEs[a]	100 (19.0)	95 (17.5)	195 (18.3)
Discontinued due to AEs	131 (24.9)	128 (23.6)	259 (24.3)
With dose reduced due to AEs	160 (30.4)	188 (34.7)	348 (32.6)
With temporary discontinuation due to AEs	406 (77.2)	322 (59.4)	728 (68.2)

SAEs – according to the Investigator's assessment (data source was from CRF page).
Percentages based on number of subjects in the per protocol population group.
AEs and SAEs are not separated out.
AE = adverse event; CRF = case report form; N = number of subjects; SAE = serious adverse event; TEAEs = treatment emergent adverse events.

a. There were 20 subjects (8 sunitinib and 12 sorafenib) who died more than 28 days after the last dose, but had Grade 5 TEAEs in the database.

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Table 5 Treatment –Emergent Non-Serious Adverse Events Reported by ≥5% of Subjects in Any Treatment Group (All Causalities)

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Number of subjects with at least one non-serious adverse event	515 (97.9)	531 (98.0)
Blood and lymphatic systems disorders	247 (47.0)	113 (20.8)
Anaemia	79 (15.0)	47 (8.7)
Leukopenia	96 (18.3)	37 (6.8)
Neutropenia	119 (22.6)	19 (3.5)
Thrombocytopenia	170 (32.3)	69 (12.7)
Endocrine disorders	30 (5.7)	7 (1.3)
Hypothyroidism	30 (5.7)	7 (1.3)
Gastrointestinal disorders	415 (78.9)	399 (73.6)
Abdominal distension	90 (17.1)	56 (10.3)
Abdominal pain	121 (23.0)	105 (19.4)
Abdominal pain upper	74 (14.1)	78 (14.4)
Ascites	76 (14.4)	64 (11.8)
Constipation	90 (17.1)	81 (14.9)
Diarrhoea	248 (47.1)	254 (46.9)
Dyspepsia	53 (10.1)	39 (7.2)
Mouth ulceration	28 (5.3)	18 (3.3)
Nausea	129 (24.5)	93 (17.2)
Stomatitis	87 (16.5)	53 (9.8)
Vomiting	103 (19.6)	61 (11.3)
General disorders and administration site conditions	354 (67.3)	311 (57.4)
Asthenia	78 (14.8)	60 (11.1)
Chest pain	21 (3.8)	30 (5.5)
Face oedema	35 (6.7)	5 (0.9)
Fatigue	171 (32.5)	115 (21.2)
Mucosal inflammation	65 (12.4)	39 (7.2)
Oedema	46 (8.7)	23 (4.2)
Oedema peripheral	71 (13.5)	46 (8.5)
Pain	25 (4.8)	29 (5.4)
Pyrexia	105 (20.0)	101 (18.6)
Hepatobiliary disorders	59 (11.2)	43 (7.9)
Hyperbilirubinaemia	59 (11.2)	43 (7.9)
Investigations	217 (41.3)	214 (39.5)
Alanine aminotransferase increased	60 (11.4)	70 (12.9)
Aspartate aminotransferase increased	84 (16.0)	92 (17.0)
Blood bilirubin increased	30 (5.7)	30 (5.5)
Gamma-glutamyltransferase increased	17 (3.2)	28 (5.2)
Neutrophil count decreased	50 (9.5)	4 (0.7)
Platelet count	29 (5.5)	9 (1.7)
Platelet count decreased	65 (12.4)	16 (3.0)
Weight decreased	44 (8.4)	115 (21.2)
White blood cells decreased	45 (8.6)	5 (0.9)
Metabolism and nutrition disorders	256 (48.7)	211 (38.9)
Decreased appetite	233 (44.3)	187 (34.5)
Hypoalbuminaemia	47 (8.9)	42 (7.7)
Musculoskeletal and connective tissue disorders	58 (11.0)	65 (12.0)

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Table 5 Treatment –Emergent Non-Serious Adverse Events Reported by ≥5% of Subjects in Any Treatment Group (All Causalities)

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Back pain	46 (8.7)	40 (7.4)
Pain in extremity	14 (2.7)	27 (5.0)
Nervous system disorders	127 (24.1)	66 (12.2)
Dizziness	48 (9.1)	17 (3.1)
Dysgeusia	69 (13.1)	15 (2.8)
Headache	43 (8.2)	40 (7.4)
Psychiatric disorders	60 (11.4)	54 (10.0)
Insomnia	60 (11.4)	54 (10.0)
Renal and urinary disorders	44 (8.4)	38 (7.0)
Proteinuria	44 (8.4)	38 (7.0)
Respiratory, thoracic and mediastinal disorders	179 (34.0)	157 (29.0)
Cough	77 (14.6)	62 (11.4)
Dysphonia	10 (1.9)	49 (9.0)
Dyspnoea	53 (10.1)	32 (5.9)
Epistaxis	63 (12.0)	25 (4.6)
Oropharyngeal pain	30 (5.7)	19 (3.5)
Skin and subcutaneous tissue disorders	299 (56.8)	403 (74.4)
Alopecia	19 (3.6)	154 (28.4)
Palmar-plantar erythrodysaesthesia syndrome	232 (44.1)	330 (60.9)
Pruritus	34 (6.5)	58 (10.7)
Rash	108 (20.5)	147 (27.1)
Yellow skin	37 (7.0)	0
Vascular disorders	109 (20.7)	95 (17.5)
Hypertension	109 (20.7)	95 (17.5)

Subjects are only counted once per treatment for each row.
MedDRA (v14.1) coding dictionary applied.
N = Total number of subjects; MedDRA = medical dictionary for regulatory activities.

A summary of treatment-related AEs reported by ≥5% of subjects in either treatment group is provided in Table 6.

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Table 6 Treatment –Emergent, Treatment-Related Adverse Events Reported by ≥5% of Subjects in Any Treatment Group (Per Protocol Population)

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Number of subjects with at least one treatment-emergent adverse event	497 (94.5)	512 (94.5)	1009 (94.5)
Blood and lymphatic systems disorders	234 (44.5)	98 (18.1)	332 (31.1)
Anaemia	64 (12.2)	34 (6.3)	98 (9.2)
Leukopenia	94 (17.9)	37 (6.8)	131 (12.3)
Neutropenia	121 (23.0)	19 (3.5)	140 (13.1)
Thrombocytopenia	167 (31.7)	65 (12.0)	232 (21.7)
Gastrointestinal disorders	345 (65.6)	347 (64.0)	692 (64.8)
Abdominal distension	36 (6.8)	20 (3.7)	56 (5.2)
Abdominal pain	49 (9.3)	57 (10.5)	106 (9.9)
Abdominal pain upper	44 (8.4)	50 (9.2)	94 (8.8)
Constipation	38 (7.2)	45 (8.3)	83 (7.8)
Diarrhoea	220 (41.8)	244 (45.0)	464 (43.4)
Dyspepsia	37 (7.0)	33 (6.1)	70 (6.6)
Nausea	108 (20.5)	69 (12.7)	177 (16.6)
Stomatitis	85 (16.2)	51 (9.4)	136 (12.7)
Vomiting	79 (15.0)	46 (8.5)	125 (11.7)
General disorders and administration site conditions	270 (51.3)	216 (39.9)	486 (45.5)
Asthenia	58 (11.0)	51 (9.4)	109 (10.2)
Face oedema	33 (6.3)	4 (0.7)	37 (3.5)
Fatigue	153 (29.1)	101 (18.6)	254 (23.8)
Mucosal inflammation	64 (12.2)	39 (7.2)	103 (9.6)
Oedema peripheral	44 (8.4)	15 (2.8)	59 (5.5)
Pyrexia	59 (11.2)	65 (12.0)	124 (11.6)
Hepatobiliary disorders	36 (6.8)	20 (3.7)	56 (5.2)
Hyperbilirubinaemia	36 (6.8)	20 (3.7)	56 (5.2)
Investigations	145 (27.6)	129 (23.8)	274 (25.7)
Alanine aminotransferase increased	39 (7.4)	47 (8.7)	86 (8.1)
Aspartate aminotransferase increased	51 (9.7)	57 (10.5)	108 (10.1)
Neutrophil count decreased	51 (9.7)	3 (0.6)	54 (5.1)
Platelet count decreased	67 (12.7)	16 (3.0)	83 (7.8)
Weight decreased	24 (4.6)	67 (12.4)	91 (8.5)
White blood cells count decreased	46 (8.7)	5 (0.9)	51 (4.8)
Metabolism and nutrition disorders	193 (36.7)	147 (27.1)	340 (31.8)
Decreased appetite	193 (36.7)	147 (27.1)	340 (31.8)
Nervous system disorders	101 (19.2)	50 (9.2)	151 (14.1)
Dizziness	30 (5.7)	10 (1.8)	40 (3.7)
Dysgeusia	66 (12.5)	14 (2.6)	80 (7.5)
Headache	22 (4.2)	30 (5.5)	52 (4.9)
Psychiatric disorders	32 (6.1)	23 (4.2)	55 (5.1)
Insomnia	32 (6.1)	23 (4.2)	55 (5.1)
Renal and urinary disorders	41 (7.8)	34 (6.3)	75 (7.0)
Proteinuria	41 (7.8)	34 (6.3)	75 (7.0)
Respiratory, thoracic and mediastinal disorders	94 (17.9)	80 (14.8)	174 (16.3)
Cough	33 (6.3)	22 (4.1)	55 (5.1)
Dysphonia	9 (1.7)	44 (8.1)	53 (5.0)
Epistaxis	58 (11.0)	21 (3.9)	79 (7.4)

