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

SYNOPSIS

Title of Study: A Phase II Open-label Rollover Study for Subjects that have Participated in a Linsitinib Trial (7487-CL-0209)

Investigators/Coordinating Investigator: The coordinating investigator for this study is [redacted], MD, PhD.

Study Center(s): This multicenter study was conducted at 12 clinical study sites, 5 sites in the United States, 2 sites in Germany, and 1 site each in Brazil, Czech Republic, Poland, Singapore and Thailand. A second site in Thailand was initiated although no patient was enrolled.

Publication Based on the Study: No manuscripts have been published based on the results of this study.

Study Period:

Study Initiation Date (Date of First Enrollment): 16 Apr 2014

Study Completion Date (Date of Last Evaluation): 21 Dec 2016

Phase of Development: Phase 2

Objectives: The objective of this study was to provide access to continued treatment for patients who participated in other studies of linsitinib that the investigator felt may benefit from continued treatment.

Methodology: Study 7487-CL-0209 was a phase 2, open-label, rollover study. This study allowed rollover by adult patients with advanced solid tumors from 42 centers who participated in linsitinib studies for continuation of treatment after the linsitinib studies had ended with respect to their primary endpoints.

Patients continued at study entry at the dose of study drug that they were currently being administered on the parent protocol. The study was designed with several arms to accommodate patients receiving various combinations of linsitinib alone or in combination with other approved cancer treatments such as erlotinib or paclitaxel, erlotinib alone, or paclitaxel alone. Dosing modifications due to toxicity were in line with the dosing modification guidance of the parent protocol.

Patients were seen in the clinic on day 1 of every fourth treatment period (i.e., every 12 weeks).

Number of Patients (Planned, Enrolled and Analyzed): A total of 13 patients were enrolled in this study from 12 different clinical study sites.

Diagnosis and Main Criteria for Inclusion: The study population consisted of adult patients with advanced solid tumors that were currently participating in a linsitinib study that ended with respect to primary and secondary analyses. Key inclusion criteria included the requirement to use highly effective contraception

consisting of the use of 2 forms of birth control if of childbearing potential by both female and male patients and the spouse/partners of male patients. There were no exclusion criteria for enrollment in this rollover study.

Test Product, Dose and Mode of Administration, Batch Numbers: Investigational treatments administered in this study included linsitinib (150, 100 or 25 mg tables, po), erlotinib (150, 100 or 25 mg tablets, po) and paclitaxel (concentrate for reconstitution, iv infusion).

Five patients received linsitinib (2 in Arm A, 2 in Arm D and 1 in Arm H) and all 8 patients in Arm C received erlotinib. Dosing of paclitaxel was not recorded.

Treatment regimens in Arms A, C, D and H are described below:

- Arm A patients received 150 mg (bid) linsitinib
- Arm C patients received 150 mg (qd) erlotinib†
- Arm D: 150 mg (bid) linsitinib plus weekly paclitaxel
- Arm H: 150 mg (bid) linsitinib x 28 days (each cycle)

† 1 patient was incorrectly identified in the listings as coming from Arm C instead of Arm B based on IRT data used to assign treatment arms. Treatment in Arm B consisted of 150 mg (bid) linsitinib plus 150 mg (qd) erlotinib (from Study OSI-906-205).

Lot numbers for linsitinib administered in this study were: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted].

Duration of Treatment (or Duration of Study, if applicable): Approximately 32 months

Reference Product, Dose and Mode of Administration, Batch Numbers: Reference products (erlotinib and paclitaxel) are described above.

Criteria for Evaluation: Safety assessments included evaluation of the incidence of AEs (TEAEs, SAEs, deaths, TEAEs leading to discontinuation), laboratory testing (hematology biochemistry, coagulation and urinalysis), vital signs, electrocardiograms and physical examinations.

The primary endpoint of the study was the number of patients with AEs. AE collection began from time of informed consent and continued through the 28-day follow-up visit. AEs were documented at each clinic visit, but may have been collected at any time. A treatment-emergent adverse event (TEAE) was defined as an AE with an onset date on or after the administration of study drug or any ongoing AE on the date of first dose that worsened in severity after administration of the study drug. There were no secondary endpoints.

Statistical Methods: No sample size calculations were done for this rollover study. The sample size was based on the number of patients remaining in the parent linsitinib studies after the respective study termination.

The safety analysis set (SAF) included all patients who took at least 1 dose of study drug.

Data from safety assessments are provided in individual patient listings.

