Name of Sponsor/Company: OSI Pharmaceuticals/ Astellas Pharma Global Development, Inc.		
Name of Finished Product: OSI-906		
Name of Active Ingredient: OSI-906		

SYNOPSIS

Title of Study:

A Phase 1 Dose Escalation Study of Intermittent Oral OSI-906 Dosing in Patients with Advanced Solid Tumors

Investigators/Coordinating Investigator:

[redacted] and [redacted] (Investigators)/[redacted], MD (Responsible Officer)

Study Center(s):

2 sites, 1 in the United States and 1 in the United Kingdom

Publication (reference):

Not applicable

Study Period:

3.2 years

Date of first enrollment (Study initiation date):

05 July 2007

Date of last evaluation (Study completion date):

20 September 2010

Phase of Development:

1

Objectives:

The primary objectives of this study were to determine the maximum tolerated dose (MTD) and establish the recommended phase 2 dose of oral OSI-906 for each intermittent dosing schedule (schedule 1 [S1], schedule 2 [S2] and schedule 3 [S3]) when administered to patients with advanced solid tumors.

The secondary objectives were to evaluate:

- the safety profile of OSI-906, including the dose-limiting toxicities (DLTs)
- the pharmacokinetic profile of OSI-906
- the effect of food on the relative bioavailability of OSI-906
- preliminary evidence of pharmacodynamic relationships with OSI-906 systemic exposure
- preliminary antitumor activity of OSI-906

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Methodology:

This was a multicenter, open-label, cohort dose escalation followed by a randomized fed-fasting expansion cohort phase 1 study in patients with advanced solid tumors. Separate cohorts of 3 to 6 eligible patients, were assigned to 1 of 3 intermittent dosing schedules (S1, OSI-906 once-daily on days 1 to 3 every 14 days; S2, OSI-906 once-daily on days 1 to 5 every 14 days; or S3, OSI-906 once-daily on days 1 to 7 every 14 days) based on accrual rate in each arm and starting at a dose of 10 mg in S1. Dose escalation proceeded independently in each schedule and was dependent on toxicity (graded using the National Cancer Institute – Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 3) in the previous cohort:

- If there were no toxicities related to OSI-906, or if the maximum grade of toxicity related to OSI-906 was Grade 1 in the first treatment period for any patient in the cohort, then dose escalation of up to 100% was implemented.
- If there was any ≥ Grade 2 toxicity related to OSI-906 in the first treatment period for any patient in the cohort, dose escalation was limited to a maximum of 50% in all future cohorts.
- If DLT occurred in any 1 patient, up to 3 additional patients were to be entered at the same dose level for a total of up to 6 evaluable patients per cohort.
    - If 1 of 6 patients had DLT in an expanded cohort, dose escalation was limited to a maximum of 30% in all future cohorts.
    - If 2 or more patients experienced DLT, the MTD was exceeded (i.e., ≥ 2 patients with DLT of a maximum of 6 evaluable patients). Dose escalation ceased and additional patients were to be treated at the next lower dose level or at an intermediate dose level, if appropriate, to determine the MTD and establish a recommended phase 2 dose of OSI-906 for each schedule.

Dosing in S2 and subsequently in S3 was initiated after review of safety and pharmacokinetic data from 6 dose levels in S1.

In addition, 2 dose-bridging cohorts were opened in S1, the first to qualitatively compare the 100-mg capsule dosage strength to the 25-mg capsule dosage strength and the second to qualitatively examine the pharmacokinetics of the 150-mg tablet dosage form compared to the 100-mg capsules. The relative bioavailability of OSI-906 under fasting and fed conditions was also examined using a standard crossover design in a separate cohort of 12 patients with advanced solid tumors (fed-fasted expansion cohort) who were randomized to take OSI-906 at a dose of 300 mg once-daily using S1 under fasting conditions in the first treatment period and under fed conditions in the second treatment period or vice versa.

Number of Patients (planned, enrolled and analyzed):

An enrollment of approximately 75 patients was planned and 79 patients were enrolled (62 in S1, 4 in S2 and 13 in S3) and treated with OSI-906 (at once-daily doses of 10 mg to 750 mg in S1, 450 mg in S2 and 450 mg

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and 600 mg in S3). All patients (100%) in each schedule were evaluable for safety; 100% in S1 and S2 and 11 of 13 (85%) in S3 were evaluable for DLT; 57 of 62 (92%) in S1 and 100% in S2 and S3 were evaluable for pharmacokinetics; and 55 of 62 (89%) in S1, 3 of 4 (75%) in S2 and 8 of 13 (62%) in S3 were evaluable for efficacy. Ten patients in S1 were enrolled in the OSI-906 dose-bridging cohorts: 3 received a dose of 300 mg (25-mg vs 100-mg capsules) and 7 received a dose of 600 mg (100-mg capsules vs 150-mg tablets). All 10 were included in the pharmacokinetic evaluable population to estimate the relative bioavailability of the dosage forms. A total of 17 patients were enrolled in the fed/fasted cohort and 12 were included in the pharmacokinetic evaluable population to determine the effect of food on OSI-906 absorption.

Diagnosis and Main Criteria for Inclusion:

Male and female patients aged ≥ 18 years were eligible for this study if they had histologically or cytologically documented malignancy that was advanced and/or metastatic and refractory to established forms of therapy or for which no effective therapy existed, a predicted life expectancy ≥ 12 weeks and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients were to have fasting glucose ≤ 125 mg/dL (7 mmol/L) at baseline, electrolytes (potassium, calcium and magnesium) within normal limits, and adequate hematopoietic, hepatic and renal function. Prior chemotherapy, hormonal therapy, and radiation therapy were permitted provided that before registration patients met criteria for time of discontinuation of such therapies and had recovered from therapy-related toxicities; previous surgery was permitted provided that wound healing had occurred prior to registration. Apart from certain types of hormonal therapy in men with prostate cancer, concurrent anticancer therapy was not permitted. Drugs that had a risk of causing QT interval prolongation as well as glucocorticoids (the exception of hormone replacement therapy or inhalers) were to be discontinued within 14 days prior to day 1 dosing and not used during the study. Patients were not eligible for the study if they had a documented history of diabetes mellitus, significant cardiac disease (unless the disease was well controlled), stroke, active seizure disorder, or previously diagnosed brain metastases. Pregnant or breast-feeding females were not eligible.