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Table 6 Treatment –Emergent, Treatment-Related Adverse Events Reported by ≥5% of Subjects in Any Treatment Group (Per Protocol Population)

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Skin and subcutaneous tissue disorders	290 (55.1)	396 (73.1)	686 (64.2)
Alopecia	19 (3.6)	151 (27.9)	170 (15.9)
Palmar-plantar erythrodysaesthesia syndrome	232 (44.1)	330 (60.9)	562 (52.6)
Pruritus	21 (4.0)	45 (8.3)	66 (6.2)
Rash	100 (19.0)	139 (25.6)	239 (22.4)
Yellow skin	35 (6.7)	0	35 (3.3)
Vascular disorders	100 (19.0)	88 (16.2)	188 (17.6)
Hypertension	100 (19.0)	88 (16.2)	188 (17.6)

Subjects are only counted once per treatment for each row
Only treatment-emergent adverse events occurring at least 5% in one of the treatment groups are presented in this table.
Percentage are based on the number of subjects in the per protocol population within each treatment group.
MedDRA (v14.0) coding dictionary applied.
AEs and SAEs are not separated out.
AE = adverse event; MedDRA = medical dictionary for regulatory activities; N = Total number of subjects; SAE = serious adverse event.

A.summary of treatment-emergent SAEs (all causalities) occurring in any treatment arm is provided in Table 7.

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Table 7 All-Causality Serious Adverse Events for the Per Protocol Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Number of subjects with at least one serious adverse event	240 (45.6)	204 (37.6)
Blood and lymphatic systems disorders	27 (5.1)	8 (1.5)
Anaemia	10 (1.9)	5 (0.9)
Disseminated intravascular coagulation	1 (0.2)	1 (0.2)
Febrile neutropenia	3 (0.6)	0
Leukopenia	1 (0.2)	0
Neutropenia	2 (0.4)	0
Splenic infarction	0	1 (0.2)
Thrombocytopenia	12 (2.3)	1 (0.2)
Cardiac disorders	5 (1.0)	7 (1.3)
Angina pectoris	0	1 (0.2)
Atrial fibrillation	0	2 (0.4)
Bradycardia	0	1 (0.2)
Cardiac arrest	1 (0.2)	0
Cardiac failure	1 (0.2)	2 (0.4)
Myocardial infarction	1 (0.2)	0
Myocardial ischaemia	0	1 (0.2)
Palpitations	1 (0.2)	0
Supraventricular tachycardia	0	1 (0.2)
Tachycardia	1 (0.2)	0
Eye disorders	1 (0.2)	1 (0.2)
Cataract	0	1 (0.2)
Diabetic retinopathy	1 (0.2)	0
Gastrointestinal disorders	82 (15.6)	54 (10.0)
Abdominal hernia	1 (0.2)	0
Abdominal pain	6 (1.1)	5 (0.9)
Abdominal pain upper	2 (0.4)	5 (0.9)
Ascites	12 (2.3)	6 (1.1)
Cheilitis	0	1 (0.2)
Constipation	1 (0.2)	1 (0.2)
Diarrhoea	10 (1.9)	9 (1.7)
Duodenal ulcer	1 (0.2)	2 (0.4)
Duodenal ulcer haemorrhage	1 (0.2)	0
Enteritis	2 (0.4)	0
Faeces discoloured	1 (0.2)	0
Gastric antral vascular ectasia	0	1 (0.2)
Gastric haemorrhage	0	1 (0.2)
Gastric ulcer	2 (0.4)	1 (0.2)
Gastric ulcer haemorrhage	1 (0.2)	1 (0.2)
Gastric varices haemorrhage	1 (0.2)	0
Gastric erosive	1 (0.2)	0
Gastritis haemorrhagic	1 (0.2)	0
Gastrointestinal haemorrhage	12 (2.3)	4 (0.7)
Gastrooesophageal reflux disease	1 (0.2)	0
Gingival bleeding	3 (0.6)	0
Glossitis	0	1 (0.2)
Haematemesis	2 (0.4)	0
Haemorrhoidal haemorrhage	1 (0.2)	0
Haemorrhoids	0	2 (0.4)
Ileus	2 (0.4)	0

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Table 7 All-Causality Serious Adverse Events for the Per Protocol Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Intestinal ischaemia	0	1 (0.2)
Melaena	1 (0.2)	2 (0.4)
Mesentric vein thrombosis	0	1 (0.2)
Nausea	4 (0.8)	2 (0.4)
Oesophageal rupture	1 (0.2)	0
Oesophageal ulcer	1 (0.2)	0
Oesophageal ulcer haemorrhage	1 (0.2)	0
Oesophageal varices haemorrhage	3 (0.6)	2 (0.4)
Pancreatic enzyme abnormality	0	1 (0.2)
Pancreatitis	0	1 (0.2)
Pancreatitis acute	2 (0.4)	1 (0.2)
Peritoneal haemorrhage	0	1 (0.2)
Rectal haemorrhage	2 (0.4)	0
Small intestine haemorrhage	1 (0.2)	0
Stomatitis	1 (0.2)	0
Upper gastrointestinal haemorrhage	11 (2.1)	7 (1.3)
Vomiting	9 (1.7)	4 (0.7)
General disorders and administration site conditions	89 (16.9)	86 (15.9)
Asthenia	10 (1.9)	3 (0.6)
Chest pain	1 (0.2)	1 (0.2)
Condition aggravated	9 (1.7)	6 (1.1)
Death	0	1 (0.2)
Device failure	1 (0.2)	0
Disease progression	55 (10.5)	62 (11.4)
Fatigue	5 (1.0)	4 (0.7)
General physical health deterioration	3 (0.6)	6 (1.1)
Generalised oedema	1 (0.2)	0
Hyperthermia	1 (0.2)	0
Malaise	2 (0.4)	0
Multi-organ failure	1 (0.2)	1 (0.2)
Oedema peripheral	1 (0.2)	0
Pain	0	1 (0.2)
Pyrexia	15 (2.9)	9 (1.7)
Hepatobiliary disorders	18 (3.4)	19 (3.5)
Acute hepatic failure	1 (0.2)	0
Bile duct obstruction	0	2 (0.4)
Bile duct stone	0	1 (0.2)
Biliary colic	1 (0.2)	0
Cholangitis	0	1 (0.2)
Cholangitis acute	1 (0.2)	0
Cholecystitis	1 (0.2)	1 (0.2)
Hepatic failure	3 (0.6)	5 (0.9)
Hepatic function abnormal	4 (0.8)	4 (0.7)
Hepatic haemorrhage	1 (0.2)	0
Hepatitis	0	1 (0.2)
Hepatorenal syndrome	0	2 (0.4)
Hepatotoxicity	1 (0.2)	0
Hyperbilirubinaemia	3 (0.6)	2 (0.4)
Hypertransaminasaemia	1 (0.2)	0
Jaundice	1 (0.2)	0

