Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

SYNOPSIS

Title of Study: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of OSI-906 in Patients with Locally Advanced or Metastatic Adrenocortical Carcinoma (OSI-906-301)

Investigators/Coordinating Investigators: [redacted] MD and [redacted], MD, PhD

Study Center(s): This multicenter study was conducted in the following locations (number of sites): Australia (1), Germany (3), France (6), United Kingdom (2), Italy (2), Netherlands (3), Poland (1), United States (14) and Canada (3).

Publication Based on the Study: Not applicable

Study Period: December 01, 2009 to July 11, 2012

Study Initiation Date (Date of First Enrollment): December 01, 2009

Study Completion Date (Date of Last Evaluation): July 11, 2012

Phase of Development: Phase 3

Objectives: The primary objective of this study was to determine the overall survival (OS) of single agent linsitinib versus placebo in patients with adrenocortical carcinoma (ACC) who received at least 1 but no more than 2 prior drug regimens.

The secondary objectives of this study were to evaluate:

- progression-free survival (PFS), disease control rate (DCR), best overall response rate (ORR) and duration of response;
- quality of life (QoL), as measured by European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30;
- the safety profile of linsitinib;
- the pharmacokinetic profile of linsitinib; and
- pharmacodynamic changes and correlations with treatment outcome.

Methodology: This multicenter, randomized, double-blind, placebo-controlled, phase 3 study evaluated single-agent linsitinib in patients with locally advanced or metastatic ACC who received at least 1 but no more than 2 prior drug regimens. Adult patients were randomized 2:1 to receive either single agent, 150 mg linsitinib (90 patients) or matching placebo (49 patients) administered orally twice daily (bid) for 21 days in a treatment period and continued until any criteria for discontinuation were met. Study subjects were stratified according to prior systemic cytotoxic chemotherapy for ACC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and use of ≥ 1 oral antihyperglycemic therapy at randomization.

Number of Patients (Planned, Enrolled and Analyzed): The planned sample size for this study was 135 patients. A total of 139 patients, 90 in the linsitinib treatment arm and 49 in the placebo treatment arm,

Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

were enrolled, randomized and included in the Full Analysis Set (FAS). One patient was randomized to the placebo treatment arm but not dosed. All efficacy analyses were performed on the FAS. The Pharmacokinetics Analysis Set (PKAS) comprised all 90 patients in the linsitinib treatment arm, and the Extended PKAS included 44 patients in the linsitinib treatment arm. The Pharmacodynamics Analysis Set (PDAS) comprised 86 patients in the linsitinib treatment arm and 47 patients in the placebo treatment arm. The Safety Analysis Set (SAF) comprised all 90 patients in the linsitinib treatment arm and 48 patients in the placebo treatment arm.

Diagnosis and Main Criteria for Inclusion: Patients ≥ 18 years of age with histologically confirmed ACC that was locally advanced or metastatic and not amenable to surgical resection were eligible for this study. Patients were to have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, radiologically-confirmed progressive disease within 6 months prior to randomization, ECOG PS ≤ 2 and a predicted life expectancy ≥ 12 weeks. Eligible patients were to have received at least 1 but no more than 2 prior drug regimens for locally advanced/metastatic ACC. In addition to 1-2 prior drug regimens, patients must have received prior mitotane, either as neoadjuvant, adjuvant or locally advanced/metastatic therapy. Prior radiation therapy was permitted provided patients had recovered from the acute, toxic effects of radiotherapy prior to randomization. A minimum of 3 weeks (21 days) must have elapsed between the end of treatment with a prior drug regimen/radiotherapy and randomization. Prior surgery was permitted provided that adequate wound healing had occurred prior to randomization. The following laboratory results were also required for study inclusion: fasting glucose ≤ 150 mg/dL (8.3 mmol/L), neutrophil count ≥ 1.5 x 10^9/L; platelet count ≥ 100 x 10^9/L; bilirubin ≤ 1.5 x upper limit of normal (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN or ≤ 5 x ULN if patient had documented liver metastases or received prior mitotane therapy and serum creatinine ≤ 1.5 x ULN or ≤ 2.0 x ULN if the patient had received prior cisplatin.

Main exclusion criteria for patients in the study included Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring insulinotropic or insulin therapy, prior insulin-like growth factor-1 receptor (IGF-1R) inhibitor therapy, malignancy other than ACC within the past 3 years (with the exception of resected basal cell or squamous cell carcinoma of the skin, cured in situ cervical carcinoma, cured ductal carcinoma in situ of the breast and/or cured superficial bladder cancer), history of significant cardiovascular disease (including second/third degree heart block, clinically significant ischemic heart disease, mean Fridericia's corrected QT interval [QTcF] interval > 450 msec at screening, poorly controlled hypertension, and congestive heart failure Class II or worse according to the New York Heart Association [NYHA] unless the disease was well-controlled), history of cerebrovascular accident (CVA) within 6 months prior to randomization or that resulted in ongoing neurologic instability, and use of drugs that have a risk of causing QT interval prolongation within 14 days prior to day 1 dosing.