Test Product, Dose and Mode of Administration, Batch Numbers:

OSI-906 was supplied as tablets (25-, 100- and 150-mg dosage strengths) or gelatin capsules (5, 25 and 100 mg dosage strengths) containing OSI-906 plus excipients. OSI-906 was administered orally once daily at doses of 10, 20, 40, 80, 150, 300, 450, 600 and 750 mg in S1 (on days 1 to 3 every 14 days), at a dose of 450 mg in S2 (on days 1 to 5 every 14 days) and at 450 and 600 mg in S3 (on days 1 to 7 every 14 days). Lot numbers [redacted] were used in this study.

Duration of Treatment (or Duration of Study, if applicable):

Patients could remain on study until disease progression or until they met other criteria for discontinuation. The median number of days on study for patients in S1 dose cohorts ranged between 25 days (at a dose of 750 mg)

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and 171 days (40 mg), with patients receiving dosing with OSI-906 for a median total of 7 days (750 mg) to 39 days (40 mg). The median number days on study for patients in S2 (450 mg) was 76 days, with patients receiving dosing with OSI-906 for a median of 30 days. The median number of days on study for patients in the S3 450-mg and 600-mg dose cohorts was 37 days and 41 days, respectively, with patients in both cohorts receiving dosing with OSI-906 for a median of 21 days.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Not applicable

Criteria for Evaluation:

The primary objectives of this study were to determine the MTD and establish the recommended phase 2 dose of oral OSI-906 for each intermittent dosing schedule (S1, S2 and S3). This was based in part on DLT.

Efficacy, for exploratory purposes only, was determined based on clinical tumor measurements and imaging methods to determine response and progression, as evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

Pharmacokinetics of OSI-906 were determined from blood and urine sample taken from patients in the dose-escalation and dose-bridging cohorts and from blood samples in the fed-fasted expansion cohorts. Assessments in plasma included $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$, C_{max}, % AUC extrapolated, t_{max}, $t_{1/2lambdaz}$, Vz/F, and CL/F and in urine included CL_R, amount excreted and percentage of dose excreted.

Pharmacodynamics, for exploratory puposes only, were determined from phospho-insulin-like growth factor 1 receptor (phospho-IGF-1R) and phospho-insulin receptor (phospho-IR) in peripheral blood mononuclear cells (PBMCs) and insulin-like growth factor 1 (IGF-1) in blood.

Safety was assessed by DLTs, adverse events (AEs), clinical laboratory evaluations (hematology, chemistry and urinalysis), vital signs, electrocardiograms (ECGs), physical examination and blood glucose monitoring.

Statistical Methods:

All analyses were performed using SAS version 9.1.3 or higher. Descriptive statistics for continuous variables included number of patients (n), mean, median, minimum and maximum. Categorical data were summarized by n and percentage. Binary outcome variables such as rates of AEs were assumed to follow binomial distribution; pharmacokinetic variables were assumed to follow LogNormal distributions; and laboratory data were assumed to follow normal distributions. Data were reported as collected. Missing data were not imputed and no adjustment for outliers was made.

Efficacy was summarized for each schedule and dose cohort by best clinical response (i.e., complete response [CR], partial response [PR], stable disease or progressive disease [PD]). Response rate (RR), calculated as the number of responders (CR + PR) divided by the total number of patients evaluable for efficacy in each cohort, and disease control rate (DCR), calculated as the number of responders and patients with stable disease

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(CR + PR + stable disease) divided by the total number of patients evaluable for efficacy in each cohort, were calculated along with associated 95% CI.

Primary pharmacokinetic analyses were conducted on plasma concentration versus time data for OSI-906 using WinNonLin (version 5.2) software. Plasma and urine pharmacokinetic parameters were calculated using a noncompartmental model for each patient and summarized by schedule and dose cohort using descriptive statistics (n, median, minimum and maximum); geometric means with 90% CI were also calculated for $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$ and C_{max}. Testing for deviation from dose proportionality of plasma pharmacokinetic parameters in S1 was done using power models, with analyses modeling $\log AUC_{0\text{-}tau}$, $\log AUC_{0\text{-}inf}$ and $\log C_{max}$ in all schedules as a function of log dose. Deviation from a slope of 1.0 was tested for significance. Relative bioavailability (100-mg capsules versus 25-mg capsules and tablets versus capsules) was assessed on day 1 of S1 and the geometric mean ratios with 90% CI were calculated for $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$ and C_{max}. The effect of food on plasma pharmacokinetics of OSI-906 was calculated for the fed-fasted expansion cohort using analysis of variance including factors for patient, treatment and period. The geometric mean ratio (fed versus fasted) and 90% CI were calculated for $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$ and C_{max} and C_{last}. A food effect was not considered to be established if the 90% CIs were contained within the equivalence limits of 80% to 125% for $AUC_{0\text{-}tau}$ (or $AUC_{0\text{-}inf}$ if appropriate), C_{max} and C_{last}. The difference in t_{max} (fasted versus fed) was analyzed using the Wilcoxon signed-rank test.

Pharmacodynamics were characterized by phospho-IGF-1R and phospho-IR inhibition in PBMCs and IGF-1 in plasma, summarized by dose cohort. Exploratory analyses were performed to correlate pharmacokinetic parameters with pharmacodynamic activity.

The number of patients who experienced DLT was summarized and the number of DLTs and description of DLTs were listed for each dose cohort. AEs were coded using the MedDRA version 9.1 by SOC and preferred term. Treatment-emergent AEs, serious AEs (SAEs), drug-related AEs and drug-related SAEs that resulted in discontinuation were summarized for each cohort. Tables were also prepared to summarize the incidence of patients with AEs combining similar preferred terms from 1 or more SOC. Each clinical laboratory parameter value was listed and values outside the normal range flagged. Hematology and biochemistry laboratory values were graded using NCI-CTCAE (Version 3) and shift tables from baseline to the maximum grade generated for each dosing cohort and schedule. Urine laboratory parameters were listed. ECG parameters including heart rate, PR interval, QRs interval, QT interval and QTc were listed and clinically significant findings flagged. QTc interval determined centrally was listed. Shift tables for change from baseline in grade of QTc interval were generated as appropriate. Physical examination abnormalities, ECOG performance status, weight, pulse rate, and blood pressure were listed by patient.

