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

PROTOCOL NO.: A4061044

PROTOCOL TITLE: A Phase 1 Study in Patients With Advanced Solid Tumor to Evaluate the Pharmacokinetics and Safety of AG-013736 at Single Doses of 5 mg, 7 mg, and 10 mg, and at Multiple Doses

Study Center: One study center in Japan took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date: 29 July 2008 to 26 April 2010

Phase of Development: Phase 1

Study Objectives:

Primary Objective:

- To evaluate plasma pharmacokinetics (PK) of axitinib (AG-013736) following single doses of 5 mg, 7 mg, and 10 mg.

Secondary Objective:

- To evaluate the safety of axitinib following single and multiple twice daily (BID) dosing.
- To evaluate plasma PK of axitinib following multiple dosing.
- To investigate the changes of the plasma concentration profiles of the pharmacodynamics (PD) indices, soluble vascular endothelial growth factor receptors (s-VEGFR1), s-VEGFR2, s-VEGFR3, stem cell factor receptor (s-KIT) and vascular endothelial growth factor (VEGF).
- To investigate the antitumor activity of axitinib.
- To investigate the effect on PK of axitinib by uridine diphosphate-glucuronosyltransferase (UGT)1A1 and cytochrome P450 (CYP) 3A4/5 gene polymorphisms. Other genes suspected to affect the PK of axitinib could also have been evaluated.

METHODS

Study Design: This study was an open-label, single-arm study in Japanese subjects with advanced solid tumors to evaluate the PK, safety, PD, and antitumor activity of axitinib. In addition, the potential effect of gene polymorphisms on the PK of axitinib was investigated.

Six subjects were to receive single dosing of axitinib, (5, 7, and 10 mg), and multiple dosing of 5 mg BID. One cycle length was 28 days. If the drug was well tolerated at 5 mg BID, the dose of axitinib was titrated from 7 mg BID up to a maximum of 10 mg BID. Subjects continued the study treatment until they experienced intolerable toxicity or progressive disease. The schedule activities are presented in Table 1 (for the single dosing regimen) and Table 2 (for the multiple dosing regimen).

Table 1. Schedule of Tests and Procedures: Single Dosing of 5 mg, 7 mg, and 10 mg Axitinib

Observation	Screening		Single Dosing					
	Within 14 Days Predose	Within 4 Days Predose	5 mg (Acceptable Range)		7 mg (Acceptable Range)		10 mg (Acceptable Range)	
			Day 1 Predose	Day 2 at 24 Hours Postdose or Later	Day 1 Predose*	Day 2 At 24 Hours Postdose or Later	Day 1 Predose*	Day 2 at 24 Hours Postdose or Later
			(-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[d]		X[d]	
ECOG PS	X		X	X	X	X	X	X
Hematology[e]	X		X[f]	X	X	X	X	X
Coagulation test[g]	X		X[f]	X	X	X	X	X
Blood chemistry[h]	X		X[f]	X	X	X	X	X
Urinalysis[i]	X[j]		X[f]	X	X	X	X	X
12-lead electrocardiogram[k]	X							
Blood samples for UGT1A1 and CYP3A4/5 test			X					
Blood samples for PK			X[l]		X[l]		X[l]	
Blood samples for PD markers[m]			X					
Pregnancy test		X						
Tumor measurements[n]	X							
Drug compliance			X		X		X	
Concomitant medications/therapies	←							→
AEs			←					→
SAEs	←							→

* Minimum of 48-hour observation after the previous single dosing was required before initiating the next single dose.
** If the tests and procedures scheduled on each single dosing on Day 2 had performed within 4 days before Day 1 of each next single dosing, these tests and procedures except for blood pressure measurement and pharmacokinetics sampling were not repeated.
AEs = Adverse events; CYP = cytochrome P450; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment;

Table 1. Schedule of Tests and Procedures: Single Dosing of 5 mg, 7 mg, and 10 mg Axitinib

PD = pharmacodynamics; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; s-KIT = stem cell factor receptor; T3 = triiodothyronine; T4 = tetraiodothyronine; s-VEGFR1 = soluble vascular endothelial growth factor receptor; VEGF = vascular endothelial growth factor receptor; UGT 1A1 = uridine diphosphate-glucuronosyltransferase.

