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

SYNOPSIS

Title of Study: A Randomized, Placebo-controlled, Double-blind Phase 2 Study of Second-line Treatment with OSI-906 in Patients with Advanced Hepatocellular Carcinoma (HCC) after Failure of First-line Treatment with Sorafenib

Coordinating Investigator: [redacted], MD, PhD

Study Center(s): Korea (3), Taiwan (1), Belgium (1), France (3), Germany (1), Italy (1), Spain (2) and the United States (3).

Publication Based on the Study: Not applicable

Study Period: January 2011 to November 2011

Study Initiation Date (Date of First Enrollment): 10 Jan 2011

Study Completion Date (Date of Last Evaluation): 04 Nov 2011

Phase of Development: 2

Objectives: The primary objective of this study was to determine the time to progression (TTP) in advanced HCC patients treated with linsitinib (Arm A) versus placebo (Arm B) after failure of first-line treatment with sorafenib.

The secondary objectives of this study were to evaluate:

- Overall survival (OS);
- Safety (including safety review for first 18 patients);
- Progression-free survival (PFS);
- Disease control rate (DCR);
- Overall response rate (ORR);
- TTP, progression- free survival (PFS), overall survival (OS), and overall response rate (ORR) in patients with hepatitis B and/or C;
- Pharmacokinetics;
- Potential relationships between exploratory biomarkers associated with the IGF-1R and IR signaling axes and other predictive and prognostic markers related to clinical outcomes; and
- TTP based on the following definitions analyzed as exploratory analyses:
    - TTPc: defined as time from randomization to progression (either radiological disease progression based on RECIST version 1.1 or symptomatic clinical progression as assessed by investigator).

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Methodology: This was a randomized, placebo-controlled, double-blind phase 2 study of linsitinib given continuously at 150 mg twice-daily dose in patients with advanced HCC who had previously failed sorafenib as first-line therapy. Adult patients with advanced HCC previously treated with sorafenib were planned for randomization in a 2 to 1 fashion to receive either single agent linsitinib (Arm A) or placebo (Arm B). Crossover to the experimental arm was not permitted at the time of progression.

- Arm A – Single agent linsitinib administered orally at a dose of 150 mg twice daily; or
- Arm B – Matching placebo administered orally twice daily.

Additionally, patients were to be stratified according to the following parameters:

- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS): 0 or 1;
- Macrovascular invasion or extra-hepatic disease: present or absent;
- Geographic region: Asia Pacific vs other; and
- Hepatitis B virus (HBV) or Hepatitis C virus (HCV) or nonviral HCC etiologies.

There was an initial safety cohort consisting of 18 patients. The study design mandated that after the 18th randomized patient was followed for at least 21 days or until death, the data monitoring committee (DMC) was to meet to confirm that the safety of linsitinib was acceptable in this population and to make any recommendations regarding the study. Dosing and randomization continued while the data on the first 18 patients were being collected, monitored and reviewed.

Specific guidelines for study drug dose modifications, including dose reduction and dose interruption, due to toxicities related to study drug were used during the study. Grading of toxicities was performed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.02.

If any toxicity requiring dose interruption recurred or developed despite the initial dose reduction to 100 mg twice daily, and resolved within 14 days to ≤ grade 1 or no more than 1 grade above screening (but no higher than grade 2), then the study drug could have been reintroduced at a dose of 75 mg twice daily. If the toxicity had not resolved within 14 days, as defined by either ≤ grade 1 or no more than 1 grade above screening (but no higher than grade 2), then the study drug was discontinued.

Number of Patients (Planned, Enrolled and Analyzed): Approximately 132 adult patients with advanced HCC previously treated with sorafenib were planned for randomization in a 2 to 1 fashion to receive either single agent linsitinib (Arm A, 88 patients) or placebo (Arm B, 44 patients). After randomizing 23 patients, the Sponsor voluntarily discontinued the study in advanced HCC. The decision to terminate the study was made solely by the Sponsor and was not requested by the DMC or any regulatory agency.