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Summary of Results/Conclusions:

Population:

A total of 79 male and female patients with various types of cancers were enrolled into the study: 62 under S1, 4 under S2, and 13 under S3. Almost all patients (90% in S1 and 100% in S2 and S3) were white/not Hispanic or Latino. Most patients (56% in S1, 75% in S2 and 69% in S3) were between the ages of 40 and 64 years, with the median age ranging between 55.0 and 61.5 years across treatment schedules. Median weight ranged between 66.4 and 78.3 kg. Most patients had an ECOG status of 0 or 1 at baseline.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

MTD and recommended phase 2 dose: No DLT was observed at doses of OSI-906 ≤ 450 mg in any treatment schedule. A total of 7 patients had DLT including 5 patients in S1 (2 at 600 mg, 3 at 750 mg) and 2 patients in S3 (both at 600 mg). Of the 5 S1 patients, 2 patients in the 600 mg cohort and 1 patient in the 750 mg cohort, had glucose intolerance (fasting glucose > 250 mg/dL or 13.9 mmol/L) (Grade 3 hyperglycemia), 1 patient (750 mg) experienced Grade 2 vomiting, and 1 patient (750 mg) had Grade 3 prolongation of QTc interval. In the S3 group, 1 patient (600 mg) had Grade 4 fatigue and 1 patient (600 mg) experienced glucose intolerance (fasting glucose > 250 mg/dL or 13.9 mmol/L) (Grade 3 hyperglycemia). Based on the observed DLT, the MTD for S1, and the recommended phase 2 dose of OSI-906 for that treatment regimen was determined to be 600 mg given once daily on days 1 to 3 every 14 days. Likewise, based on the DLT, the MTD for S3 and the recommended phase 2 dose of OSI-906 for that treatment regimen was also determined to be 600 mg, given once daily on days 1 to 7 every 14 days. The MTD and recommended phase 2 dose of OSI-906 for S2 was not identified.

Efficacy: The best overall response was assessed as either stable disease or PD in most patients in each treatment schedule. No patients had CR, and 2 patients, both in S1, had PR. The overall RR in patients in S1 was 3.6% and DCR was 43.6%. Overall RR was 0 in S2 and S3 and DCR was 2 of 3 patients in S2 and 3 of 8 patients in S3.

Plasma pharmacokinetics: Plasma concentrations of OSI-906 generally increased with increasing doses of OSI-906 (from 10 mg to 750 mg) on day 1 and day 3 of S1: median C_{max} values ranged between 0.106 and 8.02 mcg/mL on day 1 and between 0.095 and 6.55 mcg/mL on day 3 and median $AUC_{0\text{-}tau}$ between 0.408 and 84.1 mcg•h/mL on day 1 and 0.413 and 55.3 mcg•h/mL on day 3. Median $AUC_{0\text{-}inf}$ values ranged between 0.408 and 76.2 mcg•h/mL on day 1 and 0.413 and 59.1 mcg•h/mL on day 3. Median C_{last} values were ≤ 0.846 mcg/mL on day 1 and ≤ 1.20 mcg/mL on day 3; values for %AUC extrapolated were ≤ 8.88% on day 1 and ≤ 14.4% on day 3. The range of median t_{max} values was similar on day 1 (2.0 to 7.5 hours) and day 3 (2.0 to 6.0 hours) as was the range of median $t_{1/2lambdaz}$ values (2.10 to 6.08 hours on day 1; 2.17 to 4.64 hours on day 3).

Plasma concentrations of OSI-906 were similar after administration of 450 mg OSI-906 on day 1 to patients in S2 and S3, with generally higher plasma concentrations after 600 mg. The median C_{max} values for OSI-906 on

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day 1 ranged between 2.78 and 4.55 mcg/mL and were comparable to those observed at corresponding doses in S1. Values on day 5 (S2) and day 7 (S3) were also similar. Across the 2 treatment schedules (S2 and S3), median $AUC_{0\text{-}tau}$ values ranged between 24.3 and 46.6 mcg•h/mL on day 1 and between 26.2 and 31.8 mcg•h/mL on days 5 and 7. Median $AUC_{0\text{-}inf}$ values ranged between 25.5 and 50.7 mcg•h/mL on day 1 and 26.3 and 33.3 mcg•h/mL on days 5 and 7. Median C_{last} values were ≤ 0.222 mcg/mL on days 1, 5 and 7; values for %AUC extrapolated were ≤ 4.80%. The range of median t_{max} values of OSI-906 was 4.0 to 8.0 hours on day 1 and 3.0 to 3.4 hours days 5 and 7. Median $t_{1/2lambdaz}$ values were similar on day 1 (2.57 to 4.06 hours) and on days 5 and 7 (2.54 to 4.91 hours).

Accumulation: For S1, the ratio of the geometric mean (90% CI) of $AUC_{0\text{-}tau}$ on day 3 to $AUC_{0\text{-}tau}$ on day 1 ranged between 0.721 (0.336, 1.55) and 1.55 (1.14, 2.09). For S2 (450 mg OSI-906), the ratio of the geometric mean (90% CI) of $AUC_{0\text{-}tau}$ on day 5 to $AUC_{0\text{-}tau}$ on day 1 was 1.20 (0.609, 2.38). For S3, the corresponding day 7/day 1 ratios were 1.04 (0.505, 2.13) for the 450-mg dose and 1.24 (0.723, 2.11) for the 600-mg dose. These data indicate no substantial accumulation of OSI-906 in any dose schedule.

Urine pharmacokinetics: Across all dose groups in S1 (10 to 750 mg OSI-906) on day 1, the median CL_R ranged from 1.61 to 16.5 mL/h and the median amount of OSI-906 excreted ranged from 0.819 to 939 mcg (0.01% to 0.16% of dose). On day 3, the median CL_R ranged from 2.61 and 42.5 mL/h and the amount of OSI-906 excreted ranged from 2.08 to 1295 mcg (0.02% to 0.29% of dose). In S2 and S3 (450 and 600 mg OSI-906) on day 1, the median CL_R ranged from 5.56 to 13.4 mL/h and the amount of OSI-906 excreted ranged from 129 to 447 mcg (0.03% to 0.08% of dose). On days 5 and 7, the median CL_R ranged from 5.82 to 23.2 mL/h and the amount of OSI-906 excreted ranged from 209 to 816 mcg (0.01% to 0.14% of dose).

Dose proportionality: C_{max} and AUC increased in a dose-proportional manner since the 95% CI for the slope of the power model contained 1.

