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 Continuous Oral OSI-906 Dosing in Patients With Advanced Solid Tumors

Investigators/Coordinating Investigator:

[redacted] (Coordinating Investigator) and [redacted]

Study Center(s):

[redacted], United States and [redacted] United Kingdom

Publication (reference):

Not applicable

Study Period:

Approximately 4 years

Date of first enrollment (Study initiation date):

18 June 2007

Date of last evaluation (Study completion date):

13 July 2011 (Two patients [redacted] and [redacted] remained on study after database hard lock.)

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 both a once-daily (qd) and twice-daily (bid) dose regimen 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
- Preliminary evidence of pharmacodynamic relationships with OSI-906 systemic exposure
- Preliminary antitumor activity of OSI-906
- Any difference in biomarkers between archival tumor tissue and fresh tumor tissue

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- Any correlation between tumor biomarkers and treatment response in a subset of patients with locally advanced or metastatic colorectal cancer
- The safety, pharmacokinetics and preliminary antitumor activity of OSI-906 in a subset of patients with advanced solid tumors who had active Type 2 diabetes mellitus not requiring insulin or insulinotropic therapy

Methodology:

This was an open-label, uncontrolled, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of oral OSI-906 administered at 2 dose regimens (qd or bid) in patients with advanced solid tumors. The study started with an initial once-daily regimen, and initiation of a twice-daily regimen occurred after clinically significant related toxicity ≥ Grade 2 was observed in any patient at the once-daily dose regimen. The maximum starting dose for the twice-daily regimen was equal to the highest once-daily dose at which no clinically significant related toxicity ≥ Grade 2 was observed (i.e., the dose level below that at which such toxicity occurred) but divided into 2 equal oral doses. If both regimens (qd and bid) were open at the same time, patients were assigned to a regimen based on the accrual rate in each arm.

OSI-906 was evaluated in separate cohorts of at least 3 patients each, in which OSI-906 was administered for at least a 21-day treatment period; thereafter, patients could continue treatment in the absence of disease progression or unacceptable toxicity. The first patient in any cohort must have been on treatment for at least 7 days prior to the enrollment of subsequent patients in that cohort, though this rule could be modified during cohort review, pending observed toxicities. All patients in each cohort were followed for at least 21 days for assessment of DLTs.

Dose escalation proceeded independently within each dose regimen cohort and was dependent on toxicity observed during the initial 21-day treatment period in the previous cohort as follows:

- 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 21-day 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 21-day treatment period for any patient in the cohort, with the exception of nausea, vomiting or diarrhea that was not premedicated or adequately treated, dose escalation was limited to a maximum of 50%.
- 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 in the same cohort 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

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dose level, if appropriate, to determine the MTD and establish a recommended phase 2 dose of OSI-906 for each regimen.

Intrapatient dose escalation after the first 21-day treatment cycle was permitted only within each regimen (qd or bid). However, to be eligible for intrapatient dose escalation, patients must have received OSI-906 for 21 days without evidence of clinically significant related toxicity ≥ Grade 2 and the next dose level must have been cleared (i.e., without evidence that this dose was above the MTD).

Once the recommended phase 2 dose was determined, a maximum of 10 evaluable patients were to be treated at that dose level (on each regimen, as appropriate) to further evaluate the safety profile, pharmacokinetics and any preliminary evidence of antitumor activity.

If differences in DLT became apparent for particular subgroups of patients (for example, patients with prior taxane therapy), the MTD for these subgroups of patients may have been determined separately.

The need for dose interruptions, the occurrence of cumulative or persistent toxicity, and data from a concurrent study (OSI-906-102) were also considered in dose escalation decisions.

In addition to the dose-escalation cohorts described above, once the recommended phase 2 dose was determined for the twice-daily dose-escalation cohort, 2 planned expansion cohorts were opened.

The **biomarker expansion cohort** was designed to assess: (1) any difference in biomarkers between archival tumor tissue and fresh tumor tissue, (2) any correlation between tumor biomarkers and treatment response and (3) the relationship between pharmacokinetic parameters and pharmacodynamic changes in patients with locally advanced or metastatic colorectal cancer. A maximum of 20 patients evaluable for efficacy were to receive the recommended phase 2 dose of 150 mg (bid) and were required to have collection of archival tumor tissue (whole or partial block) and a fresh tumor biopsy in addition to serial blood sampling and positron emission tomography (PET) imaging.

The **diabetic expansion cohort** was designed to evaluate the safety profile and pharmacokinetics of OSI-906 in patients with advanced solid tumors who had active Type 2 diabetes mellitus not requiring insulin or insulinotropic therapy (i.e., therapy affecting the production or activity of insulin). A maximum of 12 patients evaluable for DLT were to be enrolled in this cohort and dosed according to Table 1; if a patient was not evaluable for DLT, the patient could have been replaced. If 2 or more of the first 6 patients at the starting dose experienced a DLT of glucose intolerance, then subsequent patients were dosed at the -1 dose level of 100 mg (bid). Other nonglucose intolerance DLTs were also considered in the decision to dose reduce subsequent patients if they were attributed to the patient's diabetes and/or concomitant antidiabetic therapy. If 2 or more of the first 6 patients dosed at 100 mg (bid) experienced a DLT of glucose intolerance, then an additional dose reduction was performed to the -2 level of 75 mg (bid) for the remaining patients. If 2 or more patients experienced a DLT of glucose intolerance at 75 mg (bid), then no more diabetic patients were to be enrolled. Assessment of antidiabetic therapy and the safety and tolerability of OSI-906 was performed on an

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ongoing basis. If all or the majority of patients who experienced a DLT at any dose level were identified as being treated with a particular antihyperglycemic therapy then, in consultation with the sites and the Sponsor, that particular therapy may have been excluded in further patients.

Table 1 Dose De-escalation Schema for Expansion Cohorts

Dose Level	OSI-906 Dose (mg bid)
1 (starting dose)	150
-1	100
-2	75

Number of Patients (planned, enrolled and analyzed):

Approximately 100 patients were to be enrolled. Of the 95 patients enrolled in the study, 86 patients (33 in qd regimen and 53 in bid regimen) were treated and evaluable for safety and pharmacokinetics. A total of 49 patients (27 in qd regimen and 22 in bid regimen) were evaluable for DLT and 65 patients (24 qd and 41 bid) were evaluable for efficacy [Table 2 and Table 3]. Nine patients were enrolled in the diabetic expansion cohort and 22 were enrolled into the biomarker expansion cohort.

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 (≤ 150 mg/dL [8.3 mmol/L] for diabetic expansion cohort), 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 were not to be taken 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 (except in the diabetes expansion cohort, which enrolled patients with Type 2 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 or gelatin capsules containing OSI-906 plus excipients. Capsules were available in 5-mg, 25-mg and 100-mg dosage strengths while tablets were available in 25-mg, 100-mg and 150-mg dosage strengths. OSI-906 was administered orally once daily or twice daily for 21 consecutive days

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per treatment period. The starting dose for the first dose-escalation cohort was 10 mg once daily. Dose escalations occurred as described above and included 20, 40, 75, 150, 300, 400 and 450 mg once daily and 20, 40, 75, 150 and 200 mg twice daily. The starting dose for the expansion cohorts was the recommended phase 2 dose of 150 mg twice daily. Lot numbers [redacted] and [redacted] were used in this study, and each patient may have received study drug from more than 1 lot.

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. For the once-daily OSI-906 dose groups, the median number of days on study ranged between 20 days (at a dose of 450 mg) and 196 days (20 mg), with the median number of dosing days ranging from 17 (10 mg) to 190 days (20 mg). For the twice-daily OSI-906 dose groups, the median number of days on study and dosing days ranged between 11 days (at a dose of 200 mg) and 85 days (40 mg). The number of days on study ranged between 15 and 133 in the diabetic cohort and 3 and 252 in the biomarker cohort; the number of dosing days ranged between 13 and 127 in the diabetic cohort and 3 and 252 in the biomarker cohort.