a. Subject background included the status of smoking.
b. Weight was measured on 5 mg single-dosing Day 1.
c. BP was measured twice at least 1 hour apart at the subject visit (including the screening visit). BP was measured at least twice daily during hospitalization that included measurements before each axitinib dosing. Blood pressure measurements were made with the subject in the sitting position after the subject rested for 5 minutes.
d. BP was measured at predose, 1, 2, 4, 6, 8, 10, and 24 hours post-dose. This serial BP measurement was performed on the same day of PK sampling.
e. Red blood cell count, hemoglobin, hematocrit, white blood cell count and its differential (neutrophil, eosinophil, basophil, lymphocyte, monocyte), and platelet count were measured.
f. If the predose tests (at Screening) were conducted within 4 days before single dosing of 5 mg, the test on Day 1 of 5 mg single dosing was not necessary.
g. Prothrombin time and activated partial thromboplastin times were measured.
h. Aspartate aminotransferase (AST), alanine aminotransferase , lactate dehydrogenase, alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, total bilirubin, blood urea nitrogen, creatinine, total cholesterol, glucose (fasted state), creatine phosphokinase, amylase/lipase, and thyroid stimulating hormone, free-T3, free-T4, thyroglobulin, anti-thyroid peroxidase antibody (at screening only), anti-thyroglobulin antibody (at screening only) were measured. Hypothyroidism should be treated according to the standard medical practice to maintain euthyroid state.
i. pH, urinary protein, urine sugar, urine occult blood (qualitative/semi-quantitative for all), urinary sediment (at screening only) were measured. If urinalysis (semiquantitative testing such as dipstick) revealed urinary protein ≥2+, a 24-hour urine collection was performed.
j. If urinalysis (semiquantitative testing such as dipstick) revealed urinary protein ≥1+, a 24-hour urine collection was performed. Patients with urinary protein <2 g/24 hours were enrolled.
k. Three consecutive 12-lead electrocardiograms were performed approximately 2 minutes apart to determine the mean QTc interval. Additional ECGs were performed if clinically indicated.
l. Blood samples for pharmacokinetics were collected at predose, 0.5, 1, 2, 4, 6, 8, 10, 24, and 32-hours post-dose.
m. Plasma concentrations of pharmacodynamic markers (s-VEGFR1, s-VEGFR2, s-VEGFR3, s-KIT, VEGF) were measured.
n. Any results of evaluation which was performed within 28 days before treatment initiation could be used.

Table 2. Schedule of Tests and Procedures: Multiple Dosing

Observation	Multiple Dosing								Post-Treatment (Acceptable Range)	
	Cycle 1* (Acceptable Range)				Cycle 2* (Acceptable Range)		Cycle 3 or Later* (Acceptable Range)			
	Day 1 Predose** (-4 Days)***	Day 8 (±4 Days)	Day 15 (±4 Days)	Day 22 (±4 Days)	Day 1 (±4 Days)	Day 15 (±4 Days)	Day 1 (±4 Days)	Day 15 (±4 Days)	At EOT/ Discontinuation (+4 Days)	Follow-Up 28 Days After Last Dose****
Weight[a], body temperature, pulse rate	X	X	X	X	X	X	X	X	X	-
Blood pressure[b]	X	X	X[c]	X	X	X	X	X	X	-
Home BP monitoring[d]	X (except for the hospitalization period)									
ECOG PS	X	X	X	X	X	X	X	X	X	-
Hematology[e]	X	X	X	X	X	X	X	X	X	-
Coagulation test[f]	X	X	X	X	X	X	X	X	X	-
Blood chemistry[g]	X	X	X	X	X	X	X	X	X	-
Urinalysis[h]	X	X	X	X	X	X	X	X	X	-
12-lead ECG[i]	-	-	X[j]	-	-	-	-	-	X	-
Blood samples for PK	-	-	X[k]	-	X[l]	-	X[l] Cycle 4 and 6 only	-	-	-
Blood samples for PK[m]	-	-	-	When dose was titrated/reduced						
Blood samples for PD markers[n]	-	-	-	-	X	-	X Up to Cycle 12	-	X	-
Tumor assessment[o]	-	-	-	-		-	X	-	X	-
Drug compliance	←	←	←	←	←	←	←	←	→	-
Concomitant medications/therapies	←	←	←	←	←	←	←	←	←	→
AEs	←	←	←	←	←	←	←	←	←	→
SAEs	←	←	←	←	←	←	←	←	←	→

* One cycle length was 28 days.
** Minimum of 48-hour observation after 10 mg single dosing was required before the initiation of the multiple dosing.
*** If the tests and procedures scheduled on 10 mg single dosing Day 2 had been performed within 4 days before the initiation of multiple dosing, these tests and procedures except for blood pressure measurements on Cycle 1 Day 1 were not repeated.
**** AEs was to be collected at the visit after 28 days from last dosing.
AEs = Adverse events; BP = blood pressure; BID = twice daily; CYP = cytochrome P450; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group

Table 2. Schedule of Tests and Procedures: Multiple Dosing

performance status; EOT = end of treatment; PD = pharmacodynamics; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; s-KIT = stem cell factor receptor; T3 = triiodothyronine; T4 = tetraiodothyronine; s-VEGFR1 = soluble vascular endothelial growth factor receptor; VEGF = vascular endothelial growth factor receptor; UGT 1A1 = uridine diphosphate-glucuronosyltransferase.

