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| **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:** An open-label, phase 1 dose escalation study of oral ASP8273 in subjects with non-small-cell lung cancer (NSCLC) who have epidermal growth factor receptor (EGFR) mutations

**Investigators/Coordinating Investigator:** [redacted], MD; [redacted], MD

**Study Centers:** Ten clinical sites in the United States participated in this study.

**Publication Based on the Study:** Yu H, Spira A, Horn L, Weiss J, West H, Giaccone G, et al. A phase 1, dose-escalation study of oral ASP8273 in patients with non-small cell lung cancers with epidermal growth factor receptor mutations. Clin Cancer Res. 2017;23(24):7467-73. doi: 10.1158/1078-0432.CCR-17-1447.

**Study Period:**

**Study Initiation Date (Date of First Evaluation):** 09 Apr 2014

**Study Completion Date (Date of Last Evaluation):** 11 Feb 2019; data tabulations cut-off date of 28 Jul 2017

**Phase of Development:** 1

**Objectives:** The primary objectives of the study were to assess the safety and tolerability of ASP8273 and to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) based on dose limiting toxicities (DLTs) of ASP8273. The secondary objectives were to determine the pharmacokinetics of ASP8273 (and, if applicable, its metabolite[s]), evaluate the potential inhibition of CYP3A4 by ASP8273 by using midazolam as a probe substrate, evaluate the antitumor activity of ASP8273 and determine the effect of food on the bioavailability of ASP8273. [redacted]

In May 2017, the Independent Data Monitoring Committee (IDMC) recommended discontinuing the phase 3 Study 8273-CL-0302 due to excess toxicity with limited predicted efficacy. Subsequently, Astellas voluntarily closed study randomization and announced the discontinuation of the ASP8273 treatment arm in Study 8273-CL-0302. In addition, Astellas announced the plan to terminate future development programs for ASP8273 in NSCLC. No new patients are being enrolled in ASP8273 studies.

The data presented for Study 8273-CL-0102 are based upon the data tabulations cut-off date of 28 Jul 2017.

**Methodology:** This open-label study consisted of 2 parts: Part 1: dose escalation; Part 2: RP2D expansion (including evaluation of the potential inhibition of CYP3A by ASP8273 using midazolam as a substrate), food effect and Exon 20 cohorts.

*Part 1: Dose Escalation and Response Expansion Cohorts:* In Part 1, patients enrolled in the dose escalation cohort received their assigned single oral dose on cycle 0 day 1, followed by a 2-day observation period (dosing

day inclusive). Cycle 1 started on the third day. From cycle 1 onwards, patients received oral ASP8273 once daily in a 21-day cycle.

Each of the first 2 dose levels of the dose escalation cohort consisted of at least 1 patient. If a single patient cohort had an occurrence of a Grade 2 or higher study drug-related adverse event (AE) in cycle 0 or cycle 1, 2 more patients were to be enrolled at that dose level. At subsequent dose levels, each cohort consisted of at least 3 patients. Escalation increments of 100% (i.e., dose doubling) were to occur until 1 patient experienced a DLT or 2 patients at a given dose level experienced a Grade 2 or higher study drug-related AE in cycle 0 or cycle 1. Thereafter, the dose escalation increments were to be approximately 50% (rounded to the nearest capsule strength) of the previous dose. If it was necessary to de-escalate the dose level from the 25 mg starting dose, then the lower dose level cohort was to receive 15 mg.

Bayesian Continual Reassessment Method (CRM) was used to guide the dose escalation or de-escalation based on DLT incidence. Dose levels were escalated following the dose escalation parameters with input and approval from the Dose Escalation Committee until reaching the MTD. MTD was defined as the highest dose level at which the posterior mean DLT rate was < 33%. MTD may have been declared if the next CRM–recommended dose level already had at least 6 patients and showed overall acceptable safety. Dose escalation meetings were held with the sponsor and investigators after all patients in a dose escalation cohort completed cycle 1. Decision for escalation, expansion or de-escalation were made based on the posterior mean DLT rate calculated from Bayesian CRM model and all available safety and pharmacokinetic data.

As the dose escalation cohorts proceeded, additional patients may have been enrolled in response expansion cohorts in Part 1. In the response expansion cohorts, patients received oral ASP8273 once daily in a 21-day cycle. The initial dose response expansion cohort may have been opened if a complete response (CR)/partial response (PR) was observed at a given dose level and/or if pharmacokinetic data were in the efficacious range based on nonclinical models [redacted] provided it had been cleared and deemed tolerable by the Dose Escalation Committee (i.e., DLT mean posterior rate was < 33%). Once such a response expansion cohort was opened, each subsequent higher dose level (not exceeding the MTD) also enrolled a response expansion cohort once the dose level had been cleared and deemed tolerable by the Dose Escalation Committee. Dose escalation and response expansion rules were outlined in the study protocol.

*Part 2: RP2D Expansion Cohort (Including Drug-drug Interaction with Midazolam):* In the RP2D expansion cohort, patients were enrolled to assess preliminary efficacy and safety of ASP8273 and the effect of ASP8273 on the pharmacokinetics of a CYP3A4 substrate (midazolam). Patients in this cohort received oral ASP8273 once daily in a 21-day cycle and a single 2-mg oral dose of midazolam on cycle 1 day -1 and another single 2-mg oral dose of midazolam concurrently with ASP8273 on cycle 2 day 1.

