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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Inlyta® / Axitinib

PROTOCOL NO.: A4061022

PROTOCOL TITLE: A Phase 1 Study of AG-013736 in Patients in Japan With Advanced Solid Tumors

Study Center: The study was performed at 1 center in Japan.

Study Initiation and Final Completion Dates: 06 February 2007 to 27 August 2009

Phase of Development: Phase 1

Study Objectives:

Primary Objective:

- To evaluate the clinically recommended dose of axitinib (AG-013736) in Japanese subjects by reviewing the safety of axitinib following single and multiple twice a day (BID) dosing.

Secondary Objectives:

- To evaluate the plasma pharmacokinetics (PK) of axitinib in Japanese subjects following single and multiple dosing.
- To investigate the changes of the plasma concentration profiles of the pharmacodynamics indices soluble vascular endothelial growth factor receptor (s-VEGFR) 2, s-VEGFR3, soluble stem cell factor receptor (s-KIT), and vascular endothelial growth factor (VEGF).
- To investigate the anti-tumor activity of axitinib.
- To investigate the effect on the PK of axitinib by uridine diphosphate-glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) and cytochrome P450 (CYP) 3A4 and 5 genotyping. Genes suspected to affect the PK of axitinib were also evaluated.

METHODS

Study Design: This was an open-label, non-randomized study in subjects with advanced solid tumors to evaluate the safety, PK, pharmacodynamics and anti-tumor activity of

axitinib, and genomic effects on axitinib metabolism. This study consisted of single dosing followed by multiple dosing cycles. A cycle length was 28 days and the study treatment could be continued until the subject experienced intolerable toxicity or progressive disease (PD).

Six subjects were initially enrolled and each of them received a single dose of 5 mg axitinib. After monitoring the safety of a single 5 mg dose for at least 48 hours, 5 mg BID multiple dosing was initiated. This study was to be expanded to add 6 new subjects to receive multiple dosing in Cycle 1 depending on the number of subjects experiencing dose limiting toxicities (DLTs) among the first 6 subjects. If no more than 1 of the 6 subjects experienced DLT following a single 5 mg dose and 5 mg BID multiple dosing in Cycle 1, then the study was to be expanded to include 6 additional subjects and multiple dosing was to be initiated (from Cycle 1 onwards); if 2 out of 6 subjects experienced DLT, an independent safety data monitoring committee (DMC) meeting was to be held. The DMC was to suggest the necessity of adding additional subjects to evaluate the safety of 5 mg BID multiple dosing; if 3 or more of 6 subjects experienced DLT, the maximum tolerated dose (MTD) was to be assumed to have been exceeded, and the study would not be expanded. The schedule of activities is presented in Table 1 (Cycle 1) and Table 2 (Cycle 2 onwards).

For the single dosing PK assessment, approximately 5 mL blood samples were to be collected from the first 6 subjects before dosing and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 32 hours after axitinib dosing.

For the multiple dosing PK assessment, approximately 5 mL blood samples were to be collected from all subjects at the following times:

- Cycle 1: Predose on the morning of Days 1 and 15, and 0.5, 1, 2, 4, 8 and 12 hours postdose (before the next dose).
- Cycle 2: Prior to dosing on the morning of Day 1 (immediately before the morning dose taken at the clinic).
- When the dose was increased or decreased in Cycle 2 onwards: 4-hour serial PK samples were to be collected at the visit which was performed 5 or more days after dose increase/decrease (the day prior to next dose increase/decrease). Samples were to be collected immediately before the morning dose and 1, 2, 3, and 4 hours postdose.

Table 1. Schedule of Tests and Procedures (Up to Cycle 1*)

Observation	Screening		Up to Cycle 1					
	Within 14 Days Predose	Within 4 Days Predose	Single Dosing † (Days ± Acceptable Range)		Cycle 1 (Days ± Acceptable Range)			
			Day 1 Predose	Day 2 At Least 24 Hours Postdose	Day 1 Predose	Day 8	Day 15	Day 22
			-4 Days	-	-4 Days ‡	±4 Days	±4 Days	±4 Days
Informed consent	X							
Subject background[a]	X							
Weight[b], body temperature, pulse rate	X		X	X	X	X	X	X
Blood pressure[c]	X		X[d]		X[e]	X	X[e]	X
Home blood pressure monitoring[f]					X (except the period of hospitalization)			
ECOG performance status	X		X	X	X	X	X	X
Hematology[g]	X		X[h]	X	X[h]	X	X	X
Coagulation test[i]	X		X[h]	X	X[h]	X	X	X
Blood chemistry[j]	X		X[h]	X	X[h]	X	X	X
Urinalysis[k]	X[l]		X[h]	X	X[h]	X		X
12-lead ECG[m]	X						X[n]	
Blood samples for UGT1A1 and CYP3A4/5 test			X		X[o]			
Blood samples for PK			X[p]		X[q]		X[q]	
Blood samples for pharmacodynamic markers[r]			X		X[s]			
Pregnancy test		X						
Tumor measurements[t]	X							
Drug compliance			X		←	→		
Concomitant medications/therapies	←	→						
AEs			←	→				
SAEs	←	→						

* Follow-up observations were to be made to confirm dose limiting toxicity (DLT) up through Cycle 2, as necessary, depending on the timing of onset of DLT.
† Tests and procedures for single dosing were not necessary for subjects who started from multiple dosing.
‡ For subjects who started from single dosing and had the tests and procedures on single dosing Day 2 within 4 days before Cycle 1 Day 1, the tests and procedures on Cycle 1

Table 1. Schedule of Tests and Procedures (Up to Cycle 1*)

Day 1 were not required.
AEs = adverse events; APTT = activated partial thromboplastin times; CYP = cytochrome P450; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetics; PT = prothrombin time; SAEs = serious adverse events; s-KIT = stem cell factor receptor; s-VEGFR = soluble vascular endothelial growth factor receptor; VEGF = vascular endothelial growth factor; UGT = uridine glucuronyl transferase.