a. Weight was measured every Cycle (Day 1) and EOT/discontinuation.
b. Blood pressure was measured twice at least 1 hour apart at the subject visit. Blood pressure was to be measured at least twice daily during hospitalization that included measurements before each axitinib dosing. Blood pressure measurements were made with the subject in the sitting position after the subject rested for 5 minutes.
c. Blood pressure was measured at predose, 1, 2, 4, 6, 8, 10, and 12 hours postdose (12 hours post dose measurement was made before the next dosing). These serial blood pressure measurements were performed on the same day of PK sampling
d. Subjects were issued blood pressure cuffs (provided by the Sponsor) for home monitoring. Blood pressure measurements were made at least twice daily prior to each axitinib dosing on an outpatient basis and were recorded in a subject diary. Subjects were 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, diastolic blood pressure fell below 90 mm Hg, and all symptoms related to elevated blood pressure resolved.
e. Red blood cell count, hemoglobin, hematocrit, white blood cell count and differential (neutrophil, eosinophil, basophil, lymphocyte, monocyte), platelet count were measured.
f. Prothrombin time (PT) and activated partial thromboplastin times were measured.
g. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, total bilirubin, blood urea nitrogen (BUN), creatinine, total cholesterol, glucose (fasted state), creatine phosphokinase, amylase/lipase, thyroid stimulating hormone, free-T3, free-T4, thyroglobulin were measured. Hypothyroidism was treated per standard medical practice to maintain euthyroid state.
h. pH, urinary protein, urine sugar, urine occult blood (qualitative/semi-quantitative for all). If urinalysis (semiquantitative testing such as dipstick) revealed urinary protein ≥2+, a 24-hour urine collection was performed.
i. Three consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine the mean QTc interval. Additional ECGs was performed if clinically indicated.
j. 12-lead ECG was performed at 1-3 hours postdose on Day 15 of Cycle 1.
k. Blood samples for PK were collected at predose and 0.5, 1, 2, 4, 8, and 12 hours postdose (12 hour post dose sampling was conducted before next dosing). All PK samplings was completed before the dose titration if dose was titrated to 7 mg BID on Day 15 of Cycle 1.
l. Blood samples for population pharmacokinetic analysis were collected at the clinic, prior to the morning dose and 2 hours after the dose on Day 1 of Cycle 2, Cycle 4, and Cycle 6.
m. Blood samples for PK were collected for the subjects who underwent dose titration/reduction on Day 15 of Cycle 1 or later. A 4-hour serial PK sampling was performed at subject visit, 5 days or more after dose increase/decrease (prior to the next dose increase/decrease). The collection time points for the 4-hour serial PK sampling were predose (prior to the morning dose), 1, 2, 3, and 4 hours postdose. It was not necessary to repeat 4-hour serial PK sampling when subject increased/decreased to the dose which had been previously received and 4-hour serial PK sampling had been performed.
n. Blood samples for plasma concentrations of pharmacodynamic markers (s-VEGFR1, s-VEGFR2, s-VEGFR3, s-KIT, VEGF) were collected on Day 1 of Cycle 2 to Cycle 12, and at EOT/discontinuation.
o. Tumor assessment was performed on Day 1 of every other cycle (acceptable range: ±7 days). The tumor was evaluated by the same method used at the Baseline. Acceptable range of tumor assessment at EOT/discontinuation was + 28 days. If treatment was completed/discontinued less than 8 weeks after the previous tumor assessment, another assessment was not necessary. For subjects in whom the tumor was evaluated as response by RECIST (complete response /partial response), confirmation was required at least 28 days after the response was noted.

Number of Subjects (Planned and Analyzed): Six subjects were planned for enrollment to assess the PK of axitinib by single administration of 5 mg, followed by 7, and subsequently 10 mg dose. Enrollment of additional subjects was planned in case any subject discontinued the study and did not complete the PK evaluation. A total of 6 subjects were enrolled and assigned to study treatment and all enrolled subjects were treated with axitinib.

Diagnosis and Main Criteria for Inclusion: Subjects were male or female aged 20 years and older with histologically or cytologically diagnosed advanced solid tumors with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2, with no uncontrolled hypertension, and for whom standard therapies were not effective or there were no appropriate therapies. Subjects who had central lung lesions involving major blood vessels, required anticoagulant therapy, had active epilepsy symptoms, brain metastases requiring treatment, spinal cord compression or carcinomatous meningitis were excluded from the study.

Study Treatment: Subjects received a single 5-mg dose of axitinib, followed by single 7- and 10-mg doses. After administration of each of these single doses, subjects were monitored for at least 48 hours when no additional axitinib was administered. When the monitoring period was completed following the 10 mg single dose, subjects received multiple dosages of axitinib at 5 mg BID. Axitinib was administered orally to subjects in the fed state. Doses were to be taken as close to 12 hours apart as possible and at approximately the same time each day.