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

Not applicable

Criteria for Evaluation:

Determination of the MTD and recommended phase 2 dose of oral OSI-906 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 all patients. Assessments included AUC_t, AUC_{inf}, C_{max}, % AUC extrapolated, t_{max}, $t_{1/2lambda\ z}$, V_z/F and CL/F for plasma and CL_R, amount excreted and % of dose excreted for urine.

Pharmacodynamics, for exploratory purposes 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) and other biomarkers related to the IGF-1R signaling pathway in blood. In the biomarker expansion cohort, assays for gene expression profiling were performed on tumor samples, both archival and fresh.

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.

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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 [SD] 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 response or stable disease (CR + PR + SD) divided by the total number of patients evaluable for efficacy in each cohort, were calculated along with the associated 95% confidence interval (CI) for each dose cohort.

The pharmacokinetic analyses were conducted on plasma concentration versus time data for OSI-906. WinNonLin software was used to calculate pharmacokinetic parameters. Plasma and urine pharmacokinetic parameters were summarized by regimen and dose cohort using descriptive statistics. Only those values of AUC_{inf} for which % AUC extrapolated was <20% were used for the summary. Geometric means with 90% CI were also calculated for AUC_t, AUC_{inf} and C_{max}. Testing for deviation from dose proportionality of plasma pharmacokinetic parameters was performed using power models. The analyses modeled dose-normalized $\log(AUC_t)$, $\log(AUC_{inf})$ and $\log(C_{max})$ in each regimen as a function of dose. Deviation from a slope of 1.0 was tested for significance.

Pharmacodynamics were characterized by measuring effects on phospho-IGF-1R and phospho-IR in PBMCs and plasma markers of the IGF-1R signaling pathway such as IGF-1. Exploratory analyses were performed or planned to correlate pharmacokinetic parameters with pharmacodynamic activity or patient response. Full details of pharmacodynamic analyses are reported separately.

Summaries of DLTs and AEs were prepared for each cohort. AEs were coded using the MedDRA version 9.1 by SOC and preferred term. Hematology and biochemistry laboratory values were graded using National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 3) and shift tables from baseline to the maximum grade were generated for each dosing cohort. Urine laboratory parameters were listed. ECG parameters including heart rate, PR interval, QRs interval, QT interval and QT interval corrected using Fridericia's formula (QTcF) were summarized and clinically significant findings flagged. The incidence of patients with a change from normal ECG at baseline to abnormal ECG during the study was generated. 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:

Of the 95 patients enrolled in the study, 86 patients were treated with OSI-906. For the 9 patients that did not receive study drug, 7 patients were not treated for medical or ethical reasons or noncompliance; no reason for discontinuation was reported for 2 patients. The majority of patients in each regimen stopped treatment due to disease progression (55% qd and 75% bid). Overall, 13 patients discontinued treatment due to an AE. No deaths occurred during treatment. In the subset of 31 patients enrolled in the 2 expansion cohorts, all were treated except for 2 in the biomarker cohort. The majority of patients (26) stopped treatment due to disease progression (78% in the diabetic cohort and 86% in the biomarker cohort). Overall, 2 patients, 1 in each cohort, withdrew because of an AE.

Overall, the majority of patients were male, white and not Hispanic or Latino. Patients' ages ranged from 19 to 79 years, with the majority of patients between 40 and 64 years old. Patients' weights ranged from 35.6 to 145.9 kg. The majority of patients were fully active or minimally restricted (i.e., ECOG performance status of 0 or 1). The most common cancer was colorectal [Table 4 and Table 5].

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy

No patient experienced a PR as the best clinical response. One patient in the 75-mg (bid) group experienced a PR after OSI-906 treatment began and experienced a surgical CR (i.e., disappearance of all clinical and radiological evidence of tumor) at day 882, following resection of melanoma on day 838. The patient's best overall clinical response was recorded as CR by the investigator. The patient was continuing treatment in the study at day 924. No other patient experienced a CR.

The overall RR (CR + PR) was 0% (0/24) and 2.4% (1/41) for the once-daily and twice-daily regimens of OSI-906, respectively [Table 6 and Table 7].

Overall, patient DCR (CR + PR + SD) were:

- 50% (12/24) for the once-daily dose regimens (10 to 450 mg qd)
- 46.3% (19/41) for the twice-daily dose regimens (20 to 200 mg bid)
- 33% (2/6) for the diabetic expansion cohort (150 mg bid)
- 31% (5/16) for the biomarker expansion cohort (150 mg bid)

No dose-related response was observed across dose-escalation cohorts for either treatment regimen (qd or bid) due to the small sample sizes for each cohort.

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Pharmacokinetics

In the dose-escalation cohorts:

- On day 1, median plasma OSI-906 concentrations generally increased as dose increased; however, on day 22 the highest concentrations in each regimen (150 mg bid and 300 mg qd) were not observed at the highest doses in the respective regimens.
- OSI-906 was minimally absorbed at the lower dose levels and exposure increases were not dose proportional.
- OSI-906 was rapidly absorbed with median t_{max} varying from 1.1 to 6.0 hours across all dose levels and study days (1 and 22).
- Steady-state levels based on trough OSI-906 concentrations appeared to be attained within 8 days for dose levels with measurable concentrations.
- OSI-906 was eliminated quickly with a median terminal $t_{1/2\ lambda\ z}$ ranging from 1.65 to 10.1 hours across all dose levels and study days. The estimated terminal $t_{1/2\ lambda\ z}$ was likely underestimated since the observed accumulation index following multiple dosing was generally greater than would be expected based on the observed $t_{1/2\ lambda\ z}$ which, in general, predicts little or no accumulation for either the once-daily or twice-daily regimen.
- Plasma distribution and clearance parameters were not dose dependent [Table 8 and Table 9].
- Across all dose groups and study days, urinary excretion of unchanged OSI-906 was minimal, ranging from 0.01 to 0.22% of a dose.

In the expansion cohorts:

- On day 22, OSI-906 (150 mg bid) was rapidly absorbed with t_{max} varying between 1.0 and 6.0 hours in the diabetic cohort and 1.0 and 8.0 hours in the biomarker cohort, and quickly eliminated with $t_{1/2\ lambda\ z}$ ranging from 1.97 to 8.29 hours in the diabetic cohort and 2.52 to 15.3 hours in the biomarker cohort.
- On day 22, after multiple dosing in the diabetic and biomarker cohorts at a dose of OSI-906 150 mg twice daily (recommended dose for phase 2), median AUC_{inf} was 9776 and 17454 ng•h/mL and median C_{max} was 1342 and 3645 ng/mL, respectively; median t_{max} was 2.0 and 3.0 hours and median terminal $t_{1/2\ lambda\ z}$ was 5.32 and 4.75 hours, respectively.
- Exposure to OSI-906 after dosing with capsules and tablets at 150 mg twice daily was similar, based on AUC_{inf} (24747 versus 17454 ng•h/mL) and C_{max} (3110 versus 3645 ng/mL) at day 22 for the dose-escalation cohort (capsules) versus the biomarker expansion cohort (tablets), respectively.
- An approximately 2-fold accumulation of OSI-906 in plasma was observed after twice-daily dosing at 150 mg for 22 days.

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Pharmacodynamics

Detectable phospho-IGF-1R and phospho-IR signals were present in PBMCs from 5 and 6 patients, respectively, of the 8 patients with PBMC sample sets evaluable for pharmacodynamic assessment in the 150-mg twice-daily cohort. Supportive data were available for 2 patients receiving 400 mg once daily, the MTD for the once-daily schedule. The results are summarized below:

- OSI-906 plasma exposures sufficient to inhibit IGF-1R and IR phosphorylation in PBMCs were achieved with 150 mg twice-daily dosing.
- Increases in plasma IGF-1 concentrations and their relationship to plasma OSI-906 concentrations indicate that concentrations of OSI-906 were achieved in tissues involved in regulating the growth hormone (GH)-IGF-1 signaling that may be sufficient to inhibit IGF-1R signaling.
- Collectively, these data provide evidence for target modulation by OSI-906 in cancer patients on the continuous dosing schedules.