*Food Effect Cohort:* In the food effect cohort, a single dose of the revised formulation of ASP8273 (300 mg) was to be administered to each patient on cycle 0 day 1 and cycle 0 day 4 under assigned food conditions. The 2 single doses were each followed by a 72-hour washout from ASP8273. Patients were randomized 1:1 to either Sequence I (single doses of ASP8273 RP2D dose under fasted conditions on cycle 0 day 1 and under fed conditions [high fat meal] on cycle 0 day 4) or Sequence II (single doses of ASP8273 RP2D dose under fed conditions [high fat meal] on cycle 0 day 1 and under fasted conditions on cycle 0 day 4) at enrollment. After completion of pharmacokinetic sampling following the second single dose, patients began dosing of the phase 1 formulation of ASP8273 once daily in a 21-day cycle starting on cycle 1 day 1.

*Exon 20 Cohort:* In the Exon 20 cohort, a single dose of the revised formulation of ASP8273 (300 mg) was to be received once daily in 21-day cycles until a withdraw criterion was met. In this cohort, patients were to be enrolled to assess preliminary antitumor activity and safety of ASP78273.

**Number of Patients (Planned, Enrolled and Analyzed):** The number of patients enrolled to the dose escalation part was dependent on the DLT incidence. The response expansion cohort would have enrolled up to 6 NSCLC patients who had both an EGFR activating mutation and the T790M resistant mutation. The RP2D expansion cohort was to consist of approximately 15 second-line patients who had both EGFR activating mutation and a T790M resistant mutation. The food effect cohort was to enroll approximately 12 evaluable second-line patients with both EGFR activating mutation and T790M resistance mutation. The Exon 20 cohort was to enroll approximately 20 patients. In the full analysis set (FAS; all patients who received at least 1 dose of study drug) and safety analysis set (SAF; all patients who took at least 1 dose of study medication), there were 130 patients consisting of 36 patients in the dose escalation cohort, 36 patients in the response expansion cohort, 19 patients in the RP2D cohort, 19 patients in the food effect cohort and 20 patients in the Exon 20 cohort.

**Diagnosis and Main Criteria for Inclusion:** Patients were eligible for inclusion in the study if they were ≥ 18 years old at the time of signing informed consent, agreed not to participate in another interventional study while on treatment, had Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and had histologically or cytologically confirmed metastatic or locally advanced, unresectable NSCLC.

Dose escalation patients must have had an EGFR activating mutation: Exon 18 G719X, Ex 19del, Exon 20 insertion, Exon 21 L858R, or Exon 21 L861Q on examination of an NSCLC tissue or cellular specimen and patients must have progressed on or were intolerant to prior treatment with any EGFR tyrosine kinase inhibitor (TKI) (e.g., erlotinib, gefitinib, afatinib, dacomitinib, neratinib).

Patients in the response expansion cohort, RP2D expansion cohort and food effect cohort must have progressed on or were intolerant to prior treatment with an EGFR TKI, had EGFR activating mutation (as described above) and T790M resistance mutation by local or central testing and a tumor sample obtained subsequent to EGFR TKI therapy was available for central testing and must have had at least 1 measureable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Patients were not eligible for enrollment if they had an ongoing toxicity ≥ Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.03) attributable to prior medication to treat NSCLC (except alopecia) at the time of screening, had received a prior EGFR inhibitor within 6 days prior to the first dose of study drug (e.g., erlotinib, gefitinib or afatinib), had received prior treatment with any other agent with antitumor activity, chemotherapy, radiotherapy or immunotherapy within 14 days prior to the first dose of study drug, or had received investigational therapy within 28 days or 5 half-lives, whichever was shorter, prior to the first dose of study drug.

Patients in the RP2D expansion cohort must not have had any contraindications to midazolam according to the prescribing information, taken any midazolam dose which was not specified in this protocol within 7 days of first dose or any medications or herbal supplements known to be CYP3A inhibitors (7 days) or inducer (12 days) prior to the first dose of midazolam.

Patients in the food effect cohort must not have taken any medications or herbal supplements known to be CYP3A or P-gp inhibitors within 7 days prior to the first dose of study drug or any medications or herbal supplements known to be CYP3A or P-gp inducers within 12 days prior to the first dose of study drug.

Patients in the Exon 20 cohort were to have an EGFR Exon 20 insertion mutation on examination of an NSCLC tissue or cellular specimen.

**Test Product, Dose and Mode of Administration, Batch Numbers:** ASP8273 mesilate was provided as oral capsules in 5, 25 and 100 mg strengths in bottles containing 30 capsules each. The starting dose level was 25 mg administered orally. In the dose escalation cohort, patients received their assigned single oral dose on cycle 0 day 1, followed by a 2-day observation period (dosing day inclusive). Cycle 1 started on the third day. In the dose escalation and the response expansion cohorts, patients received oral ASP8273 once daily in a 21-day cycle beginning on cycle 1 day 1. In the RP2D expansion cohort, patients received oral ASP8273 once daily in a 21-day cycle starting with cycle 1 day 1 and received a single 2-mg oral dose of midazolam on cycle 1 day -1 and another single 2-mg oral dose of midazolam concurrently with ASP8273 on cycle 2 day 1.

In the food effect cohort, a single dose of the revised formulation of ASP8273 was to be administered to each patient on cycle 0 day 1 and cycle 0 day 4 under assigned food conditions. The 2 single doses were each followed by a 72-hour washout from ASP8273. After completion of pharmacokinetic sampling following the second single dose, patients began dosing of the phase 1 formulation of ASP8273 once daily in a 21-day cycle starting on cycle 1 day 1.

In the Exon 20 cohort, a single dose of the revised formulation of ASP8273 (300 mg) was to be received once daily in 21-day cycles until a withdraw criterion was met.

Batch numbers used in this study included the following: 13075C (25 mg); CLR-9015615-003/14015C, CLR-9015615-004/14076B, CLR-9015615-005/14104C, CLR-9015615-006/15011C, CLR-9015615-007/15033A and CLR-9015615-008/15081D.