Relative bioavailability: The geometric mean ratios (90% CI) for 100-mg capsules/25-mg capsules were 0.791 (0.166, 3.762) for $C_{max,}$ 0.621 (0.109, 3.519) for $AUC_{0\text{-}tau}$ and 0.719 (0.114, 4.531) for $AUC_{0\text{-}inf}$. The geometric mean ratios (90% CI) for 150-mg tablets/100-mg capsules were 0.963 (0.615, 1.508) for $C_{max,}$ 0.798 (0.466, 1.366) for $AUC_{0\text{-}tau}$ and 0.742 (0.414, 1.329) for $AUC_{0\text{-}inf}$.

Food effect: The geometric mean ratio (fed to fasted) indicated higher C_{max} (116%) and AUC (138%) under fed condition compared to fasted condition. The 90% CI of the geometric mean for C_{max} and AUC were outside the equivalence limits of 80 to 125% indicating food effect on the pharmacokinetics of OSI-906. The median terminal half-life was similar for both treatments (4.39 vs. 4.02 hours). Comparison of the median t_{max} in the fed and fasted state indicated that food significantly delayed absorption (median difference 2.8 hours; P = 0.0005, Wilcoxon Signed-Rank test). As the effect of food on OSI-906 pharmacokinetics is moderate, OSI-906 can be administered with or without food.

Pharmacodynamics: Detectable phospho-IGF-1R and phospho-IR signals were present in PBMCs from 7 of the 11 patients with PBMC sample sets evaluable for pharmacodynamic assessment. OSI-906 inhibited IGF-1R

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and IR phosphorylation in PBMCs from patients receiving 600 mg OSI-906 in S1. Decreased IGF-1R and IR phosphorylation was observed on days 1 and 3 of dosing and returned to predose levels by day 14. These effects appeared to correlate with plasma OSI-906 concentrations. Increased total plasma IGF-1 concentrations relative to predose values were observed at doses ≥ 450 mg once daily for S1, S2 and S3. These effects were associated with higher plasma concentrations of OSI-906.

Safety Results:

Most patients experienced AEs (97% in S1, 100% in S2, 77% in S3) with ≤ 50% across treatment schedules having AEs that were considered by the investigator to be related to treatment. The most frequent treatment-related AEs during the study were nausea, vomiting, fatigue and diarrhea. At the recommended phase 2 dose for once-daily dosing using S1 and S3 regimens (600 mg), the respective incidences of these AEs were: nausea 38% and 30%, vomiting 23% and 30%, fatigue 23% and 10%, and diarrhea 23% and 30%. Most of the treatment-related AEs were of Grade 1 or 2 severity. Across treatment schedules ≤ 31% of patients had SAEs, with a total of 8 patients (6 in S1, 2 in S3) having treatment-related SAEs including hyperglycemia, hypoglycemia, nausea and vomiting, fatigue and ECG QTc interval prolonged. Two patients (1 in S1 and 1 in S3) permanently discontinued study drug due to treatment-related AEs. A total of 5 patients (4 in S1 and 1 in S2) died while on treatment or in the 30 days following the last dose of study drug. None of the deaths were considered to be related to treatment.

Ten patients had a clinically significant QTc increase with 3 having QTc interval > 500 msec while on OSI-906 treatment (maximum: 535 msec); no patient had a QTc interval increase of ≥ 100 msec. Two patients discontinued from the study due to increases in QTc interval, which occurred at doses of 600 mg (S3) and 750 mg (S1) and was considered to be treatment-related in both patients. Based on clinical study site laboratory results and home glucose monitor results, approximately 37% of the patients developed a high glucose value and approximately 30% of patients had a low (< 60 mg/dL) blood glucose value at some time while receiving OSI-906 treatment. Shifts were observed in the following clinical laboratory parameters: total hemoglobin, white blood cell count, lymphocyte count, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, creatinine, bilirubin, glucose, magnesium, inorganic phosphorus, and potassium.

CONCLUSIONS:

- The primary objectives of this study were to determine the MTD and establish the recommended phase 2 dose of oral OSI-906 for intermittent dosing schedules (S1, S2 and S3) when administered to patients with advanced solid tumors. Based on the observed safety profile of OSI-906, the recommended dose for phase 2 studies is 600 mg when given in an intermittent dosing schedule (3 to 7 days of dosing every 14 days).
- A secondary objective was to evaluate the safety profile of OSI-906, including DLT. Most of the DLTs observed in this study, namely glucose intolerance (hyperglycemia), prolonged QTc interval and fatigue, were consistent with safety considerations identified in nonclinical studies and occurred at higher dose

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levels of OSI-906. AEs that were considered to be related to OSI-906 treatment included nausea, vomiting, diarrhea, fatigue, and hyperglycemia. Approximately 13% of OSI-906 treated patients had a clinically significant QTc interval increase of ≥ 60 msec; however, none of these increases was > 100 msec.

- Another secondary objective of the study was to determine the pharmacokinetic profile of OSI-906, including the effect of food on its bioavailability. Overall, the pharmacokinetic profile of OSI-906 indicates it has a median terminal half-life between 2.17 and 6.08 hours, does not show substantial accumulation after once-daily dosing for 7 days, has a low renal clearance, and while its absorption is delayed by food, food increased the C_{max} and AUC of OSI-906 compared to fasted condition. The clinical relevance of delayed absorption and higher exposure of OSI-906 when dosed with high fat meal is unknown at this time.
- Preliminary evidence of pharmacodynamic relationships with OSI-906 systemic exposure was another secondary objective of the study. Overall, these data showed that OSI-906 plasma exposures sufficient to inhibit IGF-1R and IR phosphorylation in PBMCs, and to inhibit IGF-1R signaling in tissues involved in regulating IGF1 expression, were achieved at the 600-mg dose in S1. Collectively, these data provide evidence for target modulation by OSI-906 in cancer patients on the intermittent dosing schedule.
- The efficacy analyses in this phase 1 study were exploratory and showed only modest activity on DCR.