Test Product, Dose and Mode of Administration, Batch Numbers: Patients in the linsitinib treatment arm received 150 mg linsitinib administered orally twice daily (bid) for 21 days in a treatment period. Linsitinib

Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

was supplied as 100 or 150 mg tablets in 60 cc square high-density polyethylene (HDPE) bottles with an induction sealed liner and child-resistant closure. The following lot numbers were provided:

- Linsitinib 150 mg – [redacted], [redacted], [redacted], [redacted], [redacted]
- Linsitinib 100 mg – [redacted], [redacted], [redacted], [redacted]

Duration of Treatment (or Duration of Study, if applicable): Study drug was to be started within 5 days of randomization and continued until any criteria for discontinuation were met: relapse or disease progression as determined by radiologic evaluation by the investigator; adverse event (AE) resulting in death, requiring withdrawal from study drug and/or failure to recover from toxicity despite a dosing interruption of up to 14 days; medical or ethical reasons, including noncompliance; and patient request (excluding AE).

Reference Product, Dose and Mode of Administration, Batch Numbers: Patients in the placebo treatment arm received placebo administered orally twice daily (bid) for 21 days in a treatment period. Matching placebo tablets were the same formulation as the active tablets but an equivalent amount of lactose replaced the linsitinib. The following lot numbers were provided:

- Matching placebo (150 mg) – [redacted], [redacted], [redacted], [redacted], [redacted]
- Matching placebo (100 mg) – [redacted]

Criteria for Evaluation: OS was the primary efficacy variable and was defined as the time from the date of randomization until the documented date of death. The secondary efficacy variables included PFS, the time from randomization to the date of the first documentation of disease progression or death due to any cause, whichever occurs first; DCR, defined as the proportion of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD); best ORR, defined as the proportion of patients with a best overall response of CR or PR; and duration of response and time to deterioration in quality of life (as measured by EORTC QLQ-C30). For OS, patients who were still alive at the time of analysis were censored on the last day the patient was known to be alive. For PFS, patients who were still alive at the time of analysis and had not experienced progressive disease (PD) were censored at the last tumor assessment of CR, PR or SD.

To assess efficacy, tumor response and progression were evaluated using the new international RECIST criteria. All patients who had measurable disease according to the RECIST v1.1 criteria and who had their disease reevaluated were evaluable for response. All sites of disease were to be followed as either target or nontarget lesions, as categorized at baseline. Pathological lymph nodes were also considered target or nontarget lesions.

Pharmacokinetic data were evaluated from blood samples. Linsitinib plasma concentration (versus time) profiles were obtained and pharmacokinetic parameters were calculated including (but not limited to) AUC, C_{max} and t_{max}.

Pharmacodynamic data were to be evaluated from blood samples, fresh tumor biopsies and positron emission tomography (PET) scans. Exploratory analyses were to include analysis of fresh tumor tissue, archival tumor tissue and plasma (sufficient samples permitting), which were to be analyzed for relationships between

Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

biomarkers, including proteins and nucleic acids and the effects of linsitinib. Archival tumor tissue samples were to be analyzed for histologic/pathologic classification potentially predictive of response to linsitinib. PET imaging was to be used to assess the impact of linsitinib in up to 40 patients.

Safety was assessed via physical examination, vital signs, clinical laboratory tests (hematology and biochemistry), electrocardiograms (ECGs) and by the incidence and types of AEs/ serious adverse events (SAEs) as well as discontinuations of study drug due to AEs. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 was used to evaluate and grade all AEs until the end of the study; CTCAE v4.02 was used for patients remaining.

Statistical Methods: Analyses were performed using SAS version 9.1.3. The primary objective of this study was to determine the OS of single agent linsitinib versus placebo in patients with locally advanced or metastatic ACC who received at least 1 but no more than 2 prior drug regimens. The null hypothesis was no difference in OS between the treatment and placebo and the alternative hypothesis was a prolonged OS in either treatment arm. Hypothesis testing (i.e., for treatment effects) used a two-sided log-rank test at the 0.05 level or equivalently a one-sided log-rank test at the 0.025 level. As a sensitivity analysis, a stratified log-rank test based on the stratification factors at randomization was also to be performed if the data within each stratum were sufficient to support a stratified analysis. Kaplan-Meier survival plots were used to describe the OS in each treatment arm. Median OS and 95% confidence interval were estimated from the Kaplan-Meier curve. The corresponding hazard ratio of the treatment effect along with 95% confidence interval was calculated using a Cox proportional hazard model.

QoL and time to deterioration in QoL were summarized descriptively by visit and a repeated measurement analysis was also performed. Best ORR and DCR were analyzed using Fisher's exact test. Duration of response (CR/PR) and duration of stable disease (CR/PR/SD) were summarized descriptively for responders and SD only.