Subjects who tolerated axitinib without any treatment-related adverse events (AEs) above the Common Terminology Criteria for AEs (CTCAE [version 3.0,]) Grade 2 for consecutive 2-week periods from Day 1 of Cycle 1 had their dose titrated to 7 mg BID and then to a maximum of 10 mg BID, unless the subject had systolic blood BP >150 mm Hg or diastolic BP >90 mm Hg, or were receiving antihypertensive medication. Subjects were monitored for minimum of 2 weeks before every dose titration. Subjects who experienced hypertension, hemoptysis, proteinuria, other treatment-related nonhematological or AEs >Grade 3 (up to and including treatment-related Grade 4 hematological AEs) were considered for dosage reduction or a temporary discontinuation of axitinib treatment.

In this study, subjects continued study treatment until they experienced intolerable toxicity or progressive disease.

Efficacy, Pharmacokinetic, Pharmacodynamic, and Safety Endpoints:

Primary Endpoint:

- Plasma PK of axitinib following single dosing

Secondary Endpoints:

- AEs
- Plasma PK of axitinib following multiple dosing

- Plasma concentrations of s-VEGFR1, s-VEGFR2, s-VEGFR3, s-KIT and VEGF

- Anti-tumor effect; evaluate tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) by tumor type for subjects in whom the tumor was evaluated by RECIST

- Pharmacogenomics (PG); correlation between UGT1A1 and CYP3A4/5 genotype and PK of axitinib. Other genes suspected to affect to PK of axitinib was also evaluated

Safety Evaluations: Safety was assessed by monitoring adverse events, and laboratory test results, vital signs measurements, and electrocardiograms (ECGs).

Statistical Methods: Efficacy: The number of subjects assessed as complete response, partial response, stable disease and progressive disease according to the RECIST was summarized by tumor type.

Pharmacokinetic Analysis: Each PK parameter was summarized by cycle/day and included the set of summary statistics. For subjects who underwent dose modification, maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from Time 0 until 4 hours postdose (AUC_{4h}), time to first occurrence of C_{max} (T_{max}) and minimum plasma concentration (C_{min}) were calculated for each modified dose per subject.

Pharmacodynamics Analysis: Time profiles of individual PD parameters (plasma concentrations of s-VEGFR1, s-VEGFR2, s-VEGFR3, s-KIT, and VEGF) were summarized in graphs and tables, and descriptive statistics were calculated for measured values.

Pharmacogenomics (Genotyping): The correlation between UGT1A1 and CYP3A4/5 genotype and the PK of axitinib were investigated. Other genes suspected to affect the PK of axitinib could also have been evaluated.

RESULTS

Subject Disposition and Demography: A total of 6 subjects were assigned to study treatment and all were treated with axitinib. This study was continued until all subjects discontinued; the reason for discontinuation was lack of efficacy in all subjects (Table 3).

Table 3. Subject Disposition

Subject Category (Number of Subjects)	Axitinib (N=6)

Treated	6
Completed	0
Discontinued	6
Reason for Discontinuation	-
Related to Study Drug	-
Lack of Efficacy	6[a]

N = total number of enrolled subjects; PD = progressive disease.
a. All were assessed as having PD.

All 6 subjects were included in the each analysis set for PK, PD, PG, efficacy, and safety (Table 4).

Table 4. Data Sets Analyzed

Category (Number of Subjects)	Axitinib (N=6)
Assigned to Study Treatment	6
Analyzed for PK	6
Analyzed for PD	6
Analyzed for PG	6
Analyzed for Efficacy	-
Anti-Tumor Response	6
Analyzed for Safety	-
Adverse events	6
Laboratory data	6

N = total number of enrolled subjects; PD = pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetics.

Demography and baseline characteristics are summarized in Table 5. All (6) enrolled subjects were Japanese. Three subjects were male, 3 were female, and all were aged between 25 and 66 years, inclusive (mean age =53.8 years). No enrolled subjects were current smokers or had any kind of allergy. The baseline ECOG PS was 0 in 1 subject and 1 in 5 subjects.