Safety Results:

All patients in the study experienced at least 1 AE, with 85% in the twice-daily regimen group and 76% in the once-daily regimen group having AEs that were considered by the investigator to be related to study drug. The majority of patients in both treatment regimens experienced drug-related AEs that were of Grade 1 or 2 in severity. Overall, 8% who received the twice-daily regimen and 6% who received the once-daily regimen experienced at least 1 drug-related serious adverse event (SAE). Additionally, 8% who received the twice-daily regimen and 15% who received the once-daily regimen discontinued the study due to a drug-related AE, and 10 patients (5 in each regimen) died within 30 days following the last dose of study drug.

Across all once daily OSI-906 dose groups, the most frequently reported AEs were nausea (15 patients); vomiting (14 patients); lethargy (10 patients); diarrhea (9 patients); fatigue, anorexia, and weight decreased (8 patients each); abdominal pain (7 patients). No dose related pattern of AE occurrence was apparent [Table 10].

Across all twice daily OSI-906 dose groups, the most frequently reported AEs were fatigue (21 patients); nausea (20 patients); constipation (15 patients); hyperglycemia and hemoglobin decreased (14 patients each); abdominal pain and vomiting (13 patients each); weight decreased (12 patients); and hyponatremia (11 patients). With the exception of lethargy, which occurred at the highest OSI-906 doses only, no dose related pattern of AE occurrence was apparent [Table 11].

Similar types of AEs (e.g., nausea, vomiting, fatigue) were observed in both one-daily and twice daily regimens. Some AEs that occurred in at least 10% of patients overall for 1 treatment regimen were not reported for the other regimen. This included dyspepsia, which was only reported for the once-daily regimen and hypokalemia, aspartate aminotransferase (AST) increased and alanine aminotransferase (ALT) increased, which were only observed for the twice daily treatment regimen.

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Similar drug-related AEs (e.g., nausea, fatigue) occurred with the greatest incidence in both treatment regimens (qd and bid). No dose-related pattern of AE occurrence was apparent in the once-daily regimen, although hyperglycemia occurred at the 2 highest OSI-906 doses. In the twice-daily regimen, hyperglycemia and anorexia occurred at low and high OSI-906 doses, while all the other AEs occurred at the higher OSI-906 doses only.

For the once-daily OSI-906 regimen, 2 patients in the 400 mg (qd) dose group experienced drug-related SAEs including increased blood creatinine, mental status change and renal failure [Table 12]. For the twice-daily regimen, a total of 4 patients from the 2 highest dose groups experienced drug-related SAEs including blood creatinine increased, hyponatremia, renal failure acute, increased ALT and AST, anorexia and vomiting [Table 13].

No patient died during treatment with OSI-906. Ten patients died within 30 days of their last OSI-906 dose; all were due to disease progression and none was related to OSI-906 treatment.

Fourteen patients discontinued treatment due to AEs; those considered by the investigator to be drug-related included: vomiting; prolonged QTc; renal failure acute (2 patients); renal failure; nausea and abdominal pain; hyperglycemia; blood creatinine increased; and ALT increased, AST increased and blood bilirubin increased.

No patients had clinically significant high hemoglobin A1c levels during the study, and 17 patients had clinically significant high glucose levels; most (14) of these patients were in a twice-daily OSI-906 dose group (range 20 to 200 mg).

A total of 5 patients had clinically significant abnormalities in 1 or more ECG QTc intervals, the majority (3 patients) of which were in a twice daily dose group; however, no dose related pattern for occurrence was apparent.

All patients in the expansion cohorts (150 mg bid) had at least 1 AE, and all but 1 patient had AEs that were treatment related. Treatment-related SAEs were reported for 1 patient (11%) in the diabetic cohort and 2 patients (10%) in the biomarker cohort. One patient in each cohort withdrew from the study because of a treatment-related AE. Three patients, all in the biomarker cohort, died within 30 days of the last treatment.

MTD and Recommended Phase 2 Dose

Overall, 6 patients experienced DLTs, 3 on the once-daily regimen and 3 on the twice-daily regimen. The DLTs on the once-daily regimen included 1 patient at 400 mg with Grade 3 prolongation of QTc interval and 2 patients at 450 mg, 1 with Grade 3 hyperglycemia and 1 with Grade 2 abdominal pain and nausea that resulted in interruption of dosing for > 5 days. On the twice-daily regimen, 1 patient at 150 mg had a DLT of Grade 3 elevated AST and 2 on 200 mg had DLTs, 1 with Grade 3 hyperglycemia and 1 with Grade 4 ALT increased and AST increased and Grade 3 blood bilirubin increased. Due to the small sizes of the dose groups, the only dose levels with enough patients to ascertain the MTD were the 150-mg twice-daily (n = 10) and 400 mg once-daily (n = 6) dose groups, neither of which had 33% of patients who experienced DLTs. Two of 4 (50%) and

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2 of 3 (67%) patients experienced DLTs in the 450-mg once-daily and 200-mg twice-daily treatment regimens, respectively; therefore, the MTD for OSI-906 given once daily was determined to be 400 mg (qd) and for OSI-906 given twice daily was 150 mg (bid). The recommended phase 2 dose was 150 mg twice daily; hence, this dose was used for the expansion cohorts.

CONCLUSIONS:

Based on the results of this study, it is concluded that:

- The administration of OSI-906 in doses up to 400 mg (qd) or doses up to 150 mg (bid) were tolerated in this population of cancer patients with advanced solid tumors, with an MTD for OSI-906 of 400 mg (qd) and 150 mg (bid) in each regimen. There was a trend towards more drug-related SAEs with higher doses within and across regimens. Hyperglycemia tended to occur with OSI-906 administration without a dose-relationship, whereas increases in creatinine, QTc prolongation and increases in liver function tests (LFTs) tended to occur more often at higher doses.
- OSI-906 was absorbed in plasma and exposure increases were not dose proportional; steady-state levels were reached within 8 days. Urinary excretion of unchanged OSI-906 was minimal (0.01 to 0.22%).
- No patient experienced a PR as the best clinical response. One patient experienced a PR after OSI-906 treatment began and experienced a CR following surgical resection. No other patient experienced a CR. Among evaluable patients with measurable disease, DCRs (CR + PR + SD) were 50% and 46.3% for the once-daily and twice-daily dose groups, respectively.
- For the subpopulation of cancer patients with advanced solid tumors and diabetes or nondiabetes, no apparent differences in safety or efficacy were observed.

Date of Report: 09 Jan 2013

Table 2 Populations for Analysis and Patient Disposition (Once-daily Regimen)

	OSI-906 Dose (mg) – Once-daily Treatment Regimen								
Condition	**10 (n = 6)**	**20 (n = 3)**	**40 (n = 4)**	**75 (n = 4)**	**150 (n = 3)**	**300 (n = 4)**	**400 (n = 10)**	**450 (n = 4)**	**Total (n = 38)**
Enrolled, n (%)	6 (100)	3 (100)	4 (100)	4 (100)	3 (100)	4 (100)	10 (100)	4 (100)	38 (100)
Treated, n (%)	6 (100)	3 (100)	4 (100)	3 (75)	3 (100)	4 (100)	6 (60)	4 (100)	33 (87)
Evaluable, n (%):									
Safety	6 (100)	3 (100)	4 (100)	3 (75)	3 (100)	4 (100)	6 (60)	4 (100)	33 (87)
DLT	4 (67)	3 (100)	3 (75)	3 (75)	2 (67)	3 (75)	6 (60)	3 (75)	27 (71)
Pharmacokinetics	6 (100)	3 (100)	4 (100)	3 (75)	3 (100)	4 (100)	6 (60)	4 (100)	33 (87)
Efficacy	4 (67)	3 (100)	3 (75)	3 (75)	3 (100)	3 (75)	3 (30)	2 (50)	24 (63)
Reason off treatment, n (%):	6 (100)	3 (100)	4 (100)	3 (75)	3 (100)	4 (100)	6 (60)	4 (100)	33 (87)
Disease progression	4 (67)	2 (67)	3 (75)	2 (50)	3 (100)	3 (75)	3 (30)	1 (25)	21 (55)
Adverse event	2 (33)	0	0	0	0	1 (25)	3 (30)	1 (25)	7 (18)
Medical or ethical reasons	0	0	1 (25)	0	0	0	0	0	1 (3)
Patient request	0	1 (33)	0	1 (25)	0	0	0	2 (50)	4 (11)
Patient death	0	0	0	0	0	0	0	0	0

All patients who enrolled in the study (Enrolled population).

