PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: A4061046

PROTOCOL TITLE: Randomized, Double-Blind Phase 2 Study of Axitinib (AG 013736) With or Without Dose Titration in Patients With Metastatic Renal Cell Carcinoma

Study Center: A total of 52 centers took part in the study and enrolled subjects; 19 in the United States, 15 in Japan, 6 in the Russian Federation, 5 in Germany, 4 in the Czech Republic, and 3 in Spain.

Study Initiation, Primary Completion, and Final Completion Dates:
Study Initiation Date: 11 September 2009
Primary Completion Date (PCD): 12 October 2012
Final Completion Date: This study is still ongoing.

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To compare the objective response rate (ORR) in subjects receiving axitinib with or without dose titration (Arms A and B, respectively).

Secondary Objective: To assess the safety profile, other efficacy parameters, pharmacokinetics (PK), biomarker and/or gene expression profiling correlations with clinical outcome and/or blood pressure (BP) measurements in subjects receiving axitinib with or without dose titration (Arms A and B, respectively). Although the main study comparison is between Arms A and B, additional information such as those related to safety and biomarker/gene expression profiling correlations with clinical outcome were also assessed in the non-randomized group, Arm C. Subjects who discontinued the study during the lead-in period, prior to the point of randomization decision, were analyzed in a separate arm (additional to Arms A, B, and C).

METHODS

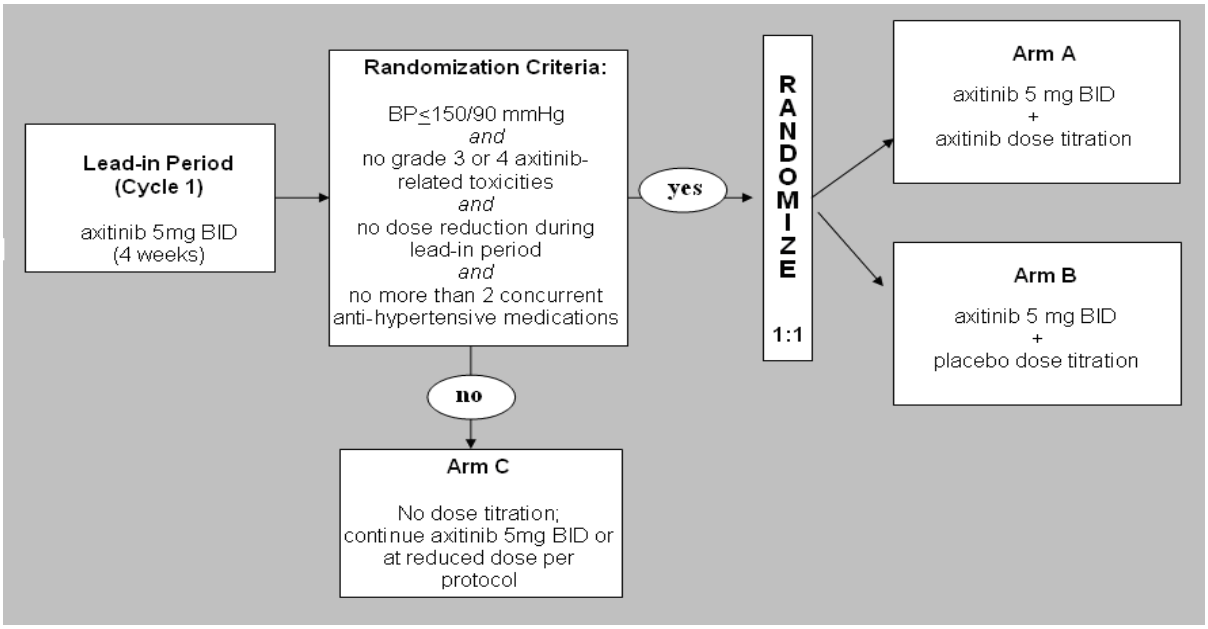
Study Design: This was a randomized, double-blind (DB), placebo-controlled, Phase 2 study of axitinib with or without dose titration in subjects with metastatic renal cell carcinoma (mRCC).

Eligible subjects were to be initially enrolled in a lead-in period (4 weeks) during which they received a starting dose of axitinib 5 mg twice a day (BID) as Cycle 1 (Figure 1). After the

lead-in period, subjects who met the randomization criteria, were to be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus [vs] 1), and randomized (1:1 ratio) to dose titration with either axitinib (Arm A) or placebo (Arm B). Subjects who did not meet randomization criteria were not to be randomized but were to continue on study without dose titration (Arm C). Once assigned to a treatment arm, subjects were to remain in the same treatment arm throughout the study; cross over to another treatment arm of the study was not permitted. Subjects were to receive treatment on an outpatient basis.

After the lead-in period (Cycle 1; Figure 1) and prior to randomization, the following randomization criteria had to be met: systolic BP (sBP) ≤150 mm Hg and diastolic BP (dBP) ≤90 mm Hg, no Grade 3 or 4 axitinib-related toxicities, no dose reduction during lead-in period, and no >2 concurrent antihypertensive medications. BP criteria were to be met and documented by 2 BP readings taken 1 hour apart, just prior to randomization (1:1 ratio), on Cycle 2 Day 1. Randomization was using a Interactive Voice Response System, and assigned to receive either axitinib + axitinib dose titration (Arm A) or axitinib + placebo dose titration (Arm B), unless otherwise contraindicated per Investigator's judgment.

Figure 1. Overview of the Study Design



BID = twice a day; BP = blood pressure.

The study duration for an individual subject included a 14-day screening period, a 4-weeks lead-in period and subsequent treatment cycles with axitinib (with active titration or placebo titration, Arm A or Arm B; or without dose titration, Arm C) until the end-of-study.

The detailed schedule of activities for the study is presented in Table 1.

Table 1. Schedule of Activities

Protocol Activity[a]	**Screening**[b] **Day -14 to Day -1**	**Prior to Lead-in Period (Cycle 1) Day -1**[c]	**Lead-in Period**[d] **(Cycle 1) Day 1**[e]	**Lead-in Period (Cycle 1) Day 4**	**Lead-in Period (Cycle 1) Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 15**	**Cycle 3 & Subsequent Odd Cycles Day 1**	**Cycle 4 & Subsequent Even Cycles Day 1**	**End of Study**	**Follow-Up 28 Days After Last Dose**[f]
Informed consent[b]	X										
Randomization (if eligible)[g]						X					
Assessment for dose titration[h]							X	(X)	(X)		
Medical and oncologic history	X										
ECOG performance status	X		X		X	X		X	X	X	X
12-lead ECG	X										
Physical examination[i]	X		X		X	X		X	X	X	
Vital signs[j]	X		X		X	X	X	X	X	X	X
Home BP monitoring[k]		X	----------Twice daily throughout the study period----------								
Collect home BP diary						X		X	X	X	(X)
Assess/record BP intervention[l]				X	X	X	X	X	X	X	
Hematology[m]	X		X			X		X	X	X	
Blood chemistry[n]	X		X			X		X	X	X	
Thyroid function testing[o]	X				X	X	X		X		
Urine protein[p]	X		X			X		X	X	X	
Pregnancy test[q]	X										
PK (serial 6-hr or sparse)[r,s,t]					X[r]		X[s]	(X)[t]			
24 hour ABPM and telemedicine[u]		X		X	X						
Brain MRI or CT scan	Day -28 to Day -1										
Tumor assessments[v]	Day -28 to Day -1							Q8 weeks X3, then Q12 weeks			
AE assessment[w]	X		Throughout the study period							X	X
Concomitant medications	X		Throughout the study period							X	
Biomarkers[x]			X		X		X	X (soluble proteins, Cycle 3 Day 1 only)	X (soluble proteins, Cycle 4 Day1 only)	X	
Genotyping[y]			X								
Survival[z]											X, Q3 months

Table 1. Schedule of Activities

ABPM = ambulatory blood pressure monitoring; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice a day; BP = blood pressure; CEC = circulating endothelial cell; CEP = circulating endothelial cell progenitor; CR = complete response; CRF = case report form; dBP = diastolic blood pressure; EC = Ethics Committee; Hgb = hemoglobin; IRB = Institutional Review Bord; LDH = lactate dehydrogenase; PK = pharmacokinetic; PR = partial response; sBP = systolic blood pressure; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1; UPC = urine protein : creatinine (ratio); WBC = white blood cell.

a. Schedule could have varied ±4 days (except where noted) to allow flexibility. Schedule of activities represents the minimum required procedures. Additional/more frequent assessments could be performed as clinically indicated and per standard medical practice.
b. Screening & baseline assessments: informed consent had been obtained prior to any procedures performed solely for study purposes.
c. Prior to lead-in period, Day -1 ABPM could be performed between Day -7 to Day -1, after enrollment eligibility had been confirmed.
d. Lead-in period was Cycle 1. Each cycle length was 4 weeks.
e. Day 1: was not to repeat Cycle 1 Day 1 assessments if they were performed and acceptable within previous 7 days.
f. Follow-up: performed 28 days after the last dose of study drug or at initiation of a new anticancer treatment, whichever occurred first.
g. Randomization criteria had to be met for randomization. After completing the lead-in period, subjects who met all of the following randomization criteria for 2 consecutive weeks during the lead-in period (Cycle 1) were to be randomized, unless otherwise contraindicated per Investigator's judgment: sBP ≤150 mm/Hg; and dBP ≤90 mm/Hg; and no Grade 3 or 4 axitinib-related toxicities; and no dose reduction during lead-in period; and no >2 concurrent antihypertensive medications. BP criteria were to be met and documented by 2 BP readings taken 1 hour apart. Subjects who did not meet randomization criteria were not to be randomized but were to continue on study without dose titration in Arm C. Once a treatment arm had been assigned, crossover to another arm was not permitted.
h. Arms A and B only. Prior to dose titration, subjects had to meet the dose titration criteria for each step of dose titration. The maximum dose level was 10 mg BID. After at least 2 consecutive weeks on the current dose, subjects satisfying the following dose titration criteria were to have their dose level increased by 1 additional dose level, unless otherwise contraindicated per the Investigator's clinical judgment: sBP ≤150 mm Hg; and dBP ≤90 mm Hg; and no Grade 3 or 4 axitinib-related toxicities; and no >2 concurrent antihypertensive medications.
i. Physical examination: included height/weight on initial examination. Subsequent targeted examinations based on signs and symptoms could be performed.
j. Vital signs included: BP taken with the subject in the seated position after the subject had been sitting quietly for 5 minutes, pulse, temperature, respiratory rate.
k. BP: BP was to be taken with the subject in the seated position after the subject had been sitting quietly for 5 minutes. All subjects were to receive home BP monitoring devices. Subjects were to take BP at least twice daily prior to taking each dose of axitinib, and BP was to be recorded in a subject diary. Subjects were to be instructed to contact their doctor immediately for guidance if their sBP rose above 150 mm Hg, dBP rose above 100 mm Hg, or if they developed symptoms perceived to be related to elevated BP (eg, headache, visual disturbance).
l. Assessed and recorded on CRF whether or not home BP measurement(s) resulted in any of the following clinical intervention(s) at any time point during the cycle: BP medication added, BP medication dose adjusted, study drug temporarily held, study drug dose adjusted, study drug permanently discontinued, hospitalization, other medical/pharmacological intervention (CRF). A CRF was to be completed each time home BP measurement(s) trigger(s) any of the above intervention(s), even if the intervention occurred outside of a clinic visit.
m. Hematology: Hgb, WBC, ANC, and platelets. All lab tests were to be performed at local labs.
n. Serum chemistry: sodium, potassium, chloride, LDH, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, BUN, creatinine, and glucose.
o. Serum or plasma thyroid function testing: TSH, total or free T3, and free T4.
p. Urine protein: if urine protein ≥2+ by semiquantitative method (eg, dipstick) then was to quantify by UPC ratio.
q. Pregnancy test (serum/urine): was to be performed within 72 hours of treatment only for women of childbearing potential. To be repeated during the study if clinically indicated or requested by the EC/IRB or required by local regulations.
r. Lead-in period Day 15 (Cycle 1 Day 15): serial 6-hour PK profiling was to be obtained from approximately 75 subjects at designated sites at the following time points: predose, 0.5, 1, 2, 4, 6 hours postdose. A BP reading was to be obtained up to 5 minutes prior to each PK draw (BP reading could be obtained by manually prompting the ABPM device and recording the time of manual prompting). Subjects were to be instructed to hold the morning axitinib dose on the day of PK sampling until the predose PK

Table 1. Schedule of Activities

had been drawn. If subjects had inadvertently taken their morning axitinib dose prior to the serial PK draw, the serial 6-hour PK collections and the ABPM were to be deferred to another day prior to Cycle 2 Day 1. Note that the Cycle 1 Day 15 ABPM was to be initiated on the same day as the Cycle 1 Day 15 serial 6-hour PK and ABPM was to be initiated prior to the first PK collection of that day. Sparse PK samples were to be collected from the remaining subjects (who were not getting serial 6-hour PKs) at the following 2 time points: predose and 1-2 hours postdose. Subjects were to be instructed to hold the morning axitinib dose on the day of PK sampling until the predose PK had been drawn. If subjects had inadvertently taken their morning axitinib dose before arriving at the clinic, then 2 PK blood samples separated by at least 2 hours were to be collected at the clinic, and the time of axitinib dosing was to be recorded.