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Diagnosis and Main Criteria for Inclusion: Male and female patients aged ≥ 18 years were eligible for this study if they had a histologically confirmed diagnosis of advanced HCC; had received prior systemic treatment for advanced HCC with sorafenib; had confirmed disease progression or had discontinued sorafenib due to a drug related toxicity; had received their last dose of sorafenib at least 14 days prior to randomization; and had an estimated life expectancy ≥ 12 weeks based on an investigator assessment of recent changes in laboratory values, performance status, and other clinical criteria. Eligible patients should have recovered from sorafenib or investigational agent related toxicity to ≤ grade 2. Eligible patients were to have an ECOG performance status of 0 to 1; a Child-Pugh Status A or B; and a Barcelona Clinic Liver Cancer (BCLC) stage B/C. Previous local therapy (e.g., surgery, radiation therapy, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) was permitted if ≥ 21 days before randomization. Patients were to have a fasting glucose ≤ 150 mg/dL (8.3 mmol/L), a platelet count ≥ 60 x 10^9/L, hemoglobin ≥ 8.5 g/dL, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, potassium within normal limits, partial prothrombin time (PTT) ≤ 2.3 x ULN (upper limit of normal), magnesium (Mg) within normal limits, and calcium (Ca) within normal limits. Adequate organ function (for a HCC population) was required: liver function test (LFT) ≤ 5 x ULN, albumin ≥ 2.8 g/dL, total bilirubin ≤ 2.8 mg/dL, creatinine ≤ 1.5 x ULN, and INR ≤ 2.3. Prior radiation therapy was permitted provided patients had recovered from the acute, toxic effects of radiotherapy prior to randomization. A minimum of 21 days must have elapsed between the end of radiotherapy and randomization. Prior surgery was permitted provided that the surgery was done ≥ 28 days prior to randomization and adequate wound healing has occurred prior to randomization.

Additionally, patients who met any of the following exclusion criteria were not eligible for randomization: Child-Pugh B (8 – 9) or C; patients who were candidates for potentially curative intervention (i.e., surgical resection or transplantation); Type 1 diabetes mellitus or Type 2 diabetes mellitus currently requiring insulinotropic or insulin therapy; prior IGF-1R therapy; patients requiring interferon; patients with uncontrolled symptomatic ascites; prior investigational agent within 21 days prior to randomization; history of poorly controlled gastrointestinal disorders that could have affected the absorption of study; history of organ allograft including liver transplant; malignancy other than HCC within the past 3 years; history (within 6 months prior to randomization) of significant cardiovascular disease unless the disease was well-controlled; history of arrhythmia that was symptomatic or required treatment (≥ Grade 3), left bundle branch block (LBBB), or asymptomatic sustained ventricular tachycardia were not allowed; QTcF interval at screening ≥ 450 msec; use of drugs that have a known risk of causing Torsades de Pointes (TdP) were prohibited within 14 days prior to randomization; use of the potent CYP1A2 inhibitors ciprofloxacin and fluvoxamine; history of cerebrovascular accident (CVA) within 6 months prior to randomization or that resulted in ongoing neurologic instability; active infection or serious underlying medical condition (including any type of active seizure disorder within 12 months prior to randomization) that would impair the ability of the patient to receive study drug; history of HIV infection or acquired immune deficiency syndrome (AIDS)-related illness or serious acute or chronic illness; history of any psychiatric or neurologic condition that might impair the patient's ability to understand or to comply with the requirements of the study or to provide informed consent; pregnant or breast-feeding females;

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symptomatic brain metastases that were not stable, required steroids, were potentially life-threatening, or that required radiation within 28 days prior to randomization; and/or history of allergic reactions attributed to compounds of similar chemical or biologic composition to study drug.

Test Product, Dose and Mode of Administration, Lot Numbers: Study drug was supplied in 60 cc HDPE bottles with induction seal liner and child-resistant closure. Each bottle contained 30 tablets of 150, 100, or 25 mg. Patients received linsitinib or matching placebo on an outpatient basis. Study drug was to be taken twice daily with food and with up to 200 mL of water. Doses were to be taken at approximately the same time each day and at regular intervals (i.e., approximately every 12 hours). If a patient missed a dose of study drug, the patient was to take the missed dose at any time up to 6 hours before the next intended dose. The missed dose was not to be combined with the next dose on that day nor be taken on a subsequent day. If the patient vomited after taking the tablet(s), the dose could have been replaced only if the tablet(s) could actually be seen and counted. Tablets were not to be split or crushed. The following lot numbers (expiry date) for linsitinib were provided: [redacted] (April 2013), [redacted] (April 2013) and [redacted] (December 2012). Lot numbers (expiry date) for matching placebo were as follows: [redacted] (October 2011), [redacted] (September 2012) and [redacted] (September 2012).

Duration of Treatment (or Duration of Study, if applicable): Treatment with study drug was planned to continue until the patient met any of the criteria for discontinuation: relapse or disease progression as determined by radiologic evaluation by the investigator; adverse event requiring withdrawal from study drug; failure to recover from toxicity despite a dosing interruption of up to 14 days; medical or ethical reasons, including noncompliance; patients with symptomatic progression who wished to discontinue the study drug for medical/ethical reasons rather than disease progression and patient request (excluding adverse events [AEs]).