DLT: dose-limiting toxicity.

Source: Table 12.1.1.2; Table 12.1.2.3

Table 3 Populations for Analysis and Patient Disposition (Twice-daily Regimen)

	OSI-906 Dose (mg) – Twice-daily Treatment Regimen					
Condition	**20 (n = 5)**	**40 (n = 3)**	**75 (n = 4)**	**150 (n = 42)**	**200 (n = 3)**	**Total (n = 57)**
Enrolled, n (%)	5 (100)	3 (100)	4 (100)	42 (100)	3 (100)	57 (100)
Treated, n (%)	5 (100)	3 (100)	3 (75)	39 (93)	3 (100)	53 (93)
Evaluable, n (%):						
Safety	5 (100)	3 (100)	3 (75)	39 (93)	3 (100)	53 (93)
DLT	3 (60)	3 (100)	3 (75)	10 (24)	3 (100)	22 (39)
Pharmacokinetics	5 (100)	3 (100)	3 (75)	39 (93)	3 (100)	53 (93)
Efficacy	3 (60)	3 (100)	3 (75)	31 (74)	1 (33)	41 (72)
Reason off treatment, n (%):	5 (100)	3 (100)	2 (50)	38 (90)	3 (100)	51 (89)
Disease progression	3 (60)	3 (100)	2 (50)	34 (81)	1 (33)	43 (75)
Adverse event	2 (40)	0	0	2 (5)	2 (67)	6 (11)
Medical or ethical reasons	0	0	0	1 (2)	0	1 (2)
Patient request	0	0	0	1 (2)	0	1 (2)
Patient death	0	0	0	0	0	0

All patients who enrolled in the study (Enrolled population).

DLT: dose-limiting toxicity.

Source: Table 12.1.1.1; Table 12.1.2.2

Table 4 Demographics and Baseline Characteristics (Once-daily Regimen)

Characteristic	OSI-906 Dose (mg) – Once-daily Treatment Regimen								
	10 (n=6)	20 (n=3)	40 (n=4)	75 (n=4)	150 (n=3)	300 (n=4)	400 (n=10)	450 (n=4)	Total (n=38)
Gender, n (%):									
Female	1 (17)	0	3 (75)	2 (50)	2 (67)	1 (25)	3 (30)	3 (75)	15 (39)
Male	5 (83)	3 (100)	1 (25)	2 (50)	1 (33)	3 (75)	7 (70)	1 (25)	23 (61)
Race/ethnicity, n (%):									
White, not Hispanic/Latino	6 (100)	3 (100)	4 (100)	4 (100)	3 (100)	4 (100)	9 (90)	3 (75)	36 (95)
White, Hispanic/Latino	0	0	0	0	0	0	0	0	0
Black	0	0	0	0	0	0	1 (10)	1 (25)	2 (5)
Asian	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0
Age (years):									
18 to 39, n (%)	1 (17)	0	0	0	0	2 (50)	0	1 (25)	4 (11)
40 to 64, n (%)	2 (33)	3 (100)	2 (50)	4 (100)	1 (33)	2 (50)	9 (90)	3 (75)	26 (68)
≥ 65, n (%)	3 (50)	0	2 (50)	0	2 (67)	0	1 (10)	0	8 (21)
Median	63.5	48.0	63.5	60.0	68.0	44.0	51.5	54.5	57.5
Minimum – maximum	38.0-76.0	41.0-64.0	47.0-68.0	52.0-63.0	64.0-69.0	19.0-59.0	42.0-69.0	34.0-60.0	19.0-76.0
Weight (kg):									
Median	69.4	98.2	71.7	62.1	61.8	73.4	70.9	69.6	70.9
Minimum – maximum	51.6-106.4	83.6-100.3	63.7-105.9	42.5-113.3	59.6-75.9	53.1-76.0	35.6-145.9	47.4-78.7	35.6-145.9
Height (cm):									
Median	177.2	175.3	165.3	163.5	163.0	170.5	167.0	165.1	169.0
Minimum – maximum	160.0-188.0	172.7-187.0	160.0-180.3	156.0-172.0	161.0-173.0	167.0-187.0	154.0-188.0	160.0-182.8	154.0-188.0
ECOG performance status, n (%):									
0	1 (17)	1 (33)	3 (75)	2 (50)	2 (67)	2 (50)	3 (30)	1 (25)	15 (39)
1	3 (50)	2 (67)	1 (25)	2 (50)	1 (33)	2 (50)	6 (60)	1 (25)	18 (47)
2	2 (33)	0	0	0	0	0	1 (10)	2 (50)	5 (13)
Cotinine test, n (%):									
Negative	5 (83)	2 (67)	4 (100)	3 (75)	2 (67)	2 (50)	4 (40)	2 (50)	24 (63)
Positive	1 (17)	1 (33)	0	1 (25)	1 (33)	2 (50)	4 (40)	1 (25)	11 (29)
Not done	0	0	0	0	0	0	2 (20)	1 (25)	3 (8)
Tumor type, n (%):									
Breast	0	0	0	0	0	0	1 (10)	0	1 (3)
Ovarian	0	0	0	1 (25)	0	0	0	0	1 (3)
Renal	1 (17)	0	0	0	1 (33)	0	0	0	2 (5)
Colorectal	0	1 (33)	2 (50)	1 (25)	2 (67)	0	4 (40)	2 (50)	12 (32)
Melanoma	0	0	0	0	0	0	1 (10)	0	1 (3)
Adrenal carcinoma	0	1 (33)	0	0	0	0	0	0	1 (3)
Sarcoma	0	0	0	0	0	1 (25)	0	0	1 (3)
Gastric	1 (17)	0	0	1 (25)	0	0	2 (20)	0	4 (11)
Pancreatic	2 (33)	0	1 (25)	1 (25)	0	1 (25)	0	0	5 (13)
Esophageal	1 (17)	0	0	0	0	1 (25)	0	0	2 (5)
Other	1 (17)	1 (33)	1 (25)	0	0	1 (25)	2 (20)	2 (50)	8 (21)

All patients who enrolled in the study (Enrolled population).

ECOG: Eastern Cooperative Oncology Group.