s. Postrandomization Day 15 (Cycle 2 Day 15) Arms A and B only: serial 6-hour PK profiling was to be obtained from approximately 12 subjects enrolled in each of Arm A and B at designated sites at the following time points: predose, 0.5, 1, 2, 4, and 6 hours postdose. Note that these 12 subjects in each of Arm A and B were among the same 75 subjects who had PK performed on Day 15 of the lead-in period (Cycle 1 Day 15). Subjects were to be instructed to hold the morning axitinib dose on the day of PK sampling until the predose PK had been drawn. If subjects had inadvertently taken their morning axitinib dose prior to the serial PK draw, the serial 6-hour PK collections were to be deferred to another day prior to Cycle 3 Day 1. Sparse PK samples were to be collected from the remaining subjects (who were not getting serial 6-hour PK) at the following 2 time points: predose and 1-2 hours postdose. Subjects were to be instructed to hold the morning axitinib dose on the day of PK sampling until the predose PK had been drawn. If subjects had inadvertently taken their morning axitinib dose before arriving at the clinic, then 2 PK blood samples separated by at least 2 hours were to be collected at the clinic and the time of axitinib dosing was to be recorded.
t. Postrandomization, posttitration to 10 mg (Arms A and B only): sparse PK sampling: If applicable, all subjects in Arms A and B who titrated up to 10 mg BID doses were to have 2 PK blood samples collected at least 4 days after starting on 10 mg BID (ie, at the next scheduled visit; regardless of which cycle [odd/even] titration to 10 mg occurred) at the following 2 time points: at predose and 1-2 hours postdose. Subjects were to be instructed to hold the morning axitinib dose until the predose PK had been drawn. If subjects had inadvertently taken their morning axitinib dose prior to the sparse PK draw, then 2 sparse PK blood samples separated by at least 2 hours were to be collected at the clinic, and the time of axitinib dosing was to be recorded.
u. A baseline ABPM was to be performed on Day -1 of the lead-in period on approximately 75 subjects at designated sites; note that these 75 subjects were also the same 75 subjects from whom serial 6-hour PK was to be collected. To allow flexibility in scheduling, Day -1 ABPM could be performed between Day -7 and Day -1, after enrollment eligibility had been confirmed. On Day 4 and Day 15 of the lead-in period (Cycle 1 Day 4, Cycle 1 Day 15), ABPM was to be performed on the same 75 subjects who had a baseline ABPM. ABPM was to be performed throughout the day. Additionally, a BP reading was to be obtained up to 5 minutes prior to each PK draw on Cycle 1 Day 15 (BP reading could be obtained by manually prompting the ABPM device and recording the time of manual prompting). Note that the Cycle 1 Day 15 ABPM was to be initiated on the same day as the Cycle 1 Day 15 serial 6-hour PK, and ABPM was to be initiated prior to the first PK collection of that day. To allow flexibility in scheduling, Day 4 ABPM could be performed between Day 3 and Day 7; Day 15 ABPM could be performed between Day 13 and Day 17, as long as the Cycle 1 Day 15 serial 6-hour PK was also performed on the same day as ABPM.
v. Radiographic tumor assessments: CT scan of chest, abdomen, and pelvis performed at Baseline and repeated every 8 weeks x 3, then every 12 weeks. A PR or CR was to be confirmed with a repeat scan at least 4 weeks, but no later than 6 weeks, after the PR/CR.
w. AE assessments: the reporting period for nonserious AEs terminated 28 days after the last dose of study treatment or upon initiation of a new anticancer treatment, whichever occurred first. Ongoing treatment-related AEs were to be followed up until resolution, return to baseline, chronicity, or initiation of subsequent anticancer treatment. The serious AEs reporting period ended 28 days after the last study treatment dose, irrespectively of start of any new anticancer treatment.
x. Biomarkers were to include blood samples for each of the following: 1) gene expression profiling in whole blood (2.5 mL); 2) gene expression profiling in CECs isolated from whole blood (9 mL); 3) enumeration and functional status of CECs/CEPs (7.5 mL); and 4) soluble proteins (6 mL).
y. Genotyping for UGT1A1 and other genes/drug metabolizing enzymes/transporters. 1 blood sample (2 mL).
z. Survival status was to be collected and recorded every 3 months after the follow-up study visit, until at least 1 year after the last subject had been randomized.

Number of Subjects (Planned and Analyzed): A total of 200 subjects were planned for enrollment in order to obtain approximately 70 randomizable subjects (35 in each, Arm A and Arm B). A total of 213 subjects were enrolled and treated during the study: 56 subjects each in Arm A and Arm B, 91 subjects in the non-randomized group, and 10 subjects in the discontinued prior to randomization group.

Diagnosis and Main Criteria for Inclusion: Males and females, 18 years and older, who were diagnosed with mRCC with clear cell component, who received no prior systemic therapy (including no prior adjuvant or neo-adjuvant). Subjects had to have ECOG performance status 0-1 and BP ≤140/90 mm Hg. Subjects with brain/central nervous system metastasis and subjects who were using >2 BP medications were excluded from the study.

Study Treatment: Axitinib and matching placebo were supplied as 1-mg and 5-mg, immediate-release, film-coated tablets for oral administration.

During the lead-in period, all enrolled subjects received a starting dose of axitinib 5 mg BID taken orally, and dose titration was not permitted; however, dose reduction was permitted. Subjects who required a dose reduction during the lead-in period, or otherwise did not meet the randomization criteria, were not randomized and continued the study without dose titration in Arm C.

Arm A Treatment: Subjects received a total dose of 7 mg of axitinib taken as 3 tablets BID (ie, axitinib 5 mg BID + 2 DB axitinib 1 mg BID). After at least 2 consecutive weeks at the 7 mg BID dose, subjects who continued to satisfy the dose titration criteria were to have their DB dose level increased by 1 additional dose level, to 10-mg axitinib taken as 2 tablets BID (ie, axitinib 5 mg BID + 1 DB axitinib 5 mg BID), which was the maximum total dose in Arm A.

Arm B Treatment: Subjects received a total dose of 5 mg of axitinib taken as 3 tablets BID (ie, axitinib 5 mg BID + 2 DB placebo for axitinib 1 mg BID). After at least 2 consecutive weeks at the 5 mg BID dose, subjects who continued to satisfy the dose titration criteria were to have their DB dose level increased by 1 additional dose level, to 5 mg axitinib taken as 2 tablets BID (ie, axitinib 5 mg BID + 1 DB placebo 5 mg BID), which was the maximum total dose in Arm B.

If a dose reduction was necessary, it was to begin by reducing the blinded treatment first, and then by reducing the open-label axitinib, if necessary.

Arm C Treatment: Non-randomized subjects received axitinib 5 mg BID or a reduced dose, as per the dose modification guideline. Dose titration was not permitted in this treatment arm.

The general dose modifications guidelines, based on the Common Terminology Criteria for Adverse Events (CTCAEs), are outlined in Table 2. Specific dose modifications were created for the management of hypertension and proteinuria, and dose interruption requirement for surgery or surgical procedures.

Table 2. Dose Modification Criteria for Drug-Related Adverse Events Other Than Hypertension or Proteinuria

Related Adverse Events	Intervention
Grade 1	Continued at same dose level
Grade 2	Continued at same dose level
Grade 3[a]	Decreased dose to 1 lower dose level.
Grade 4[b]	Interrupted dosing; re-started at 1 lower dose level as soon as improvement to CTCAE Grade ≤2. If subject required dose reduction below 2 mg BID, was to contact Sponsor for discussion.

[a] Subjects who developed Grade 3 nonhematologic toxicities that were controlled (ie, with medication) or Grade 3 asymptomatic biochemistry laboratory abnormalities could continue at the same dose level at the discretion of the Investigator.

[b] Subjects who developed Grade 4 lymphopenia or Grade 4 asymptomatic biochemistry laboratory abnormalities could continue study treatment without interruption at the discretion of the Investigator.

Permitted concomitant medications were: palliative and supportive care for disease-related symptoms (bisphosphonates, radiation), low-dose or short course of corticosteroids, antacid therapy and antihypertensive treatment.

Efficacy, Pharmacokinetic, Pharmacodynamic and Safety Endpoints:

Primary Endpoint:

- ORR (Arm A vs Arm B)

Secondary Endpoints:

- Progression free survival (PFS; Arms A and B)
- Overall survival (OS; Arms A and B)
- Overall safety profile (Arms A, B, C)
- Duration of response (DR; Arms A and B)
- BP measurements
- Plasma PK (Arms A and B)
- Biomarker and gene expression profiling correlations with response rate and/or BP measurements (Arms A, B, C)

Safety Evaluations: Safety evaluations included monitoring of adverse events (AEs), serious AEs (SAEs), laboratory evaluations (hematology, clinical chemistry, thyroid function test, and urinalysis), physical examination, 12-lead electrocardiogram (ECG), BP assessments, and 24 hour ambulatory BP monitoring (ABPM) and telemedicine at specified time points during the study (Table 1).

Statistical Methods:

Analysis Sets: The full analysis (FA) 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 that to which they were randomized. This was the primary analysis set for evaluating all efficacy endpoints as well as subject characteristics.

The safety analysis (SA) population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This analysis set was the primary 1 for evaluating treatment administration/compliance and safety.

The PK concentration population included all subjects who were treated and had at least 1 concentration on at least 1 PK assessment day. The PK parameter analysis data set included all subjects treated who had at least 1 estimated PK parameter of primary interest.

The biomarker analysis set included subjects receiving at least 1 dose of treatment, with a Cycle 1 Day 1 biomarker result for at least 1 biomarker.

Statistical Analysis: Descriptive statistics and analyses were provided for subjects overall. Baseline was defined as the last evaluation prior to the first dose of study medication.

Efficacy:

Primary Efficacy Analysis: ORR for the 2 treatment arms was compared with a 1-sided Pearson chi-square test for unstratified analyses and the Cochran-Mantel-Haenszel (CMH) test for stratified analyses. For the unstratified analyses, point estimates of the rates for each treatment arm and difference of the rates between treatment arms were provided along with the corresponding 2-sided 95% confidence intervals (CIs) using an exact method based on the F-distribution and using a normal approximation for constructing a CI for differences, respectively. For the stratified analyses, the relative risk ratio estimator was used to contrast the treatment effects on the endpoint. Both a point estimate and a 2-sided 95% CI were calculated using a normal approximation.

Secondary Efficacy Analysis: PFS in each arm was assessed using the Kaplan-Meier (KM) method in the FA population and compared with a 1-sided stratified log rank test. Estimates of the PFS curves from the KM method were presented. This method was applied to derive the median event time and a CI for the median for each treatment arm. The CI was 2-sided, had a stated coverage probability of 95%, and was calculated using normal approximation methods.

As additional sub analyses, an un-stratified log-rank test was calculated. Also, Cox proportional hazard models were used to explore the potential influences of the baseline stratification factor. Additionally, a time-dependent Cox model was fitted to the axitinib active titration arm to look at the influence of dose titration on PFS. The time-dependent covariate for dose titration was coded as less than treatment arm median weeks at a titrated

dose above 5 mg BID vs greater than or equal to treatment arm median weeks at a titrated dose above 5 mg BID.

The same analyses were done for OS as were done for PFS. Additionally, the survival probability at 1 year was estimated for each treatment arm using the KM method, and the 2-sided 95% CI for the log (-log[1-year survival probability]) was calculated using a normal approximation and then back transformed to give the CI for the 1-year survival rate itself.

Estimates of the DR curves from the KM method were presented. This method was applied to derive the median event time and a CI for the median for each treatment arm. The CI was 2-sided, had a stated coverage probability of 95%, and was calculated using normal approximation methods.

Safety: AEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The number and percentage of subjects who experienced any AE, SAE, treatment-related AE or SAE, and who discontinued because of an AE were presented. Deaths were summarized by time period (on treatment vs during follow up) and cause of death.

For hematology, biochemistry, descriptive statistics were provided for each test result and for change from Baseline by visit. Hematology and biochemistry results were graded according to the National Cancer Institute CTCAE version 3.0. For urine, descriptive statistics were provided for urine protein results and for change from Baseline by visit. For vital signs and ECOG performance status, data were summarized and listed. For ECGs, data were listed.

All concomitant medications were coded by the World Health Organization (WHO) medical dictionary. Data for concomitant medications, nondrug treatments, follow-up systemic therapy for primary diagnosis, were summarized and listed.

Pharmacokinetics: For the 6-hour PK profiles obtained in this study, standard axitinib PK parameters (maximum plasma concentration [C_{max}], time at which C_{max} is observed [T_{max}], terminal plasma elimination half life [$t_{½}$], terminal phase rate constant [k_{el}], area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration [AUC_{last}], area under the plasma concentration time curve from time 0 to 24 hours [AUC_{24}], apparent oral clearance [CL/F], and apparent oral volume of distribution during the elimination phase [V_z/F]) were estimated using non compartmental methods.