**Duration of Treatment (or Duration of Study, if applicable):** The duration of study drug administration in this study ranged from 1 to 840 days.

**Reference Product, Dose and Mode of Administration, Batch Numbers:** In the RP2D Expansion cohort, patients also received a single 2-mg oral dose of midazolam syrup on cycle 1 day -1 and another single 2-mg oral dose of midazolam syrup concurrently with ASP8273 on cycle 2 day 1 on an empty stomach defined as no food for at least 2 hours before and 1 hour after dosing.

**Criteria for Evaluation:**

*Efficacy:* Efficacy endpoints were part of the secondary objectives of the study and were evaluated using RECIST version 1.1. All analyses involving time point response were carried out based on investigator reported response. Response rates derived from time point response were considered primary and investigator reported response rates were considered supportive.

Efficacy outcomes were secondary endpoints of this study and included evaluation of target lesions:

- Overall response rate (ORR) with confirmation, defined as the proportion of patients with best overall response of CR or PR. Confirmation of CR or PR was required at the next scheduled assessment (not less than 4 weeks following the initial assessment at which CR or PR was observed).

- Disease control rate (DCR) with confirmation, defined as the proportion of patients with best overall response rate that was rated as CR, PR or stable disease (SD). For best overall response of SD, SD must have been documented as present at least once after study entry (cycle 3 day 1 assessment) and maintained for at least 6 weeks.
- Progression-free survival (PFS), defined as the time from the start of study treatment until death from any cause or radiographic disease progression, whichever occurred first. The algorithm for PFS is described in the Statistical Analysis Plan.

For evaluation of nontarget lesions: When the patient also had measurable disease, to achieve unequivocal progression on the basis of nontarget lesions, there must have been an overall level of substantial worsening in nontarget disease. This worsening must have been such that, even in the presence of SD or PR of target lesions, the overall tumor burden had increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more nontarget lesions was usually not sufficient to qualify for unequivocal progression.

As the dose escalation cohorts did not require measurable disease, some patients may have had only non-measurable lesions. In such patients, unequivocal progression was defined as a change in the non-measurable lesions sufficient to require a change in therapy. The categories of the evaluation of nontarget lesions are as follows: for CR of nontarget lesions, patients must have had disappearance of all nontarget lesions and all lymph nodes must have been non-pathological in size (< 10 mm short axis); non-CR/non-progressive disease (PD) of nontarget lesions was defined as persistence of 1 or more nontarget lesions; PD of nontarget lesions was defined as unequivocal progression of existing nontarget lesions or the appearance of 1 or more new lesions.

Best overall response was determined once all tumor response data for the patient was available. Patients were classified by best response on study as outlined in the protocol. ORR was defined as the proportion of patients whose best overall response was CR or PR. Confirmation of CR or PR was required at the next scheduled assessment (not less than 4 weeks following the initial assessment at which CR or PR was observed). For best overall response of SD, SD must have been documented as present at least once after study entry (cycle 3 day 1 assessment) and maintained for at least 6 weeks.

*Pharmacokinetics:* Pharmacokinetic endpoints were part of the secondary objectives of this study. Plasma pharmacokinetics of ASP8273, midazolam and 1-hydroxy midazolam, where applicable, were determined and included the following:

- Dose escalation, response expansion, food effect and Exon 20 insertion cohorts had standard plasma pharmacokinetic parameters of ASP8273 including but not limited to $C_{max}$, $t_{max}$, $AUC_{last}$, $AUC_{inf}$, $t_{1/2}$, CL/F and $V_z$/F estimated using noncompartmental analysis.
- RP2D expansion cohort had standard plasma pharmacokinetic parameters of midazolam, 1-hydroxy midazolam (metabolite) and ASP8273 including but not limited to $C_{max}$, $t_{max}$, $AUC_{last}$, $AUC_{inf}$, $t_{1/2}$, CL/F and $V_z$/F while each drug was given alone and in combination with each other estimated using noncompartmental analysis.

[redacted]

[redacted]

*Safety:* The primary endpoint of this study was evaluation of the safety and tolerability of ASP8273 and determination of the MTD, assessed by DLTs, incidence of AEs (including serious adverse events [SAEs] and AEs of possible hepatic origin), results from laboratory assessments (biochemistry, hematology, urinalysis, coagulation, lipid panel, and lymphocyte subpopulations) and findings from vital signs, electrocardiograms (ECGs), ECOG performance status and ophthalmologic examination.

**Statistical Methods:** For continuous variables, descriptive statistics included the number of patients (n), mean, standard deviation, median, minimum and maximum. Other percentiles were used as needed. In addition, for pharmacokinetic parameters, the coefficient of variation was calculated and, for $C_{max}$ and AUC, the geometric mean was also calculated. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data, i.e., will add up to 100%. Kaplan-Meier survival curves were displayed for time-to-event variables and median survival time were estimated with 2−sided 95% confidence interval (CI).

Summaries based on the FAS (e.g., disposition, baseline and efficacy data) were presented by planned dose level, unless specifically stated otherwise. Safety analysis and other summaries based on the SAF were presented by initial dose level received. Pharmacokinetic summaries based on the pharmacokinetic analysis set (PKAS) and [redacted] were presented by actual dose level received.

*Efficacy:* The FAS was the primary analysis set for efficacy analyses. Efficacy analysis of response variables was conducted on the FAS for the following: response variables (DCR and ORR) analyzed using exact binomial test (the response rate along with exact 95% CI using Clopper-Perason was calculated for each treatment arm); Kaplan-Meier survival plots were used to describe the PFS and estimate median PFS and 95% CI for these variables, with PFS rates provided for every 2 months for the 300-mg dose level and all patients; duration of response (DOR) was described using Kaplan-Meier plots with median and 95% CI estimated from the Kaplan-Meier curve.