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable

Criteria for Evaluation: The primary efficacy variable was time to progression (TTP). Secondary efficacy variables included overall survival (OS), progression-free status (PFS), time to progression including clinical progression (TTPc), disease control rate (DCR) and overall response rate (ORR). TTP, PFS, OS and ORR were to be also analyzed for the HBV and/or HCV subpopulations. However, efficacy evaluations were not performed for this study due to the voluntary discontinuation of the study.

Pharmacokinetics of linsitinib were determined from blood and urine sample taken from all patients. Assessments included $AUC_{0\text{-}t}$, AUC_{last}, $AUC_{0\text{-}inf}$, C_{max}, C_{last}, % AUC extrapolated, t_{max}, t_{last}, $t_{1/2}$, V_z/F and CL/F for plasma and CL_R, amount excreted and % of dose excreted for urine.

Pharmacodynamic analyses, for exploratory purposes only, were to be conducted on plasma samples to characterize biomarkers associated with IGF-1R and IR signaling axes and related pathways.

Safety was evaluated by describing the incidence of AEs, including SAEs and discontinuation of study drug due to AEs, changes in physical examination or vital signs, and incidence of abnormal clinical laboratory values.

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Additionally, a data monitoring committee (DMC) was to evaluate safety on a periodic basis during the trial. The DMC consisted of at least 2 clinicians (who were not investigators for the trial) and 1 biostatistician with expertise in oncology trials.

Statistical Methods: All analyses were performed using SAS version 8.2 or higher. For the purpose of calculating treatment emergence and inclusion in summary tables, Day 1 of the month will be considered as the imputed AE onset date if the AE onset month is non-missing and the date is missing. No adjustment for outliers was made.

The following analysis sets were planned:

1. The Full Analysis Set (FAS) consisted of all randomized patients; patients were to be analyzed according to the treatment assignment at randomization. The FAS was to be used for summaries of demographic and baseline characteristics.
2. The Per-protocol Set (PPS) included all patients in the FAS, except for those patients with major protocol violations and patients defined as unevaluable.
3. The Safety Analysis Set (SAF) consisted of all randomized patients who received at least 1 dose of study drug and for whom any data was reported after the first dose of study drug. The SAF was to be used for summaries of all safety variables and dose exposure data. Patients were to be analyzed according to treatment received.
4. The Pharmacokinetic Analysis Set (PKAS) included patients who received active drug, and for whom the pharmacokineticist determined that there was sufficient data to calculate meaningful pharmacokinetic parameters. The PKAS was to be used for all tables and graphical summaries of the pharmacokinetic data.
5. The Pharmacodynamic Analysis Set (PDAS) included patients who received active drug, and for whom the translational research scientist determined, based on sample viability, that there was sufficient data to calculate meaningful parameters for exploratory biomarkers and/or pharmacodynamic markers. The PDAS was to be used for listing pharmacodynamic blood sample collections and summarizing exploratory analysis results of plasma biomarkers.

All statistical comparisons were made using two-sided tests at the alpha = 0.05 significance level unless specifically stated otherwise. All null hypotheses were of no treatment difference. All alternative hypotheses were two-sided.

Summary of Results/Conclusions: A total of 23 patients were enrolled in the study. One patient experienced an AE prior to first dose and therefore was not included in either the SAF or the PKAS as the patient did not receive study drug. Fifteen patients were randomized to the linsitinib treatment arm of which 14 were included in the safety population and 10 in the PKAS.

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Eight patients were randomized to the placebo arm; all 8 were included in the safety population and none were included in the PKAS.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy: Data were collected by patient for tumor response, tumor assessment, and evidence of new lesions; however efficacy analyses for this study were not performed.

Pharmacokinetic Results: Median exposure (C_{max} and AUC_{0-12}) was 1205.0 ng/mL and 6270.7 h•ng/mL in Treatment Period 1 (TP1), respectively, and 1558.1 ng/mL and 16725.5 h•ng/mL in TP2, respectively. The median T_{max} occurred at 4 hours for TP1 and at 2 hours for TP2, demonstrating rapid absorption of linsitinib, particularly during TP2 [Table 3]. The median apparent clearance (Cl/F) was 19143.7 mL/hr in TP1 and 8972.5 mL/hr in TP2. Apparent volumes of distribution based on the terminal phase (Vz/F) were larger in TP1 (128993.4 mL) than in TP2 (84788.9 mL). Mean and median plasma concentrations were increased during TP2 from 0 to 4 hours and were generally higher than TP1.

The pharmacokinetic evaluation for TP1 represents single dose pharmacokinetics while the pharmacokinetic evaluation for TP2 represents steady-state pharmacokinetics. Peak absorption with t_{max} occurred within 4 hours for all patients. In many patients, terminal half-life could not be accurately calculated due to only 2 time points in the terminal phase that did not include C_{max}. In those patients, the terminal half-life was generally short with most patients ranging from 2 .7 to 6.45 hours. One patient had an extremely long terminal half-life of 19.0 hours.