The axitinib PK were summarized for approximately 75 subjects on Cycle 1 Day 15. PK on Cycle 1 Day 15 for subjects eligible for dose titration (Arms A and B) vs subjects not eligible for dose titration (Arm C) were also summarized and reported.

The study was not powered to detect differences in axitinib PK. As an exploratory analysis, the PK parameter data for the axitinib on Cycle 2 Day 15 between Arm A and Arm B were summarized and reported.

Plasma concentrations for axitinib were listed by cycle, treatment arm, nominal time, and actual time postdose. Axitinib plasma concentrations were summarized by cycle, treatment arm, and nominal time using descriptive statistics (number [n], mean, standard

deviation [SD], percent coefficient of variation [%CV], median, minimum, maximum). Linear and semi log plots of median axitinib plasma concentrations vs nominal time were prepared by cycle, and treatment arm. Similar individual subject's plasma concentrations plots (with data from all visits on the same plot) were generated. For comparisons between Arms A and B and Arm C on Cycle 1 Day 15, and comparisons between Arms A and B on Cycle 2 Day 15, linear and semi log plots of median plasma concentrations vs nominal time for axitinib were generated.

PK parameters for axitinib were listed and summarized by cycle, and treatment arm using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, and geometric mean and its associated 95% CI as well as %CV around geometric mean). PK parameters with 0 values were excluded from the calculation of geometric means (and associated 95% CIs). Dose normalized PK parameters (C_{max}, AUC_{last}, and AUC_{24}) on Cycle 2 Day 15 were compared between Arm A vs Arm B.

The correlation of changes in BP and axitinib PK were assessed. Cycle 1 Day 15 PK parameters (AUC_{24}, AUC_{last}, and C_{max}) and plasma concentrations were correlated with mean absolute BP measurements (both sBP and dBP) obtained with ABPM on Cycle 1 Day 4 and Cycle 1 Day 15. This analysis was conducted in subjects who had matched serial PK and ABPM data. Scatter plots of mean ABPM on Cycle 1 Day 4 and Cycle 1 Day 15 as well as the change in mean ABPM (change from Baseline [Cycle 1 Day -1] on Cycle 1 Day 4 and Cycle 1 Day 15) vs axitinib AUC_{24}, AUC_{last}, and C_{max} were generated. Box plots of AUC_{24}, AUC_{last} and C_{max} on Cycle 1 Day 15 in subjects with dBP (ABPM data) ≥90 mm Hg vs <90 mm Hg were generated. Similar plots for PK parameters in subjects with a BP change from Baseline of ≥15 mm Hg and <15 mm Hg (ABPM data) were also generated.

In addition, for the evaluation of the potential effect of antacids on axitinib PK, linear and semi logarithmic plots of median axitinib plasma concentration, tables with PK parameter summaries and box plots for axitinib PK parameters on Cycle 1 Day 15 in the absence and presence of antacids were also generated. Separate presentations for proton pump inhibitors (PPIs), H_2 blockers and all antacids (including locally-acting antacids, H_2 blockers, and PPIs) were generated.

For subjects in whom sparse samples (predose and 1 to 2 hour postdose) were obtained, population PK analysis was performed in accordance with the Food and Drug Administration (FDA) guidance on Population Pharmacokinetics (February 1999).

Pharmacodynamics: As the circulating endolitheal cell (CEC) biomarkers were continuously distributed, summaries were to include n, mean, SD, %CV, 25th, median, and 75th quartile, minimum and maximum.

The p-values for tests specified below were considered significant if <0.05. The Bonferroni adjustment to the comparison of p-values to a significance level were made based on 10 comparisons for the 10 individual biomarkers; the adjusted significance level was <0.05/10=0.005; comparisons were declared significant if the p-value was <0.005. If a different number of biomarkers was assayed, the adjusted significance level was changed to reflect that number.

Analysis of CEC Biomarker Levels: Comparison of Arm A to Arm B was analyzed using the Wilcoxon Rank Sum test for biomarker levels at Cycle 1 Day 1. Comparison of Arm A and Arm B for ratio to baseline across postbaseline time points was analyzed using a linear mixed effects model with terms of treatment, time, and treatment by time interaction as fixed effects, and subject as random effect in the model. If the p-value for treatment by time interaction was <0.10, the hypothesis of equal time slope was rejected. A random slope and random intercept model could be used to include treatment and time as fixed effects, and intercept and time slope as random effects. A compound symmetry variance-covariance structure could be included in the repeated measures linear mixed effects model to account for correlation among measurements made on a subject at different time points. Models incorporating other covariance structure (eg, unstructured) might have been also examined as a sensitivity analysis. If the normality assumption was not satisfied, a logarithmic transformation could have been applied.

Analysis of the Relationship Between CEC Biomarkers and Objective Response: Summary of CEC Biomarkers for Arm A, Arm B, Arm A + B, and Arm C, at Cycle 1 Day 1 and of Cycle X Day X : Cycle 1 Day 1 on each response category were provided. Fisher's exact test was used to test for association between biomarker category defined by median biomarker level at Cycle 1 Day 1 and of Cycle X Day X : Cycle 1 Day 1 and objective tumor response by treatment arm. Estimated odds ratios (OR) between the biomarker categories and its 2-sided 95% CIs were provided. Logistic regression models could be used to explore the potential influences of the baseline stratification factors and baseline subject characteristics such as age, race, and sex.

Analysis of Relationship Between CEC Biomarkers and Time to Event Endpoints: OS and PFS were compared between Arms A and B, and summarized for Arm A, Arm B, Arm A + B, and Arm C on each stratum defined biomarker at Cycle 1 Day 1 using the KM method; p-values were not displayed when N <10 in either treatment arm. The estimated hazard ratio (HR) and its 2-sided 95% CI, and median event time and its 2-sided 95% CI were reported for comparison of Arm A vs Arm B. For KM analysis of PFS and OS, comparison between 2 groups of the CEC biomarker categorized by median biomarker level at Cycle 1 Day 1 and of Cycle X Day X : Cycle 1 Day 1 were made in the similar manner as above within Arm A and Arm B. Cox proportional hazard models might be used to explore the potential influences of the baseline stratification factors and baseline subject characteristics such as age, race, and sex.

Comparison of Arm A + B combined vs Arm C were made using descriptive statistics only. Summary statistics were provided for the 2 groups of the CEC biomarker categorized by median biomarker level at Cycle 1 Day 1 and of Cycle X Day X : Cycle 1 Day 1 within Arm A + B and Arm C.

RESULTS: Note that the data reported here are based on the PCD; full data will be reported after the last subject last visit.

Subject Disposition and Demography: A summary of subject disposition and subjects analyzed is presented in Table 3.

Table 3. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Active Titration	Placebo Titration	Non-Randomized	Discontinued Prior to Randomization
Total subjects enrolled	56	56	91	10
Treated	56	56	91	10
Discontinued from treatment[a]	38	48	58	10
Adverse event	5 (8.9)	4 (7.1)	9 (9.9)	2 (20.0)
Subject died	0	0	0	0
Protocol violation	0	1 (1.8)	0	0
Lost to follow-up	0	0	1 (1.1)	0
Other	0	3 (5.4)	3 (3.3)	2 (20.0)
Objective progression or relapse	32 (57.1)	35 (62.5)	39 (42.9)	3 (30.0)
Global deterioration of health status	1 (1.8)	1 (1.8)	4 (4.4)	0
Subject refused to continue treatment for reason other than adverse event	0	4 (7.1)	2 (2.2)	3 (30.0)
Discontinued from study[b]	25	28	37	9
Adverse event	1 (1.8)	0	0	1 (10.0)
Subject died	21 (37.5)	20 (35.7)	31 (34.1)	4 (40.0)
Protocol violation	0	0	0	0
Lost to follow-up	2 (3.6)	4 (7.1)	2 (2.2)	0
Other	0	3 (5.4)	4 (4.4)	2 (20.0)
Objective progression or relapse	1 (1.8)	1 (1.8)	0	0
Global deterioration of health status	0	0	0	0
Subject refused to continue treatment for reason other than adverse event	0	0	0	2 (20.0)
Ongoing at date of cut-off	31	28	54	1
Analyzed for safety				
Adverse events	56	56	91	10
Laboratory data	56	56	91	8
Total months on treatment[c]	847.5	810.4	1429.4	7.4

Data cut-off date: 12 October 2012.
CRF = case report form.
a. Discontinued from treatment = CRF page completed when subject was no longer taking study drug.
b. Discontinued from study = CRF page completed when survival follow-up was complete, subject died or subject was lost to follow-up.
c. Months on study included all subjects (defined for each subject as: [last dose date-first dose date +1]/30.44).

A summary of demographic characteristics is presented in Table 4.

Table 4. Demographic Characteristics

	Active Titration N=56 n (%)	Placebo Titration N=56 n (%)	Non-Randomized N=91 n (%)	Discontinued Prior to Randomization N=10 n (%)
Age (years)				
n	56	56	91	10
Mean	59.7	59.6	62.9	62.9
SD	10.2	10.5	8.9	7.5
Median	60.00	62.00	63.00	61.50
Min, max	33, 81	28, 79	43, 87	49, 77
<65	38 (67.9)	38 (67.9)	54 (59.3)	6 (60.0)
≥65	18 (32.1)	18 (32.1)	37 (40.7)	4 (40.0)
Sex				
Male	37 (66.1)	45 (80.4)	55 (60.4)	6 (60.0)
Female	19 (33.9)	11 (19.6)	36 (39.6)	4 (40.0)
Race				
White	49 (87.5)	49 (87.5)	55 (60.4)	9 (90.0)
Black	0	0	2 (2.2)	0
Asian	6 (10.7)	6 (10.7)	33 (36.3)	1 (10.0)
Other	1 (1.8)	1 (1.8)	1 (1.1)	0
Weight (kg)				
n	56	56	91	10
Mean	76.2	79.9	77.7	87.7
SD	14.9	18.5	20.3	25.9
Median	73.0	79.9	77.3	81.8
Min, max	51.0, 120.6	40.9, 155,0	38.0, 145.4	62.0, 134.9
Smoking status				
Never smoked	29	26	48	7
Smoker	8	13	3	1
Ex-smoker	19	17	40	2
ECOG performance status[a]				
0	37 (66.1)	36 (64.3)		
1	19 (33.9)	20 (35.7)		
2	0	0		
ECOG performance status[b]				
0	36 (64.3)	34 (60.7)	63 (69.2)	3 (30.0)
1	20 (35.7)	22 (39.3)	27 (29.7)	7 (70.0)
2	0	0	1 (1.1)	0

Data cut-off date: 12 October 2012.
ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; N = number of subjects in each group; n = number of subjects meeting prespecified criteria; SD = standard deviation.
a. ECOG status was taken from IMPALA.
b. ECOG status was taken from the case report form and is the last measure taken prior to dosing.

Efficacy, Pharmacokinetic, and Pharmacodynamic Results:

Primary Endpoint Result: The ORR, stratified by the ECOG performance status, was statistically significantly higher in the active titration group (53.6%) compared with the placebo titration group (33.9%) (p=0.0189; 1-sided stratified CMH test). Therefore, the study achieved its primary objective and demonstrated superiority of active dose titration over placebo titration in terms of ORR. The risk ratio of active vs placebo titration, adjusted for ECOG performance status, was 1.578 (95% CI: 1.017 to 2.448). Therefore, in relative terms the estimated probability to achieve an objective response is 58% higher in the active titration group than in the placebo titration group (Table 5). A similar superior effect of active vs placebo titration was observed in the unstratified analyses.

Table 5. Summary of Best Overall Response by Treatment, Stratified Analysis - (All Randomized and Non-Randomized Subjects)

	Active Titration N=56	Placebo Titration N=56	Non-Randomized N=91
Subjects with baseline assessment (n [%])	56 (100)	56 (100)	91 (100)
Subjects with measurable disease at Baseline (n [%])	56 (100)	55 (98.2)	91 (100)
Best overall response			
Complete response (CR)	1 (1.8)	0 (0.0)	0 (0.0)
Partial response (PR)	29 (51.8)	19 (33.9)	54 (59.3)
Stable disease	13 (23.2)	24 (42.9)	23 (25.3)
Progressive disease	13 (23.2)	11 (19.6)	11 (12.1)
Not assessed	0 (0.0)	1 (1.8)	2 (2.2)
Indeterminate	0 (0.0)	0 (0.0)	1 (1.1)
Overall confirmed objective response rate (CR + PR)	30 (53.6)	19 (33.9)	54 (59.3)
95% exact CI[a]	39.7%-67.0%	21.8%-47.8%	48.5%-69.5%
Treatment comparison (active titration versus placebo titration)			
Risk ratio[b]	1.578		
95% CI of risk ratio[b]	1.017–2.448		
p-Value[c]	0.0189		

Data cut-off date: 12 October 2012.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N = number of subjects in each group; n = number of subjects meeting prespecified criteria.
a. Using exact method based on F-distribution.
b. Risk ratio and CI based on the Mantel-Haenszel estimator; risk ratio was adjusted for same stratification factors as Cochran-Mantel-Haenszel test.
c. For the overall stratified analysis the p-value was from a 1-sided Cochran-Mantel-Haenszel test stratified by ECOG performance status.

In all 213 treated subjects, the ORR was 48.4% (95% CI: 41.5% to 55.3%) (Table 6).