DOR was defined as the time from the date of the first response (CR or PR, whichever is first recorded) to the date of radiographical progression or date of censoring. If a patient had not progressed, the patient was censored at the date of the last radiographical assessment. To apply the cut-off date to DOR was to exclude from the analysis tumor assessments after the cut-off date. DOR (days) was calculated as:

(Date of documented progression or censoring) – (Date of first response for CR or PR) + 1

Select efficacy endpoints were summarized for subgroups defined on the basis of the categorized variables for age (< 65 years, ≥ 65 years), sex (female, male) and T790M mutation status (positive, negative, unknown and missing, if applicable).

*Pharmacokinetics:* The PKAS consisted of the subset of the safety population for which sufficient plasma concentration data was available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known. Plasma concentrations and pharmacokinetic parameters for ASP8273, midazolam and 1-hydroxy midazolam, where applicable, were summarized by study day in each dose within each cohort using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV). Concentration-time profiles were plotted as appropriate.

In the RP2D cohort, to determine the effect of ASP8273 on the pharmacokinetics of midazolam and 1−hydroxy midazolam (metabolite), the natural log transformed pharmacokinetics parameters $AUC_{last}$, $AUC_{inf}$ and $C_{max}$ of midazolam and 1-hydroxy midazolam were analyzed using mixed-effect model with treatment as the fixed effect and patient as the random effect. For each of the pharmacokinetics parameters, a 90% CI was constructed for the geometric mean ratio (GMR) of midazolam plus ASP8273 (cycle 2 day 1) versus midazolam alone (cycle 1 day -1), estimated from antinatural log transformation from the above mixed-effects model. A similar analysis was conducted to determine the effect of midazolam on the pharmacokinetics of ASP8273.

In the food effect cohort, to determine the effect of food on the bioavailability of ASP8273, the natural log transformed pharmacokinetics parameters $AUC_{72}$, $AUC_{inf}$ and $C_{max}$ of ASP8273 were analyzed using mixed-effect model with sequence and fed/fasted as factors. Patients nested within sequence were considered as the random effect. For each of the pharmacokinetic parameters, a 90% CI was constructed for the GMR of fed condition versus fasted condition, estimated from antinatural log transformation from the mixed-effects model.

Besides visual inspection of plots of pharmacokinetics parameters versus dose, dose proportionality was evaluated using power models as described in the statistical analysis plan.

[redacted]

*Safety:* The SAF was used for the summaries of demographic and baseline characteristics and all safety and tolerability related variables. Clinical safety data (including DLTs, treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, ECGs, and Fridericia-corrected QT interval [QTcF]) were summarized using descriptive statistics (n, mean, SD, minimum, median and maximum) or frequency distributions, as appropriate, for each cohort and dose level at each treatment visit and time point, including change from baseline. In addition TEAEs and laboratory results were graded using NCI-CTCAE v4.03, where possible and were summarized by number and percentage of patients for each visit. Shift tables of NCI-CTCAE grade change from baseline to worst postbaseline grade were also presented for both local and central laboratory data. Baseline NCI-CTCAE grade was the last nonmissing grade before the first dose. Tables for potentially clinically significant values were summarized for liver function tests and vital signs using predefined criteria for each parameter. Shift tables were also generated for changes from a normal interpretation at baseline to an abnormal interpretation obtained during treatment for each patient, cohort and dose level for ECG findings, and ophthalmologic examination as well as for changes in ECOG performance status grade.

**Summary of Results/Conclusions:**

**Population:** A total of 133 patients allocated to study drug treatment were enrolled in 1 of the cohorts. Three patients who enrolled into the study did not receive study drug. A total of 130 patients were included in the SAF and FAS, while there were 128 patients in the PKAS [redacted] [Table 1].

**Table 1 Patient Disposition by Dose Level (All Registered Patients)**

| Analysis Set n (%) | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 13) | 200 mg (n = 12) | 300 mg (n = 85) | 400 mg (n = 13) | 500 mg (n = 7) |
|---|---|---|---|---|---|---|---|
| SAF† | 1 (100) | 2 (100) | 12 (92.3) | 12 (100) | 83 (97.6) | 13 (100) | 7 (100) |
| FAS† | 1 (100) | 2 (100) | 12 (92.3) | 12 (100) | 83 (97.6) | 13 (100) | 7 (100) |
| PPS‡ | 1 (100) | 2 (100) | 10 (76.9) | 8 (66.7) | 59 (69.4) | 8 (61.5) | 4 (57.1) |
| PKAS§ | 1 (100) | 2 (100) | 12 (92.3) | 12 (100) | 81 (95.3) | 13 (100) | 7 (100) |
| [redacted] | | | | | | | |

[redacted]; FAS: full analysis set; PKAS: pharmacokinetic analysis set; PPS: per protocol set; SAF: safety analysis set.

† All patients who received at least 1 dose of study drug.

‡ All patients in the FAS who did not meet criteria for exclusion from the PPS. In addition, patients in the PPS were required to have both baseline imaging scan and at least 1 postbaseline imaging scan.

§ All patients from the SAF for whom sufficient plasma concentration data were available to facilitate derivation of at least one pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

[redacted].

Source: Table 12.1.1.2.

Overall, 98.5% (128/130) of patients in the Full Analysis Set discontinued treatment [Table 2].