Table 5. Subjects Demographics

Characteristic	Axitinib N=6
Gender, n	
Male	3
Female	3
Age (years) , n	
<18	0
18-44	1
45-64	3
≥65	2
Mean	53.8
SD	15.8
Range	25–66
Race, n	
Asian (Japanese)	6
Height (cm)	
Mean	161.9
SD	6.8
Range	151.6-70.6
Weight (kg)	
Mean	52.1
SD	11.8
Range	37.3-65.9
Smoking habit, n	
Yes	0
No	6[a]
Allergy, n	
Yes	0
No	6
ECOG Performance Status, n	
0	1
1	5

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

Efficacy, Pharmacokinetic, and Pharmacodynamic Results:

Pharmacokinetic Results: A summary of the plasma PK parameters after administration of single oral doses of axitinib (5, 7, and 10 mg [in the fed state]) is provided in Table 6. Geometric mean (coefficient of variation [CV, %]) for C_{max} after administration of a single oral dose of axitinib 5, 7 and 10 mg were 17.01 ng/mL (69.9%), 23.30 ng/mL (88.2%) and 34.91 ng/mL (114.7%), respectively. Geometric mean (CV%) for AUC_{inf} after administration of a single oral dose of axitinib 5, 7 and 10 mg were 142.0 ng∗h/mL (85.9%), 180.6 ng∗h/mL (80.2%) and 287.7 ng∗h/mL (91.1%), respectively. T_{max} and $t_{1/2}$ were similar after administration of each of the 3 dose levels.

Table 6. Axitinib Plasma Pharmacokinetic Parameters After 5, 7, and 10 mg Single-Dose

Dose (mg)	Variable	C_{max} (ng/mL)	AUC_{inf} (ng∗h/mL)	T_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
5	Geometric mean	17.01	142.0	4.100[a]	4.778[b]	35.25	206.4
	CV (%)	69.9	85.9	(3.95, 6.02)[c]	58.9	56.9	87.2
7	Geometric Mean	23.30	180.6	4.000[a]	5.088[b]	38.79	254.3
	CV (%)	88.2	80.2	(0.983, 9.88)[c]	50.9	61.8	82.8
10	Geometric Mean	34.91	287.7	4.015[a]	5.880[b]	34.74	246.3
	CV (%)	114.7	91.1	(2.05, 6.00)[c]	58.8	73.3	126.0

AUC_{inf} = area under the plasma concentration-time curve from time zero to time infinity; CV = coefficient of variation; C_{max} = maximum plasma concentration; CL/F = apparent oral clearance; T_{max} = time to first occurrence of C_{max}; $t_{1/2}$ = terminal phase plasma half life; V_z/F = apparent volume of distribution.

a. Median
b. Arithmetic mean
c. (minimum, maximum)

A summary of plasma PK parameters of axitinib after multiple oral dosing (5 mg BID in fed state) on Cycle 1 Day 15 is provided in Table 7. Geometric mean (CV%) for C_{max} and AUC_{τ} on Cycle 1 Day 15 were 21.40 ng/mL (83.7%) and 137.6 ng∗h/mL (77.9%), respectively. Median (min, max) for T_{max} on Cycle 1 Day 15 was 4.04 (3.93, 7.70) hours. The geometric mean (90% CI) of observed accumulation ratio (R_{ac}) for C_{max} and AUC were 1.257 (0.8728-1.811) and 1.372 (1.082-1.738), respectively. The observed R_{ac} was consistent with the value predicted from the mean half-life.

Table 7. Pharmacokinetic Parameters (5 mg BID at Cycle 1, Day 15)

Variable	C_{max} (ng/mL)	AUC_{τ} (ng∗h/mL)	T_{max} (h)	R_{ac}	
				C_{max}	AUC
Geometric Mean	21.40	137.6	4.040[a]	1.257	1.372
CV (%)	83.7	77.9	(3.93, 7.70)[b]	39.4	27.9
90% CI	NC	NC	NC	0.8728-1.811	1.082-1.738

N=6.
AUC_{τ} = area under the plasma concentration-time curve over dosing interval τ; CV = coefficient of variation; CI = confidence interval; C_{max} = maximum plasma concentration; N = total number of subjects; NC = Not calculated; R_{ac} = accumulation ratio; T_{max} = time to first occurrence of C_{max}; V_z/F = apparent volume of distribution.

a. Median
b. (minimum, maximum)

Plasma concentrations of soluble proteins are summarized in Table 8.

Table 8. Soluble Protein Plasma Concentrations

Soluble Protein	Visit/Day	Axitinib		
		N	Mean±SD	Median (Minimum, Maximum)
s-VEGFR1	Baseline[a] (pg/mL)	6	90.95±22.03	96.20 (60.9, 119.0)
	Cycle 2 Day 1 (pg/mL)	4	66.95±17.68	72.00 (41.8, 82.0)
	Percent change from Baseline (%)	4	–28.74±2.99	–29.15 (–31.4, –25.3)
s-VEGFR2	Baseline[a] (pg/mL)	6	8106.7±1060.3	8250.0 (6480, 9450)
	Cycle 2 Day 1 (pg/mL)	4	5460.0±1504.3	6035.0 (3290, 6480)
	Percent change from Baseline (%)	4	–37.72±14.21	–33.16 (–58.4, –26.2)
s-VEGFR3	Baseline[a] (pg/mL)	6	31616.7±10028.0	27000.0 (24600, 50400)
	Cycle 2 Day 1 (pg/mL)	4	15627.5±7266.4	15550.0 (8310, 23100)
	Percent change from Baseline (%)	4	–55.27±10.10	–56.38 (–66.2, –42.1)
s-KIT	Baseline[a] (pg/mL)	6	51666.7±10748.9	48250.0 (40900, 69500)
	Cycle 2 Day 1 (pg/mL)	4	44400.0±11869.3	43300.0 (31200, 59800)
	Percent change from Baseline (%)	4	–14.53±7.57	–14.59 (–23.7, –5.2)
VEGF	Baseline[a] (pg/mL)	6	126.80±144.52	67.80 (21.3, 414.0)
	Cycle 2 Day 1 (pg/mL)	4	246.73±142.84	249.00 (88.9, 400.0)
	Percent change from Baseline (%)	4	460.15±660.56	179.52 (37.0, 1444.6)