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Table 7 All-Causality Serious Adverse Events for the Per Protocol Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Jaundice cholestatic	1 (0.2)	1 (0.2)
Immune system disorders	0	2 (0.4)
Anaphylactic shock	0	1 (0.2)
Hypersensitivity	0	1 (0.2)
Infections and infestations	27 (5.1)	29 (5.4)
Abdominal infection	0	1 (0.2)
Anal abscess	1 (0.2)	0
Bacteraemia	2 (0.4)	0
Biliary sepsis	0	1 (0.2)
Bronchitis	0	1 (0.2)
Bronchopneumonia	0	1 (0.2)
Campylobacter infection	0	1 (0.2)
Cellulitis	2 (0.4)	0
Clostridium difficile colitis	0	1 (0.2)
Escherichia sepsis	1 (0.2)	0
Fungal oesophagitis	1 (0.2)	0
Gastroenteritis	2 (0.4)	0
Gastrointestinal infection	0	1 (0.2)
Hepatitis B	1 (0.2)	0
Herpes zoster	0	1 (0.2)
Herpes zoster opthalmic	0	1 (0.2)
Infected skin ulcer	0	1 (0.2)
Infection	1 (0.2)	1 (0.2)
Infectious peritonitis	1 (0.2)	0
Liver abscess	1 (0.2)	3 (0.6)
Lung infection	0	1 (0.2)
Osteomyelitis	1 (0.2)	0
Perineal abscess	0	1 (0.2)
Peritonitis bacterial	2 (0.4)	1 (0.2)
Pneumonia	4 (0.8)	5 (0.9)
Pulmonary tuberculosis	0	1 (0.2)
Rash pustular	0	1 (0.2)
Respiratory tract infection	0	1 (0.2)
Scrotal abscess	0	1 (0.2)
Sepsis	6 (1.1)	7 (1.3)
Septic shock	3 (0.6)	0
Tuberculosis	1 (0.2)	0
Upper respiratory tract infection	1 (0.2)	1 (0.2)
Urinary tract infection	2 (0.4)	1 (0.2)
Veillonella infection	0	1 (0.2)
Injury poisoning and procedural complications	4 (0.8)	6 (1.1)
Clavicle fracture	1 (0.2)	0
Concussion	0	1 (0.2)
Cystitis radiation	1 (0.2)	0
Fall	0	1 (0.2)
Femur fracture	0	1 (0.2)
Fracture	0	1 (0.2)
Ligament sprain	0	1 (0.2)
Radius fracture	1 (0.2)	0
Thoracic vertebral fracture	0	1 (0.2)
Traumatic liver injury	0	1 (0.2)

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Table 7 All-Causality Serious Adverse Events for the Per Protocol Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Ulna fracture	1 (0.2)	0
Investigations	4 (0.8)	5 (0.9)
Alanine aminotransferase increased	0	1 (0.2)
Aspartate aminotransferase increased	0	2 (0.4)
Blood bilirubin increased	0	1 (0.2)
Hepatic enzyme increased	0	1 (0.2)
Liver function test abnormal	0	2 (0.4)
Neutrophil count decreased	1 (0.2)	0
Platelet count decreased	4 (0.8)	1 (0.2)
White blood cell count decreased	1 (0.2)	0
Metabolism and nutrition disorder	24 (4.6)	12 (2.2)
Decreased appetite	8 (1.5)	4 (0.7)
Dehydration	8 (1.5)	3 (0.6)
Hyperammonaemia	1 (0.2)	0
Hyperkalaemia	1 (0.2)	1 (0.2)
Hypoalbuminaemia	1 (0.2)	1 (0.2)
Hypoglycaemia	3 (0.6)	4 (0.7)
Hyponatraemia	3 (0.6)	0
Hypophagia	1 (0.2)	0
Malnutrition	0	1 (0.2)
Musculoskeletal and connective tissue disorders	2 (0.4)	7 (1.3)
Back pain	1 (0.2)	3 (0.6)
Flank pain	0	1 (0.2)
Musculoskeletal pain	1 (0.2)	0
Pain in extremity	0	1 (0.2)
Rhabdomyolysis	0	1 (0.2)
Scoliosis	0	1 (0.2)
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)	13 (2.5)	7 (1.3)
Hepatic neoplasm malignant	2 (0.4)	1 (0.2)
Liver carcinoma ruptured	2 (0.4)	0
Malignant pleural effusion	0	1 (0.2)
Metastases to central nervous system	1 (0.2)	0
Nervous system neoplasm	0	1 (0.2)
Pharyngeal cancer stage unspecified	1 (0.2)	0
Tumour associated fever	0	1 (0.2)
Tumour haemorrhage	4 (0.8)	1 (0.2)
Tumour pain	1 (0.2)	1 (0.2)
Tumour rupture	2 (0.4)	1 (0.2)
Nervous system disorders	31 (5.9)	13 (2.4)
Altered state of consciousness	0	1 (0.2)
Cerebral artery embolism	0	1 (0.2)
Cerebral haemorrhage	2 (0.4)	2 (0.4)
Cerebral infarction	2 (0.4)	0
Coma	1 (0.2)	0
Convulsion	1 (0.2)	0
Diabetic hyperglycaemic coma	0	1 (0.2)
Dizziness	1 (0.2)	0
Encephalopathy	1 (0.2)	1 (0.2)
Headache	1 (0.2)	0

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Table 7 All-Causality Serious Adverse Events for the Per Protocol Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Hepatic encephalopathy	15 (2.9)	4 (0.7)
Hypoaesthesia	1 (0.2)	0
Hypoglycaemic coma	1 (0.2)	1 (0.2)
Hypoxic-ischaemic encephalopathy	0	1 (0.2)
Lacunar infarction	1 (0.2)	0
Loss of consciousness	1 (0.2)	0
Paralysis	0	1 (0.2)
Subarachnoid haemorrhage	1 (0.2)	0
Syncope	2 (0.4)	1 (0.2)
Psychiatric disorders	3 (0.6)	1 (0.2)
Alcohol withdrawal syndrome	1 (0.2)	0
Alcoholism	1 (0.2)	0
Confusional state	0	1 (0.2)
Suicide attempt	1 (0.2)	0
Renal and urinary disorders	12 (2.3)	3 (0.6)
Haematuria	1 (0.2)	0
Nephrolithiasis	1 (0.2)	0
Nephrotic syndrome	0	1 (0.2)
Proteinuria	1 (0.2)	0
Renal failure	4 (0.8)	1 (0.2)
Renal failure acute	2 (0.4)	1 (0.2)
Renal impairment	2 (0.4)	0
Renal tubular necrosis	0	1 (0.2)
Urinary retention	1 (0.2)	0
Reproductive system and breast disorders	1 (0.2)	0
Scrotal erythema	1 (0.2)	0
Respiratory thoracic and mediastinal disorders	22 (4.2)	18 (3.3)
Acute pulmonary oedema	1 (0.2)	0
Acute respiratory failure	0	2 (0.4)
Apnoea	0	1 (0.2)
Asphyxia	1 (0.2)	0
Aspiration	0	1 (0.2)
Bronchospasm	0	1 (0.2)
Chronic obstructive pulmonary disease	1 (0.2)	0
Dyspnoea	4 (0.8)	4 (0.7)
Epistaxis	2 (0.4)	0
Haemoptysis	3 (0.6)	1 (0.2)
Hiccups	0	1 (0.2)
Interstitial lung disease	0	1 (0.2)
Lung disorder	1 (0.2)	1 (0.2)
Pharyngeal haemorrhage	1 (0.2)	0
Pleural effusion	2 (0.4)	1 (0.2)
Pneumomediastinum	1 (0.2)	0
Pneumonia aspiration	1 (0.2)	0
Pneumothorax	2 (0.4)	1 (0.2)
Pulmonary alveolar haemorrhage	0	1 (0.2)
Pulmonary congestion	0	1 (0.2)
Pulmonary embolism	1 (0.2)	2 (0.4)
Respiratory failure	1 (0.2)	1 (0.2)
Respiratory tract haemorrhage	1 (0.2)	0
Upper respiratory tract inflammation	1 (0.2)	0

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Table 7 All-Causality Serious Adverse Events for the Per Protocol Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)
Skin and subcutaneous tissue disorders	9 (1.7)	9 (1.7)
Drug eruption	0	1 (0.2)
Hyperhidrosis	1 (0.2)	0
Neuropathic ulcer	1 (0.2)	0
Palmar-plantar erythrodysaesthesia syndrome	6 (1.1)	3
Rash	0	2 (0.4)
Skin exfoliation	1 (0.2)	0
Skin ulcer	0	2 (0.4)
Toxic skin eruption	0	1 (0.2)
Vascular disorders	8 (1.5)	3 (0.6)
Bleeding varicose vein	1 (0.2)	0
Deep vein thrombosis	1 (0.2)	0
Haemorrhage	1 (0.2)	2 (0.4)
Hypertension	1 (0.2)	0
Hypertensive crisis	1 (0.2)	0
Inferior vena caval occlusion	1 (0.2)	0
Intra-abdominal haemorrhage	1 (0.2)	0
Peripheral ischaemia	1 (0.2)	0
Phlebitis	0	1 (0.2)

Subjects are only counted once per treatment for each row
Includes data up to 9999 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied
MedDRA = medical dictionary for regulatory activities; N = Total number of subjects.