Table 6. Summary of Best Overall Response by Treatment, Derived Investigator's Assessment (All Subjects)

	All Subjects (N=213)		
	Stratification Category: ECOG = 0	**Stratification Category: ECOG = 1**	**Overall**
N	139	74	213
Subjects with baseline assessment (n [%])	139 (100)	74 (100)	213 (100)
Subjects with measurable disease at Baseline (n [%])	138 (99.3)	74 (100)	212 (99.5)
Complete response (CR)	1 (0.7)	0	1 (0.5)
Partial response (PR)	72 (51.8)	30 (40.5)	102 (47.9)
Stable disease	43 (30.9)	17 (23.0)	60 (28.2)
Progressive disease	18 (12.9)	20 (27.0)	38 (17.8)
Not assessed	2 (1.4)	7 (9.5)	9 (4.2)
Indeterminate	2 (1.4)	0	2 (0.9)
Overall confirmed objective response rate (CR+PR)	73 (52.5)	30 (40.5)	103 (48.4)
95% exact CI[a]	43.9%-61%	29.3 %-52.6 %	41.5 %-55.3 %

One subject did not have any target lesions at Baseline, and therefore did not have measurable disease at Baseline.
ECOG values for randomized subjects were from IMPALA.
ECOG values for subjects who were non-randomized or discontinued prior to randomization were from CRF and was the last measure taken prior to dosing.
One subject having ECOG = 2 was included in ECOG = 1 page for analysis.
% = (n/N) × 100.
Data cutoff date: 12 October 2012.
CI = confidence interval; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; N = number of subjects in each group; n = number of subjects with specified criteria.
a. Using exact method based on binomial distribution.

Secondary Endpoint Results:

Progression Free Survival: A summary of PFS is provided in Table 7. The HR (active vs placebo titration) for PFS stratified by ECOG performance status was 0.849 (95% CI: 0.535 to 1.348) in favor of active titration with a p-value of 0.2444 (1-sided stratified log-rank test). The unstratified analysis of PFS gave similar results.

Table 7. Selected Summary of Progression-Free Survival From First Dose by Treatment, Overall Stratified Analysis (All Randomized and Non-Randomized Subjects)

	Active Titration N=56	Placebo Titration N=56	Non-Randomized N=91
Subjects observed to have progressed or died due to any cause while on study (n [%])[a]	35 (62.5)	38 (67.9)	54 (59.3)
Type of event (n [%])			
Objective progression	34 (97.1)	38 (100.0)	52 (96.3)
Increase in existing lesion (target or non target)	12 (35.3)	16 (42.1)	14 (26.9)
New lesion	9 (26.5)	16 (42.1)	25 (48.1)
Increase and a new lesion	13 (38.2)	6 (15.8)	13 (25.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Death without objective progression	1 (2.9)	0 (0.0)	2 (3.7)
Subject did not progress or die due to any cause while on study (n [%])[a]	21 (37.5)	18 (32.1)	37 (40.7)
No baseline or on-study assessments	0 (0.0)	1 (5.6)	2 (5.4)
Alive, on study and progression free at the time of analysis	17 (81.0)	7 (38.9)	26 (70.3)
At least 1 on study assessment and discontinue treatment prior to documented PD on study	4 (19.0)	9 (50.0)	9 (24.3)
PD occurred after given new anti-tumor treatment	0 (0.0)	1 (5.6)	0 (0.0)
Kaplan-Meier estimates of time-to-event (months)			
Quartiles (95% CI)[b]			
25%	2.9 (1.8, 9.2)	5.4 (3.6, 8.3)	5.7 (4.6, 8.6)
50%	14.5 (9.2, 24.5)	15.7 (8.3, 19.4)	16.6 (11.2, 22.5)
75%	-(24.5,-)	24.8 (19.1,-)	28.5 (25.1,-)
Treatment comparison (active titration versus placebo titration)			
Hazard ratio[c]	0.849		
95% CI of hazard ratio	0.535–1.348		
p-Value[d]	0.2444		

Data cut-off date: 12 October 2012.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N = number of subjects; n = number of subjects meeting pre-specified criteria; PD = progressive disease.
a. On study included treatment plus 28-day follow-up period.
b. Based on Brookmeyer and Crowley method.
c. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor for active titration; a hazard ratio >1 indicates a reduction in favor of placebo titration.
d. For the overall stratified analysis the p-value is from a 1-sided log-rank test stratified by ECOG performance status. ECOG values are from IMPALA.

For all 213 treated subjects combined, 130 (61.0%) PFS events were recorded during the study and PFS was 14.6 months (95% CI: 11.5 to 17.5 months) (Table 8).

Table 8. Summary of Progression-Free Survival From First Dose - Derived Investigator's Assessment (All Subjects)

	All Subjects (N=213)		
	Stratification Category: ECOG = 0	Stratification Category: ECOG = 1	Overall
N	139	74	213
Subject observed to have progressed or died due to any cause while on study (n [%])[a]	83 (59.7)	47 (63.5)	130 (61.0)
Type of event (n [%])			
Objective progression	81 (97.6)	46 (97.9)	127 (97.7)
Increase in existing lesion (target or non target)	32 (39.5)	13 (28.3)	45 (35.4)
New lesion	31 (38.3)	19 (41.3)	50 (39.4)
Increase and a new lesion	18 (22.2)	14 (30.4)	32 (25.2)
Other	0	0	0
Death without objective progression	2 (2.4)	1 (2.1)	3 (2.3)
Subject did not progress or die due to any cause while on study (n [%])[a]	56 (40.3)	27 (36.5)	83 (39.0)
Reason for censorship (n [%])			
No baseline or on-study assessments	2 (3.6)	7 (25.9)	9 (10.8)
Alive, on study and progression free at the time of the analysis	35 (62.5)	15 (55.6)	50 (60.2)
At least 1 on study disease assessment and discontinue treatment prior to documented PD on study	18 (32.1)	5 (18.5)	23 (27.7)
PD or death occurs after ≥2 consecutive, missed assessments	0	0	0
PD occurs after given new anti-tumor treatment	1 (1.8)	0	1 (1.2)
Withdrew consent for follow-up	0	0	0
Lost to follow-up	0	0	0
Subject taking new anti-tumor therapy	0	0	0
Other	0	0	0
Kaplan-Meier estimates of time to event (months)			
Quartiles (95% CI)[b]			
25%	8.2 (5.6, 10.1)	2.3 (1.8, 4.6)	5.3 (3.6, 7.4)
50%	16.6 (13.0, 22.9)	10.3 (4.7, 16.6)	14.6 (11.5, 17.5)
75%	28.5 (25.1, -)	- (17.4, -)	28.5 (25.1, -)

ECOG values for randomized subjects are from IMPALA.
ECOG values for subjects who were non-randomized or discontinued prior to randomization are from CRF and is the last measure taken prior to dosing.
One subject having ECOG = 2 was included in ECOG = 1 page for analysis.
% = (n/N) × 100.
Data cutoff date: 12 October 2012.
CI = confidence interval; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; N = number of subjects in each group; n = number of subjects with specified criteria; PD = progression of disease.
a. On study includes treatment plus 28-day follow-up period.
b. Based on the Brookmeyer and Crowley Method.

In total, 35 (62.5%) subjects in the active titration group and 38 (67.9%) subjects in the placebo titration group had disease progression or died. To explore the potential influence of the baseline ECOG stratification factor on PFS, Cox proportional hazard models were used. The HR for the effect of baseline ECOG status (ECOG = 1 vs ECOG = 0) on PFS from first dose was 1.127 (95% CI: 0.697 to 1.823) with a p-value of 0.627. Therefore, no significant influence of baseline ECOG status was shown.

Overall Survival: A summary of OS (cut-off date: 12 October 2012) is presented in Table 9. There were 22 (39.3%) deaths (from first dose) in the active titration group, 21 (37.5%) deaths in the placebo titration group, and 31 (34.1%) deaths in the

non-randomized group, ie, at the time of analysis of the primary endpoint, most subjects were alive and the survival data were immature. The estimated HR (risk of death in the active versus placebo titration group) was 1.213 (95% CI: 0.661 to 2.229) for OS data recorded from first dose and stratified by ECOG performance status, representing an increase of 21.3% in hazard for active titration over placebo titration. Similar results were obtained for analyses of OS recorded from randomization with stratified and unstratified data. OS data was not mature at the time of data cut-off date.

Table 9. Summary of Overall Survival From First Dose by Treatment, Overall Stratified Analysis (All Randomized and Non-Randomized Subjects)

	Active Titration N=56	Placebo Titration N=56	Non-Randomized N=91
Dead (n [%])	22 (39.3)	21 (37.5)	31 (34.1)
Cause of death (n [%])			
Disease under study	21 (95.5)	18 (85.7)	26 (83.9)
Study treatment toxicity	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1(4.5)	1 (4.8)	2 (6.5)
Other	0	2 (9.5)	3 (9.7)
Alive (n [%])[a]	34 (60.7)	35 (62.5)	60 (65.9)
Alive	31 (91.2)	30 (85.7)	57 (95.0)
Subject no longer willing to participate	0 (0.0)	1 (2.9)	1 (1.7)
Lost to follow-up	3 (8.8)	4 (11.4)	2 (3.3)
Survival probability at Month 12 (95% CI)[b]	74.6 (61.0, 84.0)	81.6 (68.7, 89.6)	80.0 (70.2, 86.9)
Kaplan-Meier estimates of time-to-event (months)			
Quartiles (95% CI)[c]			
25%	11.9 (6.1, 24.7)	19.2 (10.6, 24.6)	15.6 (10.8, 29.9)
50%	- (24.7,-)	35.2 (23.7, -)	32.3 (29.9, -)
75%	NA	- (35.2, -)	-
Treatment comparison (active vs placebo titration)			
Hazard ratio[d]	1.213		
95% CI of hazard ratio	0.661–2.229		
p-Value[e]	0.7319		

Data cut-off date: 12 October 2012.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N = number of subjects, n = number of subjects meeting prespecified criteria; NA = not applicable; vs = versus.

a. Subjects who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
b. Calculated from the log (-log[12-month survival probability]) using a normal approximation and back transformation.
c. Based on the Brookmeyer and Crowley Method.
d. Assuming proportional hazards model, a hazard ratio <1 indicates a reduction in hazard rate in favor of active titration; a hazard ratio >1 indicates a reduction in favor of placebo titration.
e. For the overall stratified analysis, the p-value is based on a 1-sided log-rank test stratified by ECOG performance status.

For analysis of OS from first dose in all 213 subjects, the median OS was 35.2 months (95% CI: 32.3, -) (Table 10).

Table 10. Summary of Overall Survival From First Dose - Stratified Analysis (All Subjects)

	All Subjects (N=213)		
	Stratification Category: ECOG = 0	Stratification Category: ECOG = 1	Overall
Dead (n [%])	41 (29.5)	37 (50.0)	78 (36.6)
Cause of death (n [%])			
Disease under study	37 (90.2)	32 (86.5)	69 (88.5)
Study treatment toxicity	0	0	0
Unknown	2 (4.9)	2 (5.4)	4 (5.1)
Other	2 (4.9)	3 (8.1)	5 (6.4)
Alive (n [%])[a]	98 (70.5)	37 (50.0)	135 (63.4)
Reason for censorship (n [%])			
Alive	88 (89.8)	33 (89.2)	121 (89.6)
Subject no longer willing to participate	3 (3.1)	2 (5.4)	5 (3.7)
Lost to follow-up	7 (7.1)	2 (5.4)	9 (6.7)
Survival probability at Month 12 (95% CI[b])	86.0 (78.9, 90.8)	60.9 (48.5, 71.2)	77.5 (71.2, 82.7)
Kaplan-Meier estimates of time to event (months)			
Quartiles (95% CI)[c]			
25%	23.5 (15.6, 35.2)	7.0 (4.0, 11.4)	14.7 (10.9, 21.2)
50%	35.2 (32.3, -)	21.2 (11.7, -)	35.2 (29.9, -)
75%	- (35.2, -)	-	- (35.2, -)

Data cutoff date: 12 October 2012.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N = number of subjects; n = number of subjects with specified criteria.
a. Subjects who are not known to be dead at the time the database was closed for analysis are censored on the date they were last known to be alive.
b. Calculated from the log (-log [12-month survival probability]) using a normal approximation and back transformation.
c. Based on the Brookmeyer and Crowley Method.

Duration of Response: A summary of duration of tumor response among responders is provided in Table 11.