N = number of subjects with the given soluble protein at each visit; S.D. = standard deviation; s-KIT = soluble stem cell factor receptor; s-VEGFR = soluble vascular endothelial growth factor receptor; VEGF = vascular endthelial growth factor.

a. Plasma concentration value at Single dose Day 1 was used as the baseline value.

No subjects were identified as having heterozygous or homozygous variants for CYP3A4*1B, CYP3A4*2, CYP3A5*1B, CYP3A5*1C, CYP3A5*6, CYP3A5*7, UGT1A1*27 and UGT1A1*6. There were also no homozygous variants detected for UGT1A1*60, UGT1A1*93, or the UGT1A1 TA repeat. The relationship between PK parameters and genotype was not readily evident. For CYP3A5*3, the relationship between PK and genotype was unclear due to the limited number of subjects with this particular genotype.

Table 9. Predicted Genotype

Gene	Variant Genotyped	Axitinib N=6		
		Predicted Genotype		
		Homozygous Wild Type Number of Subjects n (%)	Heterozygous Number of Subjects n (%)	Homozygous Variant Number of Subjects n (%)
CYP3A4	1B	6 (100%)	-	-
	2	6 (100%)	-	-
CYP3A5	1B	6 (100%)	-	-
	1C	6 (100%)	-	-
	3	-	1 (16.7%)	5 (58.3%)
	6	6 (100%)	-	-
	7	6 (100%)	-	-
UGT1A1	27	6 (100%)	-	-
	*6	6 (100%)	-	-
	*60	2 (33.3%)	4 (66.7%)	-
	*93	5 (83.3%)	1 (16.7%)	-
	*36	5 (83.3%)	1 (16.7%)	-

CYP = cytochrome P450; n = number of subjects with the given genomic marker; N = total number of enrolled subjects; UGT1A1 = uridine diphosphate-glucuronosyltransferase.

Efficacy Results: Individual tumor response assessed by the Investigator is listed in Table 10.

Three (3)/6 subjects (50.0%) had a best RECIST defined response of stable disease. No subject showed RECIST defined CR or PR in this study. The target lesion size was decreased from baseline in 2 subjects (1 subject each with esophageal carcinoma and pancreatic carcinoma), with a maximum percentage decrease of 11.5% in 1 subject with pancreatic carcinoma.

Table 10. Individual Tumor Response (Investigator-Assessed)

Serial Number	Primary Diagnosis (MedDRA)	Best Overall Response (RECIST)	Maximum % Change[a] in Target Lesion Size From Baseline
1	Synovial sarcoma	SD	NA[b]
2	Oesophageal carcinoma	SD	–6.1
3	Hypopharyngeal cancer	PD	30.5
4	Gastric cancer	PD	27.2
5	Pancreatic carcinoma	SD	–11.5
6	Liposarcoma	PD	25.5

MedDRA version 13.0 coding dictionary applied.
NA = not applicable; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
a. When the sum of the longest diameter of target lesions was the smallest during the study.
b. No measurable lesion at Baseline.

Safety Results: Commonly reported all-causality nonserious AEs were fatigue, hypertension, blood TSH increased, proteinuria, palmar-plantar erythrodysasthesia syndrome (Table 11).