Source: Table 12.1.3.5; Table 12.1.3.6; Table 12.1.4.2

Table 5 Demographics and Baseline Characteristics (Twice-daily Regimen)

Characteristic	OSI-906 Dose (mg) – Twice-daily Treatment Regimen					
	20 (n=5)	40 (n=3)	75 (n=4)	150 (n=42)	200 (n=3)	Total (n=57)
Gender, n (%):						
Female	1 (20)	1 (33)	1(25)	16 (38)	1 (33)	20 (35)
Male	4 (80)	2 (67)	3 (75)	26 (62)	2 (67)	37 (65)
Race/ethnicity, n (%):						
White, not Hispanic/Latino	4 (80)	2 (67)	4 (100)	37 (88)	2 (67)	49 (86)
White, Hispanic/Latino	0	0	0	0	1 (33)	1 (2)
Black	1 (20)	0	0	4 (10)	0	5 (9)
Asian	0	0	0	1 (2)	0	1 (2)
Other	0	1 (33)	0	0	0	1 (2)
Age (years):						
18 to 39, n (%)	1 (20)	0	0	2 (5)	1 (33)	4 (7)
40 to 64, n (%)	2 (40)	3 (100)	2 (50)	25 (60)	1 (33)	33 (58)
≥ 65, n (%)	2 (40)	0	2 (50)	15 (36)	1 (33)	20 (35)
Median	64.0	56.0	65.5	60.0	55.0	60.0
Minimum - maximum	26.0-66.0	46.0-59.0	60.0-74.0	24.0-79.0	34.0-71.0	24.0-79.0
Weight (kg):						
Median	76.4	71.8	90.9	75.3	86.0	76.4
Minimum - maximum	62.3-90.0	47.4-73.2	86.5-120.3	48.3-122.8	53.9-86.9	47.4-122.8
Height (cm):						
Median	168.9	150.0	171.3	172.7	170.0	170.2
Minimum - maximum	162.6-182.9	150.0-180.3	165.1-177.8	152.4-195.6	163.0-180.0	150.0-195.6
ECOG performance status, n (%):						
0	0	0	0	15 (36)	2 (67)	17 (30)
1	3 (60)	2 (67)	4 (100)	18 (43)	1 (33)	28 (49)
2	2 (40)	1 (33)	0	9 (21)	0	12 (21)
Cotinine test, n (%):						
Negative	4 (80)	1 (33)	3 (75)	35 (83)	2 (67)	45 (79)
Positive	1 (20)	2 (67)	1 (25)	5 (12)	1 (33)	10 (18)
Not done	0	0	0	2 (5)	0	2 (4)
Tumor type, n (%):						
NSCLC	0	1 (33)	1 (25)	2 (5)	0	4 (7)
Renal	0	0	0	1 (2)	0	1 (2)
Colorectal	1 (20)	0	1 (25)	32 (76)	1 (33)	35 (61)
Melanoma	0	0	1 (25)	1 (2)	0	2 (4)
Sarcoma	0	0	0	2 (5)	1 (33)	3 (5)
Gastric	0	0	0	0	1 (33)	1 (2)
Pancreatic	1 (20)	0	0	1 (2)	0	2 (4)
Esophageal	1 (20)	0	0	0	0	1 (2)
Other	2 (40)	2 (67)	1 (25)	3 (7)	0	8 (14)

All patients who enrolled in the study (Enrolled population).

ECOG: Eastern Cooperative Oncology Group; NSCLC: non small cell lung cancer.

Source: Table 12.1.3.1; Table 12.1.3.2; Table 12.1.4.1

Table 6 Response Rates and Disease Control Rate (Once-daily Regimen)

Category	Once-daily Treatment Regimen								
	10 (n = 4)	**20 (n = 3)**	**40 (n = 3)**	**75 (n = 3)**	**150 (n = 3)**	**300 (n = 3)**	**400 (n = 3)**	**450 (n = 2)**	**Total (n = 24)**
Best clinical response, n (%)									
CR	0	0	0	0	0	0	0	0	0
PR	0	0	0	0	0	0	0	0	0
SD	2 (50)	3 (100)	0	1 (33)	2 (67)	0	2 (67)	2 (100)	12 (50)
PD	2 (50)	0	3 (100)	2 (67)	1 (33)	3 (100)	1 (33)	0	12 (50)
Overall response rate (CR + PR)									
Patients with response/patients evaluable (%)	0/4 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/2 (0)	0/24 (0)
(95% CI)	(0.0, 60.2)	(0.0, 70.8)	(0.0, 70.8)	(0.0, 70.8)	(0.0, 70.8)	(0.0, 70.8)	(0.0, 70.8)	(0.0, 84.2)	(0.0, 14.2)
DCR (CR + PR + SD)									
Patients with response/patients evaluable (%)	2/4 (50)	3/3 (100)	0/3 (0)	1/3 (33.3)	2/3 (66.7)	0/3 (0)	2/3 (66.7)	2/2 (100)	12/24 (50)
(95% CI)	(6.8, 93.2)	(29.2, 100.0)	(0.0, 70.8)	(0.8, 90.6)	(9.4, 99.2)	(0.0, 70.8)	(9.4, 99.2)	(15.8, 100.0)	(29.1, 70.9)

All patients who had measurable disease according to RECIST, who received at least 21 days of treatment and who had their disease re-evaluated (Efficacy population).

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; DCR: disease control rate; RECIST: Response Evaluation Criteria In Solid Tumors.

Note: minimal time interval required between 2 measurements for determination of SD is defined as 6 to 8 weeks.

Source: Table 12.3.2.2.2; Table 12.3.4.1

Table 7 Response Rates and Disease Control Rate (Twice-daily Regimen)

Category	Twice-daily Treatment Regimen					
	20 (n = 3)	**40 (n = 3)**	**75 (n = 3)**	**150 (n = 31)**	**200 (n = 1)**	**Total (n = 41)**
Best clinical response, n (%)						
CR	0	0	1 (33)	0	0	1 (2)
PR	0	0	0	0	0	0
SD	1 (33)	2 (67)	0	14 (45)	1 (100)	18 (44)
PD	2 (67)	1 (33)	2 (67)	17 (55)	0	22 (54)
Overall response rate (CR + PR)						
Patients with response/patients evaluable, n (%)	0/3 (0)	0/3 (0)	1/3 (33.3)	0/31 (0)	0/1 (0)	1/41 (2.4)
(95% CI)	(0.0, 70.8)	(0.0, 70.8)	(0.8, 90.6)	(0.0, 11.2)	(0.0, 97.5)	(0.1, 12.9)
DCR (CR + PR + SD)						
Patients with response/patients evaluable, n (%)	1/3 (33.3)	2/3 (66.7)	1/3 (33.3)	14/31 (45.2)	1/1 (100)	19/41 (46.3)
(95% CI)	(0.8, 90.6)	(9.4, 99.2)	(0.8, 90.6)	(27.3, 64.0)	(2.5, 100.0)	(30.7, 62.6)

All patients who had measurable disease according to RECIST, who received at least 21 days of treatment and who had their disease re-evaluated (Efficacy population).

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; DCR: disease control rate; RECIST: Response Evaluation Criteria In Solid Tumors.

Source: Table 12.3.2.2.1; Table 12.3.4.2

Table 8 Plasma OSI-906 Pharmacokinetic Parameters (Once-daily Regimen, Day 1)