Median AUC_{last} increased from TP1 to TP2 as expected with linsitinib accumulation after twice daily dosing; however, the extent of accumulation could not be determined due to insufficient data as AUC_{inf} was not estimated for all patients.

Pharmacodynamic Results: Plasma samples for at least 2 of the planned time points were received for all patients dosed in this study. All plasma samples received were assessed for total plasma concentrations of IGF-1 with the exception of 2 samples for 1 patient.

The range of total IGF-1 concentrations in plasma observed at the predose time point was similar in placebo arm (n = 8) when compared to the linsitinib arm (n = 12) [Figure 1:]. Collectively, the range of total IGF-1 concentrations in this study (23 to 144 ng/ml) were at the lower end or below the range observed in plasma from age-matched healthy donor (ages 33 to 72 years; range: 62 to 293 ng/ml; n = 44; data on file).

In the linsitinib arm, substantial increases in total IGF-1 concentrations were observed in 6 of 8 patients on day 22 or later in patients with data evaluable for these changes. In the placebo arm, 6 of 8 patients showed no substantial changes in total IGF-1 (≥ 30% increase).

Given the small number of patients evaluable for pharmacodynamic assessment, pharmacokinetic and pharmacodynamic relationships were not characterized. Archival tumor samples were received for 3 patients.

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[redacted].

Safety Results: This was a randomized, placebo-controlled, double-blind, phase 2 study of second-line treatment with linsitinib in patients with advanced HCC after failure of first-line treatment with sorafenib. One hundred thirty-two patients were planned for the trial. However, prior to enrollment completion, the study was voluntarily suspended by the Sponsor in order to review safety data in the context of 2 unexpected fatal AEs (deaths occurred on [redacted]) on study. Both cases were similar in that the patients developed hepatic and renal dysfunction shortly after being exposed to study drug and subsequently expired. In one patient, this was preceded by grade 4 hyperglycemia [redacted]; this patient also developed sepsis.

At the time of the voluntary study suspension and subsequent voluntary discontinuation, 23 patients had been enrolled, of which 22 received study drug (linsitinib n = 14; placebo n = 8). Patient demographics showed that 17 patients were classified with Child-Pugh A, 5 with Child-Pugh B liver disease, and that the enrolled patients had several comorbidities for hepatic dysfunction and abnormalities of their blood glucose. The former included hepatitis B infection (n = 8), hepatitis C infection (n = 3) and liver cirrhosis (n = 10 in the linsitinib exposed arm, n = 4 in the placebo arm). Moreover, 19 of the 22 patients treated had elevation of one or more liver enzymes prior to linsitinib or placebo treatment, and blood glucose was elevated at pretreatment in 11 patients, 6 of whom had diabetes type II at study entry. Overall, the safety evaluations were comparable between both treatment groups and the nature and severity of the AEs observed were in line with what would be expected for this patient population with advanced HCC. The numbers of patients who were treated was small however (N = 22); therefore, caution should be applied when making inferences.

In the linsitinib arm, 11/14 patients experienced elevated liver enzymes and/or elevated glucose levels while on study drug. For the placebo arm, this proportion was 4/8. Seventy-one percent (n = 10) of the patients on the linsitinib arm developed a “treatment-related AE”, with 43% (6/10) of those patients having at least “one treatment-related SAE”. For the placebo arm, these values were 50% (n = 4) and 12% (n = 1), respectively. Twenty-one percent of the patients on the linsitinib arm (n = 3) developed a drug-related hyperglycemia (2 at grade 2; 1 at grade 4), whereas no hyperglycemia cases were noted on the placebo arm. There were 3 drug-related cases of renal failure (2 with a grade 2; 1 with a grade 5) on the linsitinib arm, relative to 1 case (grade 5) on the placebo arm. Twenty-one percent (n = 3) of the patients on the linsitinib arm developed drug related hepatobiliary disorders (1 at grade 4, 2 at grade 5) versus none on the placebo arm.

The mean drug exposure on the linsitinib arm was 52 days versus 70 days for the placebo arm, yet the median time of exposure was not different (43 versus 45 days). Plasma IGF-1 levels were substantially (> 30%) increased in 6 of 8 on day 22 or later in the evaluable patients on the linsitinib arm, indirectly indicating an inhibition of IGF-1R/IR signaling in these patients. Forty-three percent (n = 6) of the patients on the linsitinib arm underwent a dose modification for drug related toxicity versus 12% (n=1) on the placebo arm. Twenty-

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nine percent (n = 4) of patients on the linsitinib arm versus zero on the placebo arm discontinued the study due to treatment-related AEs.

