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

SYNOPSIS

Title of Study: An open-label, study of the oral administration of ASP8273 in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor-naïve patients with non-small cell lung cancer harboring EGFR mutations

Investigators/Coordinating Investigator: [redacted]

Study Center(s): Eleven study sites in Japan participated in this study.

Publication Based on the Study: None

Study Period: Approximately 2.0 years.

Study Initiation Date (Date of First Enrollment): 25 Jun 2015

Study Completion Date (Date of Last Evaluation): 9 Jun 2017

Phase of Development: 2

Objectives: To determine the following in EGFR-tyrosine-kinase inhibitor (TKI)-naïve patients with non-small cell lung cancer (NSCLC) harboring EGFR activating mutations

Primary objective:

- To determine the safety of ASP8273

Secondary objectives:

- To determine the antitumor activity of ASP8273
- To determine the pharmacokinetics of ASP8273 Capsules and ASP8273 Capsules A

Methodology: This study aimed to evaluate the safety, efficacy and pharmacokinetics of ASP8273 administered as a single oral dose or multiple once daily oral doses of 300 mg (recommended phase 2 dose [RP2D] that was determined in phase 1 of the phase 1/2 study of ASP8273) in EGFR-TKI-naïve patients with NSCLC harboring EGFR activating mutations.

This study consisted of a single-dose period (cycle 0 lasting 3 days) and a multiple-dose period (from cycle 1 onwards, each cycle lasting 21 days). To compare the pharmacokinetics between ASP8273 Capsules and ASP8273 Capsules A, enrolled subjects received a single oral dose of ASP8273 Capsules A on day 1 of cycle 0 in the single-dose period and then were observed for 3 days (including the day of dosing).

In the multiple-dose period, subjects received multiple oral doses of ASP8273 Capsules during each cycle lasting 21 days.

Subjects continued to receive treatment with ASP8273 until they met the discontinuation criteria.

Number of Patients (Planned, Enrolled and Analyzed): Based on the pharmacokinetic data of ASP8273 Capsules obtained in Study 8273-CL-0101, the number of subjects necessary for pharmacokinetic comparison between ASP8273 Capsules and ASP8273 Capsules A (bioavailability [BA] evaluation), which was planned in this study, was determined to be a minimum of 14 subjects. Thirty-one (31) subjects were enrolled into the study. All 31 subjects enrolled into the study were included in the safety analysis set (SAF), full analysis set (FAS) and pharmacokinetic analysis set (PKAS).

Diagnosis and Main Criteria for Inclusion: Subjects were eligible for the study if they were ≥ 20 years of age at the time of obtaining informed consent; had Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1; had a histologically or cytologically confirmed diagnosis of Stage IIIB or IV NSCLC; were confirmed to have the deletion of exon 19 (del ex19), L858R, G719X or L861Q mutation among the EGFR activating mutations; for prior treatment for NSCLC, had not received previous treatment with EGFR-TKIs (erlotinib, gefitinib, afatinib and EGFR-TKIs under clinical investigation [e.g., neratinib, dacomitinib]. EGFR-TKIs that could inhibit EGFR with the T790M mutation [e.g., ASP8273, CO-1686, AZD9291] were also included.) and had not received more than 1 regimen of previous drug treatment (however, this did not include preoperative or postoperative therapies used within at least a 6-month interval after the last dose of the treatment); and had at least 1 measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Subjects were excluded from participation if they had persistent clinical evidence of previous antitumor treatment-related toxicity ≥ Grade 2 using the Japan Clinical Oncology Group (JCOG) Japanese translation of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (NCI-CTCAE v4.0 – JCOG) (except alopecia); had received previous treatment with intended antitumor effects or treatment with another investigational drug/medical device within 14 days before the start of the study treatment; had received strong cytochrome P450 (CYP) 3A inhibitors within 9 days prior to the start of the study treatment (for itraconazole, within 14 days prior to the start of the study treatment); had received moderate CYP3A inhibitors within 9 days prior to the start of the study treatment (only for subjects included in BA evaluation); or had received strong or moderate CYP3A inducers within 14 days prior to the start of the study treatment (only for subjects included in BA evaluation).