Exploratory biomarker analyses were limited to insulin-like growth factor (IGF)-1 concentrations; any additional biomarker analyses performed (e.g., nucleic acids or transcript levels of IGF-2, IGFBP3, insulin receptor [IR]-A, IGF binding proteins or other markers) will be submitted as an amendment to this report, as they become available.

Primary pharmacokinetic analyses for plasma concentrations versus time data obtained from the analysis of plasma samples following administration of linsitinib were calculated and presented as descriptive statistics for AUC, C_{max} and t_{max}.

Patients who received at least 1 dose of study drug were evaluated for safety according to the treatment received. The safety evaluation was based mainly on AEs, laboratory, physical examination and ECG data. Descriptive statistics were used to summarize all safety data by treatment arm. The DMC was to review the safety data at the interim analysis and during the trial on a periodic basis.

Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

Summary of Results/Conclusions:

A total of 139 patients, 90 in the linsitinib arm and 49 in the placebo treatment arm, were enrolled and randomized; all patients received study drug with the exception of 1 patient in the placebo treatment arm. In general, the baseline demographic and disease characteristics were balanced between the 2 treatment arms.

The study was unblinded based on the recommendation of the data monitoring committee (DMC) on March 19, 2012 and amended to assess safety parameters only for all active patients continuing to receive linsitinib.

The DMC reviewed unblinded safety and efficacy data from all 138 treated patients, including PFS (the secondary endpoint) and an interim analysis of the primary endpoint of OS (November 30, 2011 field data cutoff). The following observations were made: median OS was 363 days for placebo and 323 days for linsitinib ($p = 0.8875$). Per independent radiology review (IRR), PFS was 46 days for placebo and 44 days for linsitinib ($p = 0.2677$); the ORR (CR +PR) was 0% for placebo and approximately 3% (3 patients with PR) for linsitinib; and the DCR (CR + PR + SD) was 35% for placebo and 32% for linsitinib. In terms of safety, 44% of the patients receiving placebo experienced treatment-emergent adverse events (TEAEs), and 57% of the patients receiving linsitinib experienced TEAEs (notably fatigue and asthenia). No new safety findings were identified by the DMC. Based on these observations, the DMC determined that the probability of success in meeting the final desired improvement (defined as the primary endpoint of OS) was very unlikely (estimated at approximately 0.0003%). Therefore, and based on the DMC recommendations (March 19, 2012), the trial was unblinded for the remaining 6 patients who were on study treatment at that time, and these patients were informed of the risk/benefit of continued treatment. The 2 patients receiving placebo were not permitted to remain on study. The 4 other remaining patients were receiving linsitinib, and all chose to continue on treatment. The 2 patients receiving placebo experienced SD as their best overall response. Of the 4 patients receiving linsitinib, 3 patients achieved PR and 1 patient experienced SD as their best overall response.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy Results:

This study was unblinded before the prespecified primary analysis of OS was performed.

Overall, linsitinib did not improve either median OS or PFS compared to placebo treatment in this trial of patients with locally advanced or metastatic ACC. No significant differences in OS and PFS were found in the linsitinib or placebo treatment arm when analyzed by subgroups of sex, age, ECOG PS at baseline, cigarette smoking history, use of prior systemic cytotoxic chemotherapy for ACC and use of ≥ 1 noninsulinotropic oral antihyperglycemic therapy.

As assessed by both IRR and investigator review, no significant difference in tumor response was noted for the linsitinib and placebo treatment arms.

Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

As assessed by IRR, CR was not achieved by any patient in this study. In the linsitinib treatment arm, PR was achieved by 3 (3.33%) patients. At the end of the study, these patients remained on treatment (unblinded). SD of at least 6 weeks, 12 weeks and 24 weeks was achieved by 26 (28.89%), 11 (12.22%) and 3 (3.33%) patients, respectively. The overall DCR (CR + PR + SD [at least 6 weeks]) was 32.22%. In the placebo treatment arm, PR was not achieved by any patient. SD of at least 6 weeks, 12 weeks and 24 weeks was achieved by 17 (34.69%) patients, 4 (8.16%) and 0 patients, respectively. The overall DCR was 34.69%.

Similar results were seen by investigator reviewed results: CR was not achieved by any patient in this study. In the linsitinib treatment arm, PR was achieved by 3 (3.33%) patients. SD of at least 6 weeks, 12 weeks and 24 weeks was achieved by 33 (36.67%), 13 (14.44%) and 5 (5.56%) patients, respectively. The overall DCR was 36 (40.00%). In the placebo treatment arm, PR was not achieved by any patient. SD of at least 6 weeks, 12 weeks and 24 weeks was achieved by 20 (40.82%), 10 (20.41%) and 4 (8.16%) patients, respectively. The overall DCR was 40.82%.

Pharmacokinetic Results:

Linsitinib was absorbed with peak concentrations occurring at a median t_{max} of 2.0 hours for both TP 1 and TP 2. Mean and median plasma concentrations during TP 2 were generally higher than in TP 1 at all time points measured (2, 4 and 8 hours). Accordingly, mean exposure (AUC_{last}) was 6478.2 ng·h/mL in TP2 versus 2902.3 ng·h/mL in TP1. Linsitinib exposure was highly variable; AUC_{last} ranged from 483.0 to 26444.0 ng·h/mL in TP2 and 317.3 to 6188.1 ng·h/mL in TP1.

