Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP8273 mesilate		

SYNOPSIS

Title of Study: A Phase 1, Randomized, 2-period Crossover Study to Assess Bioequivalence of a Tablet Formulation versus a Capsule Formulation of ASP8273 in Subjects With Non-small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Mutations (8273-CL-0112)

Investigators/Coordinating Investigator: [redacted]

Study Center(s): 2 clinical sites in the United States participated in this study.

Publication Based on the Study: None

Study Period:

Study Initiation Date (Date of First Evaluation): 21 Mar 2017

Study Completion Date (Date of Last Evaluation): 19 Jun 2017

Phase of Development: 1

Objectives: The primary objective was to evaluate the bioequivalence of a tablet formulation versus a capsule formulation of ASP8273 following a single 300-mg dose under fasted condition in patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations.

The secondary objective was to evaluate the safety and tolerability of a tablet formulation (300 mg dose as a single dose) and a capsule formulation (300 mg as a single dose and as multiple doses) of ASP8273 in patients with NSCLC harboring EGFR mutations.

Methodology: The study consisted of 2 phases: a pharmacokinetic phase and a postpharmacokinetic phase. The pharmacokinetic phase of the study followed a randomized, 2-period, 2-sequence single dose crossover design in patients with NSCLC harboring EGFR mutations. Screening was to take place up to 28 days prior to patient enrollment on period 1 day 1. Patients were randomized to either sequence 1 (ASP8273 tablet 300 mg on day 1 of period 1/ASP8273 capsule 300 mg on day 1 of period 2) or sequence 2 (ASP8273 capsule 300 mg on day 1 of period 1/ASP8273 tablet 300 mg on day 1 of period 2). Each period was 5 days in duration with the study drug dose being administered on day 1 of each period. Pharmacokinetic samples were to be drawn in each period at predefined time points. The postpharmacokinetic phase consisted of 1 cycle (28 days) of continuous once-daily dosing (300 mg) with ASP8273 capsules and began the following day after the last pharmacokinetic sample was collected in period 2.

In May 2017, during the conduct of Study 8273-CL-0112, the Independent Data Monitoring Committee for the phase 3 Study 8273-CL-0302 recommended discontinuing that study due to excess toxicity with limited predicted efficacy. Subsequently, the sponsor voluntarily closed study randomization and announced the

discontinuation of the ASP8273 treatment arm in Study 8273-CL-0302. In addition, the sponsor terminated the ASP8273 NSCLC program, including this study (8273-CL-0112). At the time of study termination, 3 patients were enrolled and had received study drug in Study 8273-CL-0112.

Number of Patients (Planned, Enrolled and Analyzed): A total of 18 patients were planned to be enrolled. A total of 3 patients were enrolled.

Diagnosis and Main Criteria for Inclusion: The study population consisted of adult patients with histologically confirmed diagnosis of locally advanced or unresectable Stage IIIB (not amenable to receive curative treatments such as chemoradiation)/IV or metastatic NSCLC with EGFR activating mutation based on local testing, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and predicted life expectancy ≥ 12 weeks. Key exclusion criteria included an ongoing toxicity ≥ Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.03) attributable to prior medication to treat solid tumor (except alopecia) at screening; receipt of investigational therapy within 28 days or 5 half-lives prior to the first dose of study drug; receipt of any other agent with antitumor activity including chemotherapy, radiotherapy, or immunotherapy within 14 days as well as EGFR tyrosine kinase inhibitor within 6 days prior to first dose of study drug; a major surgical procedure, blood transfusions or hemopoietic factor therapy or evidence of active infection requiring systemic therapy within 14 days prior to the first dose of study drug; symptomatic central nervous system metastasis; known history of positive test results for human immunodeficiency infection, hepatitis B surface antigen or hepatitis C antibody; and known history of serious hypersensitivity reaction to ASP8273, or any component of the formulation used.

Test Product, Dose and Mode of Administration, Batch Numbers: Pharmacokinetic phase: ASP8273 300 mg (three 100-mg tablets or three 100-mg capsules as specified by sequence group) was to be administered orally. Postpharmacokinetic phase: ASP8273 300 mg (three 100-mg capsules) was to be administered orally.

Batch numbers used in this study included the following: [redacted] (tablets), [redacted] / [redacted] (capsules)

Duration of Treatment (or Duration of Study, if applicable): In the pharmacokinetic phase, patients were to receive a single dose of ASP8273 (tablets or capsules) on day 1 of each of the two 5-day periods. In the postpharmacokinetic phase, patients were to receive once-daily dosing with ASP8273 capsules for 28 days.

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

Criteria for Evaluation:

Pharmacokinetic: Plasma concentrations of ASP8273

Safety: Safety assessments included evaluation of the incidence of adverse events (AEs) (treatment-emergent adverse events [TEAEs], serious TEAEs, deaths, TEAEs leading to discontinuation), laboratory testing (hematology, biochemistry, urinalysis and coagulation), vital signs, electrocardiograms (ECGs) and ECOG performance status.

Statistical Methods: The planned statistical analyses were not performed because the amount of data collected up until study termination was deemed insufficient for this purpose. Thus, no formal statistical analyses were made and only listings were produced.

The treatment periods were defined as follows:

- Period 1 of pharmacokinetic phase: from period 1 dosing until period 2 dosing minus 1 minute
- Period 2 of pharmacokinetic phase: from period 2 dosing until collection of last pharmacokinetic sample in period 2
- Postpharmacokinetic phase: from first dosing in the postpharmacokinetic phase until end of study

Baseline, in general, was defined as the last measurement taken prior to study drug administration, unless otherwise specified.