Date of Report: 02 April 2012

Table 1 Patient Disposition

Condition	Treatment Schedule		
	S1	**S2**	**S3**
Enrolled, n (%)	62 (100)	4 (100)	13 (100)
Treated, n (%)	62 (100)	4 (100)	13 (100)
Evaluable, n (%):			
Safety	62 (100)	4 (100)	13 (100)
DLT	62 (100)	4 (100)	11 (85)
Pharmacokinetics	57 (92)	4 (100)	13 (100)
Efficacy	55 (89)	3 (75)	8 (62)
Reason off treatment, n (%):			
Disease progression	52 (84)	3 (75)	9 (69)
Adverse event	3 (5)	0	1 (8)
Medical or ethical reasons	3 (5)	0	1 (8)
Patient request	3 (5)	0	2 (15)
Patient death	1 (2)	1 (25)	0

DLT: dose-limiting toxicity; S1: schedule 1; S2: schedule 2; S3: schedule 3.

Source: Table 12.1.1.1; Table 12.1.1.2; Table 12.1.1.3; Table 12.1.2.1; Table 12.1.2.2; Table 12.1.2.3

Table 2 Demographic Characteristics

Characteristic	Treatment Schedule		
	S1 (n = 62)	S2 (n = 4)	S3 (n = 13)
Gender, n (%)			
Female	30 (48)	1 (25)	7 (54)
Male	32 (52)	3 (75)	6 (46)
Race/ethnicity, n (%)			
White, not Hispanic/Latino	56 (90)	4 (100)	13 (100)
White, Hispanic/Latino	1 (2)	0	0
Black	3 (5)	0	0
Asian	1 (2)	0	0
Other	1 (2)	0	0
Age (years)			
18 to 39, n (%)	11 (18)	0	2 (15)
40 to 64, n (%)	35 (56)	3 (75)	9 (69)
≥ 65, n (%)	16 (26)	1 (25)	2 (15)
Median	55.0	61.5	53.0
Minimum, maximum	18.0, 76.0	48.0, 71.0	28.0, 69.0
Weight (kg)			
Median	71.7	78.3	66.4
Minimum, maximum	46.0, 122.2	74.3, 101.5	47.6, 92.9
Height (cm)			
Median	170.1	179.2	165.1
Minimum, maximum	150.0, 188.0	173.0, 187.7	149.8, 187.9
ECOG performance status, n (%)			
0	16 (26)	0	4 (31)
1	44 (71)	4 (100)	8 (62)
2	2 (3)	0	1 (8)
Cotinine test, n (%)			
Negative	49 (79)	4 (100)	10 (77)
Positive	4 (6)	0	1 (8)
Not done	9 (15)	0	2 (15)
Tumor type, n (%)			
NSCLC	17 (27)	0	2 (15)
Other †	12 (19)	2 (50)	3 (23)
Sarcoma	10 (16)	0	1 (8)
Adrenocortical carcinoma	9 (15)	1 (25)	5 (38)
Colorectal	8 (13)	0	2 (15)
Breast	2 (3)	0	0
Ovarian	2 (3)	0	0
Melanoma	2 (3)	0	0
Renal	0	1 (25)	0

All patients who received at least 1 dose of OSI-906 (Safety Evaluable Population).

ECOG: Eastern Cooperative Oncology Group; NSCLC: non-small cell lung cancer; S1: schedule 1; S2: schedule 2; S3: schedule 3.

† Other not further specified in summary tables. A full by-patient listing of tumor burden at baseline is provided in Appendix 13.2.4.8

Source: Table 12.1.3.1; Table 12.1.3.2; Table 12.1.3.3; Table 12.1.3.4; Table 12.1.3.5; Table 12.1.3.6; Table 12.1.4.1; Table 12.1.4.2; Table 12.1.4.3

Table 3 Best Overall Response, Overall Response Rate and Disease Control Rate

	Treatment Schedule		
	S1 (n = 62)	**S2 (n = 4)**	**S3 (n = 13)**
Evaluable for efficacy, n (%)	55 (89)	3 (75)	8 (62)
Best overall response, n (%)			
Complete response	0	0	0
Partial response	2 (4)	0	0
Stable disease	22 (40)	2 (67)	3 (38)
Progressive disease	31 (56)	1 (33)	5 (62)
Overall response rate (CR + PR)			
Patients with response/patients evaluable, n	2/55	0/3	0/8
% (95% CI)	3.6 (0.4, 12.5)	0 (0, 70.8)	0 (0, 36.9)
Disease control rate (CR + PR + stable disease)			
Patients with response/patients evaluable, n	24/55	2/3	3/8
% (95% CI)	43.6 (30.3, 57.7)	66.7 (9.4, 99.2)	37.5 (8.5, 75.5)

All patients who had measurable disease according to RECIST, who received at least 14 days of therapy and who had their disease re-evaluated (Efficacy Population).

CR: complete response; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; S1: schedule 1; S2: schedule 2; S3: schedule 3.

Source: Table 12.3.2.1; Table 12.3.2.2; Table 12.3.2.3; Table 12.3.2.4; Table 12.3.2.5; Table 12.3.2.6; Table 12.3.3.1; Table 12.3.3.2; Table 12.3.3.3

Table 4 Ratio of $AUC_{0\text{-}tau}$ on Day 3 to $AUC_{0\text{-}tau}$ on Day 1 (S1)

Characteristic	OSI-906 Dose (mg)								
	10 (n=3)	20 (n=3)	40 (n=3)	80 (n=3)	150 (n=4)	300 † (n=6)	450 (n=4)	600 (n=13)	750 (n=6)
Evaluable, n	3	3	3	3	4	6	4	11	4
Median	1.01	1.23	0.641	0.909	1.35	1.85	1.52	1.19	0.727
Min, max	0.850, 1.19	0.646, 1.32	0.545, 1.11	0.780, 1.06	0.988, 1.66	0.831, 2.09	0.870, 1.61	0.463, 1.96	0.331, 1.58
Geometric mean (90% CI)	1.01 (0.760, 1.33)	1.02 (0.523, 1.98)	0.728 (0.390, 1.36)	0.909 (0.702, 1.18)	1.31 (1.02, 1.70)	1.55 (1.14, 2.09)	1.34 (0.951, 1.89)	1.21 (0.966, 1.52)	0.721 (0.336, 1.55)

All patients who had sufficient pharmacokinetic sampling associated with the day 1 or other appropriate OSI-906 doses (Pharmacokinetic Evaluable Population).

Max: maximum; Min: minimum; S1: schedule 1.

† Excludes patients in the fed/fasted cohort.