Test Product, Dose and Mode of Administration, Batch Numbers: ASP8273 Capsules A 100 mg (used only in the single-dose period) were hard hydroxypropyl methylcellulose (HPMC) capsules with a white to pale yellow cap and a white to pale-yellow body, containing 100 mg of ASP8273, lactose monohydrate and magnesium stearate per capsule. ASP8273 Capsules 100 mg were hard HPMC capsules with a white to pale yellow cap and a white to pale-yellow body, containing 100 mg of ASP8273 and lactose monohydrate per capsule; or, hard HPMC capsules with a yellow cap and an orange body, containing 100 mg of ASP8273, lactose monohydrate and magnesium stearate per capsule.

ASP8273 was orally administered at a dose of 300 mg once daily in the morning under fasting conditions. In principle, ASP8273 had to be administered once daily in the morning; however, if it was appropriate for subjects to take ASP8273 at other hours than in the morning based on the judgment of the principal investigator or subinvestigator, the subjects could take ASP8273 without limiting dosing to the morning hours from cycle 2 onwards. Subjects had to be fasting for at least 2 h before and 1 h after dosing, and were not allowed to take any other medications within 2 h before or after dosing with ASP8273, as much as possible.

In the single-dose period (cycle 0 lasting 3 days), subjects included in BA evaluation received a single oral dose of 3 capsules of ASP8273 Capsules 100 mg A (300 mg) on day 1 of cycle 0 and then were observed for 3 days (including the day of dosing).

In the multiple-dose period (from cycle 1 onwards, each cycle lasting 21 days), subjects included in BA evaluation received once daily oral doses of 3 capsules of ASP8273 Capsules 100 mg (300 mg) during each cycle lasting 21 days.

In subjects not included in BA evaluation, 3 capsules of ASP8273 Capsules 100 mg (300 mg) were administered as once daily oral doses during each cycle lasting 21 days.

Batch numbers used in this study included the following:

- ASP8273 Capsules A: [redacted]
- ASP8273 Capsules: [redacted]

Duration of Treatment (or Duration of Study, if applicable): The duration of study drug administration in this study ranged from 10 to 679 days.

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

Criteria for Evaluation:

Efficacy: The efficacy was assessed based on the overall response rate and disease control rate. To determine the antitumor activity of ASP8273 was secondary objective of this study. The principal investigator/subinvestigator assessed each tumor lesion (target and non-target lesions) and assessed the antitumor effects of ASP8273 on each subject using RECIST Version 1.1.

The best overall response was defined as the best response across all assessment time points. The overall response rate was defined as the proportion of subjects whose best overall response was rated as complete response (CR) or partial response (PR) among all analyzed subjects. To confirm the best overall response rated as stable disease (SD), the overall response rated as SD had to be maintained from the start of the study treatment through the week 6 assessment. The best overall response rated as CR or PR had to be confirmed by at least 2 consecutive assessments performed with a minimum interval of 4 weeks. Subjects therefore had to continue to meet the criteria for CR or PR for 4 weeks or longer. The antitumor effects were confirmed at each study site.

The disease control rate was defined as the proportion of subjects whose best overall response was rated as CR, PR or SD.

Duration of response (DOR) was defined as the time from the date of the first confirmed response CR/PR (whichever was first recorded) assessed according to RECIST 1.1 to the date of radiographical progression or date of censoring. If a subject had not progressed, the subject was censored at the date of last radiological assessment or at the date of first confirmed CR/PR if no subsequent radiological assessment was available. DOR was derived for subjects with best overall response as CR or PR (with confirmation).

Progression-free survival (PFS) was defined as the time from the start of the study treatment until death from any cause or radiographical disease progression assessed according to RECIST 1.1, whichever occurred first during study period.

Pharmacokinetic: One of the secondary objectives of this study was to determine the pharmacokinetics of ASP8273 Capsules and ASP8273 Capsules A. The plasma concentrations of unchanged ASP8273 were measured to evaluate the pharmacokinetics of ASP8273 Capsules and ASP8273 Capsules A.

Safety: The primary objective of this study was to determine the safety of ASP8273. The safety was assessed based on vital signs, adverse events (AEs), clinical laboratory tests, percutaneous oxygen saturation (SpO_2), body weight, 12-lead electrocardiogram (ECG), ophthalmologic examination, chest X-ray examination, chest computed tomography (CT) examination and ECOG performance status.

Other Measurements (EGFR Mutation Test): At the time of obtaining informed consent to participate in this study, additional separate consents were obtained from subjects to provide tumor tissue or blood samples. For EGFR mutation test using histological samples, either of the following tumor tissue samples were obtained from patients who have provided consent: tumor biopsy sample of the primary or metastatic lesions, or tumor tissue sample that had been collected and archived. For EGFR mutation test using blood samples, blood was collected from subjects who had given informed consent to provide a blood sample for the EGFR mutation test; to obtain at least 3 mL of plasma, an 8 mL blood sample were collected from the brachial vein. The obtained samples were retrieved by the facility in charge of sample retrieval and shipment, and analyzed for the EGFR mutations at the central EGFR gene testing laboratory.