For demographic and other baseline characteristics (i.e., age, sex, race, ethnicity, weight, height and body mass index), data from the listing were summarized descriptively by treatment sequence for all randomized patients. For continuous variables, descriptive statistics included the number of patients (n), median, minimum and maximum. Percentages by categories were based on the number of patients with no missing data, i.e., added up to 100%.

Pharmacokinetics: The pharmacokinetic analysis set was to include all patients who took at least 1 dose of study drug and for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

Due to the study termination, pharmacokinetic samples from a limited number of patients were available. It was decided that analyzing these samples would yield insufficient data to draw any conclusions regarding the bioequivalence objective of this study. Therefore, the pharmacokinetic samples were not analyzed and thus no statistical output could be generated.

Safety: The safety analysis set was to include all patients who took at least 1 dose of study drug.

No formal statistical testing was performed on safety data.

All AEs were coded using MedDRA version 18.0 and presented in a listing.

During the pharmacokinetic phase, all AEs with onset at any time from dosing of period 1 until the minute before dosing of period 2 were classified as treatment emergent for period 1. All AEs with onset at any time from dosing of period 2 until the minute before dosing of postpharmacokinetic phase were classified as treatment emergent for period 2.

During the postpharmacokinetic phase, all AEs with onset at any time from first dosing in that phase until last scheduled procedure were classified as treatment-emergent for the postpharmacokinetic phase.

Laboratory data (hematology, biochemistry, urinalysis and coagulation), vital signs, ECG and ECOG data and results from screening assessments were displayed in listings. In addition, NCI-CTCAE grades for hematology and biochemistry applicable parameters were programmed and included in a listing. Results from unscheduled tests were to be displayed in listings.

Summary of Results/Conclusions:

Population: The sponsor terminated the study. At the time of study termination, a total of 5 patients had been screened, 3 of whom had been randomized to study drug [Table 1].

Patient [redacted] was randomly assigned to [redacted]. After

dosing on day 1 of period 1, this patient permanently discontinued study drug due to [redacted] and thus did not receive study drug in period 2. [redacted]

Patients [redacted] and [redacted] received treatment according to their random assignment to [redacted] and completed the pharmacokinetic phase. After the clinical database had been locked, dosing diary information was obtained that had inadvertently not been entered into the clinical database. According to this dosing diary information, Patient [redacted] entered the postpharmacokinetic phase and received [redacted] This patient permanently discontinued study drug due to the study termination [Table 1] and discontinued from the postpharmacokinetic phase.

Patient [redacted] was unable to enter the postpharmacokinetic phase due to the study termination.

All 3 patients were [redacted] [Table 2], 2 of whom were < 65 years of age.

The duration of NSCLC ranged from 63 to 1336 days since the date of the locally advanced or metastatic disease diagnosis. The 3 patients had either Stage IIIB or IV NSCLC with moderately differentiated histopathology or with histopathology showing adenocarcinoma.

The EGFR status of all 3 patients was tested by a local laboratory at enrollment. According to these tests, the patients were positive for 1 or more of the following EGFR mutations: exon 18 G719X, exon 19 deletion and exon 21 L858R.

Pharmacokinetic Results:

Due to the study termination, pharmacokinetic samples from a limited number of patients were available. It was decided that analyzing these samples would yield insufficient data to draw any conclusions regarding the bioequivalence objective of this study. Therefore, the pharmacokinetic samples were not analyzed and thus no statistical output could be generated.

Safety Results:

All 3 patients reported at least 1 TEAE after taking at least 1 dose of ASP8273 capsule 300 mg. Two of the 3 patients (Patients [redacted] and [redacted] reported TEAEs during period 1 of the pharmacokinetic phase, with Patient [redacted] experiencing study drug-related TEAEs [redacted] and Patient [redacted]

None of the laboratory test results were NCI-CTCAE Grade 3 or higher. The patients' postbaseline ECOG performance status remained unchanged from that at baseline.

CONCLUSIONS:

At the time of study termination, 3 patients were enrolled and had received study drug. All 3 patients reported TEAEs after taking at least 1 dose of ASP8273 capsule 300 mg. No new safety signals for ASP8273 were detected.

Date of Report: 01 Nov 2017

Table 1 Treatment Discontinuation and Primary Reason for Discontinuation

Category	Number of Patients	
	Pharmacokinetic Phase	Postpharmacokinetic Phase
Completed treatment		
Yes	2†	0
No	1	1
Primary reason for treatment discontinuation		
Adverse event	1	0
Study terminated by sponsor	0	1

† Patient [redacted] completed the pharmacokinetic phase but was unable to enter the postpharmacokinetic phase due to the study termination and thus did not receive study drug in the postpharmacokinetic phase.

Source: Appendix 13.2.1.2

Table 2 Demographic Characteristics

Parameter Category/Statistics	Number of Patients (n = 3)
Sex, n (%)	
Male	[redacted]
Female	
Race, n (%)	
White	[redacted]
Black or African American	
Ethnicity, n (%)	
Not Hispanic or Latino	[redacted]
Hispanic or Latino	
Age, years	
Median	58
Min - Max	54 - 75
Weight (kg)	
Median	71
Min - Max	51 - 73
Height (cm)	
Median	152
Min - Max	152 - 152
BMI (kg/m^2)	
Median	30.7
Min - Max	21.9 – 31.4

BMI: body mass index (weight [kg]/height [m^2]); Max: maximum; Min: minimum

Source: Appendix 13.2.4.1