Pharmacodynamic Results

The data in this study suggest linsitinib may increase plasma IGF-1 concentrations in patients with ACC. On day 22, the median percent change in IGF-1 concentration from predose was increased by 17.4% in the linsitinib treatment arm and was decreased by 3.3% in the placebo treatment arm. On day 43, the median percent change in IGF-1 concentration from predose was increased by 15.2% in the linsitinib treatment arm and was decreased by 1.0% in the placebo treatment arm. In this study, the increase does not appear to be related to treatment outcome although a larger sample size may be needed for a definitive analysis of this type. Increases in plasma IGF-1 would be consistent with feedback increases in IGF-1 production caused by linsitinib inhibition of IGF-1R. The increases in plasma IGF-1 concentrations suggest concentrations of linsitinib sufficient to inhibit IGF-1R signaling were achieved in tissues involved in regulating IGF-1 expression in some patients.

Safety Results: In this study, a total of 90 patients received linsitinib 150 mg twice daily and 48 patients received placebo twice daily.

Few patients in either the linsitinib treatment arm (4/90 patients, 4.4%) or placebo treatment arm (1/48 patients, 2.1%) discontinued the study due to a drug-related TEAE. Patients in the linsitinib treatment arm experienced a higher number of dose reductions (12 patients, 13.3%) and dose interruptions (11 patients, 12.2%) due to drug-

Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

related toxicity, compared to patients in the placebo arm (dose reductions due to drug-related toxicity: 1 patient (2.1%); dose interruptions due to drug-related toxicity: 2 patients, 4.2%).

Generally, the nature and severity of TEAEs in both treatment arms were consistent with what would be expected in a population of patients with advanced ACC. The vast majority of patients in both treatment arms experienced at least 1 TEAE (97.8% of patients in the linsitinib treatment arm and 93.8% of patients in the placebo treatment arm). Grade 3 and 4 TEAEs were reported in 45.6% and 10.0% of patients, respectively, in the linsitinib treatment arm and in 31.3% and 2.1% of patients in the placebo treatment arm. With the exception of prolonged QTc interval (a known AE associated with linsitinib administration, reported as the preferred term of "electrocardiogram QT prolonged" in 20.0% of patients in the linsitinib treatment arm versus 6.3% in the placebo treatment arm in this study), the most common TEAEs were the same in both treatment arms: fatigue, nausea, vomiting and abdominal pain. Based on causality as determined by the investigators, 55.6% of patients in the linsitinib treatment arm and 43.8% of patients in the placebo treatment arm experienced a drug-related TEAE.

A total of 34 (37.8%) patients in the linsitinib treatment arm and 15 (31.3%) in the placebo treatment arm experienced at least 1 SAE. The most common SAEs in the linsitinib treatment arm were nausea, back pain, vomiting and dyspnea, and the most common SAEs in the placebo treatment arm were abdominal pain, malignant neoplasm progression, nausea, vomiting, asthenia and back pain. Drug-related SAEs were reported by 6.7% of patients in the linsitinib treatment arm and 2.1% in the placebo treatment arm.

Ten deaths due to an AE occurred while on treatment or within 30 days of the last dose of study drug, 5 in the placebo treatment arm (5/48 patients, 10.4%) and 5 in the linsitinib treatment arm (5/90 patients, 5.6%). In the linsitinib treatment arm, none of the deaths were considered related to study drug, and all but 1 death was due to malignant disease. The remaining death in the linsitinib arm was due to renal dysfunction (AE of renal failure). In the placebo treatment arm, 1 death (due to AEs of sepsis and megacolon) was considered related to study drug as assessed by the investigator, who remained blinded to the patient's treatment. The remaining 4 deaths were due or likely related to ACC progression (2 patients died to malignant disease, [redacted]).

CONCLUSIONS: This was a phase 3 study comparing OS for single agent linsitinib 150 mg twice daily versus placebo in patients with ACC that had received 1 or 2 prior drug regimens. A total of 139 patients with ACC were randomized in a 2:1 fashion to the linsitinib treatment arm (90 patients) or the placebo treatment arm (49 patients). Approximately 2 years after the first patient entered the study, the DMC reviewed unblinded safety and efficacy data from all 138 treated patients in an interim analysis of all data up to the field cutoff date of November 30, 2011. Subsequently, the trial was unblinded based on the efficacy data which indicated that the probability of meeting the final desired improvement in OS was highly unlikely and estimated to be

Name of Sponsor/Company: Astellas Pharma Global Development (APGD)		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

0.0003%. No new safety issues were identified by the DMC during the interim analysis. As of July 11, 2012, 4 unblinded patients in the linsitinib treatment arm were still on study.