Parameter	OSI-906 Dose (mg) – Once-daily Treatment Regimen							
	10 (n = 6)	**20 (n = 3)**	**40 (n = 4)**	**75 (n = 3)**	**150 (n = 3)**	**300 (n = 4)**	**400 (n = 6)**	**450 (n = 4)**
t_{max} (h)								
Evaluable, n	6	3	4	3	3	4	6	4
Median	2.5	2.0	2.5	3.0	3.0	3.1	3.0	3.6
Min - max	1.0 - 10.0	1.0 - 4.0	2.0 - 4.0	0.8 - 4.0	2.0 - 6.1	2.0 - 8.0	1.9 - 24.0	3.0 - 6.0
C_{max} (ng/mL)								
Evaluable, n	6	3	4	3	3	4	6	4
Median	76.6	171	420	1040	1440	2725	2905	5415
Min - max	44.8 - 112	74.1 - 192	354 - 1620	538 - 1260	1380 - 1670	1490 - 6710	594 - 4160	3020 - 10200
Geometric mean (90% CI)	72.4 (51.6, 102)	134 (56.0, 323)	564 (245, 1298)	890 (419, 1889)	1492 (1260, 1776)	2935 (1415, 6091)	2450 (1357, 4425)	5369 (2803, 10282)
AUC_{tau} (h•ng/mL)								
Evaluable, n	5	3	4	3	3	3	6	3
Median	223	630	1874	4621	9811	26527	22258	50574
Min - max	205 - 630	523 - 777	1687 - 7992	4193 - 4990	4922 - 12063	5556 - 48525	3440 - 51005	26440 - 82550
Geometric mean (90% CI)	289 (183, 458)	635 (454, 888)	2620 (1087, 6314)	4590 (3962, 5316)	8352 (3786, 18426)	19267 (2924, 126963)	19617 (8747, 43994)	47970 (18316, 125634)
AUC_{inf} (h•ng/mL)								
Evaluable, n	5	3	4	3	3	3	4	3
Median	223	599	1887	4649	10083	27944	16485	60403
Min - max	201 - 635	541 - 759	1694 - 8059	4265 - 5078	4879 - 12327	5504 - 48675	3677 - 27742	26880 - 91663
Geometric mean (90% CI)	288 (182, 457)	626 (468, 839)	2637 (1093, 6364)	4653 (4016, 5390)	8464 (3720, 19256)	19562 (2898, 132066)	12879 (4603, 36033)	52994 (18516, 151673)
CL/F (mL/h)								
Evaluable, n	5	3	4	3	3	3	4	3
Median	44789	33397	21306	16131	14876	10736	24448	7450
Min - max	15757 - 49639	26363 - 36962	4963 - 23609	14768 - 17583	12169 - 30745	6163 - 54509	14418 - 108784	4909 - 16741
$t_{1/2\ lambda\ z}$ (h)								
Evaluable, n	5	3	4	3	3	3	4	3
Median	2.20	2.22	3.10	3.64	3.85	2.53	3.52	6.91
Min - max	1.11 - 3.22	2.20 - 2.41	2.56 - 3.72	2.97 - 4.28	1.35 - 4.23	1.15 - 5.16	2.35 - 5.09	3.62 - 8.65
V_z/F (mL)								
Evaluable, n	5	3	4	3	3	3	4	3
Median	104055	106897	85173	91204	67587	79933	92471	87411
Min - max	71740 - 150546	83750 - 128718	23923 - 122544	69193 - 92359	60094 - 90737	22498 - 90122	79733 - 798673	48955 - 92930

All patients who had sufficient pharmacokinetic sampling associated with the OSI-906 doses (Pharmacokinetic analysis set).

Max: maximum; Min: minimum; CL/F: apparent body clearance after extravascular dosing; Vz/F: apparent volume of distribution during terminal phase after single or repeated extravascular dosing.

Source: Table 12.4.4.5

Table 9 Plasma OSI-906 Pharmacokinetic Parameters (Twice-daily Regimen, Day 1)

Parameter	OSI-906 Dose (mg) – Twice-daily Treatment Regimen				
	20 (n = 5)	**40 (n = 3)**	**75 (n = 3)**	**150 (n = 10)**	**200 (n = 3)**
t_{max} (h)					
Evaluable, n	5	3	3	10	3
Median	3.0	2.0	3.0	2.1	3.0
Min - max	2.0 - 4.0	1.0 - 4.0	2.0 - 4.0	1.0 - 3.2	1.2 - 3.2
C_{max} (ng/mL)					
Evaluable, n	5	3	3	10	3
Median	242	401	762	1705	2050
Min - max	121 - 284	395 - 659	629 - 1040	869 - 3090	970 - 2990
Geometric mean (90% CI)	209 (151, 289)	471 (288, 769)	793 (517, 1216)	1698 (1313, 2196)	1812 (690, 4759)
AUC_{tau} (h•ng/mL)					
Evaluable, n	5	3	3	10	3
Median	830	1761	3601	8453	12508
Min - max	366 - 1508	1093 - 1804	2437 - 5814	2557 - 11795	4668 - 17809
Geometric mean (90% CI)	878 (507, 1519)	1514 (940, 2439)	3709 (1780, 7730)	7794 (5919, 10261)	10131 3145, 32635)
AUC_{inf} (h•ng/mL)					
Evaluable, n	5	3	3	10	2
Median	861	1812	4240	9475	9680
Min - max	388 - 1624	1098 - 1815	2478 - 6742	2649 - 12411	4932 - 14428
Geometric mean (90% CI)	928 (528, 1630)	1534 (941, 2500)	4138 (1778, 9628)	8561 (6462, 11342)	8435 (NC)
CL/F (mL/h)					
Evaluable, n	5	3	3	10	2
Median	23237	22077	17687	15839	27207
Min - max	12319 - 51536	22040 - 36434	11124 - 30265	12086 - 56634	13862 - 40552
$t_{1/2\ lambda\ z}$ (h)					
Evaluable, n	5	3	3	10	3
Median	2.24	1.65	3.52	2.93	3.09
Min - max	1.64 - 3.06	1.45 - 1.83	1.80 - 4.10	2.09 - 4.58	2.55 - 6.58
V_z/F (mL)					
Evaluable, n	5	3	3	10	2
Median	59414	58429	78528	77780	105360
Min - max	39865 - 227717	52490 - 76261	65756 - 89724	37730 - 173756	61701 - 149020

All patients who had sufficient pharmacokinetic sampling associated with the OSI-906 doses (Pharmacokinetic analysis set).

Max: maximum; Min: minimum; NC: not calculated; CL/F: apparent body clearance after extravascular dosing; Vz/F: apparent volume of distribution during terminal phase after single or repeated extravascular dosing.

Source: Table 12.4.4.3.3

Table 10 Summary of Adverse Events Occurring in at Least 2 Patients in a Dose Group at Any Time During OSI-906 Treatment – Once-daily Regimen

MedDRA (v. 9.1) SOC Preferred Term	Initial OSI-906 Dose (mg) – Once-daily Regimen (n = 33)							
	10 (n = 6)	**20 (n = 3)**	**40 (n = 4)**	**75 (n = 3)**	**150 (n = 3)**	**300 (n = 4)**	**400 (n = 6)**	**450 (n = 4)**
Any AE, n (%)	**6 (100)**	**3 (100)**	**4 (100)**	**3 (100)**	**3 (100)**	**4 (100)**	**6 (100)**	**4 (100)**
Gastrointestinal disorders	**5 (83)**	**2 (67)**	**4 (100)**	**3 (100)**	**3 (100)**	**3 (75)**	**4 (67)**	**3 (75)**
Nausea	4 (67)	1 (33)	1 (25)	2 (67)	2 (67)	2 (50)	1 (17)	2 (50)
Vomiting	4 (67)	1 (33)	2 (50)	2 (67)	2 (67)	1 (25)	0	2 (50)
Diarrhoea	1 (17)	1 (33)	0	0	1 (33)	2 (50)	3 (50)	1 (25)
Abdominal pain	1 (17)	0	2 (50)	0	0	1 (25)	1 (17)	2 (50)
Investigations	**3 (50)**	**3 (100)**	**1 (25)**	**2 (67)**	**3 (100)**	**3 (75)**	**4 (67)**	**3 (75)**
Weight decreased	0	1 (33)	0	0	2 (67)	2 (50)	2 (33)	1 (25)
Electrocardiogram QT corrected interval prolonged	1 (17)	0	0	0	0	0	1 (17)	2 (50)
Haemoglobin decreased	0	0	0	0	1 (33)	0	2 (33)	1 (25)
Blood creatinine increased	0	0	0	0	0	0	2 (33)	0
Weight increased	0	2 (67)	0	0	0	0	0	0
Metabolism and nutrition disorders	**2 (33)**	**1 (33)**	**2 (50)**	**0**	**2 (67)**	**3 (75)**	**2 (33)**	**3 (75)**
Anorexia	2 (33)	0	2 (50)	0	1 (33)	1 (25)	0	2 (50)
Decreased appetite	0	0	0	0	1 (33)	2 (50)	1 (17)	0
Hyperglycaemia	0	0	0	0	0	0	1 (17)	3 (75)
Hypoalbuminaemia	0	0	0	0	0	0	2 (33)	0
Hyponatraemia	0	0	0	0	0	0	2 (33)	0
Nervous system disorders	**3 (50)**	**1 (33)**	**2 (50)**	**2 (67)**	**3 (100)**	**2 (50)**	**0**	**2 (50)**
Lethargy	2 (33)	0	0	2 (67)	3 (100)	2 (50)	0	1 (25)
Dizziness	1 (17)	0	2 (50)	0	0	0	0	1 (25)
General disorders and administration site conditions	**2 (33)**	**2 (67)**	**2 (50)**	**1 (33)**	**0**	**2 (50)**	**3 (50)**	**2 (50)**
Fatigue	1 (17)	2 (67)	2 (50)	0	0	0	1 (17)	2 (50)
Pyrexia	0	0	0	0	0	1 (25)	2 (33)	0
Oedema peripheral	0	0	0	0	0	0	2 (33)	0
Respiratory, thoracic and mediastinal disorders	**3 (50)**	**3 (100)**	**1 (25)**	**1 (33)**	**1 (33)**	**2 (50)**	**2 (33)**	**1 (25)**
Rhinitis allergic	0	2 (67)	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	**1 (17)**	**1 (33)**	**2 (50)**	**2 (67)**	**1 (33)**	**3 (75)**	**1 (17)**	**1 (25)**