a. Subject background included the status of smoking.
b. Weight was measured on Day 1 of single dosing and Day 1 of each Cycle.
c. Blood pressure was to be measured twice, separated by at least 1 hour, at subject visit (including Screening visit). Blood pressure was to be measured at least twice daily during hospitalization that included measurements before each axitinib dosing. Blood pressure measurements were to be made with the subject in the sitting position after the subject being seated quietly for 5 minutes.
d. Blood pressure was to be measured at pre dosing, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdosing.
e. Blood pressure was to be measured at pre dosing, 1, 2, 4, 6, 8, 10, and 12 hours postdosing.
f. Subjects were to be issued blood pressure cuffs (provided by the Sponsor) for home monitoring. Blood pressure measurements were to be made at least twice daily prior to each axitinib dosing on an outpatient basis and recorded in a subject diary. Subjects were to be instructed by the study staff to hold doses temporarily and contact their Physician immediately for guidance if their systolic blood pressure was elevated above 150 mm Hg, or diastolic blood pressure was elevated above 100 mm Hg, or if they developed symptoms perceived to be related to elevated blood pressure (eg, headache, visual disturbance). If subjects were unable to contact their Physician for guidance, subject were to restart dosing when systolic blood pressure fell below 140 mm Hg and diastolic blood pressure fell below 90 mm Hg, and all symptoms related to elevated blood pressure were resolved.
g. Red blood cell count, hemoglobin, hematocrit, white blood cell count and its differential, and platelet count were measured.
h. If the predose tests at the screening were conducted within 4 days before single dosing (or before multiple dosing for subjects who started from multiple dosing), the test on Day 1 in the single dosing step (or the test on Cycle 1 Day 1 for subjects who started from multiple dosing) were not necessary.
i. The PT and APTT were to be measured.
j. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total protein, albumin, sodium, potassium, chloride, total bilirubin, blood urea nitrogen (BUN), creatinine, glucose, amylase/lipase, and thyroid stimulating hormone (TSH) were measured.
k. pH, urinary protein, urine sugar, urine occult blood (qualitative for all), and urinary sediment (only at Screening) were measured. If urinalysis (semiquantitative testing, eg, dipstick) revealed urinary protein ≥1+, a 24-hour urine collection was to be performed.
l. If urinalysis (semiquantitative testing, eg, dipstick) revealed urinary protein ≥1+, a 24-hour urine collection was to be performed; subjects with total protein < 500 mg/24 hours, the subject could be enrolled.
m. Additional ECG was to be performed if required on the basis of clinical symptoms.
n. ECG was to be performed 1-3 hours after dosing.
o. Blood samples were to be collected on Cycle 1 Day 1 for subjects who started with multiple dosing.
p. Blood samples were to be collected at predose, and 0.5, 1, 2, 4, 6, 8, 12, 24, and 32 hours postdose.
q. Blood samples were to be collected at predose, and 0.5, 1, 2, 4, 8, and 12 hours postdose.
r. Plasma concentrations of s-VEGFR 2, s-VEGFR3, soluble s-KIT, and VEGF were to be measured.
s. Blood samples were to be collected Cycle 1 Day 1 for subjects who started with multiple dosing.
t. Any results of evaluation which were performed within 28 days before treatment initiation could be used.

Table 2. Schedule of Tests and Procedures (Cycle 2 Onwards, EOT/Discontinuation, and Follow-Up)

Observation	Cycle 2 or Later						At EOT/ Discontinuation (Days ± Acceptable Range)	Follow-Up 28 Days After Last Dose
	Cycle 2 (Days ± Acceptable Range)		Cycle 3 (Days ± Acceptable Range)		Cycle 4 or Later (Days ± Acceptable Range)			
	Day 1 ±4 Days	Day 15 ±4 Days	Day 1 ±4 Days	Day 15 ±4 Days	Day 1 ±4 Days	Day 15 ±4 Days	+4 Days	
Weight[a], body temperature, pulse rate	X	X	X	X	X	X	X	
Blood pressure[b]	X	X	X	X	X	X	X	
Home blood pressure monitoring[c]	X (except the period of hospitalization)							
ECOG performance status	X	X	X	X	X	X	X	
Hematology[d]	X	X	X	X	X	X	X	
Coagulation test[e]	X	X	X	X	X	X	X	
Blood chemistry[f]	X	X	X	X	X	X	X	
Urinalysis[g]	X		X		X		X	
12-lead ECG[h]							X	
Abbreviated PK sampling if dose was titrated	X[i]		When dose was titrated/reduced[j]					
Blood samples for pharmacodynamics markers[k]	X		X		X		X	
Tumor assessment[l]			X				X	
Drug compliance	←						→	
Concomitant medications/therapies	←						→	
AEs	←						→	
SAEs	←						→	

AEs = adverse events; APTT = activated partial thromboplastin times; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetics; PT = Prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; s-KIT = stem cell factor receptor; s-VEGFR = soluble vascular endothelial growth factor receptor; VEGF = vascular endothelial growth factor.

a. Weight was to be measured on Day 1 of each Cycle.

b. Blood pressure was to be measured twice, separated by at least 1 hour, at subject visit. Blood pressure was to be measured at least twice daily during the hospitalization, included measurements before each axitinib dosing. Blood pressure measurements were to be made with the subjects in the sitting

Table 2. Schedule of Tests and Procedures (Cycle 2 Onwards, EOT/Discontinuation, and Follow-Up)

position after the subject seated quietly for 5 minutes.

c. Subjects were to be issued blood pressure cuffs (provided by the Sponsor) for home monitoring. Blood pressure measurements were to be made at least twice daily prior to each axitinib dosing on an outpatient basis and recorded in a subject diary. Subjects were to be instructed by the study staff to hold doses temporarily and contact their Physician immediately for guidance if their systolic blood pressure was elevated above 150 mm Hg, or diastolic blood pressure was elevated above 100 mm Hg, or if they developed symptoms perceived to be related to elevated blood pressure (eg, headache, visual disturbance). If subjects were unable to contact their Physician for guidance, subjects were to restart dosing when systolic blood pressure fell below 140 mm Hg and diastolic blood pressure fell below 90 mm Hg, and all symptoms related to elevated blood pressure were resolved.

d. Red blood cell count, hemoglobin, hematocrit, white blood cell count and its differential, and platelet count were measured.

e. The PT and APTT were to be measured.

f. Aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, total bilirubin, blood urea nitrogen, creatinine, glucose, amylase/lipase, and thyroid stimulating hormone were to be measured.

g. pH, urinary protein, urine sugar, and urine occult blood (qualitative for all) were measured. If urinalysis (semiquantitative testing, eg, dipstick) revealed urinary protein ≥1+, a 24-hour urine collection was to be performed.

h. Additional ECG was to be performed if required on the basis of clinical symptoms.

i. Blood samples were to be collected at predose (prior to the morning dose taken at the clinic).