Linsitinib did not improve either median OS or PFS compared to placebo treatment in this trial of patients with locally advanced or metastatic ACC. Subgroup analyses also did not reveal any differences in OS or PFS between linsitinib versus placebo treatment.

As assessed by IRR and investigator review, CR was not achieved by any patient in this study. Three patients (3.33%) achieved PR in the linsitinib treatment arm versus 0 patients in the placebo treatment arm. At the end of the study, these patients remained on treatment (unblinded). No significant difference was noted in tumor response for the linsitinib and placebo treatment arms as assessed by the DCR for each arm.

Generally, the TEAE profile in both treatment arms was consistent with what would be expected in a population of patients with advanced ACC. Almost all patients in either treatment arm experienced at least 1 TEAE (97.8% of patients in the linsitinib treatment arm and 93.8% of patients in the placebo treatment arm). A higher percentage of patients experienced drug-related TEAEs in the linsitinib treatment arm versus the placebo treatment arm (55.6% and 43.8%, respectively). Eight of the 10 deaths (5 in each arm) that occurred due to an AE while on treatment or within 30 days of the last dose were due to or likely due to malignant disease. No death in the linsitinib treatment arm was considered related to study drug; 1 death in the placebo treatment arm (due to AEs of sepsis and megacolon) was considered related to study drug.

In this study, linsitinib did not improve either median OS or PFS in patients with locally advanced or metastatic ACC when compared with placebo treatment.

Date of Report: August 05, 2013

Table 1 Summary of Patient Disposition

n (%)	Linsitinib (n = 90)	Placebo (n = 49)	Total (n = 139)
FAS	90 (100.0)	49 (100.0)	139 (100.0)
SAF	90 (100.0)	48 (98.0)	138 (99.3)
PKAS	90 (100.0)	0	90 (64.7)
Extended PKAS	44 (48.9) †	0	44 (31.7) †
PDAS	86 (95.6)	47 (95.9)	133 (95.7)
Patients on treatment ‡	4 (4.4)	0	4 (2.9)
Reason off treatment			
Adverse event	12 (13.3)	2 (4.1)	14 (10.1)
Withdrawal by subject	2 (2.2)	2 (4.1)	4 (2.9)
Disease progression	69 (76.7)	41 (83.7)	110 (79.1)
Medical or ethical reasons §	3 (3.3)	4 (8.2)	7 (5.0)
Follow-up/survival ‡			
Alive	29 (32.2)	13 (26.5)	42 (30.2)
Deceased	59 (65.6)	33 (67.3)	92 (66.2)
Lost to follow-up	2 (2.2)	3 (6.1)	5 (3.6)

FAS: Full Analysis Set includes all randomized patients; PKAS: Pharmacokinetics Analysis Set includes patients who received active drug and for whom there was at least 1 measurable plasma concentration; Extended PKAS: Extended Pharmacokinetics Analysis Set includes patients who received active drug, were within the first 75 randomized patients and for whom the pharmacokineticist determined that there was sufficient data to calculate meaningful pharmacokinetic parameters; PDAS: Pharmacodynamics Analysis Set includes patients who received active drug and for whom the translational research scientist determined that there was sufficient data to calculate meaningful parameters for exploratory biomarkers and/or pharmacodynamic markers; SAF: Safety Analysis Set includes all randomized patients who received at least 1 dose of study drug and for whom any data was reported after first dose of study drug.

† A total of 58.7% of the first 75 randomized patients were included in the Extended PKAS

‡ Data as of July 11, 2012

§ Of the 7 patients discontinued due to medical or ethical reasons, 6 were due to progressive disease (PD) that did not meet Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patient [redacted] was discontinued after the study was unblinded by the data monitoring committee (DMC) and it was determined that the patient had been in the placebo treatment arm.

Source: Table 12.1.2.1

Table 2 Demographic and Baseline Characteristics

Characteristics	Linsitinib (n = 90)	Placebo (n = 49)	Total (n = 139)
Sex, n (%)			
Male	30 (33.3)	19 (38.8)	49 (35.3)
Female	60 (66.7)	30 (61.2)	90 (64.7)
Race, n (%)			
Asian	1 (1.1)	1 (2.0)	2 (1.4)
Black	5 (5.6)	3 (6.1)	8 (5.8)
White	81 (90.0)	44 (89.8)	125 (89.9)
Other †	3 (3.3)	1 (2.0)	4 (2.9)
Age (Years), n (%)			
< 60	64 (71.1)	41 (83.7)	105 (75.5)
> 60	26 (28.9)	8 (16.3)	34 (24.5)
Mean (standard deviation)	49.1 (15.38)	47.6 (13.71)	48.5 (14.78)
Median	50.0	48.0	49.0
Minimum – maximum	19.0 – 85.0	22.0 – 78.0	19.0 – 85.0
Weight (kg)			
Mean (standard deviation)	75.2 (21.20)	72.1 (16.30)	74.1 (19.63)
Median	73.6	72.2	73.6
Minimum – maximum	41.0 – 168.8	44.0 – 116.8	41.0 – 168.8
Height (cm)			
Mean (standard deviation)	168.0 (9.76)	168.4 (8.63)	168.1 (9.35)
Median	167.8	168.0	168.0
Minimum – maximum	150.0 – 195.0	152.0 – 192.0	150.0 – 195.0
ECOG Performance Status, n (%)			
0	40 (44.4)	22 (44.9)	62 (44.6)
1	45 (50.0)	26 (53.1)	71 (51.1)
2	5 (5.6)	1 (2.0)	6 (4.3)
Cigarette smoking history, n (%)			
Current smoker	11 (12.2)	6 (12.2)	17 (12.2)
Former smoker	19 (21.1)	12 (24.5)	31 (22.3)
Never smoked or < 100 cigarettes in lifetime	60 (66.7)	31 (63.3)	91 (65.5)
Time from initial diagnosis (months)			
Mean (standard deviation)	41.9 (49.66)	27.9 (28.85)	37.1 (44.06)
Median	26.5	14.9	23.4
Minimum – maximum	3.8 – 276.9	3.3 – 129.3	3.3 – 276.9