A total of 240 (45.6%) sunitinib and 204 (37.6%) sorafenib subjects had an SAE during the study. The most frequently occurring SAEs were disease progression (11.0%), pyrexia (2.3%), diarrhea and hepatic encephalopathy (1.8% each), and upper gastrointestinal hemorrhage and ascites (1.7% each). A total of 132 (25.1%) sunitinib and 86 (15.9%) sorafenib subjects had a treatment-related SAE during the study.

A summary of all-causality AEs leading to permanent discontinuation in subjects is provided in Table 8.

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Table 8. Summary of All-Causality Adverse Events Leading to Permanent Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
With at least 1 treatment-emergent AE leading to discontinuation	140 (26.6)	134 (24.7)	274 (25.7)
Being queried	1 (0.2)	2 (0.4)	3 (0.3)
Bilirubin total elevation	1 (0.2)	0	1 (0.1)
Fracture of Thoracic vertebrae N°5 with suspicion of Medullar compression	0	1 (0.2)	1 (0.1)
Liver failure due to disease progression	0	1 (0.2)	1 (0.1)
Blood and lymphatic systems disorders	4 (0.8)	4 (0.7)	8 (0.7)
Anaemia	1 (0.2)	0	1 (0.1)
Febrile neutropenia	1 (0.2)	0	1 (0.1)
Hypersplenism	1 (0.2)	0	1 (0.1)
Leukopenia	0	1 (0.2)	1 (0.1)
Splenic infarction	0	1 (0.2)	1 (0.1)
Thrombocytopenia	1 (0.2)	3 (0.6)	4 (0.4)
Cardiac disorders	2 (0.4)	3 (0.6)	5 (0.5)
Cardiac failure	1 (0.2)	2 (0.4)	3 (0.3)
Myocardial infarction	1 (0.2)	0	1 (0.1)
Palpitation	0	1 (0.2)	1 (0.1)
Eye disorders	1 (0.2)	1 (0.2)	2 (0.2)
Diabetic retinopathy	1 (0.2)	0	1 (0.1)
Retinal vein thrombosis	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders	23 (4.4)	13 (2.4)	36 (3.4)
Abdominal distension	1 (0.2)	0	1 (0.1)
Abdominal pain	1 (0.2)	0	1 (0.1)
Ascites	3 (0.6)	3 (0.6)	6 (0.6)
Diarrhoea	3 (0.6)	3 (0.6)	6 (0.6)
Gastric varices haemorrhage	1 (0.2)	0	1 (0.1)
Gastrointestinal haemorrhage	2 (0.4)	0	2 (0.2)
Gingival bleeding	2 (0.4)	1 (0.2)	3 (0.3)
Haematemesis	1 (0.2)	0	1 (0.1)
Melaena	1 (0.2)	0	1 (0.1)
Mesentric vein thrombosis	0	1 (0.2)	1 (0.1)
Mouth ulceration	1 (0.2)	0	1 (0.1)
Nausea	2 (0.4)	1 (0.2)	3 (0.3)
Oesophageal varices haemorrhage	2 (0.4)	1 (0.2)	3 (0.3)
Stomatitis	1 (0.2)	1 (0.2)	2 (0.2)
Upper gastrointestinal haemorrhage	2 (0.4)	1 (0.2)	3 (0.3)
Vomiting	0	2 (0.4)	2 (0.2)
General disorders and administration site conditions	50 (9.5)	53 (9.8)	103 (9.6)
Asthenia	4 (0.8)	2 (0.4)	6 (0.6)
Chest pain	1 (0.2)	0	1 (0.1)
Condition aggravated	11 (2.1)	6 (1.1)	17 (1.6)
Death	0	1 (0.2)	1 (0.1)
Disease progression	25 (4.8)	35 (6.5)	60 (5.6)
Fatigue	4 (0.8)	4 (0.7)	8 (0.7)
General physical health deterioration	3 (0.6)	3 (0.6)	6 (0.6)

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Table 8. Summary of All-Causality Adverse Events Leading to Permanent Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Generalised oedema	1 (0.2)	0	1 (0.1)
Multi-organ failure	1 (0.2)	1 (0.2)	2 (0.2)
Pain	0	1 (0.2)	1 (0.1)
Ulcer	0	1 (0.2)	1 (0.1)
Hepatobiliary disorder	9 (1.7)	13 (2.4)	22 (2.1)
Acute hepatic failure	1 (0.2)	0	1 (0.1)
Bile duct obstruction	0	1 (0.2)	1 (0.1)
Hepatic cirrhosis	0	1 (0.2)	1 (0.1)
Hepatic failure	1 (0.2)	3 (0.6)	4 (0.4)
Hepatic function abnormal	1 (0.2)	4 (0.7)	5 (0.5)
Hepatic haemorrhage	1 (0.2)	0	1 (0.1)
Hepatorenal syndrome	0	1 (0.2)	1 (0.1)
Hyperbilirubinaemia	4 (0.8)	2 (0.4)	6 (0.6)
Jaundice cholestatic	1 (0.2)	0	1 (0.1)
Portal vein thrombosis	0	1 (0.2)	1 (0.1)
Immune system disorders	0	1 (0.2)	1 (0.1)
Hypersensitivity	0	1 (0.2)	1 (0.1)
Infections and infestations	5 (1.0)	5 (0.9)	10 (0.9)
Gastroenteritis	1 (0.2)	0	1 (0.1)
Herpes zoster opthalmic	0	1 (0.2)	1 (0.1)
Lung infection	0	1 (0.2)	1 (0.1)
Perineal abscess	0	1 (0.2)	1 (0.1)
Pneumonia	2 (0.4)	0	2 (0.2)
Sepsis	0	1 (0.2)	1 (0.1)
Septic shock	1 (0.2)	0	1 (0.1)
Tuberculosis	1 (0.2)	1 (0.2)	2 (0.2
Injury, poisoning, and procedural complications	1 (0.2)	0	1 (0.1)
Cystitis radiation	1 (0.2)	0	1 (0.1)
Investigations	6 (1.1)	10 (1.8)	16 (1.5)
Activated partial thromboplastin time	0	1 (0.2)	1 (0.1)
Aspartate aminotransferase increased	1 (0.2)	0	1 (0.1)
Blood bilirubin	1 (0.2)	1 (0.2)	2 (0.2)
Blood bilirubin increased	0	3 (0.6)	3 (0.3)
Blood glucose decreased	1 (0.2)	0	1 (0.1)
Eastern Cooperative Oncology Group performance status worsened	0	1 (0.2)	1 (0.1)
Gamma-glutamyltransferase	1 (0.2)	0	1 (0.1)
Haemoglobin decreased	0	1 (0.2)	1 (0.1)
International normalized ratio	0	1 (0.2)	1 (0.1)
Liver function test abnormal	0	1 (0.2)	1 (0.1)
Platelet count	0	2 (0.4)	2 (0.2)
Platelet count decreased	1 (0.2)	1 (0.2)	2 (0.2)
White blood cell count decreased	1 (0.2)	0	1 (0.1)
Metabolism and nutrition disorders	4 (0.8)	2 (0.4)	6 (0.6)
Decreased appetite	1 (0.2	2 (0.4)	3 (0.3)
Dehydration	3 (0.6)	0	3 (0.3)
Musculoskeletal and connective tissue disorders	0	5 (0.9)	5 (0.5)