j. For the subjects underwent dose titration/reduction in Cycle 2 or later, 4-hour serial PK sampling was to be performed at the visit which was made 5 or more days after dose increase/decrease (the day prior to next dose increase/decrease). The collection timepoints for the 4-hour serial PK sampling were: predose (prior to the morning dose taken at the clinic) and 1, 2, 3 and 4 hours postdose. If 4-hour serial PK sampling was performed once at a particular dose, it was not required to perform another 4-hour serial PK sampling when the subject received the same dose following dose increase/decrease.

k. Plasma concentrations of s-VEGFR 2, s-VEGFR 3, s-KIT, and VEGF were to be measured. Blood samples were to be collected at Day 1 of each cycle from Cycle 2 to Cycle 12 and at end of treatment (EOT)/discontinuation.

l. Tumor assessment was to be done every other cycle (acceptable range: ±7 days) by the same method of tumor assessment used at the Baseline. Acceptable range for tumor assessment at EOT/discontinuation was +28 days. When treatment was completed/discontinued less than 8 weeks after the previous tumor assessment, no additional assessments were required. For subject in whom the tumor was evaluated as response (complete response / partial response) by RECIST required confirmation at least 28 days (+7 days) after the response was to be noted.

Number of Subjects (Planned and Analyzed): A total of 12 subjects were planned to enroll in this study. The sample size for the single dosing and multiple dosing through the end of Cycle 1 was set at 6. A total of 12 subjects were assigned to and treated with the study treatment.

Diagnosis and Main Criteria for Inclusion: Subjects aged 20 to 75 years (inclusive) with histologically or cytologically diagnosed with advanced malignant solid tumors for whom standard therapies were not effective, and no suitable therapies were available. Subjects with central lung lesions involving major blood vessels and subjects who were treated with bevacizumab or other VEGFR inhibitor(s) were excluded from the study.

Study Treatment: Axitinib was to be initially administered as a single 5 mg dose, followed by continuous 5 mg BID dosing for the first 6 subjects. Single dosing for the second and subsequent subjects was to be initiated after the first subject was monitored for at least 48 hours post single dosing.

An additional 6 subjects were to receive multiple axitinib doses of 5 mg BID depending on the number of subjects who experienced a DLT among the first 6 subjects. Axitinib was administered orally in fed state, taken as close to 12 hours apart as possible and at approximately the same time each day. One cycle length was 28 days.

The dose of axitinib could be titrated or reduced. If a subject had a dose reduction due to treatment-related toxicity, the dose normally would not be re-escalated. However, subjects who tolerated the lower dose for 8 weeks or longer without toxicities exceeding Grade 1 were to be considered for dose re-escalation and the Investigator was to discuss such cases with the Sponsor.

The axitinib tablets were film-coated immediate release tablets and contained 1 mg or 5 mg axitinib. Tablets were packed in bottles and supplied by the Sponsor.

Efficacy, Pharmacokinetic, Pharmacodynamic, and Safety Endpoints:

Primary Endpoint:

- Type and grade (Common Terminology Criteria for Adverse Events Version 3.0), timing of onset, outcome, causality with the study drug of all adverse events (AEs) observed, including abnormal laboratory values.

Secondary Endpoints:

- PK parameters of axitinib.
- Plasma concentrations of s-VEGFR2, s-VEGFR3, s-KIT, and VEGF.
- Anti-tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

- Correlation between UGT1A1 and CYP3A4/5 genotyping and PK of axitinib. Genes suspected to affect to PK of axitinib may also be evaluated.

Safety Evaluations: Safety was to be assessed by monitoring AEs, and through laboratory test results, vital signs measurements, physical examination, and electrocardiograms (ECGs). DLTs were to be assessed in the first 6 subjects following a single dose or multiple dosing in Cycle 1 to investigate the recommended clinical dose of axitinib for Japanese subjects. DLT criteria defined in this study were Grade 4 neutropenia >7 days, Grade 4 thrombocytopenia, Grade ≥3 non-hematological toxicities, hemoptysis >½ teaspoon (2.5 mL)/day unless it resolves to baseline within 7 days, and proteinuria ≥2 g/24 hours.

Statistical Methods:

No confirmatory inferential analyses were planned due to the exploratory nature of this study.

- Full Analysis Set (FAS): Subjects who received the study drug at least once. All the analyses in this study were conducted in the FAS, unless otherwise specified. This analysis set was also used as the safety analysis set.

- DLT evaluation set: Subjects who received a single dose and multiple doses and in whom DLT had been observed before the end of Cycle 1 or who had completed the Cycle 1 observations. Subjects had to have a compliance rate ≥75% in order to be included in the DLT evaluation set.

- PK, pharmacodynamics, and pharmacogenomics (PG) analysis set: Among the FAS, the subjects who completed PK, pharmacodynamics, and PG blood sampling for at least 1 day.

- Anti-tumor response analysis set: Subjects with at least 1 target lesion according to RECIST and who received at least 1 dose of study drug.

Efficacy Analysis: The number of subjects assessed as complete response (CR), partial response (PR), stable disease (SD) and PD according to the RECIST were summarized by tumor type.

PK Analysis: The axitinib PK parameter values were to be calculated for each subject, based on concentration-time data using non-compartmental analysis by WinNonlin software (Table 3).

Table 3. Pharmacokinetic Evaluation

Single dosing:	C_{max}, AUC_{last}, AUC_{inf}, AUC_{12h}, T_{max}, $t_{1/2}$, and $k_{el,}$ CL/F, and Vz/F
Multiple dosing:	
Cycle 1 Day 1	C_{max}, AUC_{tau} *, T_{max}, $t_{1/2}$, k_{el}, and C_{min}
Cycle 1 Day 15	C_{max}, AUC_{tau} *, AUC_{4h}, T_{max}, $t_{1/2}$, k_{el}, C_{min}, CL/F, $R_{ac\ (AUC)}$ and $R_{ac\ (Cmax)}$
Cycle 2 Day 1	C_{min}

τ = 12 hours postdose.
AUC = area under curve; AUC_{last} = area under the plasma concentration-time curve from zero time until the last measurable concentration; AUC_{inf} = area under the plasma concentration-time curve from time zero to time infinity; AUC_{12h} =area under the plasma concentration-time curve from zero time until 12 hours postdose; AUC_{tau} = area under the plasma concentration-time curve over dosing interval τ; AUC_{4h} = area under the plasma concentration-time curve from zero time until 4 hours postdose; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; T_{max} = time to first occurrence of C_{max}; CL/F = apparent oral clearance; k_{el} = terminal phase elimination rate constant; $t_{1/2}$ = terminal phase plasma half-life; Vz/F = apparent volume of distribution during the elimination phase; R_{ac} = accumulation ratio.