Table continued on next page

Table 10 continued

MedDRA (v. 9.1)	**Initial OSI-906 Dose (mg) – Once-daily Regimen (n = 33)**							
SOC Preferred Term	**10 (n = 6)**	**20 (n = 3)**	**40 (n = 4)**	**75 (n = 3)**	**150 (n = 3)**	**300 (n = 4)**	**400 (n = 6)**	**450 (n = 4)**
Infections and infestations	**0**	**1 (33)**	**2 (50)**	**1 (33)**	**1 (33)**	**2 (50)**	**3 (50)**	**1 (25)**
Rhinitis	0	1 (33)	0	0	1 (33)	2 (50)	1 (17)	0
Oral candidiasis	0	0	2 (50)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	**1 (17)**	**2 (67)**	**1 (25)**	**1 (33)**	**0**	**1 (25)**	**1 (17)**	**1 (25)**
Psychiatric disorders	**1 (17)**	**0**	**0**	**1 (33)**	**0**	**0**	**2 (33)**	**1 (25)**
Renal and urinary disorders	**0**	**2 (67)**	**0**	**1 (33)**	**0**	**0**	**2 (33)**	**0**
Urinary retention	0	2 (67)	0	0	0	0	0	0
Cardiac disorders	**1 (17)**	**0**	**0**	**0**	**0**	**0**	**2 (33)**	**0**

All patients who received at least 1 dose of OSI-906 (Safety analysis set). Events during follow-up are excluded.

Note: adverse events are sorted by decreasing incidence overall for the once-daily regimen, first by system organ class, then by preferred term and then alphabetically for preferred terms with the same incidence overall.

AE: adverse event.

Source: Table 12.6.1.1.4.2; Table 12.6.1.1.4.4

Table 11 Summary of Adverse Events Occurring in at Least 2 Patients in a Dose Group at Any Time During OSI-906 Treatment – Twice-daily Regimen

MedDRA (v. 9.1)	**Initial OSI-906 Dose (mg) – Twice-daily Regimen (n = 53)**				
SOC Preferred Term	**20** **(n = 5)**	**40** **(n = 3)**	**75** **(n = 3)**	**150** **(n =39)**	**200** **(n = 3)**
Any AE, n (%)	**5 (100)**	**3 (100)**	**3 (100)**	**39 (100)**	**3 (100)**
Gastrointestinal disorders	**5 (100)**	**3 (100)**	**2 (67)**	**29 (74)**	**3 (100)**
Nausea	1 (20)	0	1 (33)	16 (41)	2 (67)
Constipation	2 (40)	2 (67)	0	10 (26)	1 (33)
Abdominal pain	1 (20)	1 (33)	2 (67)	9 (23)	0
Vomiting	2 (40)	0	1 (33)	8 (21)	2 (67)
Diarrhoea	1 (20)	0	0	8 (21)	0
Abdominal pain upper	0	0	0	3 (8)	1 (33)
Abdominal distension	0	0	0	3 (8)	0
Rectal haemorrhage	0	0	0	3 (8)	0
Ascites	0	0	0	2 (5)	0
Investigations	**3 (60)**	**3 (100)**	**2 (67)**	**29 (74)**	**2 (67)**
Haemoglobin decreased	1 (20)	0	0	12 (31)	1 (33)
Weight decreased	0	1 (33)	0	10 (26)	1 (33)
Aspartate aminotransferase increased	0	1 (33)	1 (33)	5 (13)	1 (33)
Alanine aminotransferase increased	0	1 (33)	1 (33)	4 (10)	1 (33)
Gamma-glutamyltransferase increased	2 (40)	1 (33)	0	4 (10)	0
Blood creatinine increased	0	0	1 (33)	5 (13)	0
Electrocardiogram QT corrected interval prolonged	1 (20)	0	0	3 (8)	0
Blood alkaline phosphatase increased	0	1 (33)	0	2 (5)	0
Metabolism and nutrition disorders	**2 (40)**	**2 (67)**	**2 (67)**	**24 (62)**	**2 (67)**
Hyperglycaemia	2 (40)	1 (33)	0	10 (26)	1 (33)
Hyponatraemia	1 (20)	1 (33)	0	9 (23)	0
Hypokalaemia	0	0	1 (33)	8 (21)	0
Anorexia	0	1 (33)	0	6 (15)	1 (33)
Hypermagnesaemia	0	0	0	4 (10)	0
Hypoalbuminaemia	0	0	1 (33)	3 (8)	0
Hypophosphataemia	0	1 (33)	1 (33)	2 (5)	0
Hypomagnesaemia	0	0	1 (33)	2 (5)	0
Decreased appetite	0	0	0	2 (5)	0
Hypocalcaemia	0	0	0	2 (5)	0
General disorders and administration site conditions	**3 (60)**	**1 (33)**	**2 (67)**	**21 (54)**	**2 (67)**
Fatigue	2 (40)	1 (33)	2 (67)	16 (41)	0
Oedema peripheral	2 (40)	0	1 (33)	4 (10)	0
Pyrexia	0	0	1 (33)	5 (13)	1 (33)
Chest pain	1 (20)	0	0	2 (5)	0
Musculoskeletal and connective tissue disorders	**3 (60)**	**0**	**2 (67)**	**16 (41)**	**0**
Back pain	0	0	1 (33)	5 (13)	0
Pain in extremity	0	0	0	5 (13)	0
Muscular weakness	1 (20)	0	0	2 (5)	0
Musculoskeletal pain	0	0	0	3 (8)	0
Myalgia	1 (20)	0	0	2 (5)	0
Muscle spasms	0	0	0	2 (5)	0