Statistical Methods:

Efficacy: The FAS was defined as those subjects who met all of the following criteria: received at least 1 dose of ASP8273, had acceptable images for baseline tumor assessment, and evaluated for at least 1 efficacy endpoint after the start of the study treatment. Data were analyzed as described below for subjects in the FAS.

The overall response rate was calculated. Additionally, 95% confidence interval (CI) (Clopper-pearson) was presented.

The disease control rate was calculated. Additionally, 95% CI (Clopper-pearson) was presented.

The maximum shrinkage of sum of diameter from baseline in target lesion was plotted as a waterfall plot.

Median DOR and the associated 95% CI were analyzed using the method of Brookmeyer and Crowley with log-log transformation. Additionally, Kaplan-Meier plot of DOR was presented.

The median follow up time for PFS was estimated according to the Kaplan-Meier estimate of potential follow up also termed as “Reverse Kaplan-Meier”. The number of subjects who already experienced death or radiographic disease progression, the number of subjects still at risk and Kaplan-Meier estimate with 95% CI of PFS rate using Greenwood’s formula with log-log transformation were presented at given time points. Additionally, median PFS and the associated 95% CI were analyzed using the method of Brookmeyer and Crowley with log-log transformation. Kaplan-Meier plot of PFS was presented.

As other analyses, the number and percentage of patients with each overall response (i.e., CR, PR, progressive disease [PD] and SD) at each visit, the number and percentage of patients with CR or PR at each visit, the number and percentage of patients with CR or PR or SD at each visit, and the proportion of patients whose maximum shrinkage from baseline in target lesion was equal to or more than 30% (If there was no target lesion at baseline for Central Review, then these subjects were not included in the denominator.) were presented.

Pharmacokinetic: The PKAS was defined as those subjects who received at least 1 dose of ASP8273 and in whom drug concentration was measured at least 1 time point after the start of the study treatment. Using measured plasma concentrations of the unchanged drug in subjects included in the PKAS, the pharmacokinetic parameter values and summary statistics were calculated.

In cycles 0, 1, and 3, non-compartmental model analysis was performed on individual subject data of the plasma concentrations of unchanged ASP8273 to estimate the pharmacokinetic parameters listed below. The parameters were calculated using actual time data. The analysis in cycle 0 was based on the data of plasma concentrations of unchanged ASP8273 up to 48 h postdose (i.e., cycle 0 day 3).

Subjects included in BA evaluation (BA evaluation group)

- Cycle 0: AUC_{inf}, AUC_{last}, AUC_{24h}, AUC_{48h}, C_{max}, C_{24h}, CL/F, λ_z, MRT_{inf}, t_{max}, $t_{1/2}$, V_z/F
- Cycle 1 (day 1): AUC_{last}, AUC_{24h}, C_{max}, C_{24h}, CL/F, λ_z, t_{max}, t_{last}, $t_{1/2}$, V_z/F
- Cycle 1 (day 8, 15): C_{trough}
- Cycle 1 (day 21): AUC_{tau}, C_{max}, C_{24h}, CL/F, t_{max}, PTR, $R_{ac}(C_{max})$, $R_{ac}(AUC)$
- Cycle 3 (day 1): C_{trough}

Subjects not included in BA evaluation (Not BA evaluation group)

- Cycle 1 (day 15, 21): C_{trough}
- Cycle 3 (day 1): C_{trough}

For pharmacokinetic parameters calculated above, number of subjects, arithmetic mean, standard deviation (SD), coefficient of variation (CV[%]), median, minimum, and maximum were calculated. The geometric mean (GM) was also calculated for pharmacokinetic parameters excluding t_{max}, but the GM was not calculated for missing values or values reported as "zero (0)".

For confirmation of accumulation (only for subjects included in BA evaluation), the geometric mean ratio (GMR) of AUC_{tau} values on cycle 1 day 21 to those in cycle 1 day 1 and its 90% CI were calculated.

For comparison of formulations (only for subjects included in BA evaluation), the GMR of AUC_{24} (cycle 0 day 1) of ASP8273 Capsules A to AUC_{24} (cycle 1 day 1) of ASP8273 Capsules and the 90% CI, and the GMR of C_{max} (cycle 0 day 1) of ASP8273 Capsules A to C_{max} (cycle 1 day 1) of ASP8273 Capsules and the 90% CI were calculated.