Single dosing and multiple dosing was to be analyzed using descriptive statistics. The terminal half-life in multiple dose periods was not evaluated because the terminal elimination phase was not adequately characterized following multiple dosing for all subjects.

Pharmacodynamic Analysis: The time profiles of individual plasma concentrations of s-VEGFR2, s-VEGFR3, s-KIT, and VEGF were to be summarized in figures and tables, and descriptive statistics were to be calculated for measured values.

Pharmacogenomics (Genotyping): The potential correlation between UGT1A1 and CYP 3A4/5 genotype and the PK of axitinib were to be investigated.

RESULTS

Subject Disposition and Demography: A total of 12 Japanese subjects were assigned to the study treatment and all were treated with axitinib. This study was continued until all subjects discontinued due to intolerable toxicity or PD. The reason for discontinuation was lack of efficacy in all except 1 subject who discontinued due to a treatment-related adverse event (Table 4). The first 6 subjects had treatment compliance ≥75% and, therefore, were included in the assessment for DLT, according to the protocol.

Table 4. Subject Disposition and Subject Analyzed

Subject Category Number of Subjects (%)	Axitinib
Enrolled	12
Treated	12 (100)
Completed	0
Discontinued	12 (100)
Reason for Discontinuation	
Related to Study Drug	
Adverse Event	1 (8.3)
Lack of Efficacy	11[a] (91.7)
Subject Analyzed	
Full Analysis Set	12 (100)
Analyzed for PK	12 (100)
Analyzed for Pharmacodynamics	12 (100)
Analyzed for Pharmacogenomics	12 (100)
Analyzed for Safety	
Dose limiting toxicity	6 (100)
Adverse events	12 (100)
Laboratory data	12 (100)

PD = progressive disease; PK = pharmacokinetics.
a. All were assessed as having PD.

Demography and baseline characteristics are summarized in Table 5.

Table 5. Subject Demography and Baseline Characteristics

Characteristic	Axitinib N=12
Gender, n (%)	
Male	7 (58.3)
Female	5 (41.7)
Age (years), n (%)	
<18	0
18-44	2 (16.7)
45-64	6 (50.0)
≥65	4 (33.3)
Mean	60.2
SD	13.1
Range	32-75
Race, n (%)	
Asian (Japanese)	12 (100)
Height (cm)	
Mean	162.7
SD	9.8
Range	148.7-180.2
Weight (kg)	
Mean	59.7
SD	13.4
Range	43.6-83.2
Smoking habit, n (%)	
Yes	1 (8.3)
No	11[a] (91.7)
Allergy, n (%)	
Yes	4 (33.3)
No	8 (66.7)
ECOG-PS, n (%)	
0	6 (50.0)
1	5 (41.7)
2	1 (8.3)

ECOG-PS = Eastern Cooperative Oncology Group Performance status; N = total number of subjects, n = number of subjects in specified category, SD = standard deviation
a. This included 9 ex-smokers.

Efficacy, Pharmacokinetic, and Pharmacodynamic Results: Primary endpoint in the study was safety.

Secondary Efficacy Endpoint: Ten (83.3%) out of 12 subjects had a best RECIST defined response of SD. The target lesion size was decreased from Baseline in 9 subjects (5/6 with colorectal cancer [CRC], 1/2 with renal cell carcinoma [RCC], 1/1 with ovarian cancer, 1/1 with non-small cell lung cancer [NSCLC], and 1/1 with thymoma malignant) (Table 6).

Table 6. Individual Tumor Response (Investigator-Assessed)

Serial Number	Primary Diagnosis (MedDRA)	Best Overall Response (RECIST)	Maximum % Change in Target Lesion Size[a] From Baseline
1	Colorectal cancer	SD	–12.9
2	Rectosigmoid cancer	SD	–5.7
3	Ovarian cancer	SD	–9.2
4	Liposarcoma	PD	46.8
5	Non-small cell lung cancer	SD	–27.9
6	Rectal cancer	SD	–2.5
7	Thymoma malignant	SD	–24.5
8	Rectal cancer	SD	0.5
9	Rectal cancer	SD	–30.3
10	Renal cell carcinoma	SD	–1.9
11	Renal cell carcinoma	PD	46.6
12	Colon cancer	SD	–35.9

MedDRA version 12.1 was used.
MedDRA = Medical Dictionary for Regulatory Activities; PD = progressive disease; SD = stable disease; RECIST = Response Evaluation Criteria in Solid Tumors.
a. When the sum of the longest diameter of target lesions was the lowest during the study.

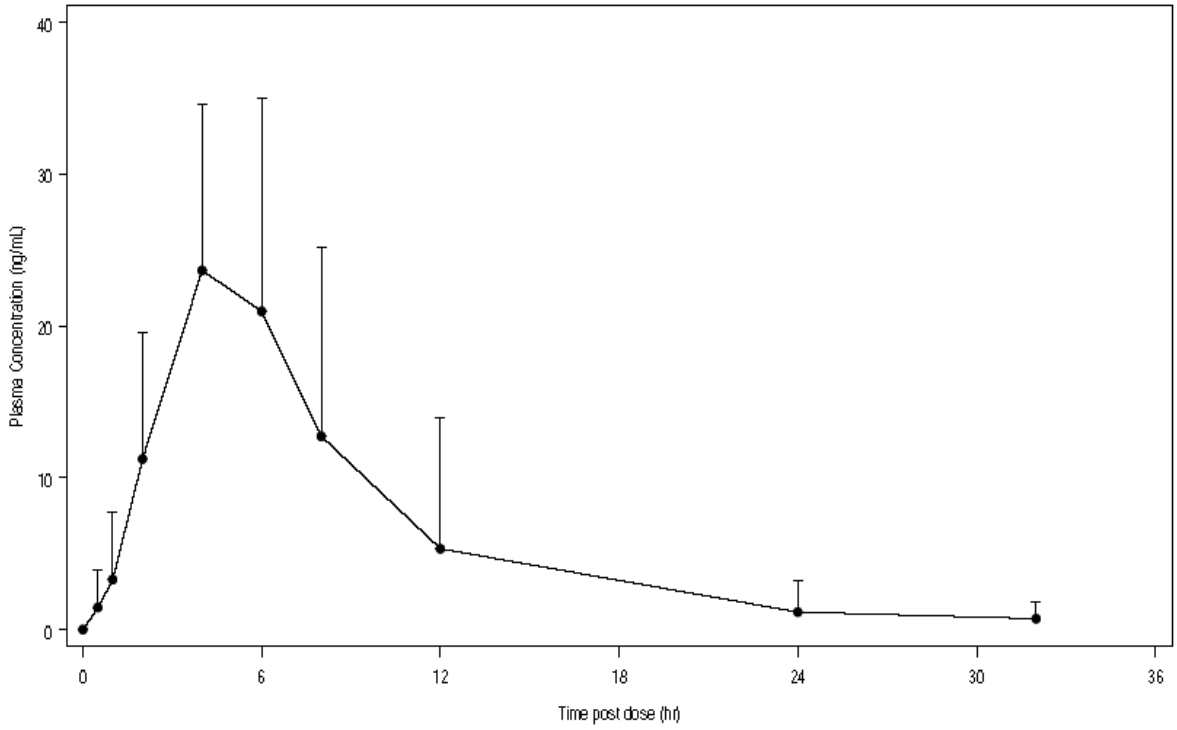
PK Parameter of Axitinib: A summary of plasma PK parameters after administration of a single oral 5-mg dose of axitinib (fed state) is provided in Table 7 and the mean plasma concentration profile is presented in Figure 1.