All randomized patients (Full Analysis Set)

ECOG: Eastern Cooperative Oncology Group

† Other includes all races not listed in White, Black, Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander.

Source: Tables 12.1.3.1 and 12.1.3.2

Table 3 Efficacy Results

Efficacy Variables	Linsitinib (n = 90)	Placebo (n = 49)	Hazard Ratio † (95% CI)	P-value ‡
OS				
Number of events, n (%)	59 (65.6)	33 (67.3)	0.938 [0.611, 1.440]	0.7708
Median (days) [95% CI]	323 [256, 507]	356 [249, 556]		
25% and 75% Quartiles	147; 717	164; 590		
PFS (IRR)				
Number of events, n (%)	73 (81.1)	44 (89.8)	0.825 [0.563, 1.207]	0.3035
Median (days) [95% CI]	44 [43, 61]	46 [43, 64]		
25% and 75% Quartiles	42; 86	42; 85		
PFS (Investigator)				
Number of events, n (%)	78 (86.7)	45 (91.8)	0.975 [0.674, 1.412]	0.8923
Median (days) [95% CI]	44 [43, 83]	46 [43, 85]		
25% and 75% Quartiles	42; 92	42; 106		
DCR, n (%) [95% CI]				
Per IRR	29 (32.22) [22.8, 42.9]	17 (34.69) [21.7, 49.6]	NC	NC
Per Investigator	36 (40.00) [29.8, 50.9]	20 (40.82) [27.0, 55.8]		
ORR, n (%) [95% CI]				
Per IRR	3 (3.33) [0.7, 9.4]	0	NC	NC
Per Investigator	3 (3.33) [0.7, 9.4]	0		

All randomized patients (Full Analysis Set)

DCR: disease control rate; IRR: independent radiology review; NC: not calculated; ORR: overall response rate; OS: overall survival; PFS: progression-free survival

† Hazard ratio for linsitinib treatment arm versus placebo treatment arm. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of linsitinib.

‡ P-value from an unstratified log-rank test

Source: Table 12.3.1.1, Table 12.3.1.2, Table 12.3.1.3, Table 12.3.3.1 and Table 12.3.3.2

Table 4 Linsitinib Pharmacokinetic Parameters

Treatment Period Statistic	AUC_{last} (h·ng/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{last} (ng/mL)	t_{last} (h)	MRT_{last} (h)
Treatment Period 1, day 1						
n	38	44	44	44	44	44
Mean	2902.3	822.8	2.4	228.1	7.4	3.6
Standard deviation	1559.7	461.0	1.1	296.1	1.3	0.7
Coefficient of variation	53.7	56.0	46.5	129.8	17.6	18.8
Minimum	317.3	85.2	1.8	9.5	3.3	2.5
Median	2571.7	782.5	2.0	130.2	7.9	3.5
Max	6188.1	1883.0	8.2	1592.8	8.3	6.5
Geometric mean	2408.8	673.1	2.3	130.3	7.3	3.5
Treatment Period 2, day 1						
n	33	40	40	40	40	40
Mean	6478.2	1360.9	2.3	696.8	6.9	652.4
Standard deviation	5701.6	1032.7	1.0	907.4	2.2	878.4
Coefficient of variation	88.0	75.9	42.4	130.2	31.5	134.6
Minimum	483.0	80.9	0.7	18.8	0.7	14.8
Median	5580.1	1091.1	2.0	332.4	7.9	289.4
Max	26444.0	4542.8	4.0	4542.8	8.1	4198.8
Geometric mean	4599.9	980.3	2.1	343.5	6.1	300.9

Patients who received active drug, were within the first 75 randomized patients and for whom the pharmacokineticist determined that there was sufficient data to calculate meaningful pharmacokinetic parameters (Extended Pharmacokinetics Analysis Set)

Note: only day 1 in treatment period 1 has AUC_{inf} and $t_{1/2}$, which were not summarized if extrapolation is more than 20% in AUC_{inf}.