The deaths on study or within 30 days of the last dose of study drug were equally distributed between the 2 arms, i.e., 4 patients (29%) on the linsitinib arm and 2 patients (25%) on the placebo arm. One death in a patient treated on the linsitinib arm was considered attributable to a drug-related toxicity of hepatic and renal failure preceded by grade 4 hyperglycemia. Among the patients who died there was a total of 8 AEs resulting in death, 4 of these AEs were considered related to study drug by the investigator. Three of the four patients in the linsitinib arm who died on study presented with concurrent renal and liver failure that were considered drug-related versus one patient on the placebo arm. Of note is the fact that in 4 patients, the change in blood glucose to more than 1.5 x ULN was temporally close to the rise in LFTs. In all 4 patients the LFTs were elevated at baseline.

Compared to the other studies in the linsitinib development program (n = 513 as of 5 January 2012, excluding patients in the current OSI-906-206 report), the rates for elevations in ASTs (50% versus10%), in ALT (31.8% versus 11.1%), in bilirubin (31.8% versus 6.4%), in glucose (31.8% versus 15.8%) and in serum creatinine (13.6% versus 4.9%) were much higher on the OSI-906-206 study. However, these data should be interpreted with caution due to the limited number of patients in this study.

CONCLUSIONS: In general, on study, without reaching statistical significance, there was a pattern of increased adverse events observed on the linsitinib arm with more drug-related AEs and SAEs observed, more instances of hyperglycemia, of hepatobiliary disorders, of drug-related dose modifications, and of patients discontinuing study due to treatment-related AEs. When comparing OSI-906-206 with the linsitinib program as a whole, the same aforementioned trend seems to be present (linsitinib Investigator's Brochure).

At study entry, 19/22 patients had several factors that predisposed them for hepatic, renal and glucose metabolism -related events, including hepatitis B and C, cirrhosis known to lead to hyperinsulinemia and/or peripheral insulin resistance, diabetes type II known to be associated with renal impairment, hyperglycemia and hepatic dysfunction, and older age. In 4 patients, there was a temporal association observed between the rise in glucose and the rise in LFTs. Also, in 2 patients, deaths due to liver failure occurred within 38 days of the start of dosing. Both cases were similar in that the patients developed hepatic and renal dysfunction shortly after being exposed to study drug and subsequently expired. In one patient, this was preceded by grade 4 hyperglycemia [redacted], and this patient also developed sepsis. The data do not provide a clear difference in on-study disposition between the patients with HCC on the linsitinib arm versus the placebo arm that would allow us to identify those patients with HCC who would be at a higher risk for developing significant side effects on linsitinib.

In response to these events, a number of additional analyses were conducted in the OSI-906-206 study population relative to potential hepatic toxicities. These included an investigation of baseline demographics that may predispose to hepatic or glycemic toxicities, analyses of all AEs and SAEs including relevant laboratory

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values for the entire safety population, a specific subset analysis for all renal, hepatic, cardiac (QTc, arrhythmias), neurologic, psychiatric and glycemic AEs ≥ grade 3, and a detailed evaluation of glycemic changes with respect to hepatic dysfunction. These analyses and conclusions are presented within Section 9 of the study report. The overall conclusion was that there were no clearly differentiating baseline factors observed for patient deaths in this study, and no apparent relationship between abnormal blood glucose values and observed LFT abnormalities. Overall, the observed events suggest a pattern of (S)AEs that is not unlike one that could be expected for such a population with advanced HCC and their underlying disease and comorbidities. However, the combined inhibition of IGF-1R and IR in these patients with advanced HCC with limited liver, glycemic and/or renal reserve and the observed data supports a notion that linsitinib may induce significant changes in the aforementioned physiological systems. Complex interactions between baseline deficits in hepatic, glycemic and/or renal function may contribute to a smaller therapeutic window for linsitinib in patients with advanced HCC. Therefore, linsitinib may have more untoward reactions in subjects with advanced HCC with two or more hepatic, glycemic, or renal co-morbidities. As such, linsitinib should be used with considerable caution in such patients.

Date of Report: 06 December 2012

Table 1 Patient Disposition

	Linsitinib (n = 15)	**Placebo (n = 8)**	**Total (n = 23)**
	n (%)	n (%)	n (%)
Full Analysis Set population	15 (100)	8 (100)	23 (100)
Safety population	14 (93)	8 (100)	22 (96)
Pharmacokinetic Analysis Set	10 (67)	0	10 (43)
Patients on treatment	0	0	0
Reasons off treatment (Safety Analysis Set)			
Disease progression radiologic evaluation	5 (33)	7 (88)	12 (52)
Symptomatic disease progression	2 (13)	0	2 (9)
Adverse event	4 (27)	0	4 (17)
Medical or ethical reasons	3 (20)	0	3 (13)
Patient request	0	1 (12)	1 (4)
Missing	0	0	0
Follow-up/survival			
Alive	4 (27)	2 (25)	6 (26)
Lost to follow-up	0	0	0
Deceased	11 (73)	6 (75)	17 (74)
Missing	0	0	0