Table 7. Axitinib Plasma Pharmacokinetic Parameters (Single Dose)

	C_{max} (ng/mL) N=6	AUC_{inf} (ng•h/mL) N=6	T_{max} (h) N=6	$t_{½}$ (h) N=6	CL/F (L/h) N=6	V_z/F (L) N=6
Geometric Mean	28.59	181.3	4.0[a]	4.8[b]	27.57	186.56
CV %	33.25	69.7	(2, 6)[c]	23.9	42.66	49.97

AUC_{inf} = area under the plasma concentration-time curve from time zero to time infinity; C_{max} = maximum plasma concentration; CV = coefficient of variation; CL/F = apparent oral clearance; T_{max} = time to first occurrence of C_{max}; $t_{1/2}$ = terminal phase plasma half-life; Vz/F = apparent volume of distribution during the elimination phase.
a. Median.
b. Arithmetic mean.
c. Minimum, maximum.

Figure 1. Mean Axitinib Plasma Concentration (Single Dose) Linear Plot



A summary of plasma PK parameters of axitinib after multiple oral dosing (5 mg BID in the fed state) on Cycle 1 Day 15 (5 mg BID in the fed state) is provided in Table 8.

Table 8. Axitinib Plasma Pharmacokinetic Parameters (Cycle 1, Day 15)

	C_{max} (ng/mL) N=11[a]	AUC_{tau} (ng•h/mL) N=11[a]	AUC_{4h} (ng•h/mL) N=11[a]	T_{max}(h) N=11[a]
Geometric Mean	27.01	149.8	59.4	4.0[b]
CV (%)	56.13	66.7	55.3	(1, 4)[c]

AUC_{tau} = area under the plasma concentration-time curve over dosing interval τ; AUC_{4h} = area under the plasma concentration-time curve from zero time until 4 hours postdose; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects assessed.

a. One subject was excluded from summary statistics because the Day 14 morning axitinib dose was not administered.
b. Median.
c. Minimum, maximum.

Mean axitinib plasma concentration profiles for Cycle 1 Day 1 and Day 15 are presented in Figure 2 and Figure 3, respectively.

Figure 2. Mean Axitinib Plasma Concentration (Cycle 1 Day 1) Linear Plot

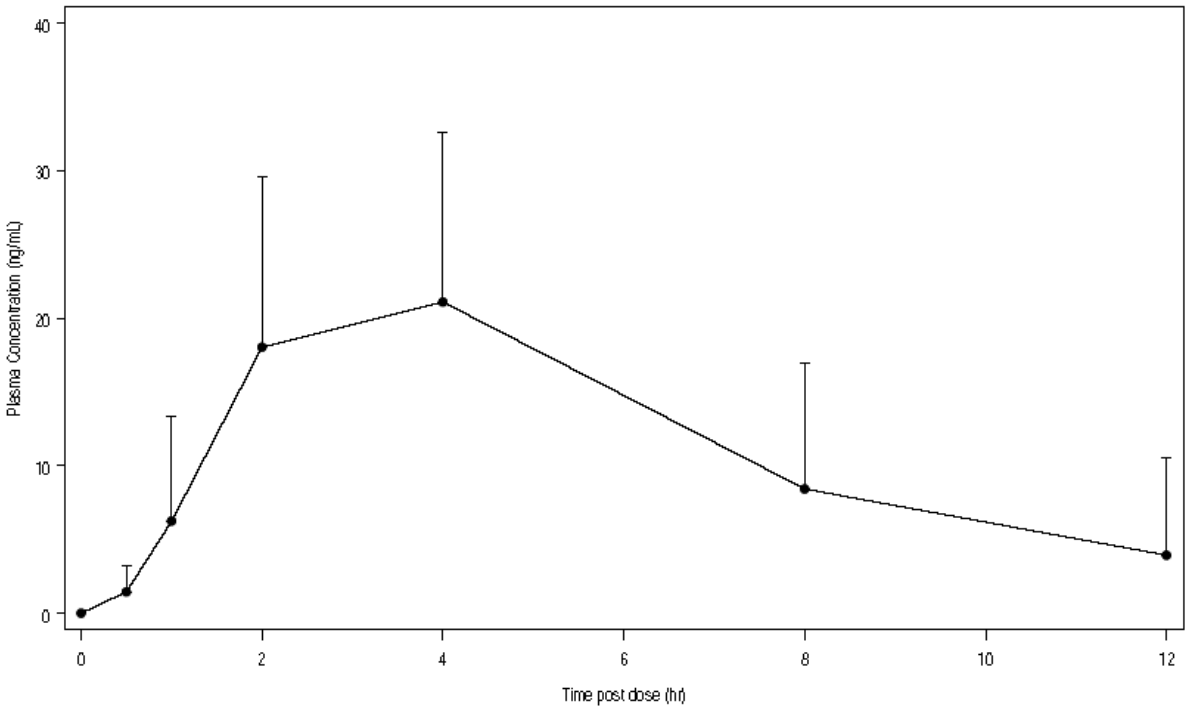
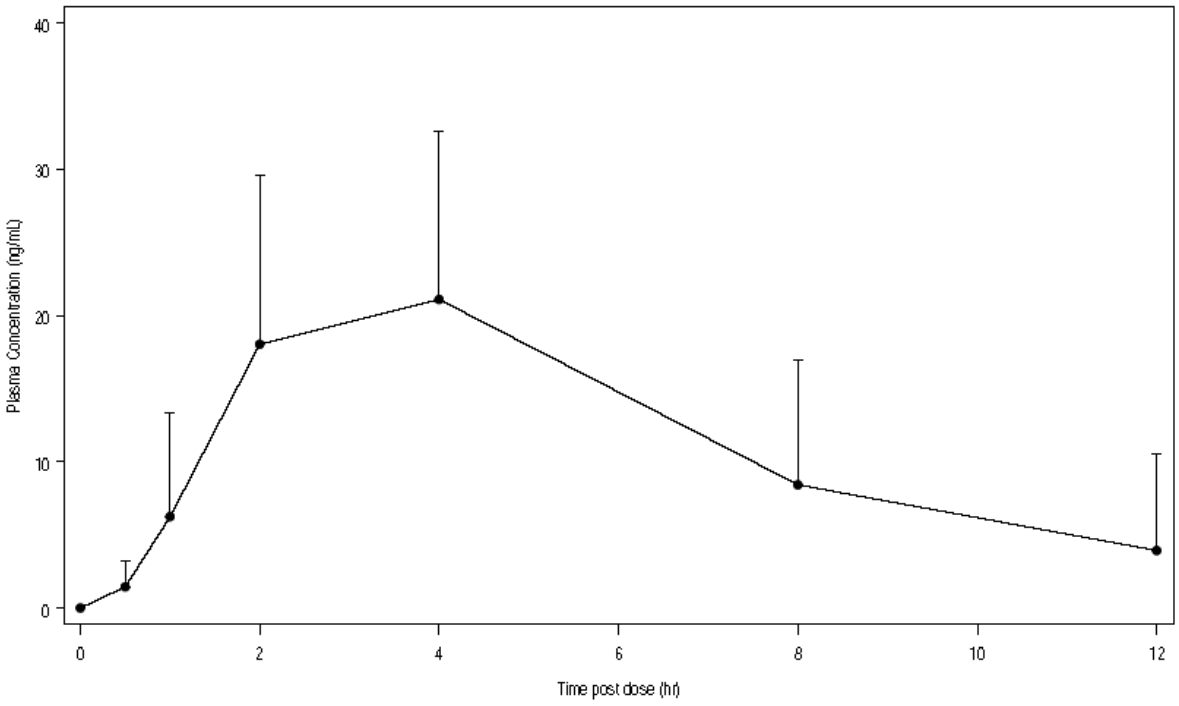