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

System Organ Class and MedDRA Preferred Term	Axitinib N=6
Number of subjects: evaluable for AEs n (%)	6
Number of subjects: with AEs n (%)	6 (100.0)
Endocrine disorders	1 (16.7)
Thyroiditis chronic	1 (16.7)
Eye disorders	1 (16.7)
Eye irritation	1 (16.7)
Gastrointestinal disorders	4 (66.7)
Abdominal pain upper	1 (16.7)
Ascites	1 (16.7)
Cheilitis	1 (16.7)
Constipation	2 (33.3)
Diarrhoea	3 (50.0)
Nausea	2 (33.3)
Stomatitis	2 (33.3)
General disorders and administration site conditions	5 (83.3)
Chest pain	1 (16.7)
Fatigue	5 (83.3)
Mucosal inflammation	1 (16.7)
Oedema	2 (33.3)
Hepatobiliary disorders	1 (16.7)
Jaundice cholestatic	1 (16.7)
Infections and infestations	2 (33.3)
Nasopharyngitis	2 (33.3)
Paronychia	1 (16.7)
Injury, poisoning and procedural complications	2 (33.3)
Contusion	1 (16.7)
Fracture	1 (16.7)
Investigations	6 (100.0)
Alanine aminotransferase increased	1 (16.7)
Aspartate aminotransferase increased	2 (33.3)
Blood alkaline phosphatase increased	3 (50.0)
Blood amylase increased	3 (50.0)
Blood cholesterol increased	2 (33.3)
Blood lactate dehydrogenase increased	3 (50.0)
Blood potassium increased	1 (16.7)
Blood thyroid stimulating hormone decreased	2 (33.3)
Blood thyroid stimulating hormone increased	4 (66.7)
Blood urine present	1 (16.7)
Lipase increased	1 (16.7)
Neutrophil count decreased	2 (33.3)
Platelet count decreased	1 (16.7)
Thyroglobulin increased	1 (16.7)
Thyroxine free decreased	2 (33.3)
Thyroxine free increased	1 (16.7)
Tri-iodothyronine free decreased	2 (33.3)
Weight decreased	1 (16.7)
White blood cell count decreased	2 (33.3)
Metabolism and nutrition disorders	3 (50.0)
Decreased appetite	3 (50.0)
Musculoskeletal and connective tissue disorders	3 (50.0)

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

System Organ Class and MedDRA Preferred Term	Axitinib N=6
Back pain	1 (16.7)
Myalgia	2 (33.3)
Neck pain	1 (16.7)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	2 (33.3)
Cancer pain	2 (33.3)
Nervous system disorders	4 (66.7)
Dizziness	1 (16.7)
Headache	2 (33.3)
Neuropathy peripheral	3 (50.0)
Somnolence	1 (16.7)
Renal and urinary disorders	4 (66.7)
Proteinuria	4 (66.7)
Reproductive system and breast disorders	1 (16.7)
Menstruation irregular	1 (16.7)
Respiratory, thoracic and mediastinal disorders	3 (50.0)
Cough	1 (16.7)
Dysphonia	2 (33.3)
Epistaxis	2 (33.3)
Skin and subcutaneous tissue disorders	5 (83.3)
Dermatitis	1 (16.7)
Dermatitis acneiform	1 (16.7)
Haemorrhage subcutaneous	1 (16.7)
Palmar-plantar erythrodyasthesia syndrome	4 (66.7)
Pruritus	1 (16.7)
Rash	3 (50.0)
Telangiectasia	1 (16.7)
Urticaria	1 (16.7)
Vascular disorders	5 (83.3)
Hypertension	5 (83.3)
Hypotension	2 (33.3)

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (version 13.0) coding dictionary applied.
AE = adverse events; n = number of subjects with AEs; N = total number of enrolled subjects.

Treatment-related AEs are summarized in Table 12.

Table 12. Summary of Treatment-Emergent Adverse Events (Treatment Related, All Cycles)

System Organ Class Preferred Term	Axitinib (N=6) n (%)
Any AEs	6 (100.0)
Endocrine disorders	1 (16.7)
Thyroiditis chronic	1 (16.7)
Eye disorders	1 (16.7)
Eye irritation	1 (16.7)
Gastrointestinal disorders	4 (66.7)
Ascites	1 (16.7)
Cheilitis	1 (16.7)
Constipation	2 (33.3)
Diarrhoea	3 (50.0)
Nausea	1 (16.7)
Stomatitis	2 (33.3)
General disorders and administration site conditions	5 (83.3)
Fatigue	5 (83.3)
Mucosal inflammation	1 (16.7)
Oedema	2 (33.3)
Infections and infestations	1 (16.7)
Paronychia	1 (16.7)
Investigations	5 (83.3)
Blood amylase increased	2 (33.3)
Blood cholesterol increased	2 (33.3)
Blood potassium increased	1 (16.7)
Blood thyroid stimulating hormone increased	4 (66.7)
Lipase increased	1 (16.7)
Neutrophil count decreased	2 (33.3)
Platelet count decreased	1 (16.7)
Thyroglobulin increased	1 (16.7)
Thyroxine free decreased	2 (33.3)
Tri-iodothyronine free decreased	2 (33.3)
Weight decreased	1 (16.7)
White Blood cell count decreased	2 (33.3)
Metabolism and nutrition disorders	2 (33.3)
Decreased appetite	2 (33.3)
Musculoskeletal and connective tissue disorders	2 (33.3)
Myalgia	2 (33.3)
Nervous system disorders	2 (33.3)
Headache	2 (33.3)
Neuropathy peripheral	1 (16.7)
Somnolence	1 (16.7)
Renal and urinary disorders	4 (66.7)
Proteinuria	4 (66.7)
Reproductive system and breast disorders	1 (16.7)
Menstruation irregular	1 (16.7)
Respiratory, thoracic and mediastinal disorders	3 (50.0)
Dysphonia	2 (33.3)
Epistaxis	2 (33.3)
Skin and subcutaneous tissue disorders	5 (83.3)
Dermatitis	1 (16.7)
Dermatitis acneiform	1 (16.7)