MRT: mean residence time

Source: Table 12.4.2

Table 5 Most Common Treatment-emergent Adverse Events (Occurring in ≥ 10% of Patients in Any Treatment Arm)

MedDRA (v12.0)	Linsitinib (n = 90)		Placebo (n = 48)	
Preferred Term, n (%)	All Grades	Grades 3/4	All Grades	Grades 3/4
Fatigue	30 (33.3)	6 (6.7)	11 (22.9)	1 (2.1)
Nausea	24 (26.7)	6 (6.7)	15 (31.3)	1 (2.1)
Vomiting	19 (21.1)	3 (3.3)	10 (20.8)	2 (4.2)
Abdominal pain	18 (20.0)	2 (2.2)	10 (20.8)	7 (14.6)
Electrocardiogram QT prolonged	18 (20.0)	0	3 (6.3)	0
Back pain	17 (18.9)	7 (7.8)	6 (12.5)	3 (6.3)
Constipation	13 (14.4)	0	9 (18.8)	0
Diarrhoea	13 (14.4)	1 (1.1)	4 (8.3)	0
Dyspnoea	12 (13.3)	3 (3.3)	6 (12.5)	1 (2.1)
Pyrexia	12 (13.3)	1 (1.1)	5 (10.4)	0
Oedema peripheral	11 (12.2)	2 (2.2)	5 (10.4)	1 (2.1)
Hyperglycaemia	10 (11.1)	3 (3.3)	5 (10.4)	0
Hypokalaemia	10 (11.1)	4 (4.4)	3 (6.3)	2 (4.2)
Cough	9 (10.0)	0	5 (10.4)	0
Headache	9 (10.0)	0	9 (18.8)	0
Hypertension	7 (7.8)	1 (1.1)	5 (10.4)	1 (2.1)

All randomized patients who received at least 1 dose of study drug and for whom any data was reported after first dose of study drug (Safety Analysis Set)

Treatment-emergent adverse events reported from the first dosing of study drug to the last dose + 30 days. Sorting order: descending in frequency of linsitinib All Grades column. For each preferred term, each subject was only counted once.

Source: Table 12.6.1.1.4

Table 6 Treatment-emergent Serious Adverse Events Reported in 2 or More Patients

MedDRA (v12.0) SOC Preferred Term	Number of Patients (%) †										
	Linsitinib (n = 90)						Placebo (n = 48)				
	Any Grade	1	2	3	4	5	Any Grade ‡	2	3	4	5
Total patients with any SAE	**34 (37.8)**	**0**	**1 (1.1)**	**24 (26.7)**	**4 (4.4)**	**5 (5.6)**	**15 (31.3)**	**0**	**9 (18.8)**	**1 (2.1)**	**5 (10.4)**
Gastrointestinal Disorders	**10 (11.1)**	**0**	**3 (3.3)**	**7 (7.8)**	**0**	**0**	**8 (16.7)**	**0**	**6 (12.5)**	**1 (2.1)**	**1 (2.1)**
Abdominal pain	2 (2.2)	0	1 (1.1)	1 (1.1)	0	0	6 (12.5)	0	4 (8.3)	2 (4.2)	0
Nausea	4 (4.4)	0	1 (1.1)	3 (3.3)	0	0	2 (4.2)	1 (2.1)	1 (2.1)	0	0
Vomiting	3 (3.3)	0	0	3 (3.3)	0	0	2 (4.2)	1 (2.1)	1 (2.1)	0	0
Diarrhoea	2 (2.2)	0	2 (2.2)	0	0	0	0	0	0	0	0
General Disorders and Administrative Site Conditions	**5 (5.6)**	**1 (1.1)**	**0**	**3 (3.3)**	**1 (1.1)**	**0**	**6 (12.5)**	**1 (2.1)**	**4 (8.3)**	**0**	**1 (2.1)**
Pyrexia	2 (2.2)	1 (1.1)	0	1 (1.1)	0	0	1 (2.1)	1 (2.1)	0	0	0
Asthenia	0	0	0	0	0	0	2 (4.2)	0	2 (4.2)	0	0
Fatigue	1 (1.1)	0	0	1 (1.1)	0	0	1 (2.1)	0	1 (2.1)	0	0
Oedema peripheral	1 (1.1)	0	0	1 (1.1)	0	0	1 (2.1)	0	1 (2.1)	0	0
Pain	1 (1.1)	0	0	1 (1.1)	0	0	1 (2.1)	0	1 (2.1)	0	0
Musculoskeletal and Connective Tissue Disorders	**6 (6.7)**	**0**	**0**	**5 (5.6)**	**1 (1.1)**	**0**	**3 (6.3)**	**0**	**3 (6.3)**	**0**	**0**
Back pain	4 (4.4)	0	0	3 (3.3)	1 (1.1)	0	2 (4.2)	0	2 (4.2)	0	0
Muscular weakness	1 (1.1)	0	0	1 (1.1)	0	0	1 (2.1)	0	1 (2.1)	0	0
Respiratory, Thoracic and Mediastinal Disorders	**6 (6.7)**	**0**	**1 (1.1)**	**3 (3.3)**	**1 (1.1)**	**1 (1.1)**	**2 (4.2)**	**0**	**2 (4.2)**	**0**	**0**
Dyspnoea	3 (3.3)	0	1 (1.1)	1 (1.1)	1 (1.1)	0	1 (2.1)	0	1 (2.1)	0	0
Pulmonary embolism	2 (2.2)	0	0	1 (1.1)	1 (1.1)	0	0	0	0	0	0
Respiratory failure	2 (2.2)	0	0	0	1 (1.1)	1 (1.1)	0	0	0	0	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	**4 (4.4)**	**0**	**0**	**1 (1.1)**	**0**	**3 (3.3)**	**3 (6.3)**	**0**	**0**	**0**	**3 (6.3)**
Malignant neoplasm progression	2 (2.2)	0	0	0	0	2 (2.2)	3 (6.3)	0	0	0	3 (6.3)
Infections and Infestations	**2 (2.2)**	**0**	**1 (1.1)**	**1 (1.1)**	**0**	**0**	**4 (8.3)**	**0**	**2 (4.2)**	**1 (2.1)**	**1 (2.1)**
Pneumonia	1 (1.1)	0	1 (1.1)	0	0	0	1 (2.1)	0	1 (2.1)	0	0