Figure 3. Mean Axitinib Plasma Concentration (Cycle 1 Day 15) Linear Plot



Summary for accumulation ratio (R_{ac}) for C_{max} and area under the plasma concentration-time curve over dosing interval τ (AUC_{tau}) of axitinib following 5 mg BID dosing are provided in Table 9.

Table 9. Accumulation Ratio (R_{ac}) for Axitinib following 5 mg BID dosing

	R_{ac} C_{max} N=11[a]	R_{ac} AUC_{tau} N=11[a]
Geometric Mean	1.389	1.481
CV (%)	32.534	31.768
90% CI	1.180-1.634	1.266-1.731

AUC_{tau} = area under the plasma concentration-time curve over dosing interval τ; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects assessed; R_{ac} = accumulation ratio; CI = confidence interval

a. One subject was excluded from summary statistics at Cycle 1 Day 15 because the Day 14 axitinib morning dose was not administered

Plasma Concentrations of s-VEGFR2, s-VEGFR3, s-KIT, and VEGF: All subjects had a decrease in s-VEGFR2 plasma concentration at Cycle 2 Day 1; the mean ± standard deviation (SD; median, range) percent change from Baseline was –34.76±14.99% (-41.73%, -53.2% to –10.1%). Individual changes at Cycle 3 and in later cycles were gradual in most of subjects; the mean ± SD (median, range) percent change from Baseline at study discontinuation was -34.85±14.12% (–40.57%, –53.0% to –8.4%).

All subjects were noted to have a decrease of s-VEGFR3 plasma concentration at Cycle 2 Day 1 and the mean ± SD (median, range) percent change from Baseline was –45.55±22.20% (–52.50%, –93.7% to –15.6%). Changes at Cycle 3 showed a slight increase compared to Cycle 2 Day 1 in all subjects and thereafter varied from individual to individual until study discontinuation. The mean ± SD (median, range) percent change from Baseline at study discontinuation was –44.36±37.14% (–65.48%, –81.2% to 39.4%).

There were no consistent changes in s-KIT plasma concentrations between subjects. In general, there was little change in mean s-KIT plasma concentration with the mean ± SD (median, range) percent change from Baseline being -0.60±15.62% (-0.26%, –23.8% to 33.5%) at Cycle 2 Day 1 and –4.59 ± 16.08% (4.66%, –31.2% to 12.9%) at study discontinuation.

All subjects had an increase of VEGF plasma concentration at Cycle 2 Day 1 and the mean ± SD (median, range) percent change from Baseline was 288.06±287.28% (266.92%, 14.9% to 1030.4%). VEGF plasma concentration fluctuated and individually varied; the maximum mean ± SD (median, range) change was 398.14±423.40% (292.06%, –43.9% to 1113.9%) at Cycle 4 Day 1, and the mean ± SD (median, range) percent at the discontinuation 123.00±167.50% (43.48%, –15.5% to 423.1%)

Pharmacogenomics: For CYP3A4*1B, CYP3A4*2, CYP3A5*1B, CYP3A5*1C, CYP3A5*6, CYP3A5*7, UGT1A1*27, UGT1A1*36, and *37, none of the 12 subjects were heterozygous or homozygous variants (wt/v, v/v). For UGT1A1*28, *6, *60 and *93, none of the 12 subjects were homozygous variants (Table 10).

No correlation between pharmacokinetic parameters and genotype was observed. However, this may have been due to the limited number of subjects in this study.

Table 10. Predicted Genotype

Gene	Variant Genotyped	N	Axitinib		
			Predicted Genotype		
			Homozygous Wild Type, Number of Subjects (%)	Heterozygous, Number of Subjects (%)	Homozygous Variant, Number of Subjects (%)
CYP3A4	*1B	12	12 (100)	-	-
	*2	12	12 (100)	-	-
CYP3A5	*1B	12	12 (100)	-	-
	*1C	12	12 (100)	-	-
	*3	12	1 (8.3)	4 (33.3)	7 (58.3)
	*6	12	12 (100)	-	-
	*7	12	12 (100)	-	-
UGT1A1	*27	12	12 (100)	-	-
	*28	12	7 (58.3)	5 (41.7)	-
	*6	12	6 (50.0)	6 (50.0)	-
	*60	12	7 (58.3)	5 (41.7)	-
	*93	12	7 (58.3)	5 (41.7)	-

CYP = cytochrome P450; N = number of subjects with the given genomic marker; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1 family, polypeptide A1.