Safety: The SAF was defined as all subjects who received at least 1 dose of ASP8273. Data were analyzed as described below for subjects in the SAF. The number and percentage of subjects with all AEs and study drug-related AEs were summarized, as classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Summary statistics were calculated and frequency was tabulated according to the data characteristics of the following parameters: laboratory values, bone turnover markers, vital signs, SpO_2, body weight, 12-lead ECG, ophthalmologic examination, chest X-ray examination, chest CT examination and ECOG performance status. Using NCI-CTCAE grade (V.4.03), AEs, including abnormal clinical laboratory values, were graded and sodium values were graded as hyponatraemia. The number and percentage of subjects with potentially clinically significant values in liver function tests during the investigational period were presented.

Subgroups of Interest: Some efficacy and safety variables were summarized for the subgroups defined on the basis of the categorized variables for sex (female, male), age (< 75, ≥ 75), del ex19 at local laboratory (only for

efficacy; yes, others), L858R at local laboratory (only for efficacy; yes, others), tobacco history (never used tobacco, current tobacco user, former tobacco user) and existence of brain metastasis at baseline (yes, no).

Other Analyses (EGFR Mutation Test): Using histological samples, the frequencies were tabulated for the status (presence or absence) of the following EGFR mutations: EGFR activating mutations (del ex19, L858R, L861Q, S768I, G719A, G719S, G719C, exon20 insertion mutation), EGFR-T790M mutation. Using blood samples, the frequencies were tabulated for the status (presence or absence) of the following EGFR mutations: EGFR-T790M mutation, EGFR activating mutations (del ex19, L858R).

Summary of Results/Conclusions:

Population: All 31 subjects who enrolled into the study received at least one dose of the study drug. The same number of subjects, 31, was included in the SAF, FAS and PKAS. These analysis sets consisted of 16 subjects in BA evaluation group and 15 subjects in Not BA evaluation group [Table 1].

Overall, 100.0% (31/31) of subjects discontinued treatment; the primary reason for discontinuation was PD (54.8%, 17/31) followed by study terminated by sponsor (25.8%, 8/31) [Table 2].

Overall, the majority of subjects in the study were female (61.3%, 19/31) and < 75 years of age (80.6%, 25/31). The ECOG performance status was grade 0 or 1. The BA evaluation group (16 subjects) had equal number of male and female subjects [Table 3].

Overall, the majority of subjects (77.4%, 24/31) were definitively diagnosed with NSCLC based on histological diagnosis. A total of 96.8% (30/31) of subjects had pathologic diagnosis of adenocarcinoma and 1 subject had pathologic diagnosis of squamous cell carcinoma. All but 1 subject had Stage IV NSCLC.

EGFR mutation status in the total population was found for the following: EGFR activating mutations for del ex19 (41.9%, 13 subjects), L858R (45.2%, 14 subjects), L861Q (6.5%, 2 subjects) and other type of EGFR activating mutation (16.1%, 5 subjects).

Among 12 subjects from whom informed consent for EGFR tissue sample collection was obtained, the central-tissue EGFR mutation test was performed in 11 subjects. EGFR mutation positive at baseline was reported for the following: T790M (18.2%, 2 subjects), del ex19 (18.2%, 2 subjects), L858R (63.6%, 7 subjects) and L861Q (9.1%, 1 subject). All 11 subjects showed EGFR mutation negative for G719X, S768I and insertion ex20. Among 20 subjects from whom informed consent for blood sample collection was obtained, the central-plasma EGFR mutation test was performed in 18 subjects. EGFR mutation positive at baseline was reported for the following: Del ex19 (11.1%, 2 subjects) and L858R (22.2%, 4 subjects). There were no subjects who were positive for EGFR T790M mutation.

When comparing between EGFR status based on local testing and that based on central-tissue testing among subjects in whom the central-tissue EGFR mutation test was performed, similar results were observed.

The median duration of exposure was 216.0 days for 300 mg and 335.0 days for all-doses (including dose decreased to 200 or 100 mg). Dose decrease from 300 mg was experienced by 25.8% (8/31) of subjects and drug interruption of 300 mg by 67.7% (21/31) of subjects. The mean compliant rate with study drug was 94.99%.