Table 11. Selected Summary of Duration of Tumor Response Among Responders by Treatment – (All Randomized and Non-Randomized Subjects)

	Active Titration N=30	Placebo Titration N=19	Non-Randomized N=54
Subjects observed to have progressed or died due to any cause while on study (n [%])[a]	13 (43.3)	10 (52.6)	26 (48.1)
Type of event (n [%])			
Objective progression	13 (100.0)	10 (100.0)	25 (96.2)
Increase in existing lesion (target or non target)	5 (38.5)	4 (40.0)	10 (40.0)
New lesion	5 (38.5)	4 (40.0)	9 (36.0)
Increase and a new lesion	3 (23.1)	2 (20.0)	6 (24.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Death without objective progression	0 (0.0)	0 (0.0)	1 (3.8)
Subject did not progress or die due to any cause while on study (n [%])[a]	17 (56.7)	9 (47.4)	28 (51.9)
No baseline or on-study assessments	0 (0.0)	0 (0.0)	0 (0.0)
Alive, on study and progression free at the time of analysis	17 (100.0)	8 (88.9)	28 (100.0)
At least 1 on study assessment and discontinued treatment prior to documented PD on study	0 (0.0)	0 (0.0)	0 (0.0)
PD occurred after given new anti-tumor treatment	0 (0.0)	1 (11.1)	0 (0.0)
Kaplan-Meier estimates of time-to-event (months)			
Quartiles (95% CI)[b]			
25%	9.4 (6.5, 20.6)	11.1 (6.4, 21.2)	12.0 (7.0, 16.8)
50%	- (10.8, -)	21.2 (11.1, 25.8)	23.3 (15.7, 28.6)
75%	NA	25.8 (21.2, 25.8)	28.6 (23.3,-)

Data cut-off date: 12 October 2012.
CI = confidence interval; N = number of subjects; n = number of subjects meeting prespecified criteria; NA = not applicable; PD = progressive disease.
a. On study included treatment plus 28-day follow-up period.
b. Based on Brookmeyer and Crowley method.

Pharmacokinetic Results: The axitinib plasma PK parameter values at steady state on Cycle 1 Day 15 are summarized in Table 12.

Table 12. Summary of Axitinib Steady-State Pharmacokinetic Parameters Following Administration of Multiple Doses of Axitinib (5 mg BID) in Subjects With Advanced Renal Cell Carcinoma

Treatment	C_{max}[a] (ng/mL)	AUC_{last}[a] (ng•hr/mL)	AUC_{24}[a] (ng•hr/mL)	CL/F (L/hr)	V_z/F (L)	$t_{½}$ (hr)
Axitinib (N=73)	30.9 (25.9, 36.8)	107 (89.1, 129)	268 (213, 338)	37.3 (29.6, 47.0)	146 (115, 186)	3.98 (129)

Values reported are geometric mean with 95% CI for C_{max}; AUC_{last}; AUC_{24}; CL/F; and V_z/F; arithmetic mean with %CV for $t_{½}$.
One subject was excluded from summary statistics for all PK parameters because all the sample concentrations were BLQ. Five subjects were excluded from summary statistics for all PK parameters because of errors in sample collection. AUC_{24}, CL/F, V_z/F could not be reported for N=20 subjects due to non-estimable half-life.
AUC_{24} = area under the plasma concentration versus time curve from 0 to 24 hrs; AUC_{last} = area under the plasma concentration versus time curve from 0 to time of the last quantifiable concentration; BLQ = below limit of quantification; CI = confidence interval; C_{max} = maximal plasma concentration; CL/F = apparent oral clearance; CV = coefficient of variation; N = number of subjects; PK = pharmacokinetics; $t_{½}$ = plasma terminal elimination half-life; V_z/F = apparent volume of distribution during the elimination phase.
a. Dose normalized to 5 mg dose.

Arms A and B included subjects who were eligible for dose titration above the 5 mg BID starting dose on Cycle 2 Day 1; Arm C included subjects not eligible for dose titration on Cycle 2 Day 1. The axitinib steady-state plasma concentrations following multiple oral 5 mg BID dosing on Cycle 1 Day 15 are compared in subjects eligible for dose titration (Arms A and B) vs those that were not (Arm C) (Table 13).

Table 13. Comparison of Axitinib Steady-State Pharmacokinetic Parameters on Cycle 1 Day 15 Following Administration of Multiple Doses of Axitinib (5 mg BID) in Subjects Eligible or Not Eligible for Dose Titration

Treatment Arm	C_{max}[a] (ng/mL)	AUC_{last}[a] (ng•hr/mL)	AUC_{24}[a] (ng•hr/mL)	CL/F (L/hr)	V_z/F (L)	$t_{1/2}$ (hr)
Eligible for dose-titration (Arms A + B; N=39)	25.3 (20.1, 31.9)	78.4 (62.2, 98.7)	181 (138, 237)	55.3 (42.2, 72.4)	158 (113, 219)	2.42 (94)
Not eligible for dose-titration (Arm C; N=34)	38.7 (30.2, 49.6)	154 (120, 197)	432 (321, 581)	23.1 (17.2, 31.2)	133 (92.8, 192)	5.87 (116)

Values reported are geometric mean with 95% CI for C_{max}, AUC_{last}, AUC_{24}, CL/F, and V_z/F, arithmetic mean with %CV for $t_{½}$.
One subject was excluded from summary statistics for all PK parameters because all the sample concentrations were BLQ. Five subjects were excluded from summary statistics for all PK parameters because of sample collection error. AUC_{24}, CL/F, V_z/F and $t_{½}$ could not be reported for N=20 subjects due to non-estimable plasma half-life.
AUC_{24} = area under the plasma concentration versus time curve from 0 to 24 hrs; AUC_{last} = area under the plasma concentration versus time curve from 0 to time of the last quantifiable concentration; BLQ = below limit of quantification; CI = confidence interval; C_{max} = maximal plasma concentration; CL/F = apparent oral clearance; CV = coefficient of variation; N = number of subjects; PK = pharmacokinetics; $t_{½}$ = plasma terminal elimination half-life; V_z/F = apparent volume of distribution during the elimination phase.
a. Dose normalized to 5 mg dose.

In Cycle 2, subjects in Arms A and B had their dose increased with either axitinib (Arm A) or placebo (Arm B). Therefore, PK data on Cycle 2 Day 15 represents steady-state PK for axitinib at the up-titrated dose. The corresponding axitinib steady-state plasma PK parameter values in these 2 arms are summarized in Table 14.

Table 14. Comparison of Axitinib Steady-State Pharmacokinetic Parameters in Arms A and B on Cycle 2 Day 15 Following Multiple Oral Doses of Axitinib

Treatment Arm	C_{max}[a] (ng/mL)	AUC_{last}[a] (ng•hr/mL)	AUC_{24}[a] (ng•hr/mL)	CL/F (L/hr)	V_z/F (L)	$t_{½}$ (hr)
Axitinib dose titration (Arm A; N=16)	31.7 (21.6, 46.6)	105 (70.2, 158)	259 (150, 445)	54.2 (31.5, 93.1)	158 (98.4, 254)	2.48 (77)
Placebo dose titration (Arm B; N=20)	23.1 (16.4, 32.5)	78.4 (54.5, 113)	161 (102, 255)	61.9 (39.2, 97.9)	217 (145, 324)	2.81 (60)

Values reported are geometric mean with 95% CI for C_{max}, AUC_{last}, AUC_{24}, CL/F, and V_z/F, arithmetic mean with %CV for $t_{½}$.
Five subjects were excluded from summary statistics for all PK parameters because of sample collection error. AUC_{24}, CL/F, V_z/F and $t_{½}$ could not be reported for N=12 subjects due to non-estimable half-life.
AUC_{24} = area under the plasma concentration versus time curve from 0 to 24 hrs; AUC_{last} = area under the plasma concentration versus time curve from 0 to time of the last quantifiable concentration; BID = twice a day; BLQ = below limit of quantification; CI = confidence interval; C_{max} = maximal plasma concentration; CL/F = apparent oral clearance; CV = coefficient of variation; N = number of subjects; PK = pharmacokinetics; $t_{½}$ = plasma terminal elimination half-life; V_z/F = apparent volume of distribution during the elimination phase.
a. Dose normalized to 7 mg dose for subjects in Arm A and to 5 mg for subjects in Arm B.

Correlation Between Ambulatory Blood Pressure and Axitinib Pharmacokinetics: The mean dBP represented the average of 24 hour diastolic ABPM on Cycle 1 Day 15. In addition, the mean change in dBP was estimated as the difference between the mean dBP at Baseline and at Cycle 1 Day 15. The geometric mean C_{max} and AUC_{24} are higher in subjects with mean diastolic ABPM ≥90 mm Hg than those in subjects with mean diastolic ABPM <90 mm Hg. A similar outcome was observed when using mean change in dBP (from Baseline) instead of absolute dBP values. The geometric mean C_{max} and AUC_{24} were higher in subjects with mean change from Baseline of diastolic ABPM ≥15 mm Hg than those subjects with mean change of baseline of diastolic ABPM <15 mm Hg. A weak correlation was observed between axitinib plasma steady-state exposure and mean absolute diastolic ABPM on Cycle 1 Day 15 (R^2=0.126). A similar observation was seen with the use of mean change of diastolic ABPM on Cycle 1 Day 15 from Baseline (R^2=0.225).

Pharmacodynamic Results:

Plasma Levels of Circulating Endolitheal Cells: There were no statistically significant findings.

Correlation Between Circulating Endolitheal Cells and Response According to Response Evaluation Criteria in Solid Tumors Criteria: The comparison of CEC values at Baseline and ratios to Baseline at each time point, between subjects having a response and those without a response, there were no statistically significant findings. For cluster of differentiation (CD)146 +/CD105 + vascular endothelial growth factor receptor (pVEGFR) + expressing cells at Baseline, the ORR was higher in 62.5% of subjects with <median values (OR = 4.44, 95% CI = 1.1 to 17.7, p=0.047) compared to 27.3% of subjects with greater than or equal to median values for the combined active titration and placebo titration groups. No other findings were statistically significant.

Analysis of PFS by Median CEC Values at Baseline and by Median Ratios to Baseline: There were no statistically significant findings.

Analysis of OS by Median CEC Values at Baseline and by Median Ratios to Baseline: There were 3 significant observations for the combined active + placebo titration groups: at Baseline, subjects with less than median CD31+/146+ platelet-derived growth factor receptor β (pPDGFRβ) expressing cells had a longer OS than subjects with greater than or equal to median values; at Baseline, subjects with less than median CD31 +/146 + pVEGFR expressing cells had a longer OS than subjects with greater than or equal to median values; for the Cycle 2 Day 15/Cycle 1 Day 1 ratio, subjects with less than median CD31 +/CD146 + pVEGFR expressing cells had a shorter OS than subjects with greater than or equal to median values.

Kaplan-Meier OS Curves Comparing Less Than Median CEC Values Versus Greater Than or Equal to Median Values at Baseline Amongst Treatment Arms: There were no statistically significant findings.

Pharmacogenomics Results:

Baseline Characteristics: The baseline characteristics were similar between active titration and placebo titration groups.

Analysis of PFS by Vascular Endothelial Growth Factor (VEGF)-A or VEGFR3 Genotype: When all subjects were grouped together, median PFS was longer for the reference G/G genotype (22.17 weeks) vs G/A genotype (11.50 weeks) or A/A genotype (8.57 weeks). For the VEGFR3 rs448012 polymorphism, when all subjects were grouped together, median PFS was longer for subjects with the reference G/G genotype (19.42 weeks) compared to subjects with the G/C genotype (10.28 weeks). However, PFS for the C/C genotype was not significantly different (17.51 weeks). There were no other consistent trends of genotype effect on PFS.

Analysis of OS by VEGF-A or VEGFR3 Genotype: When all subjects were grouped together, there were no significant associations of genotype vs OS. There were no other consistent trends of genotype effect on OS.

Analysis of ORR by VEGF-A or VEGFR3 Genotype: When all subjects were grouped together, there were no significant associations of genotype vs ORR. For the VEGFR3 polymorphism rs448012, in the combined active + placebo titration group, subjects with the reference G/G genotype had an increased ORR (67.7%) compared to subjects with the G/C genotype (31.8%). However, ORR was not different for these genotypes in the non-randomized group. There were no other consistent trends of genotype effect on ORR.

Analysis of Postbaseline dBP <90 mmHg According to VEGF-A or VEGFR3 Genotype: For active titration, placebo titration, combined active titration + placebo titration, and non-randomized groups, no significant observations of association of genotype vs postbaseline dBP <90 mmHg were reported, other than 1 significant observation for a genotype where N=1.

Analysis of Post-Baseline dBP Increase of >15 mmHg According to VEGF-A or VEGFR3 Genotype: For active titration, placebo titration, combined active titration + placebo titration,

and non-randomized groups, for the VEGF-A rs699947 polymorphism, in the non-randomized group only, there was a higher chance of an observed ≥15 mm Hg increase in dBP for subjects with the A/C genotype (OR = 5.40; p=0.022) and C/C genotype (OR = 8.25; p=0.034) compared to the reference A/A genotype. There were no other significant observations of association of genotype vs postbaseline dBP increase of 15 mm Hg.

Analysis of ≥Grade 3 Hypertension by VEGF-A or VEGFR3 Genotype: For active titration, placebo titration, non-randomized, and combined active titration + placebo titration, for the VEGFR3 rs307821 polymorphism, in the non-randomized group only, subjects with the G/T genotype had a lower chance of a ≥Grade 3 hypertension event (OR = 0.19; p=0.043) than subjects with the reference G/G genotype. There were no other consistent trends of genotype effect with ≥Grade 3 hypertension.

Safety Results: An overall summary of treatment-emergent AEs (TEAEs) is provided in Table 15.