Source: Table 12.4.4.3

Table 5 Ratio of $AUC_{0\text{-}tau}$ on Day 5 (S2) or Day 7 (S3) to $AUC_{0\text{-}tau}$ on Day 1

Characteristic	Treatment Schedule/OSI-906 Dose (mg)		
	S2	S3	
	450 (n = 4)	450 (n = 3)	600 (n = 10)
Evaluable, n	4	3	7
Median	1.36	0.992	1.06
Min, max	0.658, 2.05	0.694, 1.62	0.568, 4.80
Geometric mean (90% CI)	1.20 (0.609, 2.38)	1.04 (0.505, 2.13)	1.24 (0.723, 2.11)

All patients who had sufficient pharmacokinetic sampling associated with the day 1 or other appropriate OSI-906 doses (Pharmacokinetic Evaluable Population).

Max: maximum; Min: minimum; S2: schedule 2; S3: schedule 3.

Source: Table 12.4.4.4

Table 6 Comparison of Dose-normalized Pharmacokinetic Parameters of OSI-906 (All schedules, Day 1 and Day 3)

	OSI-906 Dose (mg)								
Characteristic	**10**	**20**	**40**	**80**	**150**	**300 †**	**450**	**600 ‡**	**750**
Day 1									
n	3	3	3	3	4	5	10	12	4
Geometric mean $AUC_{0\text{-}inf}$	0.362	0.764	2.26	3.59	8.94	18.2	23.3	53.2	75.5
Geometric mean AUC_{inf}/dose	0.036	0.038	0.057	0.045	0.060	0.061	0.052	0.089	0.101
Slope (95% CI)	All doses: 1.19 (1.06, 1.31) *; 150 to 600 mg only: 1.26 (0.78. 1.75)								
n	3	3	3	3	4	6	11	16	6
Geometric mean C_{max}	0.0983	0.166	0.388	0.730	1.26	2.63	2.74	4.78	8.66
Geometric mean C_{max}/dose	0.010	0.008	0.010	0.009	0.008	0.009	0.006	0.008	0.012
Slope (95% CI)	All doses: 0.96 (0.84, 1.09); 150 to 600 mg only: 0.92 (0.42, 1.41)								
Day 3									
n	3	3	3	3	4	6	2	4	4
Geometric mean AUC_{inf}	0.366	0.777	1.64	3.28	11.9	30.0	15.9	74.4	53.5
Geometric mean AUC_{inf}/dose	0.037	0.039	0.041	0.041	0.079	0.100	0.035	0.124	0.071
Slope (95% CI)	1.24 (1.06, 1.41) *								
n	3	3	3	3	4	6	4	6	4
Geometric mean C_{max}	0.0664	0.171	0.312	0.681	1.75	3.48	3.71	7.25	6.13
Geometric mean C_{max}/dose	0.007	0.009	0.008	0.009	0.012	0.012	0.008	0.012	0.008
Slope (95% CI)	1.08 (0.94, 1.22)								

All patients who had sufficient pharmacokinetic sampling associated with the day 1 or other appropriate OSI-906 doses (Pharmacokinetic Evaluable Population).

† Excludes patients in the fed/fasted cohort.

‡ Excludes patients in the dose bridging (tablet vs capsule) cohort

Statistically significant deviation from dose proportionality * P = 0.004 (day 1); P = 0.009 (day 3), based on Power model used to model $\log_{(conc)}$ as a function of $\log_{(dose)}$ with t-test for test of deviation from 1.0.

Source: Table 12.4.3.1; Table 12.4.3.2; Table 12.4.3.3

Table 7 Relative Bioavailability of 300 mg OSI-906 Administered as 25-mg Capsules Versus 100-mg Capsules (S1, Day 1)

Parameter	25-mg Capsules (n = 3)		100-mg Capsules (n = 3)		Geometric Mean Ratio 100-mg Capsules/ 25-mg Capsules	90% CI of Ratio
	n	Geometric Mean	n	Geometric Mean		
C_{max} (mcg/mL)	3	2.96	3	2.34	0.791	0.166, 3.762
$AUC_{0\text{-}tau}$ (mcg•h/mL)	3	23.5	3	14.6	0.621	0.109, 3.519
$AUC_{0\text{-}inf}$ (mcg•h/mL)	3	24.0	3	17.2	0.719	0.114, 4.531

All patients who had sufficient pharmacokinetic sampling associated with the day 1 or other appropriate OSI-906 doses (Pharmacokinetic Evaluable Population).

Source: Table 12.4.1.1

Table 8 Relative Bioavailability of 600 mg OSI-906 Administered as 150-mg Tablets Versus 100-mg Capsules (S1, Day 1)

Parameter	150-mg Tablets (n = 7)		100-mg Capsules (n = 6)		Geometric Mean Ratio 150-mg Tablets/ 100-mg Capsules	90% CI of Ratio
	n	Geometric Mean	n	Geometric Mean		
C_{max} (mcg/mL)	16	4.78	7	4.61	0.963	0.615, 1.508
$AUC_{0\text{-}tau}$ (mcg•h/mL)	16	49.6	7	39.5	0.798	0.466, 1.366
$AUC_{0\text{-}inf}$ (mcg•h/mL)	16	58.7	7	43.6	0.742	0.414, 1.329

All patients who had sufficient pharmacokinetic sampling associated with the day 1 or other appropriate OSI-906 doses (Pharmacokinetic Evaluable Population).

Source: Table 12.4.1.2

Table 9 Relative Bioavailability of OSI-906 Administered under Fed and Fasted Conditions (S1 Fed-Fasted Cohort, Day 1)

Parameter	Fed		Fasted		Geometric Mean Ratio Fed/Fasted (90% CI of Ratio) (%)
	n	Geometric Mean	n	Geometric Mean	
C_{max} (mcg/mL)	12	2.08	12	1.79	116.2 (80.5, 167.7)
AUC_{tau} (mcg•h/mL)	12	15.2	12	11.0	138.4 (103.3, 185.4)
AUC_{inf} (mcg•h/mL)	12	15.8	11	11.7	126.0 (97.5, 162.9)
C_{last} (mcg/mL)	12	0.0474	12	0.0477	99.4 (51.9, 190.3)
T_{max}	12	4.0	12	1.0	2.8*†

All patients who had sufficient pharmacokinetic sampling associated with the day 1 or other appropriate OSI-906 doses (Pharmacokinetic Evaluable Population).

S1: schedule 1.

† Value is for median difference, fed-fasted

Statistically significant difference from fed to fasted * P = 0.0005 using Wilcoxon signed rank text.