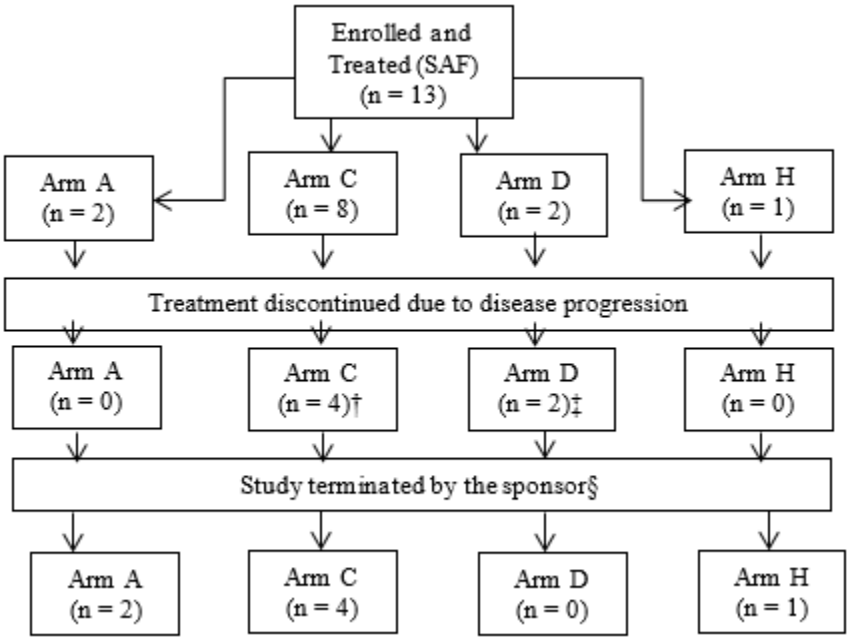
The coding dictionary used to summarize AEs by system organ class (SOC) and preferred term (PT) was MedDRA v16.1. Toxicity grade was defined according to NCI-CTCAE v4.03.

Summary of Results/Conclusions:

Population: Of the 13 patients enrolled in this study, there were 2 patients in Arm A, 8 in Arm C, 2 in Arm D and 1 in Arm H [Figure 1]. All 13 patients received study drug and were included in the SAF.

A subgroup of patients from 5 sponsor-initiated studies and several investigator–initiated studies were allowed, under this protocol, an additional 32 months of continued treatment until product expiration. The sponsor notified the clinical sites approximately 10 months prior to study termination that no further manufacturing was planned and alternative treatment should be secured for the patients remaining in the study who have not progressed or otherwise discontinued prior to study termination. All 13 patients had discontinued from the study due to progressive disease or were transitioned to therapy other than linsitinib.

Figure 1 Disposition of Patients



Arm A: 150 mg (bid) linsitinib (from Study OSI-906-301); Arm C: 150 mg (qd) erlotinib (from Studies OSI–906-205 or OSI-906-207); Arm D: 150 mg (bid) linsitinib plus weekly paclitaxel (from Study OSI–906–202); Arm H: 150 mg (bid) linsitinib x 28 days (each cycle) (from Study SARC-022-CTEP 8945); IRT: Interactive Response Technology; SAF: safety analysis set.

† 1 patient was incorrectly identified in the listings as coming from Arm C instead of Arm B based on the IRT data used to assign treatment arms. Treatment in Arm B consisted of 150 mg (bid) linsitinib plus 150 mg (qd) erlotinib (from Study OSI-906-205).

‡ 1 of these 2 patients discontinued the study on study day 62 due to disease progression, but had experienced an SAE of ileus on study day 49 and received a last dose of study drug on day 51.

§ These patients were transitioned to therapy other than linsitinib.

Source: Appendix 13.1.1, Protocol 7487-CL-0209, Sections 2.2.1 and 5.1.1; and Appendices 13.2.1.1 and 13.2.7.5

Of the 13 patients enrolled in this study, 11 (84.6%) patients were female and 2 (15.4%) patients were male. Eight (61.5%) patients were White (ethnicity for 1 of these 8 patients was Hispanic or Latino), 2 (15.4%) patients were Asian and 3 (23.1%) patients did not have race data collected. Patient ages ranged from 47 to 78 years. Patient weights ranged from 51.7 to 105.0 kg and patient heights ranged from 148 to 173 cm.

Efficacy Results: There were no formal efficacy endpoints, although patients were followed for continued clinical benefit as evaluated by the investigator and radiographic assessment.

Safety Results:

All 13 patients in the SAF experienced at least 1 AE during the rollover study, no patient died, 6 patients experienced an SAE and 1 patient discontinued the study due to a TEAE (ileus) [Table 1].

Table 1 Overall Summary of Safety During the Rollover Study

	Arm A (n = 2)	Arm C (n = 8)†	Arm D (n = 2)	Arm H (n = 1)
Any AE	2 (100%)	8 (100%)	2 (100%)	1 (100%)
Any TEAE	2 (100%)	6 (75.0%)	1 (50.0%)	1 (100%)
Deaths	0	0	0	0
Serious TEAEs	1 (50.0%)	3 (37.5%)	1 (50.0%)	1 (100%)
TEAEs Leading to Discontinuation	0	0	1 (50.0%)	0

All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF).

A TEAE was defined as an AE with an onset date on or after the administration of study drug or any ongoing AE that worsened in severity up to 30 days after administration of the last dose of study drug.