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Table 8. Summary of All-Causality Adverse Events Leading to Permanent Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Arthritis	0	1 (0.2)	1 (0.1)
Back pain	0	1 (0.2)	1 (0.1)
Flank pain	0	1 (0.2)	1 (0.1)
Pain in extremity	0	1 (0.2)	1 (0.1)
Rhabdomyolysis	0	1 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)	13 (2.5)	2 (0.4)	15 (1.4)
Cancer pain	1 (0.2)	0	1 (0.1)
Hepatic neoplasm malignant	4 (0.8)	1 (0.2)	5 (0.5)
Liver carcinoma ruptured	2 (0.4)	0	2 (0.2)
Metastases to central nervous system	1 (0.2)	0	1 (0.1)
Nervous system neoplasm	0	1 (0.2)	1 (0.1)
Tumour haemorrhage	3 (0.6)	0	3 (0.3)
Tumour rupture	2 (0.4)	0	2 (0.2)
Nervous system disorder	9 (1.7)	4 (0.7)	13 (1.2)
Cerebral artery embolism	0	1 (0.2)	1 (0.1)
Coma	1 (0.2)	0	1 (0.1)
Encephalopathy	1 (0.2)	0	1 (0.1)
Hepatic encephalopathy	4 (0.8)	3 (0.6)	7 (0.7)
Hypoaesthesia	1 (0.2)	0	1 (0.1)
Nervous system disorder	1 (0.2)	0	1 (0.1)
Subarachnoid haemorrhage	1 (0.2)	0	1 (0.1)
Psychiatric disorders	1 (0.2)	2 (0.4)	3 (0.3)
Anxiety	0	1 (0.2)	1 (0.1)
Confusional state	1 (0.2)	1 (0.2)	2 (0.2)
Renal and urinary disorders	2 (0.4)	4 (0.7)	6 (0.6)
Proteinuria	0	1 (0.2)	1 (0.1)
Renal failure	1 (0.2)	1 (0.2)	2 (0.2)
Renal failure acute	0	1 (0.2)	1 (0.1)
Renal impairment	1 (0.2)	0	1 (0.1)
Renal tubular necrosis	0	1 (0.2)	1 (0.1)
Respiratory thoracic and mediastinal disorders	5 (1.0)	9 (1.7)	14 (1.3)
Acute pulmonary oedema	1 (0.2)	0	1 (0.1)
Acute respiratory failure	0	1 (0.2)	1 (0.1)
Apnoea	0	1 (0.2)	1 (0.1)
Dyspnoea	1 (0.2)	2 (0.4)	3 (0.3)
Haemoptysis	1 (0.2)	0	1 (0.1)
Interstitial lung disease	0	1 (0.2)	1 (0.1)
Pleural effusion	0	1 (0.2)	1 (0.1)
Pulmonary alveolar haemorrhage	0	1 (0.2)	1 (0.1)
Pulmonary embolism	0	1 (0.2)	1 (0.1)
Respiratory failure	1 (0.2)	1 (0.2)	2 (0.2)
Respiratory tract haemorrhage	1 (0.2)	0	1 (0.1)
Skin and subcutaneous tissue disorders	4 (0.8)	7 (1.3)	11 (1.0)
Drug eruption	0	1 (0.2)	1 (0.1)
Erythema multiforms	0	1 (0.2)	1 (0.1)
Palmar-plantar erythrodysaesthesia syndrome	3 (0.6)	3 (0.6)	6 (0.6)
Rash	0	1 (0.2)	1 (0.1)

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Table 8. Summary of All-Causality Adverse Events Leading to Permanent Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Skin toxicity	1 (0.2)	0	1 (0.1)
Toxic skin eruption	0	1 (0.2)	1 (0.1)
Vascular disorders	3 (0.6)	1 (0.2)	4 (0.4)
Hypertension	0	1 (0.2)	1 (0.1)
Intra-abdominal haemorrhage	1 (0.2)	0	1 (0.1)
Peripheral ischaemia	1 (0.2)	0	1 (0.1)
Vena cava	1 (0.2)	0	1 (0.1)

Subjects are only counted once per treatment for each row.
Percentages are based on the number of subjects in the Per Protocol Population with in each treatment group.
MedDRA (v14.0) coding dictionary applied.
MedDRA = medical dictionary for regulatory activities; N = Total number of subjects.

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A summary of treatment-emergent AEs leading to temporary discontinuation in subjects is provided in Table 9.

Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Number of subjects with at least 1 treatment-emergent AE resulting in temporary discontinuation	403 (76.6)	318 (58.7)	721 (67.5)
Being queried	2 (0.4)	1 (0.2)	3 (0.3)
Digital cellulitis left hand	0	1 (0.2)	1 (0.1)
Post surgery wound pain	1 (0.2)	0	1 (0.1)
Right femoral shaft fracture (Pathological fracture), post surgery implant failure	1 (0.2)	0	1 (0.1)
Sputum expectorate difficulty	1 (0.2)	0	1 (0.1)
Blood and lymphatic systems disorders	155 (29.5)	24 (4.4)	179 (16.8)
Anaemia	27 (5.1)	8 (1.5)	35 (3.3)
Bone marrow failure	1 (0.2)	0	1 (0.1)
Coagulopathy	2 (0.4)	0	2 (0.2)
Febrile neutropenia	2 (0.4)	0	2 (0.2)
Haematotoxicity	1 (0.2)	0	1 (0.1)
Leukocytosis	0	1 (0.2)	1 (0.1)
Leukopenia	29 (5.5)	1 (0.2)	30 (20.8)
Lymphopenia	2 (0.4)	0	2 (0.2)
Microangiopathic haemolytic anaemia	1 (0.2)	0	1 (0.1)
Neutropenia	65 (12.4)	6 (1.1)	71 (6.6)
Pancytopenia	2 (0.4)	0	2 (0.2)
Thrombocytopenia	95 (18.1)	12 (2.2)	107 (10.0)
Cardiac disorders	2 (0.4)	5 (0.9)	7 (0.7)
Atrial fibrillation	0	2 (0.4)	2 (0.2)
Bradycardia	0	1 (0.2)	1 (0.1)
Cardiac failure congestive	1 (0.2)	1 (0.2)	2 (0.2)
Diastolic dysfunction	0	1 (0.2)	1 (0.1)
Myocardial ischaemia	0	1 (0.2)	1 (0.1)
Tachycardia	1 (0.2)	0	1 (0.1)
Ear and labyrinth disorders	1 (0.2)	1 (0.2)	2 (0.2)
Ear pain	0	1 (0.2)	1 (0.1)
Tinnitus	0	1 (0.2)	1 (0.1)
Vertigo	1 (0.2)	0	1 (0.1)
Eye disorders	4 (0.8)	1 (0.2)	5 (0.5)
Cataract	0	1 (0.2)	1 (0.1)
Conjuctival haemorrhage	1 (0.2)	0	1 (0.1)
Conjuctivitis	2 (0.4)	0	2 (0.2)
Periorbital oedema	1 (0.2)	0	1 (0.1)
Gastrointestinal disorders	130 (24.7)	113 (20.8)	243 (22.8)
Abdominal discomfort	1 (0.2)	0	1 (0.1)
Abdominal distension	3 (0.6)	2 (0.4)	5 (0.5)
Abdominal hernia	1 (0.2)	0	1 (0.1)
Abdominal pain	15 (2.9)	15 (2.8)	30 (2.8)
Abdominal pain upper	4 (0.8)	8 (1.5)	12 (1.1)
Anal haemorrhage	0	1 (0.2)	1 (0.1)