Source: Table 12.4.4.7

Table 10 Summary of Adverse Events Occurring in Any Treatment Schedule at Any Time

MedDRA (v. 9.1) SOC Preferred Term	Treatment Schedule S1 (n = 62)	S2 (n = 4)	S3 (n = 13)
Any AE, n (%)	**60 (97)**	**4 (100)**	**10 (77)**
Gastrointestinal disorders	**41 (66)**	**4 (100)**	**6 (46)**
Nausea	23 (37)	2 (50)	5 (38)
Vomiting	19 (31)	2 (50)	5 (38)
Constipation	12 (19)	0	1 (8)
Diarrhoea	10 (16)	1 (25)	3 (23)
Abdominal pain	10 (16)	0	0
Abdominal pain upper	5 (8)	0	0
Dyspepsia	4 (6)	0	0
Abdominal distension	3 (5)	0	1 (8)
General disorders and administration site conditions	**38 (61)**	**3 (75)**	**4 (31)**
Fatigue	26 (42)	3 (75)	4 (31)
Pyrexia	8 (13)	1 (25)	1 (8)
Oedema peripheral	6 (10)	0	0
Chest pain	3 (5)	1 (25)	0
Respiratory, thoracic and mediastinal disorders	**27 (44)**	**3 (75)**	**1 (8)**
Dyspnoea	11 (18)	2 (50)	0
Cough	9 (15)	1 (25)	0
Haemoptysis	7 (11)	0	0
Dyspnoea exertional	3 (5)	1 (25)	1 (8)
Pleural effusion	3 (5)	0	0
Productive cough	3 (5)	0	0
Musculoskeletal and connective tissue disorders	**24 (39)**	**2 (50)**	**5 (38)**
Back pain	7 (11)	1 (25)	1 (8)
Pain in extremity	5 (8)	0	2 (15)
Arthralgia	4 (6)	0	1 (8)
Musculoskeletal pain	4 (6)	0	1 (8)
Flank pain	3 (5)	0	0
Metabolism and nutrition disorders	**23 (37)**	**2 (50)**	**4 (31)**
Anorexia	10 (16)	2 (50)	1 (8)
Hyperglycaemia	8 (13)	0	1 (8)
Hypokalaemia	3 (5)	0	0
Hyponatraemia	3 (5)	0	0
Infections and Infestations	**20 (32)**	**1 (25)**	**1 (8)**
Upper respiratory tract infection	9 (15)	0	1 (8)
Investigations	**19 (31)**	**3 (75)**	**4 (31)**
Weight decreased	5 (8)	3 (75)	1 (8)
Weight increased	5 (8)	0	1 (8)
Nervous system disorders	**19 (31)**	**0**	**2 (15)**
Headache	10 (16)	0	0
Dizziness	6 (10)	0	0
Skin and subcutaneous tissue disorders	**13 (21)**	**0**	**1 (8)**
Pruritis	4 (6)	0	0
Rash	3 (5)	0	0
Psychiatric disorders	**10 (16)**	**1 (25)**	**1 (8)**
Anxiety	3 (5)	1 (25)	0
Renal and urinary disorders	**8 (13)**	**0**	**0**
Proteinuria	4 (6)	0	0

Table continued on next page

MedDRA (v. 9.1) SOC Preferred Term	Treatment Schedule S1 (n = 62)	S2 (n = 4)	S3 (n = 13)
Vascular disorders	**6 (10)**	**1 (25)**	**0**
Blood and lymphatic system disorders	**5 (8)**	**2 (50)**	**2 (15)**
Anaemia	4 (6)	2 (50)	1 (8)
Cardiac disorders	**4 (6)**	**0**	**0**
Eye disorders	**3 (5)**	**0**	**0**

All patients who received at least 1 dose of OSI-906 (Safety Evaluable Population).

Note: Table includes AEs by SOC or preferred term observed in ≥ 3 patients in S1 (5%) or in ≥ 2 patients in S2 (50%) or S3 (15%). For each AE in each schedule, the corresponding number (%) of patients with the AE in other schedules is shown.

AEs are ordered by frequency in the S1 cohort, then by frequency in the S3 cohort, then by frequency in the S2 cohort.

AE: adverse event; S1: schedule 1; S2: schedule 2; S3: schedule 3.

Source: Table 12.6.1.1.4.7

Table 11 Summary of Treatment-related Adverse Events Occurring in at Least 2 Patients at Any Dose of OSI-906 at Any Time (S1, S2 and S3)

MedDRA (v. 9.1) Preferred Term	Treatment Schedule/OSI-906 Dose (mg)											
	S1									S2	S3	
	10	20	40	80	150	300	450	600	750	450	450	600
n	3	3	3	3	4	23	4	13	6	4	3	10
Any AE, n (%)	1 (33)	0	1 (33)	1 (33)	1 (25)	9 (39)	2 (50)	11 (85)	5 (83)	1 (25)	1 (33)	5 (50)
Nausea	0	0	0	0	1 (25)	2 (9)	1 (25)	5 (38)	3 (50)	0	1 (33)	3 (30)
Vomiting	0	0	0	0	0	0	0	3 (23)	4 (67)	0	1 (33)	3 (30)
Diarrhoea	0	0	1 (33)	0	1 (25)	1 (4)	0	3 (23)	1 (17)	0	0	3 (30)
Fatigue	0	0	0	1 (33)	1 (25)	3 (13)	1 (25)	3 (23)	0	0	0	1 (10)
Hyperglycaemia	0	0	0	0	0	3 (13)	0	2 (15)	1 (17)	0	0	1 (10)

All patients who received at least 1 dose of OSI-906 (Safety Evaluable Population).

AE: adverse event; S1: schedule 1; S2: schedule 2; S3: schedule 3.