**Table 2 Treatment Discontinuation and Primary Reason for Discontinuation (FAS)**

| n (%) | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 12) | 200 mg (n = 12) | 300 mg (n = 83) | 400 mg (n = 13) | 500 mg (n = 7) | Total (n = 130) |
|---|---|---|---|---|---|---|---|---|
| Discontinued Treatment | 1 (100) | 2 (100) | 12 (100) | 12 (100) | 81 (97.6) | 13 (100) | 7 (100) | 128 (98.5) |
| Primary Reason | | | | | | | | |
| AE | 0 | 0 | 1 (8.3) | 1 (8.3) | 9 (10.8) | 3 (23.1) | 2 (28.6) | 16 (12.3) |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| LOE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| LTF | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PD | 0 | 2 (100) | 11 (91.7) | 11 (91.7) | 64 (77.1) | 9 (69.2) | 4 (57.1) | 101 (77.7) |
| Protocol Violation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Withdrawal by Patient | 1 (100) | 0 | 0 | 0 | 3 (3.6) | 0 | 1 (14.3) | 5 (3.8) |
| Study Terminated by Sponsor | 0 | 0 | 0 | 0 | 4 (4.8) | 1 (7.7) | 0 | 5 (3.8) |
| Other | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 0 | 1 (0.8) |

All patients who received at least 1 dose of study drug (FAS).

AE: adverse event; FAS: full analysis set; LOE: lack of efficacy; LTF: lost to follow-up; PD: progressive disease.

Source: Table 12.1.1.3.

The majority of patients in the study were female (72.3%, 94/130), White (71.5%, 93/130) and < 65 years of age (53.1%, 69/130) Table 3. Similarly, in the 300-mg dose group, the majority of patients were female (73.5%, 61/83), White (72.3%, 60/83) and < 65 years of age (53.0%, 44/83).

Overall, the median duration of NSCLC was 665.0 days at baseline, with a median of 501.5 days since the date of the locally advanced or metastatic disease diagnosis. A total of 94.6% (123/130) of patients had Stage IV NSCLC and 96.2% (125/130) of patients had histopathology showing adenocarcinoma.

Based on local EGFR status testing at baseline, positive EGFR status in the total population, except for the Exon 20 cohort, was found for the following: Exon 18 G719x (3.6%, 4 patients), Exon 19 deletion (56.4%, 62 patients), Exon 20 insertion (1.8%, 2 patients), Exon 21 L858R (25.5%, 28 patients) and T790M resistant mutation (80.0%, 88 patients).

Prior therapies for NSCLC, which included known and investigational anticancer agents either alone or in combination, were received by 98.5% (128/130) patients overall. For all but 12 patients, the prior therapy regimen included an EGFR TKI. The most common prior therapy for NSCLC was erlotinib, received by 78.5% of patients (102/130). Other therapies include afatinib, dacomitinib, gelfitinib, Paraplatin (carboplatin) + Taxol (paclitaxel), Gemzar (gemcitabine) + Platinol (cisplatin), Tarceva (erlotinib) + Avastin (bevacizumab), Tarceva (erlotinib) + Avastin (bevacizumab) + Alimta (pemetrexed), Alimta (pemetrexed) + Platinol (cisplatin), Alimta (pemetrexed) + Paraplatin (carboplatin) and other prior regimens for NSCLC including known and investigational anticancer agents administered as single agents or in combination with other agents.

A total of 14 (10.8%) patients received prior nonmedication therapy such as a chest tube for pneumothorax. A total of 40 (30.8%) patients received concomitant nonmedication therapy such as surgery for cataracts and whole brain radiation for brain metastases.

Overall, a median of 6 treatment cycles were completed with a median dose of 300 mg and a median duration of 127 days. Dose decreases were experienced by 16.0% of patients (21/130) and dose interruptions by 45% of patients (59/130). A mean of 96.55% of patients were considered compliant with study drug, 86.0% of patients (112/130) were > 80% compliant.