Full Analysis Set includes all randomized patients. Safety Analysis Set includes all randomized patients who took at least one dose of study medication. Pharmacokinetic Analysis Set includes patients who received active drug, and for whom the pharmacokineticist determined there was sufficient data to calculate meaningful pharmacokinetic parameters.
Source: Table 12.1.2.1

Table 2 Demographic Characteristics

Characteristic	Linsitinib (n = 15)	Placebo (n = 8)	Total (n = 23)
Gender, n (%)			
Female	2 (13)	3 (38)	5 (22)
Male	13 (87)	5 (62)	18 (78)
Race, n (%)†			
White	9 (60)	6 (75)	15 (65)
Asian	5 (33)	2 (25)	7 (30)
Other	1 (7)	0	1 (4)
Age (years)			
< 60	5 (33)	2 (25)	7 (30)
≥ 60	10 (67)	6 (75)	16 (70)
Mean (standard deviation)	62.1 (11.8)	65.1 (6.6)	63.1 (10.2)
Median	65.0	67.5	67.0
Minimum – maximum	33.0 – 76.0	55.0 – 72.0	33.0 – 76.0
Weight (kg)			
Mean (standard deviation)	68.3 (17.3)	74.0 (18.8)	70.3 (17.7)
Median	61.1	78.3	66.0
Minimum – maximum	52.0 – 117.0	47.0 – 98.5	47.0 – 117.0
Height (cm)			
Mean (standard deviation)	169.2 (8.0)	166.5 (4.9)	168.3 (7.1)
Median	169.4	168.0	169.0
Minimum – maximum	156.1 – 180.0	157.0 – 172.0	156.1 – 180.0
ECOG performance status			
0	3 (20)	4 (50)	7 (30)
1	12 (80)	4 (50)	16 (70)
Cigarette smoking history			
Never smoked or < 100 cigarettes in lifetime	4 (27)	2 (25)	6 (26)
Former smoker	5 (33)	4 (50)	9 (39)
Current smoker	6 (40)	2 (25)	8 (35)
Time from initial diagnosis (months)			
Mean (standard deviation)	28.6 (22.2)	18.3 (13.3)	25.0 (19.9)
Median	28.0	11.0	27.0
Minimum – maximum	4.0 – 83.0	5.0 – 38.0	4.0 – 83.0
Child-Pugh total score			
Mean (standard deviation)	6.1 (0.8)	5.4 (0.5)	5.9 (0.8)
Median	6.0	5.0	6.0
Minimum – maximum	5.0 – 7.0	5.0 – 6.0	5.0 – 7.0
BCLC Staging			
Intermediate HCC (BCLC B)	0	2	
Advanced HCC (BCLC C)	15	6	

All randomized patients (Full Analysis Set).
BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group.
†4 sites were in region of Asia Pacific; 8 sites were considered the region of Non-Asia Pacific and 3 sites were in the United States.
Source: Table 12.1.3.1, Table 12.1.3.2 and Table 13.2.4.8.

Table 3 Summary of Pharmacokinetic Parameters of Linsitinib for Treatment Period 1 and Treatment Period 2

Parameter	Treatment Period 1	Treatment Period 2
C_{max} (ng/mL)		
Evaluable, n	10	9
Median	1205.0	1558.1
Minimum – maximum	282.0 – 3354.6	263.6 – 2630.8
%CV	71.6	44.3
Geometric mean	1014.6	1398.5
t_{max} (hr)		
Evaluable, n	10	9
Median	4.0	2.0
Minimum – maximum	1.0 – 4.0	0.9 – 4.0
%CV	35.2	55.6
Geometric mean	3.0	2.1
AUC_{last} (hr•ng/mL)		
Evaluable, n	10	9
Median	5938.0	9311.4
Minimum – maximum	1844.4 – 16743.2	1583.6 – 15753.4
%CV	68.3	45.1
Geometric mean	5711.6	8660.9
AUC_{0-12} (hr•ng/mL)		
Evaluable, n	4	4
Median	6270.7	16725.5
Minimum – maximum	2941.1 – 17731.7	9258.4 – 17225.2
%CV	78.1	25.6
Geometric mean	5724.0	14531.6
CL/F (mL/h)		
Evaluable, n	3	4
Median	19143.7	8972.5
Minimum – maximum	8049.5 – 22573.6	8708.2 – 16201.6
%CV	45.8	34.2
Geometric mean	15151.9	10322.3
V_z/F (mL)		
Evaluable, n	3	4
Median	128993.4	84788.9
Minimum – maximum	31607.5 – 144187.5	62087.4 – 239407.6
%CV	60.1	69.5
Geometric mean	83771.2	101671.6