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Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Ascites	7 (1.3)	8 (1.5)	15 (1.4)
Cheilitis	1 (0.2)	1 (0.2)	2 (0.2)
Constipation	3 (0.6)	2 (0.4)	5 (0.5)
Diarrhoea	43 (8.2)	52 (9.6)	95 (8.9)
Dry mouth	1 (0.2)	1 (0.2)	2 (0.2)
Duodenal ulcer	1 (0.2)	0	1 (0.1)
Dyspepsia	5 (1.0)	2 (0.4)	7 (0.7)
Dysphagia	1 (0.2)	2 (0.4)	3 (0.3)
Enteritis	0	1 (0.2)	1 (0.1)
Faeces discoloured	1 (0.2)	1 (0.2)	2 (0.2)
Frequent bowl movements	1 (0.2)	0	1 (0.1)
Gastric haemorrhage	0	1 (0.2)	1 (0.1)
Gastric ulcer	3 (0.6)	2 (0.4)	5 (0.5)
Gastritis	2 (0.4)	1 (0.2)	3 (0.3)
Gastritis erosive	1 (0.2)	0	1 (0.1)
Gastrointestinal haemorrhage	10 (1.9)	3 (0.6)	13 (1.2)
Gingival bleeding	5 (1.0)	1 (0.2)	6 (0.6)
Gingival pain	0	1 (0.2)	1 (0.1)
Gingival ulceration	1 (0.2)	0	1 (0.1)
Glossitis	1 (0.2)	1 (0.2)	2 (0.2)
Haematemesis	3 (0.6)	1 (0.2)	4 (0.4)
Haemtochezia	1 (0.2)	1 (0.2)	2 (0.2)
Haemorrhoidal haemorrhage	2 (0.4)	1 (0.2)	3 (0.3)
Haemorrhoids	1 (0.2)	2 (0.4)	3 (0.3)
Hyperchlorhydria	1 (0.2)	0	1 (0.1)
Ileus	1 (0.2)	0	1 (0.1)
Inguinal hernia	1 (0.2)	0	1 (0.1)
Intestinal ischaemia	0	1 (0.2)	1 (0.1)
Melaena	3 (0.6)	1 (0.2)	4 (0.4)
Mouth ulceration	1 (0.2)	0	1 (0.1)
Nausea	12 (2.3)	6 (1.1)	18 (1.7)
Oesophageal discomfort	1 (0.2)	0	1 (0.1)
Oesophageal rupture	1 (0.2)	0	1 (0.1)
Oesophageal ulcer	1 (0.2)	0	1 (0.1)
Oesophageal ulcer haemorrhage	1 (0.2)	0	1 (0.1)
Oesophageal varices haemorrhage	2 (0.4)	1 (0.2)	3 (0.3)
Oral pain	1 (0.2)	0	1 (0.1)
Pancreatic enzyme abnormality	0	1 (0.2)	1 (0.1)
Pancreatitis	0	1 (0.2)	1 (0.1)
Pancreatitis acute	2 (0.4)	1 (0.2)	3 (0.3)
Periodontitis	4 (0.8)	0	4 (0.4)
Peritonitis	1 (0.2)	0	1 (0.1)
Proctalgia	0	1 (0.2)	1 (0.1)
Rectal haemorrhage	2 (0.4)	0	2 (0.2)
Reflux oesophagitis	1 (0.2)	0	1 (0.1)
Small intestinal haemorrhage	2 (0.4)	0	2 (0.2)
Stomatitis	18 (3.4)	3 (0.6)	21 (2.2)
Toothache	3 (0.6)	0	3 (0.3)
Upper gastrointestinal haemorrhage	6 (1.1)	5 (0.9)	11 (1.0)

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Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Vomiting	16 (3.0)	11 (2.0)	27 (2.5)
General disorders and administration site conditions	92 (17.5)	53 (9.8)	145 (13.6)
Asthenia	20 (3.8)	9 (1.7)	29 (2.7)
Chest pain	3 (0.6)	1 (0.2)	4 (0.4)
Chills	1 (0.2)	1 (0.2)	2 (0.2)
Condition aggravated	3 (0.6)	3 (0.6)	6 (0.6)
Device failure	1 (0.2)	0	1 (0.1)
Face oedema	3 (0.6)	0	3 (0.3)
Fatigue	25 (4.8)	11 (2.0)	36 (3.4)
Gait disturbance	1 (0.2)	0	1 (0.1)
General physical health deterioration	3 (0.6)	4 (0.7)	7 (0.7)
Influenza like illness	1 (0.2)	0	1 (0.1)
Malasie	2 (0.4)	4 (0.7)	6 (0.6)
Mucosal inflammation	8 (1.5)	7 (1.3)	15 (1.4)
Oedema	1 (0.2)	0	1 (0.1)
Oedema peripheral	6 (1.1)	5 (0.9)	11 (1.0)
Pain	7 (1.3)	2 (0.4)	9 (0.8)
Pyrexia	19 (13.6)	13 (2.4)	32 (3.0)
Hepatobiliary disorders	32 (6.1)	24 (4.4)	56 (5.2)
Bile duct obstruction	0	2 (0.4)	2 (0.2)
Biliary colic	1 (0.2)	0	1 (0.1)
Cholangitis	0	1 (0.2)	1 (0.1)
Cholangitis acute	1 (0.2)	0	1 (0.1)
Cholecystitis	1 (0.2)	0	1 (0.1)
Cholelithiasis	1 (0.2)	0	1 (0.1)
Hepatic failure	1 (0.2)	1 (0.2)	2 (0.2)
Hepatic function abnormal	6 (1.1)	6 (1.1)	12 (1.1)
Hepatic pain	1 (0.2)	0	1 (0.1)
Hepatic vein thrombosis	1 (0.2)	0	1 (0.1)
Hepatitis	0	2 (0.4)	2 (0.2)
Hepatitis acute	1 (0.2)	0	1 (0.1)
Hepatorenal syndrome	0	1 (0.2)	1 (0.1)
Hepatotoxicity	0	2 (0.4)	2 (0.2)
Hyperbilirubinaemia	18 (3.4)	9 (1.7)	27 (2.5)
Jaundice	3 (0.6)	4 (0.7)	7 (0.7)
Jaundice cholestatic	0	1 (0.2)	1 (0.1)
Immune system disorders	1 (0.2)	3 (0.6)	4 (0.4)
Anaphylactic shock	0	1 (0.2)	1 (0.1)
Hypersensitivity	1 (0.2)	2 (0.4	3 (0.3)
Infections and infestations	29 (5.5)	23 (4.2)	52 (4.9)
Abscess	0	1 (0.2)	1 (0.1)
Acute tonsillitis	0	1 (0.2)	1 (0.1)
Anal abscess	1 (0.2)	0	1 (0.1)
Bacteraemia	1 (0.2)	0	1 (0.1)
Biliary sepsis	0	1 (0.2)	1 (0.1)
Bronchitis	0	1 (0.2)	1 (0.1)
Bronchopneumonia	0	1 (0.2)	1 (0.1)
Cellulitis	1 (0.2)	0	1 (0.1)

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Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Folliculitis	0	1 (0.2)	1 (0.1)
Fungal oesophagitis	1 (0.2)	0	1 (0.1)
Gastroenteritis	1 (0.2)	0	1 (0.1)
Gastroenteritis viral	1 (0.2)	0	1 (0.1)
Gingival infection	1 (0.2)	0	1 (0.1)
HIV infection	0	1 (0.2)	1 (0.1)
Hand foot and mouth disease	0	1 (0.2)	1 (0.1)
Hepatitis viral	2 (0.4)	0	2 (0.2)
Herpes zoster	1 (0.2)	0	1 (0.1)
Infected skin ulcer	0	1 (0.2)	1 (0.1)
Infection	3 (0.6)	0	3 (0.3)
Influenza	1 (0.2)	0	1 (0.1)
Liver abscess	2 (0.4)	3 (0.6)	5 (0.5)
Localised infection	1 (0.2)	0	1 (0.1)
Lower respiratory tract infection	0	1 (0.2)	1 (0.1)
Lung infection	1 (0.2)	0	1 (0.1)
Oral candidiasis	0	1 (0.2)	1 (0.1)
Peritonitis bacterial	3 (0.6)	0	3 (0.3)
Pharyngitis	1 (0.2)	2 (0.4)	3 (0.3)
Pneumonia	2 (0.4)	2 (0.4)	4 (0.4)
Rash pustular	0	1 (0.2)	1 (0.1)
Sepsis	2 (0.4)	2 (0.4)	4 (0.4)
Staphylococcal infection	1 (0.2)	0	1 (0.1)
Tooth abscess	2 (0.4)	0	2 (0.2)
Upper respiratory tract infection	2 (0.4)	4 (0.7)	6 (0.6)
Urinary tract infection	1 (0.2)	1 (0.2)	2 (0.2)
Wound infection	1 (0.2)	0	1 (0.1)
Injury, poisoning, and procedural complications	5 (1.0)	2 (0.4)	7 (0.7)
Contusion	2 (0.4)	0	2 (0.2)
Procedural pain	0	1 (0.2)	1 (0.1)
Radius fracture	1 (0.2)	0	1 (0.1)
Rib fracture	0	1 (0.2)	1 (0.1)
Traumatic liver injury	0	1 (0.2)	1 (0.1)
Ulna fracture	1 (0.2)	0	1 (0.1)
Wound complication	1 (0.2)	0	1 (0.1)
Investigations	118 (22.4)	58 (10.7)	176 (16.5)
Alanine aminotransferase	3 (0.6)	3 (0.6)	6 (0.6)
Alanine aminotransferase increased	14 (2.7)	14 (2.6)	28 (2.6)
Ammonia increased	2 (0.4)	0	2 (0.2)
Aspartate aminotransferase	3 (0.6)	4 (0.7)	7 (0.7)
Aspartate aminotransferase decreased	1 (0.2)	0	1 (0.1)
Aspartate aminotransferase increased	31 (5.9)	25 (4.6)	56 (5.2)
Bilirubin conjugated increased	1 (0.2)	0	1 (0.1)
Blood albumin decreased	0	1 (0.2)	1 (0.1)
Blood alkaline phosphatase	0	2 (0.4)	2 (0.2)
Blood alkaline phosphatase increased	1 (0.2)	2 (0.4)	3 (0.3)
Blood amylase increased	1 (0.2)	0	1 (0.1)
Blood bilirubin	1 (0.2)	2 (0.4)	3 (0.3)