Table 15. Overall Summary of All-Causality and Treatment-Related Treatment-Emergent Adverse Events According to Study Arm

	Active Titration N=56		Placebo Titration N=56		Non-Randomized N=91		Discontinued Prior to Randomization N=10	
	All Grades		All Grades		All Grades		All Grades	
	n	%	n	%	n	%	n	%
All-Causality TEAEs								
Number of AEs	713		689		1578		64	
Subjects with AEs	55	98.2	51	91.1	91	100.0	9	90.0
Subjects with SAEs	15	26.8	13	23.2	35	38.5	2	20.0
Subjects with Grade 3 or Grade 4 events	34	60.7	26	46.4	73	80.2	7	70.0
Subjects with Grade 5 events	2	3.6	0		8	8.8	0	
Subjects discontinued treatment due to AEs	7	12.5	6	10.7	11	12.1	2	20.0
Subjects with dose reduced due to AEs	15	26.8	8	14.3	16	17.6	1	10.0
Subjects with temporary discontinuation due to AEs	28	50.0	25	44.6	71	78.0	4	40.0
Treatment-Related TEAEs								
Number of AEs	512		481		1176		49	
Subjects with AEs	53	94.6	48	85.7	90	98.9	8	80.0
Subjects with SAEs	10	17.9	4	7.1	15	16.5	1	10.0
Subjects with Grade 3 or Grade 4 events	30	53.6	16	28.6	63	69.2	6	60.0
Subjects with Grade 5 events	0		0		1	1.1	0	
Subjects discontinued treatment due to AEs	4	7.1	2	3.6	6	6.6	1	10.0
Subjects with dose reduced due to AEs	15	26.8	6	10.7	15	16.5	1	10.0
Subjects with temporary discontinuation due to AEs	25	44.6	18	32.1	64	70.3	4	40.0

Includes data up to 28 days after last dose of study drug.
Except for the number of AEs, subjects were counted only once per treatment in each row.
Data cut-off date: 12 October 2012.
AE = adverse event; N = number of subjects; n = number of subjects meeting prespecified criteria; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

All-Causality Treatment-Emergent Adverse Events: A summary of nonserious all-causality TEAEs reported in ≥5% of subjects in any treatment group is presented in Table 16.

Table 16. Treatment-Emergent Nonserious Adverse Events Reported in ≥5% of Subjects in any Treatment Group (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Active Titration n (%)	Placebo Titration n (%)	Non-Randomized n (%)	Discontinued Prior to Randomization n (%)
Number (%) of subjects evaluable for adverse events	56	56	91	10
Number (%) of subjects with adverse events	55 (98.2)	50 (89.3)	91 (100.0)	9 (90.0)
Being queried	0	0	0	1 (10.0)
Transient ischemic attack	0	0	0	1 (10.0)
Blood and lymphatic system disorders	7 (12.5)	6 (10.7)	20 (22.0)	2 (20.0)
Anaemia	4 (7.1)	3 (5.4)	8 (8.8)	1 (10.0)
Lymphopenia	0	0	2 (2.2)	1 (10.0)
Thrombocytopenia	4 (7.1)	3 (5.4)	14 (15.4)	0
Cardiac disorders	0	1 (1.8)	0	2 (20.0)
Sinus tachycardia	0	1 (1.8)	0	2 (20.0)
Ear and labyrinth disorders	0	3 (5.4)	3 (3.3)	0
Tinnitus	0	3 (5.4)	3 (3.3)	0
Endocrine disorders	18 (32.1)	13 (23.2)	41 (45.1)	2 (20.0)
Hypothyroidism	18 (32.1)	13 (23.2)	41 (45.1)	2 (20.0)
Gastrointestinal disorders	41 (73.2)	41 (73.2)	78 (85.7)	5 (50.0)
Abdominal discomfort	1 (1.8)	0	6 (6.6)	0
Abdominal distension	1 (1.8)	3 (5.4)	3 (3.3)	0
Abdominal pain	9 (16.1)	7 (12.5)	11 (12.1)	1 (10.0)
Abdominal pain upper	4 (7.1)	2 (3.6)	10 (11.0)	0
Cheilitis	1 (1.8)	2 (3.6)	5 (5.5)	0
Constipation	10 (17.9)	8 (14.3)	27 (29.7)	3 (30.0)
Diarrhoea	34 (60.7)	35 (62.5)	57 (62.6)	1 (10.0)
Dry mouth	6 (10.7)	1 (1.8)	7 (7.7)	0
Dyspepsia	6 (10.7)	5 (8.9)	18 (19.8)	0
Dysphagia	0	2 (3.6)	2 (2.2)	1 (10.0)
Flatulence	7 (12.5)	3 (5.4)	3 (3.3)	0
Gastritis	2 (3.6)	2 (3.6)	8 (8.8)	0
Gastrooesophageal reflux disease	1 (1.8)	3 (5.4)	4 (4.4)	0
Haemorrhoids	1 (1.8)	1 (1.8)	3 (3.3)	1 (10.0)
Nausea	21 (37.5)	19 (33.9)	31 (34.1)	2 (20.0)
Proctalgia	2 (3.6)	0	5 (5.5)	0
Stomatitis	9 (16.1)	4 (7.1)	17 (18.7)	0
Vomiting	17 (30.4)	11 (19.6)	23 (25.3)	2 (20.0)
General disorders and administration site conditions	34 (60.7)	32 (57.1)	58 (63.7)	5 (50.0)
Asthenia	6 (10.7)	5 (8.9)	6 (6.6)	0
Chest pain	4 (7.1)	2 (3.6)	6 (6.6)	0
Chills	2 (3.6)	1 (1.8)	5 (5.5)	0
Fatigue	25 (44.6)	26 (46.4)	49 (53.8)	4 (40.0)
General physical health deterioration	0	0	1 (1.1)	1 (10.0)
Mucosal inflammation	11 (19.6)	7 (12.5)	13 (14.3)	0
Oedema peripheral	4 (7.1)	4 (7.1)	14 (15.4)	0
Pain	3 (5.4)	3 (5.4)	4 (4.4)	0
Pyrexia	4 (7.1)	3 (5.4)	4 (4.4)	0
Infections and infestations	14 (25.0)	12 (21.4)	28 (30.8)	1 (10.0)
Nasopharyngitis	4 (7.1)	3 (5.4)	15 (16.5)	0
Rhinitis	3 (5.4)	6 (10.7)	4 (4.4)	0
Sinusitis	4 (7.1)	2 (3.6)	2 (2.2)	0
Upper respiratory tract infection	4 (7.1)	3 (5.4)	5 (5.5)	0
Urinary tract infection	2 (3.6)	1 (1.8)	10 (11.0)	1 (10.0)

Table 16. Treatment-Emergent Nonserious Adverse Events Reported in ≥5% of Subjects in any Treatment Group (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Active Titration n (%)	Placebo Titration n (%)	Non-Randomized n (%)	Discontinued Prior to Randomization n (%)
Investigations	26 (46.4)	22 (39.3)	53 (58.2)	2 (20.0)
Alanine aminotransferase increased	4 (7.1)	9 (16.1)	12 (13.2)	0
Aspartate aminotransferase increased	4 (7.1)	10 (17.9)	11 (12.1)	0
Blood alkaline phosphatase increased	3 (5.4)	4 (7.1)	6 (6.6)	2 (20.0)
Blood creatinine increased	1 (1.8)	6 (10.7)	14 (15.4)	1 (10.0)
Blood glucose decreased	3 (5.4)	4 (7.1)	1 (1.1)	0
Blood glucose increased	4 (7.1)	7 (12.5)	10 (11.0)	2 (20.0)
Blood potassium increased	3 (5.4)	3 (5.4)	4 (4.4)	0
Blood thyroid stimulating hormone increased	8 (14.3)	7 (12.5)	9 (9.9)	0
Blood triglycerides increased	2 (3.6)	2 (3.6)	5 (5.5)	0
Fibrin d dimer increased	0	1 (1.8)	0	1 (10.0)
Haemoglobin decreased	1 (1.8)	1 (1.8)	5 (5.5)	0
Weight decreased	15 (26.8)	12 (21.4)	25 (27.5)	1 (10.0)
Metabolism and nutrition disorders	28 (50.0)	24 (42.9)	49 (53.8)	3 (30.0)
Decreased appetite	21 (37.5)	16 (28.6)	35 (38.5)	3 (30.0)
Dehydration	3 (5.4)	4 (7.1)	5 (5.5)	0
Hyperglycaemia	5 (8.9)	3 (5.4)	5 (5.5)	0
Hyperkalaemia	5 (8.9)	1 (1.8)	4 (4.4)	0
Hyperlipidaemia	0	0	6 (6.6)	0
Hyperuricaemia	1 (1.8)	0	9 (9.9)	0
Hypoalbuminaemia	3 (5.4)	1 (1.8)	2 (2.2)	0
Hypoglycaemia	0	3 (5.4)	2 (2.2)	0
Hyponatraemia	4 (7.1)	1 (1.8)	4 (4.4)	1 (10.0)
Hypophosphataemia	1 (1.8)	2 (3.6)	4 (4.4)	1 (10.0)
Musculoskeletal and connective tissue disorders	27 (48.2)	23 (41.1)	56 (61.5)	2 (20.0)
Arthralgia	11 (19.6)	9 (16.1)	16 (17.6)	0
Back pain	13 (23.2)	8 (14.3)	15 (16.5)	0
Bone pain	3 (5.4)	2 (3.6)	4 (4.4)	0
Flank pain	1 (1.8)	3 (5.4)	2 (2.2)	0
Groin pain	0	0	1 (1.1)	1 (10.0)
Muscle spasms	2 (3.6)	2 (3.6)	5 (5.5)	0
Muscular weakness	3 (5.4)	2 (3.6)	2 (2.2)	0
Musculoskeletal chest pain	3 (5.4)	3 (5.4)	2 (2.2)	0
Musculoskeletal pain	7 (12.5)	4 (7.1)	15 (16.5)	0
Musculoskeletal stiffness	1 (1.8)	3 (5.4)	3 (3.3)	0
Myalgia	4 (7.1)	3 (5.4)	8 (8.8)	0
Neck pain	4 (7.1)	4 (7.1)	5 (5.5)	0
Pain in extremity	7 (12.5)	5 (8.9)	23 (25.3)	2 (20.0)
Nervous system disorders	24 (42.9)	21 (37.5)	42 (46.2)	2 (20.0)
Dizziness	8 (14.3)	10 (17.9)	12 (13.2)	1 (10.0)
Dysgeusia	9 (16.1)	5 (8.9)	20 (22.0)	1 (10.0)
Dyskinesia	0	0	0	1 (10.0)
Headache	8 (14.3)	12 (21.4)	26 (28.6)	0
Hypoaesthesia	2 (3.6)	0	3 (3.3)	1 (10.0)
Paraesthesia	5 (8.9)	3 (5.4)	3 (3.3)	1 (10.0)
Peripheral sensory neuropathy	4 (7.1)	1 (1.8)	3 (3.3)	0
Psychiatric disorders	9 (16.1)	10 (17.9)	19 (20.9)	3 (30.0)
Anxiety	3 (5.4)	3 (5.4)	7 (7.7)	0
Confusional state	1 (1.8)	1 (1.8)	0	2 (20.0)
Delirium	0	0	0	1 (10.0)
Depression	3 (5.4)	4 (7.1)	6 (6.6)	0
Insomnia	2 (3.6)	4 (7.1)	7 (7.7)	1 (10.0)

Table 16. Treatment-Emergent Nonserious Adverse Events Reported in ≥5% of Subjects in any Treatment Group (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Active Titration n (%)	Placebo Titration n (%)	Non-Randomized n (%)	Discontinued Prior to Randomization n (%)
Renal and urinary disorders	12 (21.4)	11 (19.6)	39 (42.9)	2 (20.0)
Haemoglobinuria	2 (3.6)	3 (5.4)	5 (5.5)	1 (10.0)
Proteinuria	11 (19.6)	11 (19.6)	39 (42.9)	2 (20.0)
Respiratory, thoracic and mediastinal disorders	22 (39.3)	26 (46.4)	63 (69.2)	4 (40.0)
Cough	7 (12.5)	8 (14.3)	17 (18.7)	0
Dysphonia	18 (32.1)	20 (35.7)	44 (48.4)	3 (30.0)
Dyspnoea	6 (10.7)	7 (12.5)	26 (28.6)	1 (10.0)
Epistaxis	4 (7.1)	3 (5.4)	11 (12.1)	0
Oropharyngeal pain	3 (5.4)	2 (3.6)	7 (7.7)	0
Skin and subcutaneous tissue disorders	24 (42.9)	21 (37.5)	55 (60.4)	0
Alopecia	2 (3.6)	3 (5.4)	14 (15.4)	0
Dry skin	7 (12.5)	3 (5.4)	7 (7.7)	0
Erythema	0	2 (3.6)	6 (6.6)	0
Hyperkeratosis	2 (3.6)	4 (7.1)	5 (5.5)	0
Palmar-plantar erythrodysaesthesia syndrome	18 (32.1)	10 (17.9)	40 (44.0)	0
Pruritus	2 (3.6)	6 (10.7)	12 (13.2)	0
Rash	4 (7.1)	8 (14.3)	19 (20.9)	0
Vascular disorders	34 (60.7)	26 (46.4)	77 (84.6)	5 (50.0)
Hypertension	34 (60.7)	24 (42.9)	75 (82.4)	5 (50.0)
Hypotension	0	8 (14.3)	9 (9.9)	0

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v15.0) coding dictionary applied.
Data cutoff date: 12 October 2012.
MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0); n = number of subjects with adverse events.