Pharmacokinetics Analysis Set
Source: Table 12.4.2

Table 4 Summary of Adverse Events

Characteristics, n (%)	Linsitinib (n = 14)	Placebo (n = 8)	Total (n = 22)
Patients with at least 1 AE	12 (86)	6 (75)	18 (82)
Patients with at least 1 treatment-related AE	10 (71)	4 (50)	14 (64)
AEs regardless of causality by worst severity			
Grade 1	1 (7)	2 (25)	3 (14)
Grade 2	2 (14)	1 (12)	3 (14)
Grade 3	3 (21)	1 (12)	4 (18)
Grade 4	2 (14)	0	2 (9)
Grade 5	4 (29)	2 (25)	6 (27)
Treatment-related AEs by worst severity			
Grade 1	1 (7)	1 (12)	2 (9)
Grade 2	3 (21)	1 (12)	4 (18)
Grade 3	2 (14)	1 (12)	3 (14)
Grade 4	2 (14)	0	2 (9)
Grade 5	2 (14)	1 (12)	3 (14)

All patients who took at least 1 dose of study drug (Safety Analysis Set).
AE: adverse event.
Source: Table 12.6.1.1.1

Table 5 Summary of Treatment Emergent Adverse Events Reported in 3 or More Patients

MedDRA (v13.1) SOC Preferred Term	Number of Patients (%)											
	Linsitinib (n = 14)						Placebo (n = 8)					
	Any Grade	1	2	3	4	5	Any Grade	1	2	3	4	5
Total patients with any AE	**12 (86)**	**1 (7)**	**2 (14)**	**3 (21)**	**2 (14)**	**4 (29)**	**6 (75)**	**2 (25)**	**1 (12)**	**1 (12)**	**0**	**2 (25)**
Gastrointestinal disorders	**10 (71)**	**5 (36)**	**3 (21)**	**2 (14)**	**0**	**0**	**4 (50)**	**2 (25)**	**0**	**2 (25)**	**0**	**0**
Abdominal pain	3 (21)	2 (14)	0	1 (7)	0	0	2 (25)	1 (12)	1 (12)	0	0	0
Constipation	3 (21)	2 (14)	1 (7)	0	0	0	2 (25)	1 (12)	1 (12)	0	0	0
Nausea	3 (21)	3 (21)	0	0	0	0	2 (25)	1 (12)	1 (12)	0	0	0
Metabolism and nutrition disorders	**8 (57)**	**2 (14)**	**2 (14)**	**2 (14)**	**2 (14)**	**0**	**4 (50)**	**3 (38)**	**0**	**1 (12)**	**0**	**0**
Decreased appetite	5 (36)	3 (21)	1 (7)	1 (7)	0	0	3 (38)	2 (25)	0	1 (12)	0	0
Hyperglycaemia	4 (29)	0	2 (14)	1 (7)	1 (7)	0	0	0	0	0	0	0
General disorders and administration site conditions	**8 (57)**	**1 (7)**	**1 (7)**	**6 (43)**	**0**	**0**	**3 (38)**	**1 (12)**	**1 (12)**	**1 (12)**	**0**	**0**
Asthenia	5 (36)	0	1 (7)	4 (29)	0	0	1 (12)	0	0	1 (12)	0	0
Oedema peripheral	5 (36)	3 (21)	2 (14)	0	0	0	0	0	0	0	0	0
Investigations	**7 (50)**	**1 (7)**	**1 (7)**	**3 (21)**	**2 (14)**	**0**	**1 (12)**	**1 (12)**	**0**	**0**	**0**	**0**
Aspartate aminotransferase increased	4 (29)	1 (7)	0	3 (21)	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	3 (21)	1 (7)	1 (7)	1 (7)	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	**6 (43)**	**2 (14)**	**3 (21)**	**1 (7)**	**0**	**0**	**2 (25)**	**1 (12)**	**0**	**1 (12)**	**0**	**0**
Back pain	3 (21)	1 (7)	2 (14)	0	0	0	1 (12)	1 (12)	0	0	0	0
Infections and infestations	**4 (29)**	**0**	**3 (21)**	**0**	**0**	**1 (7)**	**2 (25)**	**1 (12)**	**1 (12)**	**0**	**0**	**0**
Bronchitis	3 (21)	0	3 (21)	0	0	0	0	0	0	0	0	0
Hepatobiliary disorders †	**4 (29)**	**0**	**0**	**0**	**1 (7)**	**3 (21)**	**1 (12)**	**0**	**0**	**0**	**0**	**1 (12)**
Nervous system disorders †	**4 (29)**	**1 (7)**	**0**	**1 (7)**	**2 (14)**	**0**	**1 (12)**	**1 (12)**	**0**	**0**	**0**	**0**
Renal and urinary disorders	**4 (29)**	**0**	**2 (14)**	**0**	**0**	**2 (14)**	**1 (12)**	**0**	**0**	**0**	**0**	**1 (12)**
Renal failure	3 (21)	0	1 (7)	0	0	2 (14)	1 (12)	0	0	0	0	1 (12)
Respiratory, thoracic and mediastinal disorders †	**4 (29)**	**2 (14)**	**1 (7)**	**1 (7)**	**0**	**0**	**1 (12)**	**0**	**0**	**1 (12)**	**0**	**0**
Skin and subcutaneous tissue disorders †	**3 (21)**	**1 (7)**	**2 (14)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