**Table 3 Demographic and Baseline Characteristics (SAF)**

| Parameter Category/ Statistics | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 12) | 200 mg (n = 12) | 300 mg (n = 83) | 400 mg (n = 13) | 500 mg (n = 7) | Total (n = 130) |
|---|---|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | | | |
| Male | 0 | 1 (50.0) | 4 (33.3) | 1 (8.3) | 22 (26.5) | 6 (46.2) | 2 (28.6) | 36 (27.7) |
| Female | 1 (100) | 1 (50.0) | 8 (66.7) | 11 (91.7) | 61 (73.5) | 7 (53.8) | 5 (71.4) | 94 (72.3) |
| Race, n (%) | | | | | | | | |
| White | 0 | 0 | 9 (75.0) | 8 (66.7) | 60 (72.3) | 12 (92.3) | 4 (57.1) | 93 (71.5) |
| Black or African American | 0 | 0 | 1 (8.3) | 1 (8.3) | 8 (9.6) | 1 (7.7) | 0 | 11 (8.5) |
| Asian | 1 (100) | 2 (100) | 2 (16.7) | 2 (16.7) | 12 (14.5) | 0 | 2 (28.6) | 21 (16.2) |
| Other | 0 | 0 | 0 | 1 (8.3) | 3 (3.6) | 0 | 1 (14.3) | 5 (3.8) |
| Ethnicity, n (%) | | | | | | | | |
| Hispanic or Latino | 0 | 0 | 0 | 1 (8.3) | 2 (2.4) | 0 | 1 (14.3) | 4 (3.1) |
| Not Hispanic or Latino | 1 (100) | 2 (100) | 12 (100) | 11 (91.7) | 80 (96.4) | 13 (100) | 6 (85.7) | 125 (96.2) |
| Missing | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 0 | 1 (0.8) |
| Age, years | | | | | | | | |
| Mean (SD) | 82 | 66 (15.6) | 69.2 (11.0) | 55.9 (11.2) | 62.4 (9.6) | 63.5 (5.2) | 62.0 (8.5) | 62.7 (9.9) |
| Median | 82 | 66 | 68 | 60 | 64.0 | 65.0 | 64.0 | 64.0 |
| Min - Max | 82-82 | 55-77 | 50-85 | 38-71 | 42-81 | 55-71 | 47-72 | 38-85 |
| Age Group, years, n (%) | | | | | | | | |
| < 65 | 0 | 1 (50.0) | 4 (33.3) | 9 (75.0) | 44 (53.0) | 6 (46.2) | 5 (71.4) | 69 (53.1) |
| ≥ 65 | 1 (100) | 1 (50.0) | 8 (66.7) | 3 (25.0) | 39 (47.0) | 7 (53.8) | 2 (28.6) | 61 (46.9) |
| Weight (kg) | | | | | | | | |
| Mean (SD) | 55.5 | 48.5 (16.1) | 61.7 (8.0) | 62.0 (11.0) | 71.2 (17.9) | 68.6 (14.2) | 73.0 (18.5) | 68.8 (16.6) |
| Median | 55.5 | 48.5 | 60.3 | 60.3 | 68.6 | 65.7 | 67.0 | 66.6 |
| Min - Max | 56-56 | 37-60 | 53-80 | 44-81 | 42-136 | 48-94 | 48-102 | 37-136 |
| Height (cm) | | | | | | | | |
| Mean (SD) | 162.6 | 156.7 (9.4) | 162.6 (6.8) | 161.8 (7.3) | 165.8 (8.8) | 170.4 (9.4) | 166.4 (8.4) | 165.5 (8.7) |
| Median | 162.6 | 156.7 | 162.5 | 161.1 | 165.0 | 172.7 | 165.1 | 165.0 |
| Min - Max | 163-163 | 150-163 | 153-175 | 150-172 | 147-190 | 152-185 | 155-176 | 147-190 |
| BMI ($kg/m^2$) | | | | | | | | |
| Mean (SD) | 21.0 | 19.5 (4.2) | 23.3 (2.4) | 23.8 (4.9) | 25.8 (5.5) | 23.6 (4.4) | 26.4 (6.8) | 25.0 (5.2) |
| Median | 21.0 | 19.5 | 22.5 | 23.2 | 25.2 | 23.4 | 24.6 | 24.1 |
| Min - Max | 21-21 | 17-23 | 19-27 | 18-35 | 17-49 | 17-32 | 19-38 | 17-49 |

All enrolled patients who received study drug (SAF).

BMI: body mass index (weight [kg]/height [$m^2$]); Max: maximum; Min: minimum; SAF: safety analysis set.

Source: Table 12.1.2.1.1.

**Efficacy/Pharmacokinetic/[redacted] Results:**

*Efficacy Results:* The ORR for derived ASP8273 response assessments with confirmation in all patients regardless of mutation and dose was 27.7% (36/130; 95% CI: 20.2%, 36.2%) and DCR was 55.4% (72/130; 95% CI: 46.4%, 64.1%) for derived ASP8273 response assessments with confirmation [Table 4].

**Table 4 Derived Response Assessment with Confirmation (FAS)**

| | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 12) | 200 mg (n = 12) | 300 mg (n = 63) | 400 mg (n = 13) | 500 mg† (n = 7) | Exon 20 (n = 20) | Total (n = 130) |
|---|---|---|---|---|---|---|---|---|---|
| Best Overall Response, n (%) | | | | | | | | | |
| CR‡ | 0 | 0 | 0 | 0 | 1 (1.6) | 0 | 0 | 0 | 1 (0.8) |
| PR‡ | 0 | 0 | 4 (33.3) | 3 (25.0) | 21 (33.3) | 4 (30.8) | 2 (28.6) | 1 (5.0) | 35 (26.9) |
| SD§ | 0 | 0 | 4 (33.3) | 7 (58.3) | 17 (27.0) | 2 (15.4) | 1 (14.3) | 5 (25.0) | 36 (27.7) |
| PD | 0 | 2 (100) | 2 (16.7) | 2 (16.7) | 17 (27.0) | 5 (38.5) | 1 (14.3) | 12 (60.0) | 41 (31.5) |
| NE | 1 (100) | 0 | 2 (16.7) | 0 | 2 (3,2) | 1 (7.7) | 2 (28.6) | 0 | 8 (6.2) |
| ND | 0 | 0 | 0 | 0 | 5 (7.9) | 1 (7.7) | 1 (14.3) | 2 (10.0) | 9 (6.9) |
| ORR (CR + PR) | | | | | | | | | |
| n (%) | 0 | 0 | 4 (33.3) | 3 (25.0) | 22 (34.9) | 4 (30.8) | 2 (28.6) | 1 (5.0) | 36 (27.7) |
| 95% CI (%)¶ | (0, 97.5) | (0, 84.2) | (9.9, 65.1) | (5.5, 57.2) | (23.3, 48.0) | (9.1, 61.4) | (3.7, 71.0) | (0.1, 24.9) | (20.2, 36.2) |
| DCR (CR + PR + SD at Week 12) | | | | | | | | | |
| n (%) | 0 | 0 | 8 (66.7) | 10 (83.3) | 39 (61.9) | 6 (46.2) | 3 (42.9) | 6 (30.0) | 72 (55.4) |
| 95% CI (%)¶ | (0, 97.5) | (0, 84.2) | (34.9, 90.1) | (51.6, 97.9) | (48.8, 73.9) | (19.2, 74.9) | (9.9, 81.6) | (11.9, 54.3) | (46.4, 64.1) |

All enrolled patients who received the study drug (FAS).