Efficacy/Pharmacokinetic Results:

Efficacy Results: Best overall response rate over the entire exposure period is presented in Table 4. Based on the best response across all assessment time points, CR was observed in 3.2% (1/31) of subjects, PR in 48.4% (15/31) of subjects, SD in 41.9% (13/31) of subjects and PD in 3.2% (1/31) of subjects. The overall response rate over the entire exposure period was 51.6% (16/31; 95% CI: 33.1, 69.8) and disease control rate was 93.5% (29/31; 95% CI: 78.6, 99.2).

Overall, 56.7% of subjects (17/30) had maximum shrinkage from baseline (≥ 30%) in target lesion.

The median DOR was 13.7 months (95% CI: 8.3, - [undetermined]).

The median duration of PFS was 11.3 months (95% CI: 7.2, 18.0).

The overall response rate at each visit was ≥ 40.7% until cycle 31 day 1. The disease control rate at each visit was ≥ 96.3% until cycle 9 day 1, ≥ 71.4 % until cycle 25 day 1, and ≥ 50.0% until cycle 31 day 1. The results showed a sustained antitumor activity of ASP8273.

Subgroup analyses were performed on efficacy outcomes for sex, age, tobacco history, del ex19 at local laboratory, L858R at local laboratory and existence of brain metastasis at baseline. The data showed that both the overall response rate and disease control rate were similar in male and female subjects: 50.0% (6/12) vs 52.6% (10/19), 91.7% (11/12) vs 94.7% (18/19), respectively. The data showed that the overall response rate was higher in subjects < 75 years than in those ≥ 75 years while disease control rate was similar regardless of subject's age < 75 or ≥ 75 years: 56.0% (14/25) vs 33.3% (2/6), 92.0% (23/25) vs 100% (6/6), respectively. The data showed that both the overall response rate and disease control rate were higher in subjects who never used tobacco and the current tobacco users than in the former tobacco users: 58.8% (10/17) and 66.7% (2/3) vs 36.4% (4/11), 100% (17/17) and 100% (3/3) vs 81.8% (9/11), respectively. The data showed that the overall response rate was higher in subjects without brain metastasis than in those with brain metastasis while the disease control rate was similar regardless of subjects with or without brain metastasis at baseline: 40.0% (4/10) vs 57.1% (12/21), 100% (10/10) vs 90.5% (19/21), respectively. The data showed that both the overall response rate and disease control rate were slightly higher in subjects without del ex19 based on local testing than in those with del ex19 based on local testing: 55.6% (10/18) vs 46.2% (6/13), 100% (18/18) vs 84.6% (11/13), respectively. The data showed that both the overall response rate and disease control rate were slightly higher in subjects with L858R based on local testing than in those without L858R based on local testing: 57.1% (8/14) vs 47.1% (8/17), 100% (14/14) vs 88.2% (15/17), respectively.

Pharmacokinetic Results: On cycle 0 day 1 to day 3 after a single dose of ASP8273 Capsules A at dosage of 300 mg, median AUC_{inf} was 12965.95 ng•h/mL, median C_{max} was 1285.01 ng/mL, median t_{max} was 3.97 hours and median $t_{1/2}$ was 10.99 hours. On cycle 1 day 1 after a single dose of ASP8273 Capsules at dosage of 300 mg, median AUC_{24h} was 13596.11 ng•h/mL, median C_{max} was 1522.08 ng/mL, median t_{max} was 2.93 hours and median $t_{1/2}$ was 8.22 hours. On cycle 1 day 21 after multiple doses of ASP8273 Capsules at dosage of 300 mg, median AUC_{tau} was 24881.67 ng•h/mL, median C_{max} was 1945.25 ng/mL and median t_{max} was 2.94 hours.

Steady state was achieved within 8 days by visual check of the figure and it is reasonable according to $t_{1/2}$. The increase at day 43 would be due to variability of pharmacokinetic concentration.

The GMRs (Capsule A on day 1 cycle 0 / Capsule on day 1 cycle 1) for AUC_{24h} and C_{max} were 96.46% (90% CI: 86.89, 107.09) and 100.98% (90% CI: 92.81, 109.88), respectively [Table 5]. The results demonstrated that the oral bioavailability of ASP8273 Capsule A is comparable to that of ASP8273 Capsule.

Safety Results:

All 31 subjects included in the SAF reported 1 or more treatment-emergent AEs (TEAEs). All 31 subjects reported 1 or more study drug-related TEAEs [Table 6].