All patients who took at least 1 dose of study drug (Safety Analysis Set).
AE: adverse event; SOC: system organ class.
†No specific preferred terms within the SOC were reported by ≥ 3 patients.
Source: Table 12.6.1.1.2

Table 6 Summary of Serious Adverse Events and Discontinuations Due to Adverse Events

Characteristics, n (%)	Linsitinib (n = 14)	Placebo (n = 8)	Total (n = 22)
Patients with at least 1 SAE	9 (64)	3 (38)	12 (55)
Patients with at least 1 treatment-related SAE	6 (43)	1 (12)	7 (32)
Patients who discontinued study due to treatment-related AEs	4 (29)	0	4 (18)
Patients who died on treatment or within 30 days	4 (29)	2 (25)	6 (27)

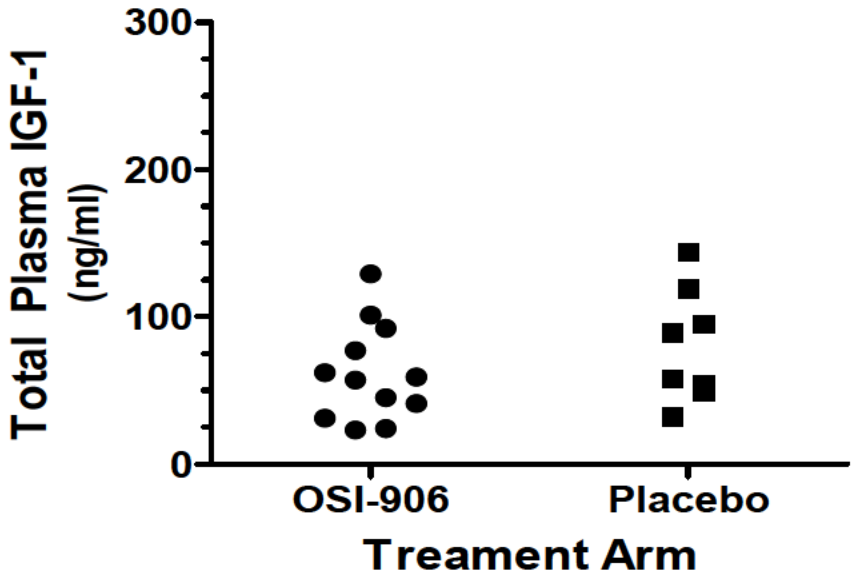
SAE: serious adverse event.
All patients who took at least 1 dose of study drug (Safety Analysis Set).
Source: Table 12.6.1.1.1

Table 7 Deaths on Treatment or Within 30 Days of Last Dose of Study Drug

Patient Number	Days on Study Drug	Date of Last Dose	Date of Death	Cause of Death	Adverse Event(s) Resulting in Death	Relationship to Study Drug
Linsitinib						
[redacted]	55	[redacted]	[redacted]	Other†	Hepatic failure Renal failure	Not related Not related
[redacted]	83	[redacted]	[redacted]	Other‡	Cirrhosis alcoholic	Related
[redacted]	7	[redacted]	[redacted]	Other§	Sepsis	Not related
[redacted]	29	[redacted]	[redacted]	Study drug related toxicity	Hepatic failure Renal failure	Related Related
Placebo						
[redacted]	74	[redacted]	[redacted]	Other¶	Renal failure	Related
[redacted]	44	[redacted]	[redacted]	Other¶	Hepatic function abnormal	Not related

† [redacted]
‡ [redacted]
§ [redacted]
¶ [redacted]
Source: Listing 13.2.7.4

Figure 1: **Predose Total IGF-1 Concentrations in Plasma in the OSI-906 and Placebo Treatment Arms**



IGF-1: insulin-like growth factor 1.
Data are shown for patients with plasma samples evaluable for assessment prior to dosing on day 1 (predose).
Total plasma IGF-1 concentrations were shown.