Safety Results: All-causality treatment-emergent AEs are summarized in Table 11. Overall, commonly reported AEs in all cycles were decreased appetite, fatigue, diarrhea, stomatitis, and increased blood thyroid stimulating hormone.

Table 11. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class and MedDRA Preferred Term	Axitinib n (%)
Number (%) of subjects: evaluable for AEs	12
Number (%) of subjects: with AEs	12 (100.0)
Blood and lymphatic system disorders	1 (8.3)
Lymphopenia	1 (8.3)
Neutropenia	1 (8.3)
Cardiac disorders	1 (8.3)
Palpitations	1 (8.3)
Ear and labyrinth disorders	1 (8.3)
Ear discomfort	1 (8.3)
Endocrine disorders	1 (8.3)
Hyperthyroidism	1 (8.3)
Gastrointestinal disorders	12 (100.0)
Abdominal discomfort	1 (8.3)
Abdominal pain	5 (41.7)
Constipation	6 (50.0)
Diarrhoea	10 (83.3)
Dyspepsia	2 (16.7)
Nausea	4 (33.3)
Proctalgia	1 (8.3)
Stomatitis	9 (75.0)
Toothache	2 (16.7)
General disorders and administration site conditions	11 (91.7)
Face oedema	1 (8.3)
Fatigue	10 (83.3)
Generalised oedema	1 (8.3)
Pyrexia	1 (8.3)
Thirst	1 (8.3)
Infections and infestations	5 (41.7)
Herpes zoster	1 (8.3)
Nasopharyngitis	3 (25.0)
Onychomycosis	1 (8.3)
Tinea infection	1 (8.3)
Investigations	12 (100.0)
Alanine aminotransferase increased	3 (25.0)
Aspartate aminotransferase increased	6 (50.0)
Blood albumin decreased	1 (8.3)
Blood alkaline phosphatase increased	6 (50.0)
Blood amylase increased	1 (8.3)
Blood bilirubin increased	3 (25.0)
Blood creatinine increased	1 (8.3)
Blood glucose increased	5 (41.7)
Blood thyroid stimulating hormone decreased	4 (33.3)
Blood thyroid stimulating hormone increased	9 (75.0)
Blood urea increased	1 (8.3)
Blood urine present	7 (58.3)
Haemoglobin decreased	1 (8.3)
Lipase increased	5 (41.7)
Platelet count decreased	5 (41.7)
Thyroxine free decreased	1 (8.3)
Thyroxine free increased	3 (25.0)

Table 11. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class and MedDRA Preferred Term	Axitinib n (%)
Tri-iodothyronine free increased	3 (25.0)
Urine bilirubin increased	2 (16.7)
Weight decreased	4 (33.3)
White blood cell count decreased	3 (25.0)
Metabolism and nutrition disorders	11 (91.7)
Decreased appetite	11 (91.7)
Hypoalbuminaemia	1 (8.3)
Musculoskeletal and connective tissue disorders	5 (41.7)
Arthralgia	1 (8.3)
Back pain	3 (25.0)
Musculoskeletal pain	2 (16.7)
Musculoskeletal stiffness	1 (8.3)
Myalgia	1 (8.3)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	3 (25.0)
Tumour associated fever	1 (8.3)
Tumour pain	2 (16.7)
Nervous system disorders	6 (50.0)
Dysgeusia	1 (8.3)
Headache	3 (25.0)
Lacunar infarction	1 (8.3)
Post herpetic neuralgia	1 (8.3)
Somnolence	2 (16.7)
Psychiatric disorders	2 (16.7)
Insomnia	2 (16.7)
Renal and urinary disorders	6 (50.0)
Proteinuria	6 (50.0)
Respiratory, thoracic and mediastinal disorders	11 (91.7)
Cough	4 (33.3)
Dysphonia	7 (58.3)
Dyspnoea	2 (16.7)
Dyspnoea exertional	1 (8.3)
Epistaxis	3 (25.0)
Haemoptysis	1 (8.3)
Nasal mucosal disorder	1 (8.3)
Skin and subcutaneous tissue disorders	10 (83.3)
Alopecia	1 (8.3)
Erythema	1 (8.3)
Palmar-plantar erythrodysaesthesia syndrome	8 (66.7)
Rash	3 (25.0)
Vascular disorders	6 (50.0)
Hypertension	6 (50.0)

Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
MedDRA (version 12.1) coding dictionary applied.
AEs = adverse events, MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with AEs.

A total of 222 all-causality AEs and 167 treatment-related AEs were reported for the 12 subjects enrolled in the study. Seven subjects reported all-causality CTCAE Grade 3 or 4 AEs and these 7 subjects had at least 1 treatment-related Grade 3 or 4 AEs (Table 12).

Table 12. Overall Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

Number of Subjects (%)	Axitinib			
	All Cycles N=12	Single dose N=6	Cycle 1 N=12	Cycle 1-3 N=12
	Treatment-Related	Treatment-Related	Treatment-Related	Treatment-Related
Subjects with at least 1 AE	12 (100)	2 (33.3)	12 (100)	12 (100)
Number of AEs	167	3	78	132
Subjects with at least 1 SAE	0	0	0	0
Subjects with grade 3 or 4 AEs	7 (58.3)	0	2 (16.7)	5 (41.7)
Subjects with grade 5 AEs	0	0	0	0
Discontinuation due to AEs	1 (8.3)	0	0	0
Temporary discontinuation/dose reduction due to AEs	9 (75.0)	0	4 (33.3)	6 (50.0)

AE = adverse event; N = number of subjects assessed; SAE = serious adverse event.

Serious AEs (SAEs) are summarized in Table 13.

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class and MedDRA Preferred Term	Axitinib n (%)
Number (%) of subjects: evaluable for AEs	12
Number (%) of subjects: with AEs	5 (41.7)
Cardiac disorders	1 (8.3)
Cardiac tamponade	1 (8.3)
Gastrointestinal disorders	2 (16.7)
Intestinal obstruction	2 (16.7)
General disorders and administration site conditions	2 (16.7)
Pyrexia	2 (16.7)
Infections and infestations	1 (8.3)
Liver abscess	1 (8.3)

Subjects were only counted once per treatment for each row.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with SAEs.