AE: adverse event; Arm A: 150 mg (bid) linsitinib (from Study OSI–906–301); Arm C: 150 mg (qd) erlotinib (from Studies OSI–906–205 or OSI–906–207); Arm D: 150 mg (bid) linsitinib plus weekly paclitaxel (from Study OSI–906–202); Arm H: 150 mg (bid) linsitinib x 28 days (each cycle) (from Study SARC–022–CTEP 8945); IRT: Interactive Response Technology; SAF: safety analysis set; TEAE: treatment−emergent adverse event.

† 1 patient was incorrectly identified in the listings as coming from Arm C instead of Arm B based on IRT data used to assign treatment arms. Treatment in Arm B consisted of 150 mg (bid) linsitinib plus 150 mg (qd) erlotinib (from Study OSI-906-205).

Source: Appendices 13.2.7.1, 13.2.7.3, 13.2.7.4 and 13.2.7.5

SAEs were experienced by 1 (50.0%) patient in Arm A, 3 (37.5%) patients in Arm C, 1 (50.0%) patient in Arm D and 1 (100%) patient in Arm H as described in [Table 2].

Table 2 List of SAEs by Patient

Treatment Group	MedDRA (v16.1) Preferred Term	Onset/ Stop Day (Last Dose Day)	NCI-CTCAE Grade	Outcome	Relationship to Linsitinib/ Erlotinib/ Paclitaxel
Arm A Linsitinib	Atrial fibrillation	-28/-26	3	Recovered	No/No/No
	Hypertensive crisis	735/736	3	Recovered	Yes/No/No
Arm C† Erlotinib	Transient ischaemic attack	169/174	2	Recovered	No/No/No
Arm C Erlotinib	Pneumonia	681/690	3	Recovered	No/No/No
Arm C Erlotinib	Viral infection	251/259	2	Recovered	No/No/No
Arm D Linsitinib/ paclitaxel	Vomiting	17/19	3	Recovered	No/No/No
	Ileus‡	49/62	4	Resolved with sequelae	No/No/No
Arm H Linsitinib	Cholecystitis acute	342/345	3	Recovered	No/No/No

All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF).

A TEAE was defined as an AE with an onset date on or after the administration of study drug or any ongoing AE that worsened in severity up to 30 days of the last dose of administration of the study drug.

Footnotes continued on next page

AE: adverse event; Arm A: 150 mg (bid) linsitinib (from Study OSI–906–301); Arm C: 150 mg (qd) erlotinib (from Studies OSI–906–205 or OSI–906–207); Arm D: 150 mg (bid) linsitinib plus weekly paclitaxel (from Study OSI–906–202); Arm H: 150 mg (bid) linsitinib x 28 days (each cycle) (from Study SARC–022–CTEP 8945); IRT: Interactive Response Technology; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for AE; SAF: safety analysis set.

† 1 patient was incorrectly identified in the listings as coming from Arm C instead of Arm B based on IRT data used to assign treatment arms. Treatment in Arm B consisted of 150 mg (bid) linsitinib plus 150 mg (qd) erlotinib (from Study OSI-906-205).

‡ This patient discontinued study drug (last dose day 51) due to this SAE and discontinued the study on day 62 due to disease progression.

Source: Appendix 13.2.7.4

One patient in Arm D (linsitinib/paclitaxel) of the study experienced an SAE of ileus (NCI–CTCAE grade 4) on study day 49, had a last dose of study drug on day 51 and discontinued the study on day 62 (due to disease progression). The patient received 150 mg (bid) linsitinib plus weekly paclitaxel. The SAE was not considered to be related to either linsitinib or paclitaxel. The patient recovered with sequelae.

Of the AEs considered to be associated with linsitinib treatment, at least 1 patient receiving linsitinib in this rollover study reported the following: [redacted]

There were 2 elevated glucose values reported in patients who received linsitinib during the rollover study and both returned to within normal limits at the next study visit. No AEs were reported for hyperglycemia.

One patient had an ALT on study day 652 of 120 U/L (< 3.5 times the upper limit of normal) that returned to within normal limits on day 680. The last dose of study drug for this patient was taken on study day 651. No AEs were reported for increased ALT or AST values.

Three patients had at least 1 serum creatinine level greater than the upper limit of normal (1 patient each in Arms A, C and D). No AEs were reported for increased serum creatine values.

A TEAE of hypertension was reported for 1 patient in Arm C (patient actually received linsitinib/erlotinib) on study day 169 that was not considered to be related to study drug. Study drug dose was not changed. This patient's blood pressure was 170/90 on study days 169 and 183. The patient discontinued the study due to disease progression on study day 183.

Five female patients receiving linsitinib had a QTcF interval > 430 ms and 3 of these patients had a QTcF interval > 450 ms. No patient had a QTcF interval > 469 ms. One patient in Arm A (150 mg bid linsitinib) had an AE of ECG QT prolonged (NCI–CTCAE grade 1) that started on study day −56 and resolved on day −29. The event was considered to be related to linsitinib treatment.

No patient had a positive pregnancy test during the study. The majority of female patients were at least 2 years postmenopausal or surgically sterile.

CONCLUSIONS: This study allowed continuation of study treatment from prior studies. No new safety signals for linsitinib were detected.

Date of Report: 10 Apr 2017