Table continued on next page

Table 11 continued

MedDRA (v. 9.1)	**Initial OSI-906 Dose (mg) – Twice-daily Regimen (n = 53)**				
SOC Preferred Term	**20** **(n = 5)**	**40** **(n = 3)**	**75** **(n = 3)**	**150** **(n =39)**	**200** **(n = 3)**
Nervous system disorders	**0**	**0**	**2 (67)**	**12 (31)**	**3 (100)**
Lethargy	0	0	0	7 (18)	3 (100)
Dizziness	0	0	0	3 (8)	0
Headache	0	0	1 (33)	2 (5)	0
Respiratory, thoracic and mediastinal disorders	**0**	**1 (33)**	**1 (33)**	**14 (36)**	**0**
Dyspnoea	0	1 (33)	1 (33)	4 (10)	0
Cough	0	0	0	5 (13)	0
Productive cough	0	0	0	3 (8)	0
Epitaxis	0	0	0	2 (5)	0
Pleural effusion	0	0	0	2 (5)	0
Pulmonary embolism	0	0	0	2 (5)	0
Skin and subcutaneous tissue disorders	**0**	**2 (67)**	**1 (33)**	**11 (28)**	**0**
Hyperhidrosis	0	1 (33)	0	3 (8)	0
Pruritus	0	0	0	4 (10)	0
Drug eruption	0	0	0	2 (5)	0
Infections and infestations	**2 (40)**	**0**	**2 (67)**	**7 (18)**	**1 (33)**
Urinary tract infection	2 (40)	0	1 (33)	4 (10)	0
Blood and lymphatic system disorders	**1 (20)**	**1 (33)**	**1 (33)**	**8 (21)**	**0**
Lymphopenia	1 (20)	0	1 (33)	6 (15)	0
Anaemia	0	0	0	2 (5)	0
Renal and urinary disorders	**1 (20)**	**0**	**0**	**6 (15)**	**0**
Cardiac disorders	**1 (20)**	**0**	**1 (33)**	**3 (8)**	**0**
Tachycardia	0	0	0	2 (5)	0
Ventricular arrythmia	0	0	0	2 (5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (60)**	**1 (33)**	**0**	**1 (3)**	**0**
Cancer pain	3 (60)	1 (33)	0	1 (3)	0
Psychiatric disorders	**0**	**0**	**0**	**4 (10)**	**0**
Insomnia	0	0	0	2 (5)	0
Injury, poisoning and procedural complications	**0**	**0**	**1 (33)**	**2 (5)**	**0**
Reproductive system and breast disorders	**0**	**0**	**0**	**3 (8)**	**0**
Vascular disorders	**1 (20)**	**0**	**0**	**2 (5)**	**0**
Ear and labyrinth disorders	**0**	**0**	**0**	**2 (5)**	**0**

All patients who received at least 1 dose of OSI-906 (Safety analysis set). Events during follow-up are excluded.

Note: adverse events are sorted by decreasing incidence overall for the twice-daily regimen, first by system organ class, then by preferred term and then alphabetically for preferred terms with the same incidence overall.

AE: adverse event.

Source: Table 12.6.1.1.4.5; Table 12.6.1.1.4.6

Table 12 Summary of Serious Adverse Events at Any Time During OSI-906 Treatment – Once-daily Treatment Regimen

Treatment Regimen/ Preferred Term MedDRA (v. 9.1)	**Initial OSI-906 Dose (mg) – Once-daily Regimen (n = 33)**							
	10 (n = 6)	**20 (n=3)**	**40 (n = 4)**	**75 (n = 3)**	**150 (n = 3)**	**300 (n = 4)**	**400 (n = 6)**	**450 (n = 4)**
Any SAE, n (%)	**4 (67)**	**0**	**1 (25)**	**0**	**0**	**3 (75)**	**2 (33)**	**1 (25)**
Abdominal pain	1 (17)	0	0	0	0	0	1 (17)	0
Headache	0	0	1 (25)	0	0	1 (25)	0	0
Vomiting	0	0	1 (25)	0	0	1 (25)	0	0
Anaemia	0	0	0	0	0	1 (25)	0	0
Blood creatinine increased	0	0	0	0	0	0	1 (17) †	0
Chest pain	0	0	0	0	0	0	1 (17)	0
Chronic obstructive pulmonary disease	0	0	0	0	0	0	0	1 (25)
Confusional state	0	0	0	0	0	0	0	1 (25)
Constipation	1 (17)	0	0	0	0	0	0	0
Dehydration	1 (17)	0	0	0	0	0	0	0
Dizziness	0	0	1 (25)	0	0	0	0	0
Dysphagia	1 (17)	0	0	0	0	0	0	0
Fatigue	1 (17)	0	0	0	0	0	0	0
Haematemesis	1 (17)	0	0	0	0	0	0	0
Haemoglobin decreased	0	0	0	0	0	0	1 (17)	0
Hyperbilirubinaemia	1 (17)	0	0	0	0	0	0	0
Jaundice cholestatic	0	0	0	0	0	1 (25)	0	0
Mental status changes	0	0	0	0	0	0	1 (17) †	0
Metastases to central nervous system	0	0	1 (25)	0	0	0	0	0
Nausea	0	0	1 (25)	0	0	0	0	0
Renal failure	0	0	0	0	0	0	1 (17) †	0
Renal failure acute	0	0	0	0	0	0	1 (17) †	0
Urinary tract infection	0	0	0	0	0	0	0	1 (25)

All patients who received at least 1 dose of OSI-906 (Safety analysis set). Follow-up events are excluded.

Note: adverse events are sorted by decreasing incidence overall for the once-daily regimen by preferred term and then alphabetically for preferred terms with the same incidence overall.

SAE: serious adverse event.

† SAE considered by the investigator to be related to study drug.

Source: Table 12.6.1.3.2.5; Table 12.6.1.3.2.6; Table 12.6.1.3.8.5; Table 12.6.1.3.8.6; Appendix 13.2.7.2

Table 13 Summary of Serious Adverse Events at Any Time during OSI-906 Treatment – Twice-daily Treatment Regimen

	Initial OSI-906 Dose (mg) – Twice-daily Regimen (n = 53)				
Treatment Regimen/ Preferred Term MedDRA (v. 9.1)	**20 (n = 5)**	**40 (n = 3)**	**75 (n = 3)**	**150 (n = 39)**	**200 (n = 3)**
Any SAE, n (%)	**2 (40)**	**1 (33)**	**1 (33)**	**17 (44)**	**1 (33)**
Dyspnoea	0	1 (33)	1 (33)	1 (3)	0
Vomiting	0	0	0	2 (5) †	1 (33) †
Aspartate aminotransferase increased	0	0	0	1 (3)	1 (33) †
Back pain	0	0	0	2 (5)	0
Urinary tract infection	0	0	0	2 (5)	0
Abdominal pain	1 (20)	0	0	0	0
Abdominal pain upper	0	0	0	1 (3)	0
Alanine aminotransferase increased	0	0	0	0	1 (33) †
Angina pectoris	0	0	1 (33)	0	0
Anorexia	0	0	0	0	1 (33) †
Asthenia	0	0	0	1 (3)	0
Blood creatinine increased	0	0	0	1 (3) †	0
Cancer pain	1 (20)	0	0	0	0
Constipation	0	0	0	1 (3)	0
Death	0	0	0	1 (3)	0
Dehydration	0	0	0	1 (3)	0
Deep vein thrombosis	1 (20)	0	0	0	0
Disorientation	0	0	0	1 (3)	0
Faecal incontinence	0	0	0	1 (3)	0
Fall	0	0	0	1 (3)	0
Gastrointestinal haemorrhage	0	0	0	1 (3)	0
Haematemesis	0	0	0	1 (3)	0
Hyperbilirubinaemia	1 (20)	0	0	0	0
Hypercalcaemia	0	0	0	1 (3)	0
Hyponatraemia	0	0	0	1 (3) †	0
Infection	1 (20)	0	0	0	0
Muscular weakness	0	0	0	1 (3)	0
Musculoskeletal pain	0	0	0	1 (3)	0
Performance status decreased	0	0	0	1 (3)	0
Pulmonary embolism	0	0	0	1 (3)	0
Pyrexia	0	0	0	0	1 (33)
Rash morbilliform	0	0	0	1 (3)	0
Rectal haemorrhage	0	0	0	1 (3)	0
Renal failure acute	0	0	0	1 (3) †	0
Small intestinal obstruction	0	0	0	1 (3)	0
Vaginal haemorrhage	0	0	0	1 (3)	0
Varices oesophageal	0	0	0	1 (3)	0
Weight decreased	0	0	0	1 (3)	0

All patients who received at least 1 dose of OSI-906 (Safety analysis set). Follow-up events are excluded.

Note: adverse events are sorted by decreasing incidence overall for the twice-daily regimen by preferred term and then alphabetically for preferred terms with the same incidence overall.

† Serious adverse event considered by the investigator to be related to study drug in 1 patient.

Source: Table 12.6.1.3.2.2; Table 12.6.1.3.2.3; Table 12.6.1.3.8.3