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Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Blood bilirubin increased	10 (1.9)	7 (1.3)	17 (1.6)
Blood creatine	1 (0.2)	0	1 (0.1)
Blood creatinine	1 (0.2)	1 (0.2)	2 (0.2)
Blood creatinine increased	1 (0.2)	1 (0.2)	2 (0.2)
Blood potassium increased	1 (0.2)	0	1 (0.1)
Blood sodium decreased	1 (0.2)	0	1 (0.1)
Blood thyroid stimulating hormone increased	1 (0.2)	0	1 (0.1)
Electrocardiogram QT prolonged	0	1 (0.2)	1 (0.1)
Gamma-glutamyltransferase	2 (0.4)	0	2 (0.2)
Gamma-glutamyltransferase increased	6 (1.1)	3 (0.6)	9 (0.8)
Haemoglobin	1 (0.2)	0	1 (0.1)
Haemoglobin decreased	4 (0.8)	1 (0.2)	5 (0.5)
Hepatic enzyme increased	0	1 (0.2)	1 (0.1)
International normalised ratio	1 (0.2)	1 (0.2)	2 (0.2)
Liver function test abnormal	0	1 (0.2)	1 (0.1)
Lymphocyte count decreased	1 (0.2)	0	1 (0.1)
Neutrophil count	14 (2.7)	1 (0.2)	15 (1.4)
Neutrophil count decreased	25 (4.8)	0	25 (2.3)
Occult blood positive	1 (0.2)	0	1 (0.1)
Platelet count	19 (3.6)	1 (0.2)	20 (1.9)
Platelet count decreased	37 (7.0)	3 (0.6)	40 (30.7)
Prothrombin time prolonged	1 (0.2)	1 (0.2)	2 (0.2)
Tri-idothyronine decreased	1 (0.2)	0	1 (0.1)
Waist circumference increased	0	1 (0.2)	1 (0.1)
Weight decreased	1 (0.2)	2 (0.4)	3 (0.3)
White blood cell count	11 (2.1)	0	11 (1.0)
White blood cell count decreased	9 (1.7)	0	9 (0.8)
Metabolism and nutrition disorders	41 (7.8)	31 (5.7)	72 (6.7)
Decreased appetite	26 (4.9)	15 (2.8)	41 (3.8)
Dehydration	5 (1.0)	2 (0.4)	7 (0.7)
Gout	0	1 (0.2)	1 (0.1)
Hyperammonaemia	1 (0.2)	1 (0.2)	2 (0.2)
Hyperamylasaemia	0	1 (0.2)	1 (0.1)
Hyperkalaemia	2 (0.4)	1 (0.2)	3 (0.3)
Hyperuricaemia	1 (0.2)	0	1 (0.1)
Hypoalbuminaemia	6 (1.1)	1 (0.2)	7 (0.7)
Hypocalcaemia	1 (0.2)	0	1 (0.1)
Hypoglycaemia	0	2 (0.4)	2 (0.2)
Hypokalaemia	3 (0.6)	4 (0.7)	7 (0.7)
Hypomagnesaemia	0	1 (0.2)	1 (0.1)
Hyponatraemia	6 (1.1)	1 (0.2)	7 (0.7)
Hypophagia	2 (0.4)	0	2 (0.2)
Hypophosphataemia	0	2 (0.4)	2 (0.2)
Tumour lysis syndrome	0	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	9 (1.7)	10 (1.8)	19 (1.8)
Arthralgia	0	2 (0.4)	2 (0.2)
Back pain	2 (0.4)	2 (0.4)	4 (0.4)

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Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Bone pain	0	1 (0.2)	1 (0.1)
Flank pain	0	2 (0.4)	2 (0.2)
Musculoskeletal chest pain	1 (0.2)	0	1 (0.1)
Musculoskeletal pain	1 (0.2)	0	1 (0.1)
Myalgia	3 (0.6)	0	3 (0.3)
Osteoarthritis	1 (0.2)	1 (0.2)	2 (0.2)
Pain in extremity	1 (0.2)	1 (0.2)	2 (0.2)
Scoliosis	0	1 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)	4 (0.8)	2 (0.4)	6 (0.6)
Liver carcinoma ruptured	2 (0.4)	0	2 (0.2)
Tumour haemorrhage	1 (0.2)	1 (0.2)	2 (0.2)
Tumour pain	1 (0.2)	0	1 (0.1)
Tumour rupture	0	1 (0.2)	1 (0.1)
Nervous system disorders	30 (5.7)	17 (3.1)	47 (4.4)
Altered state of consciousness	0	1 (0.2)	1 (0.1)
Amnesia	0	1 (0.2)	1 (0.1)
Cerebral ischaemia	1 (0.2)	0	1 (0.1)
Convulsion	1 (0.2)	1 (0.2)	2 (0.2)
Depressed level of consciousness	0	1 (0.2)	1 (0.1)
Dizziness	6 (1.1)	1 (0.2)	7 (0.7)
Dysgeusia	1 (0.2)	0	1 (0.1)
Encephalopathy	1 (0.2)	1 (0.2)	2 (0.2)
Headache	6 (1.1)	3 (0.6)	9 (0.8)
Hepatic encephalopathy	8 (1.5)	4 (0.7)	12 (1.1)
Hypoglycaemic coma	1 (0.2)	0	1 (0.1)
Lacunar infarction	1 (0.2)	0	1 (0.1)
Lethargy	5 (1.0)	2 (0.4)	7 (0.7)
Memory impairment	0	1 (0.2)	1 (0.1)
Peripheral sensory neuropathy	1 (0.2)	0	1 (0.1)
Sciatica	0	1 (0.2)	1 (0.1)
Somnolence	0	1 (0.2)	1 (0.1)
Syncope	1 (0.2)	0	1 (0.1)
Psychiatric disorders	7 (1.3)	2 (0.4)	9 (0.8)
Confusional state	3 (0.6)	0	3 (0.3)
Delirium	1 (0.2)	0	1 (0.1)
Depressed mood	1 (0.2)	0	1 (0.1)
Insomnia	0	2 (0.4)	2 (0.2)
Listless	1 (0.2)	0	1 (0.1)
Suicide attempt	1 (0.2)	0	1 (0.1)
Renal and Urinary disorders	17 (3.2)	10 (1.8)	27 (2.5)
Dysuria	0	1 (0.2)	1 (0.1)
Haematuria	3 (0.6)	0	3 (0.3)
Haemorrhage urinary tract	1 (0.2)	1 (0.2)	2 (0.2)
Micturition urgency	1 (0.2)	0	1 (0.1)
Nephrolithiasis	1 (0.2)	0	1 (0.1)
Pollakiuria	1 (0.2)	0	1 (0.1)
Proteinuria	7 (1.3)	7 (1.3)	14 (1.3)
Renal failure	1 (0.2)	1 (0.2)	2 (0.2)