Source: Table 12.6.1.2.2.1; Table 12.6.1.2.2.2; Table 12.6.1.2.2.3; Table 12.6.1.2.2.5; Table 12.6.1.2.2.6

Table 12 Summary of Serious Adverse Events (S1, S2, S3)

MedDRA (v. 9.1) Preferred Term	Treatment Schedule/OSI-906 Dose (mg)											
	S1									S2	S3	
	10	20	40	80	150	300	450	600	750	450	450	600
n	3	3	3	3	4	23	4	13	6	4	3	10
Any SAE, n	0	0	0	0	2 (50)	6 (26)	1 (25)	3 (23)	4 (67)	1 (25)	1 (33)	3 (30)
Hyperglycaemia	0	0	0	0	0	1 (4)	0	2 (15)	1 (17)	0	0	1 (10)
Fatigue	0	0	0	0	0	1 (4)	0	0	0	1 (25)	0	1 (10)
Pneumonia	0	0	0	0	1 (25)	0	0	0	1 (17)	1 (25)	0	0
Cerebral ischemia	0	0	0	0	0	1 (4)	0	0	0	0	1 (33)	0
Dyspnoea	0	0	0	0	0	1 (4)	0	0	0	1 (25)	0	0
Nausea	0	0	0	0	0	1 (4)	0	1 (8)	0	0	0	0
Pyrexia	0	0	0	0	1 (25)	0	1 (25)	0	0	0	0	0
Vomiting	0	0	0	0	0	1 (4)	0	1 (8)	0	0	0	0
Constipation	0	0	0	0	0	0	0	1 (8)	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	0	1 (10)
Back pain	0	0	0	0	0	0	0	0	0	0	0	1 (10)
ECG QTc interval prolonged	0	0	0	0	0	0	0	0	1 (17)	0	0	0
Intestinal obstruction	0	0	0	0	0	0	0	0	1 (17)	0	0	0
Hypoglycaemia	0	0	0	0	0	0	0	0	1 (17)	0	0	0
Hypokalaemia	0	0	0	0	0	0	0	0	1 (17)	0	0	0
Respiratory failure	0	0	0	0	0	0	0	0	0	1 (25)	0	0
Abdominal pain	0	0	0	0	0	1 (4)	0	0	0	0	0	0
Blood creatinine increased	0	0	0	0	0	1 (4)	0	0	0	0	0	0
Bronchiolitis	0	0	0	0	0	1 (4)	0	0	0	0	0	0
Bronchopneumonia	0	0	0	0	0	1 (4)	0	0	0	0	0	0
Confusional state	0	0	0	0	0	1 (4)	0	0	0	0	0	0
Renal failure acute	0	0	0	0	0	1 (4)	0	0	0	0	0	0
Pleural effusion	0	0	0	0	0	1 (4)	0	0	0	0	0	0
Anaemia	0	0	0	0	1 (25)	0	0	0	0	0	0	0
Infection	0	0	0	0	1 (25)	0	0	0	0	0	0	0
Urinary tract infection	0	0	0	0	1 (25)	0	0	0	0	0	0	0

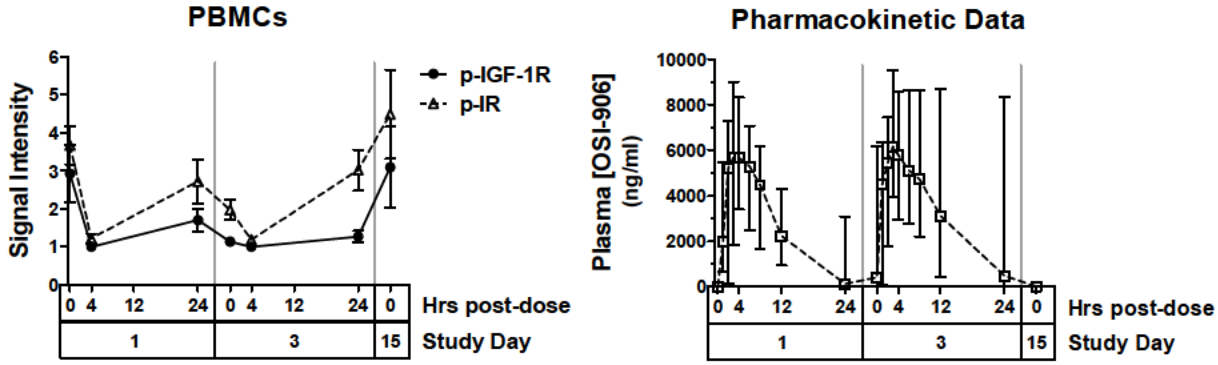
All patients who received at least 1 dose of OSI-906 (Safety Evaluable Population).

ECG: electrocardiogram; QTc: QT corrected; S1: schedule 1; S2: schedule 2; S3: schedule 3; SAE: serious adverse event.

Each preferred term is listed in order of overall frequency, then by dose group, then alphabetically.

Source: Table 12.6.1.3.2.1; Table 12.6.1.3.2.2; Table 12.6.1.3.2.3; Table 12.6.1.3.2.5; Table 12.6.1.3.2.6

Figure 1 **Effects of 600 mg OSI-906 on IGF-1R and IR Phosphorylation in PBMCs (S1)**



Patients in the 600 mg S1 cohort with PBMC sample sets evaluable for pharmacodynamic assessment and with detectable p-IGF-1R and p-IR signals (n = 7).

Samples obtained prior to dosing (predose) are labeled 0 hours.

Left: Signal intensity for IGF-1R and IR phosphorylation in PBMCs is graphed relative to assay background (set at intensity of 1); p-IGF-1R and p-IR data are shown as mean (standard error).

Right: Pharmacokinetic data are shown as median (range) (n = 9).

IGF-1R: insulin-like growth factor 1 receptor; IR: insulin receptor; PBMCs: peripheral blood mononuclear cells; p-IGF-1R: phospho-insulin-like growth factor 1 receptor; p-IR: phospho-insulin receptor; S1: schedule 1.

Source: Attachment 2 Figure 7-1

Figure 2 **Effects of OSI-906 on Total Plasma IGF-1 Levels and Relationships to Plasma OSI-906 Exposure (S1, S2 and S3)**

Patients with plasma samples evaluable for pharmacodynamic assessment (n = 54).

Left: Total plasma IGF-1 levels shown were those observed 24 hours after the last dose on day 3 (S1), day 5 (S2) or day 7 (S3) and are shown as percentages of predose levels.

Right: The changes in plasma IGF-1 were plotted against minimum plasma OSI-906 concentrations for each individual patient. The curve was the result of nonlinear regression analysis.

On both graphs, horizontal dashed lines indicate predose levels (100%) ± 30% (2 intrapatient assay coefficients of variation)

C_{min}: minimum plasma concentration; IGF1/IGF-1: insulin-like growth factor 1; S1: schedule 1; S2: schedule 2; S3: schedule 3.

Source: Attachment 2 Figure 7-2