Table 12. Summary of Treatment-Emergent Adverse Events (Treatment Related, All Cycles)

System Organ Class Preferred Term	Axitinib (N=6) n (%)
Haemorrhage subcutaneous	1 (16.7)
Palmar-plantar erythrodysaesthesia syndrome	4 (66.7)
Pruritus	1 (16.7)
Rash	3 (50.0)
Telangiectasia	1 (16.7)
Urticaria	1 (16.7)
Vascular disorders	5 (83.3)
Hypertension	5 (83.3)

MedDRA (version 13.0) coding dictionary applied.
SAEs and AEs are not separated out in this table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with AEs; SAE = serious adverse events.

No SAEs was reported other than 1 disease progression (gastric cancer) resulted in death.

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=6
Number of subjects: evaluable for AEs n (%)	6
Number of subjects: with AEs n (%)	1 (16.7)
General disorders and administration site conditions	1 (16.7)
Disease progression	1 (16.7)

Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
MedDRA (version 13.0) coding dictionary applied.
AE = adverse events; MedDRA = medical Dictionary for Regulatory Activities, n = number of subjects with AEs; N = total number of enrolled subjects.

Discontinuations: No subject discontinued the study due to an AE. Four (4) of the 6 total subjects temporarily discontinued the study drug due to AEs and 2 of them also had dose reductions. Frequently observed AEs which caused temporary discontinuations were hypertension (4 subjects), proteinuria (1 subject), dysphonia (1 subject), and palmar-plantar erythrodyasthesia syndrome (1 subject). The reasons for dose reductions were proteinuria and palmar-plantar erythrodyasthesia syndrome (1 subject each).

Deaths: There was 1 death reported in this study, a 57-year-old female subject died on the study on Day 72 due to disease progression (gastric cancer, not-related to the study drug).

Electrocardiogram, Clinical Laboratory and Vital Sign Results: The mean changes (±SD) of ECG QTc interval from the baseline were 0.4±11.1 msec at Cycle 1 Day 15 and -13.1±9.2 msec at the end of treatment /discontinuation. No subject had a clinically significant abnormal ECG value throughout the study.

All 6 subjects had at least 1 post baseline laboratory test value abnormal regardless of the baseline abnormality. Decreased lymphocytes (%) was observed in all 6 subjects. Thyroid stimulating hormone (TSH) abnormal was the most commonly reported laboratory test abnormality; Increased TSH was reported in 5/6 subjects and decreased TSH was reported in 3/6 subjects. Other common abnormalities reported in >50% of subjects were decreased hemoglobin (4 subjects) and increased basophils (%; 4 subjects).
Elevations in mean BP were observed with the peak at 8 to 10 hours postdose. Five subjects reported hypertension as an AE, and 3/6 experienced at least 1 Grade 3 event. However, these events were controllable with antihypertensive agents.

CONCLUSIONS:

- C_{max} and AUC were increased dose-proportionally for axitinib single 5, 7, and 10 mg doses in subjects with solid tumors.

- Axitinib was absorbed with peak plasma axitinib concentrations observed at 4 hours after dosing in fed state and had an elimination half-life of 4.778-5.880 hours. The R_{ac} for C_{max} and AUC was consistent with the value predicted from mean half-life of the drug.

- Common treatment-related AEs (>50%) were fatigue, hypertension, blood TSH increased, proteinuria, and palmar-plantar erythrodysaesthesia syndrome. Common Grade 3 treatment-related AEs were hypertension. No SAEs was reported other than 1 disease progression resulted in death (gastric cancer, not-related to the study drug). No subject discontinued the study due to a AEs. Overall, axitinib was well tolerated in this study.

- Axitinib increased VEGF and decreased plasma s-VEGFR1, s-VEGFR2, s-VEGFR3, and s-KIT concentrations. The changes in s-KIT were less pronounced relative to s-VEGFR1, 2, and 3.

- Correlations between PK and CYP3A4/5 and UGT genotypes were not readily evident; however, this may have been due to the limited number of subjects.

- The best tumor response according to RECIST was stable disease in 3 of 6 subjects. Three subjects entered ≥12 cycles of study treatment (with a maximum of 17 cycles) before progressive disease was noted.