Table continued on next page

Table 6 continued

MedDRA (v12.0) SOC Preferred Term	Number of Patients (%) †										
	Linsitinib (n = 90)						Placebo (n = 48)				
	Any Grade	1	2	3	4	5	Any Grade ‡	2	3	4	5
Metabolism and Nutrition Disorders	**4 (4.4)**	**0**	**0**	**4 (4.4)**	**0**	**0**	**2 (4.2)**	**0**	**2 (4.2)**	**0**	**0**
Dehydration	1 (1.1)	0	0	1 (1.1)	0	0	1 (2.1)	0	1 (2.1)	0	0
Hyperglycaemia	2 (2.2)	0	0	2 (2.2)	0	0	0	0	0	0	0
Hyperkalaemia	1 (1.1)	0	0	1 (1.1)	0	0	1 (2.1)	0	1 (2.1)	0	0
Nervous System Disorders	**6 (6.7)**	**0**	**0**	**6 (6.7)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Syncope	2 (2.2)	0	0	2 (2.2)	0	0	0	0	0	0	0
Renal and Urinary Disorders	**3 (3.3)**	**0**	**1 (1.1)**	**1 (1.1)**	**0**	**1 (1.1)**	**1 (2.1)**	**1 (2.1)**	**0**	**0**	**0**
Renal failure	2 (2.2)	0	0	1 (1.1)	0	1 (1.1)	0	0	0)	0	0
Cardiac disorders §	**3 (3.3)**	**0**	**0**	**3 (3.3)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Endocrine disorders §	**1 (1.1)**	**0**	**1 (1.1)**	**0**	**0**	**0**	**2 (4.2)**	**0**	**2 (4.2)**	**0**	**0**
Blood and Lymphatic System Disorders	**2 (2.2)**	**1 (1.1)**	**0**	**1 (1.1)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Anaemia	2 (2.2)	1 (1.1)	0	1 (1.1)	0	0	0	0	0	0	0
Ear and Labyrinth Disorders §	**2 (2.2)**	**0**	**0**	**2 (2.2)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Injury, Poisoning and Procedural Complications	**1 (1.1)**	**0**	**0**	**1 (1.1)**	**0**	**0**	**1 (2.1)**	**0**	**1 (2.1)**	**0**	**0**
Femur fracture	1 (1.1)	0	0	1 (1.1)	0	0	1 (2.1)	0	1 (2.1)	0	0
Investigations §	**1 (1.1)**	**0**	**0**	**1 (1.1)**	**0**	**0**	**1 (2.1)**	**0**	**1 (2.1)**	**0**	**0**
Psychiatric Disorders	**1 (1.1)**	**0**	**0**	**0**	**1 (1.1)**	**0**	**1 (2.1)**	**0**	**1 (2.1)**	**0**	**0**
Confusional state	1 (1.1)	0	0	0	1 (1.1)	0	1 (2.1)	0	1 (2.1)	0	0

All randomized patients who received at least 1 dose of study drug and for whom any data was reported after first dose of study drug (Safety Analysis Set)

Treatment-emergent adverse events reported from the first dosing of study drug to the last dose + 30 days.

Sorting order: descending in frequency of combined total of drug and placebo SAEs by SOC and within that descending order by preferred term.

SAE: serious adverse event

† For each preferred term, each subject was only counted once at a maximum grade.

‡ No Grade 1 treatment-emergent SAEs were reported in the placebo treatment arm.

§ No specific preferred terms within the SOC were reported by ≥ 2 patients.

Source: Table 12.6.1.3.1