Treatment-Emergent Treatment-Related Adverse Events: A summary of all treatment-related TEAEs reported in ≥5% of subjects in any treatment group is provided in Table 17.

Table 17. Treatment-Emergent Treatment-Related Adverse Events Reported in ≥5% of Subjects in any Treatment Group

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Active Titration n (%)	Placebo Titration n (%)	Non-Randomized n (%)	Discontinued Prior to Randomization n (%)
Number (%) of subjects evaluable for adverse events	56	56	91	10
Number (%) of subjects with adverse events	53 (94.6)	47 (83.9)	89 (97.8)	8 (80.0)
Being queried	0	0	0	1 (10.0)
Transient ischemic attack	0	0	0	1 (10.0)
Blood and lymphatic system disorders	7 (12.5)	5 (8.9)	16 (17.6)	1 (10.0)
Anaemia	4 (7.1)	2 (3.6)	4 (4.4)	0
Lymphopenia	0	0	2 (2.2)	1 (10.0)
Thrombocytopenia	4 (7.1)	3 (5.4)	12 (13.2)	0
Cardiac disorders	0	1 (1.8)	0	2 (20.0)
Sinus tachycardia	0	1 (1.8)	0	2 (20.0)
Endocrine disorders	18 (32.1)	13 (23.2)	41 (45.1)	2 (20.0)
Hypothyroidism	18 (32.1)	13 (23.2)	41 (45.1)	2 (20.0)
Gastrointestinal disorders	38 (67.9)	37 (66.1)	70 (76.9)	4 (40.0)
Abdominal distension	1 (1.8)	3 (5.4)	1 (1.1)	0
Abdominal pain	8 (14.3)	3 (5.4)	7 (7.7)	1 (10.0)
Abdominal pain upper	4 (7.1)	1 (1.8)	5 (5.5)	0
Cheilitis	1 (1.8)	1 (1.8)	5 (5.5)	0
Constipation	5 (8.9)	7 (12.5)	18 (19.8)	1 (10.0)
Diarrhoea	32 (57.1)	32 (57.1)	56 (61.5)	1 (10.0)
Dry mouth	5 (8.9)	1 (1.8)	6 (6.6)	0
Dyspepsia	3 (5.4)	2 (3.6)	14 (15.4)	0
Flatulence	6 (10.7)	2 (3.6)	3 (3.3)	0
Gastritis	2 (3.6)	2 (3.6)	6 (6.6)	0
Gastrooesophageal reflux disease	0	3 (5.4)	4 (4.4)	0
Haemorrhoids	1 (1.8)	0	3 (3.3)	1 (10.0)
Nausea	18 (32.1)	15 (26.8)	28 (30.8)	2 (20.0)
Stomatitis	9 (16.1)	3 (5.4)	17 (18.7)	0
Vomiting	14 (25.0)	10 (17.9)	19 (20.9)	2 (20.0)
General disorders and administration site conditions	32 (57.1)	29 (51.8)	48 (52.7)	4 (40.0)
Asthenia	5 (8.9)	4 (7.1)	4 (4.4)	0
Fatigue	23 (41.1)	24 (42.9)	42 (46.2)	4 (40.0)
Mucosal inflammation	11 (19.6)	7 (12.5)	13 (14.3)	0
Oedema peripheral	2 (3.6)	3 (5.4)	10 (11.0)	0
Pain	2 (3.6)	3 (5.4)	0	0
Infections and infestations	2 (3.6)	7 (12.5)	3 (3.3)	0
Rhinitis	2 (3.6)	6 (10.7)	3 (3.3)	0
Upper respiratory tract infection	0	3 (5.4)	0	0
Investigations	22 (39.3)	20 (35.7)	47 (51.6)	2 (20.0)
Alanine aminotransferase increased	4 (7.1)	9 (16.1)	12 (13.2)	0
Aspartate aminotransferase increased	3 (5.4)	9 (16.1)	11 (12.1)	0
Blood alkaline phosphatase increased	0	4 (7.1)	6 (6.6)	2 (20.0)
Blood creatinine increased	1 (1.8)	3 (5.4)	10 (11.0)	1 (10.0)
Blood glucose decreased	3 (5.4)	4 (7.1)	1 (1.1)	0
Blood glucose increased	4 (7.1)	7 (12.5)	7 (7.7)	1 (10.0)
Blood potassium increased	3 (5.4)	3 (5.4)	4 (4.4)	0
Blood thyroid stimulating hormone increased	8 (14.3)	7 (12.5)	9 (9.9)	0
Fibrin D dimer increased	0	1 (1.8)	0	1 (10.0)
Weight decreased	14 (25.0)	10 (17.9)	25 (27.5)	1 (10.0)

Table 17. Treatment-Emergent Treatment-Related Adverse Events Reported in ≥5% of Subjects in any Treatment Group

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Active Titration n (%)	Placebo Titration n (%)	Non-Randomized n (%)	Discontinued Prior to Randomization n (%)
Metabolism and nutrition disorders	21 (37.5)	16 (28.6)	44 (48.4)	3 (30.0)
Decreased appetite	17 (30.4)	13 (23.2)	34 (37.4)	3 (30.0)
Hyperkalaemia	3 (5.4)	1 (1.8)	3 (3.3)	0
Hyperlipidaemia	0	0	5 (5.5)	0
Hyperuricaemia	0	0	8 (8.8)	0
Hypoalbuminaemia	3 (5.4)	1 (1.8)	1 (1.1)	0
Hyponatraemia	1 (1.8)	0	2 (2.2)	1 (10.0)
Hypophosphataemia	1 (1.8)	2 (3.6)	4 (4.4)	1 (10.0)
Musculoskeletal and connective tissue disorders	18 (32.1)	14 (25.0)	32 (35.2)	2 (20.0)
Arthralgia	9 (16.1)	5 (8.9)	11 (12.1)	0
Back pain	6 (10.7)	4 (7.1)	5 (5.5)	0
Bone pain	3 (5.4)	2 (3.6)	1 (1.1)	0
Groin pain	0	0	0	1 (10.0)
Muscular weakness	3 (5.4)	0	1 (1.1)	0
Musculoskeletal pain	2 (3.6)	3 (5.4)	6 (6.6)	0
Musculoskeletal stiffness	0	3 (5.4)	2 (2.2)	0
Myalgia	4 (7.1)	1 (1.8)	5 (5.5)	0
Neck pain	2 (3.6)	3 (5.4)	2 (2.2)	0
Pain in extremity	3 (5.4)	2 (3.6)	13 (14.3)	2 (20.0)
Nervous system disorders	18 (32.1)	13 (23.2)	37 (40.7)	1 (10.0)
Dizziness	5 (8.9)	5 (8.9)	6 (6.6)	1 (10.0)
Dysgeusia	9 (16.1)	5 (8.9)	20 (22.0)	1 (10.0)
Headache	7 (12.5)	6 (10.7)	22 (24.2)	0
Hypoaesthesia	1 (1.8)	0	2 (2.2)	1 (10.0)
Paraesthesia	3 (5.4)	1 (1.8)	3 (3.3)	1 (10.0)
Psychiatric disorders	2 (3.6)	4 (7.1)	8 (8.8)	2 (20.0)
Confusional state	0	1 (1.8)	0	1 (10.0)
Depression	1 (1.8)	3 (5.4)	3 (3.3)	0
Insomnia	1 (1.8)	1 (1.8)	6 (6.6)	1 (10.0)
Renal and urinary disorders	11 (19.6)	10 (17.9)	38 (41.8)	1 (10.0)
Haemoglobinuria	2 (3.6)	3 (5.4)	4 (4.4)	0
Proteinuria	10 (17.9)	10 (17.9)	37 (40.7)	1 (10.0)
Respiratory, thoracic and mediastinal disorders	20 (35.7)	23 (41.1)	55 (60.4)	4 (40.0)
Cough	4 (7.1)	4 (7.1)	7 (7.7)	0
Dysphonia	18 (32.1)	18 (32.1)	44 (48.4)	3 (30.0)
Dyspnoea	4 (7.1)	5 (8.9)	17 (18.7)	1 (10.0)
Epistaxis	4 (7.1)	3 (5.4)	11 (12.1)	0
Oropharyngeal pain	3 (5.4)	1 (1.8)	7 (7.7)	0
Skin and subcutaneous tissue disorders	24 (42.9)	19 (33.9)	53 (58.2)	0
Alopecia	2 (3.6)	2 (3.6)	13 (14.3)	0
Dry skin	7 (12.5)	3 (5.4)	6 (6.6)	0
Palmar-plantar erythrodysaesthesia syndrome	18 (32.1)	10 (17.9)	40 (44.0)	0
Pruritus	2 (3.6)	6 (10.7)	11 (12.1)	0
Rash	3 (5.4)	7 (12.5)	17 (18.7)	0
Vascular disorders	34 (60.7)	24 (42.9)	75 (82.4)	5 (50.0)
Hypertension	34 (60.7)	24 (42.9)	75 (82.4)	5 (50.0)

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v15.0) coding dictionary applied.
Data cutoff date: 12 October 2012.
MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0); n = number of subjects with adverse events.

All-Causality Serious Adverse Events: A summary of all-causality SAEs reported during the study is presented in Table 18.

Table 18. Treatment-Emergent Serious Adverse Events (All-Causalities)

System Organ Class Preferred Term	Active Titration N=56 n (%)	Placebo Titration N=56 n (%)	Non-Randomized N=91 n (%)	Discontinued Prior to Randomization N=10 n (%)
Number of subjects with at least 1 SAE	15 (26.8)	13 (23.2)	35 (38.5)	2 (20.0)
Being queried	0	0	1 (1.1)	0
Transient ischemic attack	0	0	1 (1.1)	0
Blood and lymphatic system disorders	1 (1.8)	0	1 (1.1)	0
Neutropenia	1 (1.8)	0	0	0
Anaemia	0	0	1 (1.1)	0
Cardiac disorders	1 (1.8)	0	6 (6.6)	0
Myocardial ischaemia	1 (1.8)	0	0	0
Acute myocardial infarction	0	0	1 (1.1)	0
Angina pectoris	0	0	2 (2.2)	0
Coronary artery stenosis	0	0	1 (1.1)	0
Diastolic dysfunction	0	0	1 (1.1)	0
Myocardial infarction	0	0	2 (2.2)	0
Ear and labyrinth disorders	0	0	1 (1.1)	0
Tinnitus	0	0	1 (1.1)	0
Endocrine disorders	0	0	1 (1.1)	0
Hypothyroidism	0	0	1 (1.1)	0
Eye disorders	0	0	1 (1.1)	0
Cataract	0	0	1 (1.1)	0
Gastrointestinal disorders	5 (8.9)	5 (8.9)	7 (7.7)	0
Diarrhoea	2 (3.6)	1 (1.8)	1 (1.1)	0
Nausea	2 (3.6)	0	0	0
Vomiting	2 (3.6)	1 (1.8)	1 (1.1)	0
Diverticulum intestinal haemorrhagic	1 (1.8)	0	0	0
Abdominal distension	0	1 (1.8)	0	0
Abdominal pain	0	1 (1.8)	1 (1.1)	0
Abdominal pain upper	0	0	1 (1.1)	0
Ascites	0	2 (3.6)	0	0
Crohn's disease	0	0	1 (1.1)	0
Enterocolitis	0	1 (1.8)	1 (1.1)	0
Gastrointestinal hypomotility	0	0	1 (1.1)	0
Gingivitis	0	0	1 (1.1)	0
Ileus	0	0	1 (1.1)	0
Intestinal obstruction	0	1 (1.8)	0	0
Pancreatitis	0	0	1 (1.1)	0
General disorders and administration site conditions	2 (3.6)	4 (7.1)	8 (8.8)	0
Disease progression	1 (1.8)	1 (1.8)	6 (6.6)	0
General physical health deterioration	1 (1.8)	1 (1.8)	0	0
Chest pain	0	0	1 (1.1)	0
Fatigue	0	0	1 (1.1)	0
Pyrexia	0	2 (3.6)	1 (1.1)	0
Hepatobiliary disorders	1 (1.8)	0	2 (2.2)	0
Cholecystitis chronic	1 (1.8)	0	0	0
Biliary colic	0	0	1 (1.1)	0
Cholelithiasis	0	0	1 (1.1)	0
Infections and infestations	2 (3.6)	4 (7.1)	5 (5.5)	0
Cystitis	1 (1.8)	1 (1.8)	0	0
Lung abscess	1 (1.8)	0	0	0
Pneumonia	1 (1.8)	2 (3.6)	1 (1.1)	0
Appendicitis	0	1 (1.8)	0	0
Infection	0	0	1 (1.1)	0
Lung infection	0	0	1 (1.1)	0

Table 18. Treatment-Emergent Serious Adverse Events (All-Causalities)