CI: confidence interval; CR: complete response; DCR: disease control rate; FAS: full analysis set; ND: not done; NE: not evaluable; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease.

† In the 500-mg dose group, 2 patients had dose decreases and 7 patients discontinued the study (2 due to AEs, 4 due to PD and 1 patient withdrew consent).

‡ Confirmation of CR or PR was required not less than 4 weeks following the initial assessment at which CR or PR was observed. For SD, SD must have been documented as present at least once after study entry (cycle 3 day 1 assessment) and maintained for at least 6 weeks.

§ Durable SD at week 12

¶ Exact 95% CI was estimated using the binomial distribution.

Source: Tables 12.3.1.1.1.

Overall, in patients with T790M positive mutation at study entry, ORR was 35.2% (31/88) (95% CI: 25.3%, 46.1%) and DCR was 64.8% (57/88; 95% CI: 53.9%, 74.7%) based on local testing. For patients who were positive for T790M mutation at study entry in the ASP8273 300-mg dose group, ORR was 36.2% (21/58; 95% CI: 24.0%, 49.9%) and DCR was 63.8% (37/58; 95% CI: 50.1%, 76.0%) based on local testing. The 1 patient in the 300-mg dose cohort who was T790M negative at study entry did not achieve a response. At the time of the data tabulations cut-off, there were 9 (6.9%) patients who did not have postbaseline imaging assessments. [redacted]

Patients in the Exon 20 cohort were enrolled based on local results indicating the presence of the Exon 20 insertions. These results were not centrally confirmed. [redacted]

Derived DOR with confirmation ranged from 1.4 to 26.5 months in the total population and in the ASP8273 300-mg dose group. Median DOR in the ASP8273 300-mg dose group was 8.6 months.

The median duration of PFS was 5.6 months (95% CI: 4.0, 6.9) for combined ASP8273 doses and cohorts (n = 130) and 6.8 months (95% CI: 4.1, 8.5) for the ASP8273 300-mg dose level (n = 63). In all dose cohorts, 45.3% of patients were progression free at 6 months and 24.2% of patients were progression free at 12 months. In the ASP8273 300-mg dose group, 53.8% of patients were progression free at 6 months and 27.6% of patients were progression free at 12 months.

In the ASP8273 300-mg dose group, the median duration of PFS for patients who were T790M mutation positive at study entry was 7.0 months (95% CI: 5.3, 8.5) based on local testing (n = 58). At 6 months, 55.0% of patients in the ASP8273 300-mg dose group who were T790M mutation positive at study entry were progression free based on local testing.

Subgroup analyses were conducted on efficacy outcomes for age categories (< 65 and ≥ 65 years) and sex (female, male). In patients < 65 years of age (n = 32) in the ASP8273 300-mg dose group, ORR was 34.4% (95% CI: 18.6%, 53.2%) and DCR at week 12 was 62.5% (95% CI: 43.7%, 78.9%). In patients ≥ 65 years (n = 31) in the ASP8273 300-mg dose group, ORR was 35.5% (95% CI: 19.2%, 54.6%) and DCR at week 12 was 61.3% (95% CI: 42.2%, 78.2%). In female patients (n = 47) in the ASP8273 300-mg dose group, ORR was 42.6% (95% CI: 28.3%, 57.8%) and DCR at week 12 was 61.7% (95% CI: 46.4%, 75.5%). In male patients (n = 16) in the ASP8273 300-mg dose group, ORR was 12.5% (95% CI: 1.6%, 38.3%) and DCR at week 12 was 62.5% (95% CI: 35.4%, 84.8%).

In patients < 65 years of age (n = 32) in the ASP8273 300-mg dose group, the median duration of PFS was 6.8 months (95% CI: 3.0, 9.8). In patients ≥ 65 years of age (n = 31) in the ASP8273 300-mg dose group, the median duration of PFS was 7.0 months (95% CI: 3.2, 10.0). In female patients (n = 47) in the ASP8273 300-mg dose group, the median duration of PFS was 7.2 months (95% CI: 4.1, 10.0). In male patients (n = 16) in the ASP8273 300-mg dose group, the median duration of PFS was 5.6 months (95% CI: 1.7, 8.8).

*Pharmacokinetic Results:* For the dose escalation cohort (dose levels 25 mg to 500 mg), the median plasma $AUC_{inf}$, $C_{max}$ and $t_{max}$ values after single-dose ASP8273 on cycle 0 day 1 ranged from 4380 to 40400 h·ng/mL, 589 to 2710 ng/mL and 1 to 3 hours, respectively. The terminal elimination half-life in the 25-mg through 500-mg dose groups ranged from 6 hours to 14 hours. The median plasma $AUC_{24}$, $C_{max}$ and $t_{max}$ values at steady state (cycle 2 day 1) ranged from 6210 to 39400 h·ng/mL, 623 to 2390 ng/mL and 1 to 4 hours, respectively.

For the response expansion cohort, median $AUC_{24}$, $C_{max}$ and $t_{max}$ values for dose levels from ASP8273 100 mg to 400 mg on cycle 1 day 1 ranged from 3970 to 17500 h·ng/mL, 605 to 1750 ng/mL and 2 to 3 hours, respectively, and on cycle 2 day 1 ranged from 6880 to 28600 h·ng/mL, 597 to 2110 ng/mL and from 2 to 4 hours, respectively.