The most common TEAEs occurring in ≥ 20% of subjects were diarrhoea (77.4%), peripheral sensory neuropathy (48.4%), nausea, hyponatraemia (38.7%, each), alanine aminotransferase increased, decreased appetite (32.3%, each), vomiting, dry skin (29.0%, each), dry mouth, upper respiratory tract infection, aspartate aminotransferase increased (25.8%, each), constipation, and cystitis (22.6%, each) [Table 7].

Maximum NCI-CTCAE grade 3 or higher TEAEs were experienced by 67.7% (21/31) of subjects. The most common (occurring in 2 or more subjects) maximum NCI-CTCAE grade 3 or higher TEAEs were hyponatraemia (29.0%), anaemia, alanine aminotransferase increased (9.7%, each), neutropenia, diarrhoea, pneumonia bacterial, and hypoalbuminaemia (6.5%, each). Four subjects (12.9%) experienced maximum NCI-CTCAE grade 4 TEAEs: pericardial effusion, sepsis, hyponatraemia, and metastases to meninges.

There were no deaths during the study.

Serious TEAEs were reported in 38.7% (12/31) of subjects. The most common (occurring in 2 or more subjects) serious TEAEs were pyrexia and pneumonia bacterial (6.5%, each) [Table 8]. The majority of serious TEAEs were considered by the investigator to be unrelated to study drug. Study drug-related serious TEAEs were reported in 9.7% (3/31) of subjects: hepatotoxicity, alanine aminotransferase increased, aspartate aminotransferase increased, and dehydration reported in 1 subject each.

TEAEs leading to permanent discontinuation of study drug were reported in 3.2% (1/31) of subjects. The TEAE leading to permanent discontinuation of study drug was peripheral sensory neuropathy (3.2%, 1/31).

TEAEs leading to dose reduction were reported in 22.6% (7/31) of subjects. The TEAE leading to dose reduction occurring in 2 or more subjects was only alanine aminotransferase increased (6.5%, 2/31).

TEAEs leading to drug interruption were reported in 58.1% (18/31) of subjects. The TEAE leading to drug interruption occurring in 2 or more subjects was pneumonia bacterial and alanine aminotransferase increased (6.5%, 2/31, each).

As potentially clinically significant values in liver enzymes, alkaline phosphatase > 1.5 x upper limit of normal (ULN) was reported in 9 subjects (29.0%); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN was reported in 22.6% (7/31) of subjects; ALT > 5 x ULN was reported in 3 subjects, and AST > 5 x ULN was reported in 1 subject; and ALT > 10 x ULN was reported in 1 subject. There was no subject with ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN.

Baseline ECOG performance status was grade 1 for 41.9% (13/31) of subjects. No ECOG performance status of grade 3 was reported during the study. ECOG performance status of grade 4 was reported in 3.4% (1/29) of subjects only at discontinuation.

Shifts from normal or abnormal (not clinically significant) ophthalmologic results (baseline) to abnormal (clinically significant) were observed in 5 subjects.

Shifts from normal ECG results (baseline) to abnormal (clinically significant) were observed in 2 subjects.

No notable change from baseline was observed over time in vital signs. There was no increase in the number of subjects with abnormal (clinically significant) postbaseline in chest X-ray and CT examinations.

CONCLUSIONS:

ASP8273 was well tolerated at dosage of 300 mg in this study. A sustained antitumor activity of ASP8273 was observed in EGFR tyrosine kinase inhibitor-naïve patients with NSCLC harboring EGFR Mutations. Pharmacokinetic results demonstrated the comparable bioavailability between two ASP8273 formulations.

Date of Report: 18 Apr 2018

Table 1 Analysis Sets (All Registered Subjects)

Analysis Set, n (%)	BA (N=16)	Not BA (N=15)	Total (N=31)
Drug taken	16 (100)	15 (100)	31 (100)
SAF †	16 (100)	15 (100)	31 (100)
FAS ‡	16 (100)	15 (100)	31 (100)
PKAS §	16 (100)	15 (100)	31 (100)

† Subjects who took at least 1 dose of ASP8273

‡ The FAS was defined as those subjects who met all of the following criteria:

Received at least 1 dose of ASP8273

Had acceptable images for baseline tumor assessment

Evaluated for at least 1 efficacy endpoint after the start of the study treatment

§ Subjects who received at least one dose of ASP8273 and in whom drug concentration was measured at least 1 time point after the start of the study treatment.