System Organ Class Preferred Term	Active Titration N=56 n (%)	Placebo Titration N=56 n (%)	Non-Randomized N=91 n (%)	Discontinued Prior to Randomization N=10 n (%)
Osteomyelitis	0	0	1 (1.1)	0
Peritonitis bacterial	0	0	1 (1.1)	0
Postoperative wound infection	0	0	1 (1.1)	0
Injury, poisoning and procedural complications	0	1 (1.8)	2 (2.2)	0
Lumbar vertebral fracture	0	1 (1.8)	0	0
Overdose	0	0	1 (1.1)	0
Postoperative hernia	0	0	1 (1.1)	0
Postoperative wound complication	0	0	1 (1.1)	0
Road traffic accident	0	1 (1.8)	0	0
Investigations	0	2 (3.6)	0	0
Blood creatinine increased	0	2 (3.6)	0	0
Blood sodium decreased	0	1 (1.8)	0	0
Metabolism and nutrition disorders	4 (7.1)	1 (1.8)	7 (7.7)	1 (10.0)
Dehydration	4 (7.1)	0	3 (3.3)	1 (10.0)
Decreased appetite	1 (1.8)	1 (1.8)	2 (2.2)	0
Hypercalcaemia	0	0	0	1 (10.0)
Hypokalaemia	0	0	1 (1.1)	0
Hyponatraemia	0	0	1 (1.1)	0
Musculoskeletal and connective tissue disorders	1 (1.8)	1 (1.8)	1 (1.1)	0
Back pain	1 (1.8)	0	1 (1.1)	0
Haemarthrosis	0	1 (1.8)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (1.8)	0	0
Metastases to central nervous system	0	1 (1.8)	0	0
Nervous system disorders	2 (3.6)	2 (3.6)	3 (3.3)	0
Cerebrovascular insufficiency	1 (1.8)	0	0	0
Syncope	1 (1.8)	0	0	0
Encephalopathy	0	1 (1.8)	0	0
Headache	0	1 (1.8)	1 (1.1)	0
Presyncope	0	0	1 (1.1)	0
Somnolence	0	0	1 (1.1)	0
Psychiatric disorders	0	1 (1.8)	0	0
Delirium	0	1 (1.8)	0	0
Renal and urinary disorders	1 (1.8)	0	3 (3.3)	1 (10.0)
Renal colic	1 (1.8)	0	0	0
Postrenal failure	0	0	1 (1.1)	0
Renal failure	0	0	0	1 (10.0)
Renal failure acute	0	0	1 (1.1)	0
Urinary retention	0	0	2 (2.2)	0
Reproductive system and breast disorders	0	0	1 (1.1)	0
Pelvic prolapse	0	0	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders	2 (3.6)	2 (3.6)	2 (2.2)	0
Atelectasis	1 (1.8)	0	0	0
Dyspnoea	1 (1.8)	1 (1.8)	0	0
Cough	0	1 (1.8)	0	0
Pleural effusion	0	0	1 (1.1)	0
Pulmonary hypertension	0	0	1 (1.1)	0
Pulmonary oedema	0	0	1 (1.1)	0
Skin and subcutaneous tissue disorders	1 (1.8)	0	0	0
Dermatitis	1 (1.8)	0	0	0
Surgical and medical procedures	0	0	1 (1.1)	0
Incisional hernia repair	0	0	1 (1.1)	0
Vascular disorders	0	1 (1.8)	4 (4.4)	1 (10.0)
Circulatory collapse	0	0	1 (1.1)	0
Hypertension	0	1 (1.8)	1 (1.1)	0
Hypertensive crisis	0	0	0	1 (10.0)

Table 18. Treatment-Emergent Serious Adverse Events (All-Causalities)

System Organ Class Preferred Term	Active Titration N=56 n (%)	Placebo Titration N=56 n (%)	Non-Randomized N=91 n (%)	Discontinued Prior to Randomization N=10 n (%)
Hypotension	0	0	1 (1.1)	0
Orthostatic hypotension	0	0	1 (1.1)	0

MedDRA (v15.0) coding dictionary applied.
Subjects were only counted once per treatment for each row.
Data source is from CRF page.
Data cutoff date: 12 October 2012.
CRF = case report form; MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0); N = number of subjects in each group; n = number of subjects with adverse events; SAE = serious adverse event.

Treatment-Related Serious Adverse Events: A summary of treatment-related SAEs reported during the study is presented in Table 19.

Table 19. Treatment-Emergent Treatment-Related Serious Adverse Events

System Organ Class Preferred Term	Active Titration N=56 n (%)	Placebo Titration N=56 n (%)	Non-Randomized N=91 n (%)	Discontinued Prior to Randomization N=10 n (%)
Number of subjects with at least 1 SAE	10 (17.9)	4 (7.1)	15 (16.5)	1 (10.0)
Being queried	0	0	1 (1.1)	0
Transient ischemic attack	0	0	1 (1.1)	0
Cardiac disorders	1 (1.8)	0	2 (2.2)	0
Myocardial ischaemia	1 (1.8)	0	0	0
Angina pectoris	0	0	1 (1.1)	0
Diastolic dysfunction	0	0	1 (1.1)	0
Ear and labyrinth disorders	0	0	1 (1.1)	0
Tinnitus	0	0	1 (1.1)	0
Endocrine disorders	0	0	1 (1.1)	0
Hypothyroidism	0	0	1 (1.1)	0
Gastrointestinal disorders	5 (8.9)	2 (3.6)	4 (4.4)	0
Diarrhoea	2 (3.6)	1 (1.8)	1 (1.1)	0
Nausea	2 (3.6)	0	0	0
Vomiting	2 (3.6)	1 (1.8)	0	0
Diverticulum intestinal haemorrhagic	1 (1.8)	0	0	0
Abdominal distension	0	1 (1.8)	0	0
Abdominal pain upper	0	0	1 (1.1)	0
Enterocolitis	0	1 (1.8)	0	0
Gingivitis	0	0	1 (1.1)	0
Pancreatitis	0	0	1 (1.1)	0
General disorders and administration site conditions	0	1 (1.8)	2 (2.2)	0
Chest pain	0	0	1 (1.1)	0
Pyrexia	0	1 (1.8)	1 (1.1)	0
Infections and infestations	1 (1.8)	1 (1.8)	2 (2.2)	0
Lung abscess	1 (1.8)	0	0	0
Pneumonia	1 (1.8)	0	0	0
Appendicitis	0	1 (1.8)	0	0
Osteomyelitis	0	0	1 (1.1)	0
Postoperative wound infection	0	0	1 (1.1)	0
Metabolism and nutrition disorders	2 (3.6)	1 (1.8)	4 (4.4)	0
Dehydration	2 (3.6)	0	1 (1.1)	0
Decreased appetite	0	1 (1.8)	2 (2.2)	0
Hypokalaemia	0	0	1 (1.1)	0
Musculoskeletal and connective tissue disorders	0	1 (1.8)	0	0
Haemarthrosis	0	1 (1.8)	0	0
Nervous system disorders	1 (1.8)	0	1 (1.1)	0
Cerebrovascular insufficiency	1 (1.8)	0	0	0
Presyncope	0	0	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders	2 (3.6)	0	1 (1.1)	0
Atelectasis	1 (1.8)	0	0	0
Dyspnoea	1 (1.8)	0	0	0
Pulmonary hypertension	0	0	1 (1.1)	0
Skin and subcutaneous tissue disorders	1 (1.8)	0	0	0
Dermatitis	1 (1.8)	0	0	0
Vascular disorders	0	1 (1.8)	2 (2.2)	1 (10.0)
Circulatory collapse	0	0	1 (1.1)	0
Hypertension	0	1 (1.8)	1 (1.1)	0
Hypertensive crisis	0	0	0	1 (10.0)

MedDRA (v15.0) coding dictionary applied. Subjects were only counted once per treatment for each row. Data source is from CRF page. Data cutoff date: 12 October 2012.
CRF = case report form; MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0); N = number of subjects in each group; n = number of subjects with adverse events; SAE = serious adverse event.

Permanent Discontinuations due to Adverse Events: A summary of AEs that led to treatment discontinuation in ≥2% of subjects in any treatment group is presented in Table 20.

Table 20. Summary of Adverse Events That led to Treatment Discontinuation in ≥2% of Subjects in any Treatment Group

System Organ Class Preferred Term	Active Titration N=56 n (%) No. of Subjects (%)	Placebo Titration N=56 n (%) No. of Subjects (%)	Non-Randomized N=91 n (%) No. of Subjects (%)	Discontinued Prior to Randomization N=10 n (%) No. of Subjects (%)
Any AEs	7 (12.5)	6 (10.7)	11 (12.1)	2 (20.0)
General disorders and administration site conditions	1 (1.8)	2 (3.6)	3 (3.3)	1 (10.0)
General physical health deterioration	1 (1.8)	1 (1.8)	1 (1.1)	1 (10.0)
Disease progression	0 (0.0)	1 (1.8)	2 (2.2)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	2 (2.2)	1 (10.0)
Hypertension	0 (0.0)	0 (0.0)	1 (1.1)	1 (10.0)

% = (n/N) × 100.
MedDRA (v15.0) coding dictionary applied.
Data cutoff date: 12 October 2012.
AE = adverse event; MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0); N = number of subjects in each group; n = number of subjects with adverse events; No. = number.

Deaths: Similar percentages of subjects died across treatment groups. The most common cause of death was disease under study. No subject died due to study treatment toxicity. A summary of causes of death is presented in Table 21.

Table 21. Causes of Death

	Active Titration N=56		Placebo Titration N=56		Non-Randomized N=91		Discontinued Prior to Randomization N=10	
	n	%	n	%	n	%	n	%
Subjects who died	22	39.3	21	37.5	31	34.1	4	40.0
Subjects who died on-study[a]	2	3.6	1	1.8	8	8.8	0	
Disease under study	2	3.6	0		5	5.5	0	
Study treatment toxicity	0		0		0		0	
Unknown	0		0		0		0	
Other	0		1	1.8	3	3.3	0	
Acute circulatory failure	0		0		1	1.1	0	
Pneumonia	0		0		1	1.1	0	
Fatal disease progression	0		1	1.8	0		0	
General physical health deterioration	0		0		1	1.1	0	
Subjects who died during follow-up[b]	20	35.7	20	35.7	23	25.3	4	40.0
Disease under study	19	33.9	18	32.1	21	23.1	4	40.0
Study treatment toxicity	0		0		0		0	
Unknown	1	1.8	1	1.8	2	2.2	0	
Other	0		1	1.8	0		0	
Upper GI bleed	0		1	1.8	0		0	

Data cut-off date: 12 October 2012.
GI = gastrointestinal; N = number of subjects; n = number of subjects meeting prespecified criteria.
a. On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
b. Follow-up deaths are those that occurred >28 days after the last dose of study drug.

Vital Signs, Laboratory Findings, and Other Observations Related to Safety: In general, there were no clinically relevant observations regarding results of vital sign assessments in this study.

There were no clinically-significant hematological and biochemistry abnormalities reported.

In the active titration group, the proportion of subjects whose TSH values shifted to postbaseline TSHs ≥10 IU/mL was higher than in the placebo group (41.8% and 19.6%, respectively). In the non-randomized group, the TSH values of 51.6% of subjects shifted to TSH values ≥10 IU/mL.

Urine protein values for 2 (3.6%) subjects in the active titration group shifted from Grade 0 to Grade 3 and for 1 (1.8%) subject from Grade 0 to Grade 4; values for 1(1.8%) subject shifted from Grade 1 to Grade 3. In the placebo titration group, urine protein values for 3 (5.5%) subjects shifted from Grade 0 to Grade 3. In the non-randomized group, urine protein values for 10 (11.1%) subjects shifted from Grade 0 to Grade 3 and for 1 (1.1%) subject from Grade 0 to Grade 4.

Discontinuations from study due to an abnormal laboratory test were reported for 1 subject in the placebo titration group (increased blood creatinine, SAE, unrelated to study drug), and for 1 subject in the non-randomized group (proteinuria, AE, related to study drug).

CONCLUSIONS:

- The primary objective of the study was achieved and the ORR was significantly higher in the active titration arm compared to the placebo titration arm. There were no statistically significant differences in secondary efficacy endpoints, PFS or OS, between the 2 randomized arms. The overall median PFS was 14.6 months.

- The most common all-causality, all grade AEs in the randomized arms were diarrhea, hypertension, and fatigue. More hypertension was reported in active titration arm than in the placebo titration arms; rates of diarrhea and fatigue were similar in both arms. In general, the non-randomized arm had more all-causality, all grade AEs. Overall, the AEs observed in treatment-naïve subjects with advanced RCC in this study were consistent with the risk/benefit profile observed in completed studies in previously-treated subjects with advanced RCC; there were no new or unexpected AEs in this study.

- The axitinib PK in treatment- naïve subjects with advanced RCC is consistent with that observed in previously-treated subjects with advanced RCC subjects receiving a starting dose of 5 mg BID.

- There were no significant associations of genotype vs ORR (primary objective) or OS (secondary objective). For some polymorphisms it was shown that median PFS for the G/G genotype was longer than for other genotypes. No significant observations of association of genotype vs postbaseline DBP <90 mm Hg were reported.