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Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Renal failure acute	1 (0.2)	0	1 (0.1)
Renal impairment	2 (0.4)	0	2 (0.2)
Urinary retention	2 (0.4)	0	2 (0.2)
Reproductive system and breast disorders	4 (0.8)	5 (0.9)	9 (0.8)
Balanoposthitis	0	1 (0.2)	1 (0.1)
Genital rash	0	1 (0.2)	1 (0.1)
Menorrhagia	1 (0.2)	0	1 (0.1)
Scrotal erythema	1 (0.2)	2 (0.4)	3 (0.3)
Scrotal haematocoele	1 (0.2)	0	1 (0.1)
Scrotal swelling	0	1 (0.2)	1 (0.1)
Scrotal ulcer	1 (0.2)	0	1 (0.1)
Respiratory thoracic and mediastinal disorders	31 (5.9)	16 (3.0)	47 (4.4)
Asthma	1 (0.2)	0	1 (0.1)
Bronchial haemorrhage	0	1 (0.2)	1 (0.1)
Bronchospasm	1 (0.2)	1 (0.2)	2 (0.2)
Chronic obstructive pulmonary disease	1 (0.2)	0	1 (0.1)
Cough	2 (0.4)	1 (0.2)	3 (0.3)
Dysphonia	0	2 (0.4)	2 (0.2)
Dyspnoea	4 (0.8)	4 (0.7)	8 (0.7)
Epistaxis	3 (0.6)	2 (0.4)	5 (0.5)
Haemoptysis	6 (1.1)	2 (0.4)	8 (0.7)
Laryngeal haemorrhage	1 (0.2)	0	1 (0.1)
Lung disorder	1 (0.2)	0	1 (0.1)
Nasal inflammation	1 (0.2)	0	1 (0.1)
Oropharyngeal discomfort	1 (0.2)	0	1 (0.1)
Oropharyngeal pain	4 (0.8)	0	4 (0.4)
Pharyngeal erythema	0	1 (0.2)	1 (0.1)
Pharyngeal ulceration	1 (0.2)	0	1 (0.1)
Pleural effusion	2 (0.4)	3 (0.6)	5 (0.5)
Pneumomediastinum	1 (0.2)	0	1 (0.1)
Pneumonia aspiration	1 (0.2)	0	1 (0.1)
Pneumothorax	1 (0.2)	0	1 (0.1)
Pulmonary congestion	0	1 (0.2)	1 (0.1)
Pulmonary embolism	0	2 (0.4)	2 (0.2)
Respiratory tract haemorrhage	0	1 (0.2)	1 (0.1)
Upper respiratory tract inflammation	1 (0.2)	0	1 (0.1)
Skin and subcutaneous tissue disorders	90 (17.1)	135 (24.9)	225 (21.1)
Acne	1 (0.2)	0	1 (0.1)
Alopecia	1 (0.2)	0	1 (0.1)
Dermatitis	1 (0.2)	0	1 (0.1)
Dermatitis acneiform	0	2 (0.4)	2 (0.2)
Dermatitis allergic	1 (0.2)	0	1 (0.1)
Drug eruption	0	6 (1.1)	6 (0.6)
Erythema	2 (0.4)	0	2 (0.2)
Haemorrhage subcutaneous	1 (0.2)	0	1 (0.1)
Hyperhidrosis	1 (0.2)	0	1 (0.1)
Hyperkeratosis palmaris and plantaris	0	1 (0.2)	1 (0.1)
Increased tendency to bruise	1 (0.2)	0	1 (0.1)
Livedo reticularis	1 (0.2)	0	1 (0.1)

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Table 9. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation (Per Protocol Population)

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Neuropathic ulcer	1 (0.2)	0	1 (0.1)
Palmar-plantar erythrodysaesthesia syndrome	73 (13.9)	114 (21.0)	187 (17.5)
Petechiae	4 (0.8)	0	4 (0.4)
Pruritus	0	1 (0.2)	1 (0.1)
Rash	6 (1.1)	24 (4.4)	30 (2.8)
Rash generalised	0	2 (0.4)	2 (0.2)
Skin exfoliation	1 (0.2)	1 (0.2)	2 (0.2)
Skin lesion	1 (0.2)	0	1 (0.1)
Skin reaction	0	1 (0.2)	1 (0.1)
Skin ulcer	4 (0.8)	5 (0.9)	9 (0.8)
Surgical and medical procedure	0	1 (0.2)	1 (0.1)
Tooth extraction	0	1 (0.2)	1 (0.1)
Vascular disorders	23 (4.4)	7 (1.3)	30 (2.8)
Diabetic vascular disorder	1 (0.2)	0	1 (0.1)
Haemorrhage	2 (0.4)	1 (0.2)	3 (0.3)
Hypertension	19 (3.6)	7 (1.3)	26 (2.4)
Hypotension	1 (0.2)	0	1 (0.1)

Subjects are only counted once per treatment for each row.
Percentages are based on the number of subjects in the Per Protocol Population with in each treatment group.
MedDRA (v14.0) coding dictionary applied.
MedDRA = medical dictionary for regulatory activities; N = Total number of subjects.

A summary of on-study deaths is provided in Table 10.

A total of 176 (16.5%) subjects died due to any cause during the study and within 28 days after the last dose of study medication. The number of on-study deaths was 93 (17.7%) for sunitinib and 83 (15.3%) for sorafenib.

The most common cause of death was disease under study (141 [80.1%] subjects; 70 [75.3%] sunitinib subjects and 71 [85.5%] sorafenib subjects). The percentage of deaths due to study treatment toxicity was higher for sunitinib (18.3%) than sorafenib (2.4%) subjects. There was a higher percentage of deaths due to unknown or other causes for sorafenib (12.0%) than sunitinib (7.6%) subjects.

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Table 10. Summary of Deaths on Study (Per Protocol Population)

Number (%) of Subjects	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Died			
Death from all cause	93 (17.7)	83 (15.3)	176 (16.5)
Cause of death			
Disease under study	70 (75.3)	71 (85.5)	141 (80.1)
Study treatment toxicity	17 (18.3)	2 (2.4)	19 (10.8)
Unknown	1 (1.1)	2 (2.4)	3 (1.7)
Other	6 (6.5)	8 (9.6)	14 (8.0)[a]

Deaths that occurred within 28 days after the last dose of study medication are defined as on-study deaths.
Data source is CRF page.
Subjects who died may have more than 1 cause of death recorded on the CRF. One sunitinib subject had disease under study and study treatment toxicity (dehydration) for cause of death.
Percentages based on the total number of subjects in the per protocol population within each treatment group, except for cause of death, where it was based on the number of deaths.
N=number of subjects; CRF=Case Report Form; GI = gastrointestinal.

a. Other causes of death were listed as 2 pneumonia, 2 sepsis, asphyxia, hepatic encephalopathy, septic shock, cardiac attack, lung infection, heart failure, aspiration, diabetes mellitus, hepatorenal syndrome, and upper GI bleeding.

A summary of deaths during follow-up is provided in Table 11. A total of 640 (59.9%) subjects died due to any cause during follow-up: 337 (64.1%) subjects for sunitinib and 303 (55.9%) subjects for sorafenib.

The most common cause of death was disease under study (597 [93.3%] subjects; 317 [94.1%] sunitinib subjects and 280 [92.4%] sorafenib subjects).

Table 11. Summary of Deaths During Follow-up (Per Protocol Population)

Number (%) of Subjects	Sunitinib (N=526)	Sorafenib (N=542)	Total (N=1068)
Died			
Death from all cause	337 (64.1)	303 (55.9)	640 (59.9)
Cause of death			
Disease under study	317 (94.1)	280 (92.4)	597 (93.3)
Study treatment toxicity	0	2 (<1.0)	2 (<1.0)
Unknown	9 (2.7)	15 (5.0)	24 (3.8)
Other	11 (3.3)	6 (2.0)	17 (2.7)
Lost to follow-up	9 (1.7)	20 (3.7)	29 (2.7)

Deaths that occurred after 28 days after the last dose of study medication are defined as follow-up deaths.
Data source is CRF page.
Subjects who died may have more than 1 cause of death recorded on the CRF.
Percentages are based on the total number of subjects in the Per Protocol Population within each treatment group except for 'Cause of Death' where it's on the number of deaths.
N = number of subjects; CRF = Case Report Form.

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CONCLUSIONS:

- Sunitinib did not demonstrate superiority in OS compared with sorafenib in subjects with advanced HCC. The study did not achieve non-inferiority after failing to show superiority.

- PFS and TTP were longer for the sunitinib group compared to the sorafenib group.

- The frequency of AEs was higher and severity of AEs was greater with sunitinib than sorafenib.

- There were more Grade ≥3 AEs that were considered at least possibly study drug related in the sunitinib arm than in the sorafenib arm.

- The types, frequencies, and seriousness of reported events were similar to the known safety profile of sunitinib.

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