Source: Table 12.1.1.3

Table 2 Study Discontinuation (All Registered Subjects)

Parameter	Category, n (%)	BA (N=16)	Not BA (N=15)	Total (N=31)
Treatment Discontinuation	Yes	16 (100.0)	15 (100.0)	31 (100.0)
	No	0	0	0
Primary Reason for Discontinuation †	Progressive Disease	9 (56.3)	8 (53.3)	17 (54.8)
	Adverse Event	0	1 (6.7)	1 (3.2)
	Protocol Violation	0	0	0
	Lost to Follow-up	0	0	0
	Withdrawal by Subject	1 (6.3)	0	1 (3.2)
	Randomized/Registered but Never Received/Dispensed Study Drug	0	0	0
	Death	0	0	0
	Lack of Efficacy	1 (6.3)	0	1 (3.2)
	Study Terminated by Sponsor	3 (18.8)	5 (33.3)	8 (25.8)
	Pregnancy	0	0	0
	Other	2 (12.5)	1 (6.7)	3 (9.7)

† Only the primary reason for discontinuation was collected.

Source: Table 12.1.1.5

Table 3 Demographic and Other Baseline Characteristics (SAF)

Parameter	Category/ Statistic	BA (N=16)	Not BA (N=15)	Total (N=31)
Sex, n (%)	Male	8 (50.0)	4 (26.7)	12 (38.7)
	Female	8 (50.0)	11 (73.3)	19 (61.3)
Race, n (%)	Asian	16 (100)	15 (100)	31 (100)
Age (Years)	Mean	63.9	62.7	63.3
	SD	15.9	8.3	12.6
	Min	31	48	31
	Median	69.0	63.0	64.0
	Max	82	77	82
Age Group (Years) , n (%)	<75	12 (75.0)	13 (86.7)	25 (80.6)
	≥75	4 (25.0)	2 (13.3)	6 (19.4)
Weight (kg)	Mean	55.08	58.53	56.75
	SD	10.56	11.75	11.10
	Min	34.2	41.9	34.2
	Median	56.70	59.20	58.90
	Max	75.1	82.4	82.4
Height (cm)	Mean	159.18	158.70	158.95
	SD	9.38	10.00	9.52
	Min	145.0	141.9	141.9
	Median	160.35	157.40	158.90
	Max	173.4	178.0	178.0
ECOG Performance Status, n (%)	Grade 0	7 (43.8)	11 (73.3)	18 (58.1)
	Grade 1	9 (56.3)	4 (26.7)	13 (41.9)
	Grade 2	0	0	0
	Grade 3	0	0	0
	Grade 4	0	0	0
Tobacco History, n (%)	Never Used Tobacco	8 (50.0)	9 (60.0)	17 (54.8)
	Current Tobacco User	1 (6.3)	2 (13.3)	3 (9.7)
	Former Tobacco User	7 (43.8)	4 (26.7)	11 (35.5)
Any investigational agents or other drug treatment for underlying disease prior to first dose?, n (%)	No	11 (68.8)	14 (93.3)	25 (80.6)
	Yes	5 (31.3)	1 (6.7)	6 (19.4)
Any radiation therapy for underlying disease prior to first dose?, n (%)	No	9 (56.3)	13 (86.7)	22 (71.0)
	Yes	7 (43.8)	2 (13.3)	9 (29.0)
Any surgeries performed to treat underlying disease prior to first dose?, n (%)	No	11 (68.8)	7 (46.7)	18 (58.1)
	Yes	5 (31.3)	8 (53.3)	13 (41.9)

Source: Table 12.1.2.1.2

Table 4 Best Overall Response Rate Over the Entire Exposure Period (FAS)

Parameter		Total (N=31)
Best Overall Response ‡, n (%)	CR	1 (3.2)
	PR	15 (48.4)
	SD	13 (41.9)
	PD	1 (3.2)
	Not Evaluated	1 (3.2)
	Non-CR/Non-PD	0
	Total	31
Analysis ‡	Overall Response Rate (CR + PR), n (%)	16 (51.6)
	95% CI †	33.1%, 69.8%
	Disease Control Rate (CR + PR + SD), n (%)	29 (93.5)
	95% CI †	78.6%, 99.2%

CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.

† Based on exact binomial confidence interval (Clopper-Pearson).

‡ The denominator for percentage calculation was number of subjects who had best overall response.

Source: Table 12.3.1.1.1.1

Table 5 Comparison of Primary Pharmacokinetic Parameters of ASP8273 300 mg in BA Evaluation Group (C_{max} and AUC_{24h}) (PKAS)

Parameter	Comparison	Geometric LS Mean Ratio (%) †	90% CI of Ratio (%) †
AUC_{24h} (ng•h/mL)	Capsule A / Capsule	96.46	(86.89, 107.09)
C_{max} (ng/mL)	Capsule A / Capsule	100.98	(92.81, 109.88)

LS: least squares.