All SAEs (Table 14) were considered not related to the study drug.

Table 14. Serious Adverse Events

Serial Number	Daily Dose	AE (MeDRA Preferred Term)	CTCAE-Grade	Onset Cycle/Day[a]	Causality[b]	Drug Action	Outcome[c]
1	5 mg[d]	Intestinal obstruction	3	Cycle 4/13	Not related	No action	Still present[e]
2	NA	Pseudomembranous colitis	NA	Post therapy	Not related	No action	Resolved
3	6 mg	Cardiac tamponade	4	Cycle 5/20	Not related	Stopped temporarily	Resolved[f]
4	6 mg	Intestinal obstruction	3	Cycle 4/25	Not related	Stopped temporarily	Still present[g]
5	5 mg	Pyrexia	2	Cycle 1/3	Not related	Stopped temporarily	Resolved
	5 mg	Liver abscess	3	Cycle 1/3	Not related	Stopped temporarily	Resolved
6	14 mg	Pyrexia	2	Cycle 2/15	Not related	Stopped temporarily	Resolved

CTCAE Version 3.0 was adopted.
AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable.

a. Day relative to the date of first dose in multiple dosing.
b. Investigator causality.
c. Outcome recorded in the study database.
d. This event occurred while the subject was pending dose for fatigue.
e. This event was reported as resolved in the safety database at the follow-up observation.
f. The outcome was entered in the study database as "resolved" after the pericardial fluid removal: however, it was entered as "resolving" in the safety database as the subject was still being hospitalized.
g. The event was reported as resolving in the safety database at the follow-up observation.

Discontinuations and Deaths: One subject permanently discontinued the study due to an AE. Proteinuria initially occurred in this subject in Cycle 1 Day 6 as a Grade 2 event. Due to Grade 3 proteinuria (6.4 g/day and 9.2 g/day respectively) the subject temporarily discontinued study twice, and permanently discontinued the study in Cycle 4 when a third Grade 3 proteinuria (7.8 g/day) was experienced. At the follow-up observation, proteinuria still persisted, but was alleviated to Grade 2. The event, coded as a Grade 3 proteinuria, was considered to be treatment-related.

A total of 10/12 subjects temporarily discontinued the study drug due to an AE and 5/12 subjects also had dose reductions. Frequently observed AEs which caused temporary discontinuations were fatigue (6 subjects) followed by diarrhea and pyrexia (3 subjects each).

No deaths occurred during the study.

All 12 subjects had at least 1 post-baseline abnormal laboratory test value regardless of the baseline abnormality. Abnormal TSH was the most commonly reported laboratory test abnormality; increased TSH was reported in 11/12 subjects and decreased TSH was reported in 6/12 subjects. Other common abnormalities reported in ≥50% of subjects were increased glucose level (9 subjects), positive urine blood (7 subjects), decreased lymphocytes (%; 6 subjects), and increased neutrophils (%; 6 subjects). CTCAE Grade 3 hypoalbuminemia, alkaline phosphatase, hyperglycemia, and lipase results were recorded in 1 subject each at the planned laboratory tests. No other test results were recorded as CTCAE Grade 3 or higher after the treatment.

All subjects had baseline hematology test results (hemoglobin, platelets, white blood cells, neutrophils, lymphocytes, and prothrombin time) ≤ CTCAE Grade 2. No subjects reported events related to coagulation factors.

A total of 7/12 subjects reported urine protein (qualitative) at the planned laboratory tests; 3/12 subjects had CTCAE Grade 1, 4/12 subjects had CTCAE Grade 2. Although no subject reported urine protein ≥ CTCAE Grade 3 by qualitative test, 1 subject was re-graded as CTCAE Grade 3 after urinary protein > 3.5 g/ 24 hours was confirmed at a 24 hour urine collection.

Elevation of blood pressure was observed with the peak at 8 to 12 hours postdose. Maximum mean ± SD increases from the baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 16.2±18.3 mm Hg and 7.2±9.1 mm Hg with absolute values of 137.8±24.7 mm Hg and 81.0±9.7 mm Hg, respectively at 12 hours after administration of a single dose; 12.8±16.5 mm Hg and 9.3±8.1 mm Hg with absolute values of 133.8±21.9 mm Hg and 82.3±12.8 mm Hg, respectively at 8 hours postdose on Cycle 1 Day 1. The change from Baseline was smaller at 8 hours postdose on Cycle 1 Day 15 (SBP: 6.7±12.6 mm Hg and DBP: 2.2±8.8 mm Hg) with absolute values of 128.8±16.1 mm Hg and 81.2±7.7 mm Hg, respectively. Blood pressure subsequently remained relatively stable following adequate anti-hypertensive treatment.

The mean changes (±SD) of ECG QTc interval from the baseline were –26.3±20.1 msec at Cycle 1 Day 15 and 1.3±15.9 msec at study discontinuation. No subject had a QTc interval ≥480 msec or had QTc interval increased ≥30 msec.

CONCLUSIONS:

- Only 1 subject experienced a DLT (Grade 3 proteinuria and Grade 3 fatigue) in this study. Common treatment-related AEs occurring in ≥50% subjects were decreased appetite, fatigue, diarrhea, blood TSH increased, stomatitis, palmar-plantar erythrodysaesthesia syndrome, blood urine present, dysphonia, and hypertension. Common Grade 3 treatment-related AEs were fatigue and hypertension. There were no treatment-related SAEs or deaths reported in this study. One subject discontinued the study due to an AE (treatment-related proteinuria). Overall, axitinib was well tolerated in this study.

- The peak plasma axitinib concentration was reached at a median of 4 hours postdose in the fed state and axitinib was eliminated from plasma with a mean half-life of 4.8 hours. The mean (90% CI) for axitinib R_{ac} for AUC_{tau} was 1.481 (1.266 - 1.731); the observed R_{ac} was consistent with the value predicted from the mean half-life of the drug.

- Axitinib treatment increased VEGF and decreased plasma s-VEGFR2 and s-VEGFR3 concentrations; in contrast, axitinib had little effect on s-KIT plasma concentrations.

- No correlations between PK and CYP3A4/5 and UGT genotypes were observed; however, this may have been due to the limited number of subjects.

- The best tumor response (RECIST) was "stable disease" in 10/12 subjects. Four subjects entered ≥9 cycles of study treatment (with a maximum of 29 cycles) before PD was noted.

- The clinically recommended starting dose for Japanese subjects was determined to be 5 mg BID.