An analysis of variance was performed on natural log-transformed parameters with formulation as a factor.

† Estimate and CI are transformed back to the raw scale and are expressed as fraction.

Source: Table 12.4.4

Table 6 Overview of TEAEs (SAF)

n (%)	300 mg ‡ (N=31)
TEAEs	31 (100)
Drug-Related † TEAEs	31 (100)
TEAEs Leading to Deaths	0
Drug-Related † TEAEs Leading to Deaths	0
Serious TEAEs	12 (38.7)
Drug-Related † Serious TEAEs	3 (9.7)
TEAEs Leading to Permanent Discontinuation of Study Drug	1 (3.2)
Drug-Related † TEAEs Leading to Permanent Discontinuation of Study Drug	1 (3.2)
TEAEs Leading to Drug Interruption	18 (58.1)
Drug-Related † TEAEs Leading to Drug Interruption	13 (41.9)

A TEAE was defined as an AE observed after starting administration of the study drug.

TEAE: treatment-emergent adverse event.

† Possible or probable, as assessed by the investigator

‡ initial dose level

Source: Table 12.6.1.1.1

Table 7 Most Common (≥ 10%) TEAEs (SAF)

MedDRA v16.1 SOC PT, n (%)	**300 mg † (N=31)**
Overall	**31 (100)**
Blood and Lymphatic System Disorders	**9 (29.0)**
Anaemia	5 (16.1)
Gastrointestinal Disorders	**27 (87.1)**
Constipation	7 (22.6)
Diarrhoea	24 (77.4)
Dry mouth	8 (25.8)
Nausea	12 (38.7)
Stomatitis	6 (19.4)
Vomiting	9 (29.0)
General Disorders and Administration Site Conditions	**14 (45.2)**
Fatigue	4 (12.9)
Malaise	5 (16.1)
Pyrexia	5 (16.1)
Infections and Infestations	**23 (74.2)**
Cystitis	7 (22.6)
Upper respiratory tract infection	8 (25.8)
Investigations	**17 (54.8)**
Alanine aminotransferase increased	10 (32.3)
Aspartate aminotransferase increased	8 (25.8)
Blood creatinine increased	4 (12.9)
Platelet count decreased	4 (12.9)
Metabolism and Nutrition Disorders	**17 (54.8)**
Decreased appetite	10 (32.3)
Hyponatraemia	12 (38.7)
Nervous System Disorders	**22 (71.0)**
Dysgeusia	5 (16.1)
Peripheral sensory neuropathy	15 (48.4)
Skin and Subcutaneous Tissue Disorders	**16 (51.6)**
Dry skin	9 (29.0)
Rash	6 (19.4)

A TEAE was defined as an AE observed after starting administration of the study drug.

TEAE: treatment-emergent adverse event.

† initial dose level

Source: Table 12.6.1.2.9.1

Table 8 Serious TEAEs (SAF)

MedDRA v16.1 SOC PT, n (%)	**300 mg † (N=31)**
Overall	**12 (38.7)**
Cardiac Disorders	**2 (6.5)**
Cardiac failure	1 (3.2)
Pericardial effusion	1 (3.2)
Gastrointestinal Disorders	**1 (3.2)**
Enterocolitis	1 (3.2)
General Disorders and Administration Site Conditions	**2 (6.5)**
Pyrexia	2 (6.5)
Hepatobiliary Disorders	**1 (3.2)**
Hepatotoxicity	1 (3.2)
Infections and Infestations	**4 (12.9)**
Lung infection	1 (3.2)
Pneumonia bacterial	2 (6.5)
Sepsis	1 (3.2)
Urinary tract infection	1 (3.2)
Investigations	**1 (3.2)**
Alanine aminotransferase increased	1 (3.2)
Aspartate aminotransferase increased	1 (3.2)
Metabolism and Nutrition Disorders	**1 (3.2)**
Dehydration	1 (3.2)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**1 (3.2)**
Metastases to meninges	1 (3.2)
Skin and Subcutaneous Tissue Disorders	**1 (3.2)**
Excessive granulation tissue	1 (3.2)

A TEAE was defined as an AE observed after starting administration of the study drug.

TEAE: treatment-emergent adverse event.

† initial dose level

Source: Table 12.6.1.2.3.1