Coadministration of ASP8273 (300 mg once daily) with a single 2-mg dose of midazolam resulted in a decrease in midazolam and 1–hydroxy midazolam systemic exposure compared with midazolam alone [Table 5]. Midazolam $AUC_{last}$ decreased approximately 24% (geometric least squares mean [GLSM] ratio: 76%; 90% CI: 60%, 96%), $AUC_{inf}$ decreased approximately 18% (GLSM ratio: 82%; 90% CI: 65%, 103%) and $C_{max}$ decreased 31% (GLSM ratio: 69%; 90% CI: 57%, 84%) compared with midazolam alone. The 1–hydroxy midazolam $AUC_{last}$ decreased approximately 44% (GLSM ratio: 56%; 90% CI: 48%, 67%), $AUC_{inf}$ decreased

approximately 40% (GLSM ratio: 60%; 90% CI: 51%, 69%) and $C_{max}$ decreased approximately 47% (GLSM ratio: 53%; 90% CI: 40%, 69%) compared with midazolam alone.

**Table 5 Statistical Assessment of the Effect of ASP8273 (300 mg) on the Pharmacokinetics of Midazolam (2 mg) and 1-Hydroxy Midazolam, RP2D Expansion Cohort (PKAS)**

| | Parameter | n/n | GLSM Ratio (%) † | 90% CI of Ratio (%) † |
|---|---|---|---|---|
| Midazolam ‡ | $AUC_{last}$ (h·ng/mL) | 13/13 | 75.76 | (59.83, 95.94) |
| | $AUC_{inf}$ (h·ng/mL) | 13/13 | 81.52 | (64.62, 102.83) |
| | $C_{max}$ (ng/mL) | 13/13 | 69.00 | (56.71, 83.94) |
| 1-hydroxy midazolam § | $AUC_{last}$ (h·ng/mL) | 13/13 | 56.36 | (47.75, 66.52) |
| | $AUC_{inf}$ (h·ng/mL) | 13/13 | 59.70 | (51.38, 69.38) |
| | $C_{max}$ (ng/mL) | 13/13 | 52.68 | (40.28, 68.89) |

A subset of the Safety Analysis Set population for which sufficient plasma concentration data was available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known (PKAS).

CI: confidence interval; GLSM: geometric least squares mean; PKAS: pharmacokinetic analysis set; SAF: safety analysis set.

† The difference of GLSMs of log-transformed pharmacokinetic parameters between Midazolam + ASP8273 and Midazolam alone and its 90% CI are back-transformed to the raw scale and are expressed as percents.

‡ Patients with midazolam pharmacokinetic parameters for both midazolam + ASP8273 and midazolam alone are included in the analysis.

§ Patients with 1-hydroxy midazolam pharmacokinetic parameters for both midazolam + ASP8273 and midazolam alone are included in the analysis.

Source: Tables 12.4.4.1 and 12.4.4.2.

Concomitant administration with midazolam resulted in no change in the systemic exposure of ASP8273 (Table 6). The GLSM ratios of $AUC_{24}$ was 104 (90% CI: 96%, 113%) and $C_{max}$ was 102 (90% CI: 94%, 111%), respectively.

**Table 6 Statistical Assessment of the Effect of Midazolam (2 mg) on the Pharmacokinetics of ASP8273 (300 mg), RP2D Expansion Cohort (PKAS)**

| Parameter | n/n | GLSM Ratio (%) † | 90% CI of Ratio (%) † |
|---|---|---|---|
| $AUC_{24}$ (h·ng/mL) | 12/12 | 104.20 | (96.21, 112.86) |
| $C_{max}$ (ng/mL) | 12/12 | 102.24 | (94.27, 110.89) |

A subset of the Safety Analysis Set population for which sufficient plasma concentration data was available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known (PKAS).

Patients with ASP8273 pharmacokinetic parameters for both midazolam + ASP8273 and ASP8273 alone are included in the analysis

CI: confidence interval; GLSM: geometric least squares mean; PKAS: pharmacokinetic analysis set; SAF: safety analysis set.

† The difference of GLSMs of log-transformed pharmacokinetic parameters between Midazolam + ASP8273 and ASP8273 alone and its 90% CI are back-transformed to the raw scale and are expressed as percentages.

Source: Table 12.4.4.3.

The statistical assessment of food effect on the pharmacokinetics of ASP8273 300 mg provided GLSM ratios of 99% (90% CI: 86%, 114%) for $AUC_{72}$, 100% (87%, 115%) for $AUC_{inf}$ and 94% (81%, 109%) for $C_{max}$, indicating no effect of a high-fat meal on ASP8273 bioavailability (Table 7). The median $t_{max}$ under fed conditions (4 hours; range: 1 to 6 hours) occurred approximately 2 hours later than the median $t_{max}$ under fasted conditions (2 hours; range: 1 to 6 hours).

**Table 7 Statistical Assessment of Food Effect on the Oral Bioavailability of ASP8273 (300 mg), Food Effect Cohort (PKAS)**

| Parameter | n (Fed) / n (Fasted) † | GLSM Ratio (%) ‡ | 90% CI of Ratio (%) ‡ |
|---|---|---|---|
| $AUC_{72}$ (h·ng/mL) | 17/17 | 99.38 | (86.27, 114.49) |
| $AUC_{inf}$ (h·ng/mL) | 17/17 | 100.18 | (87.10, 115.23) |
| $C_{max}$ (ng/mL) | 17/17 | 93.83 | (80.80, 108.97) |

A subset of the Safety Analysis Set population for which sufficient plasma concentration data was available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known (PKAS).

CI: confidence interval; GLSM: geometric least squares mean; PKAS: pharmacokinetic analysis set; SAF: safety analysis set.

† Patients with ASP8273 pharmacokinetic parameters for both food conditions (fasted and fed) are included in the analysis.

‡ The difference of GLSMs of log-transformed pharmacokinetic parameters is obtained from the Mixed Effect Model using fasted status and sequence as factors and patient nested within sequence as random effect. The difference was exponentiated back to normal scale as in percentage.

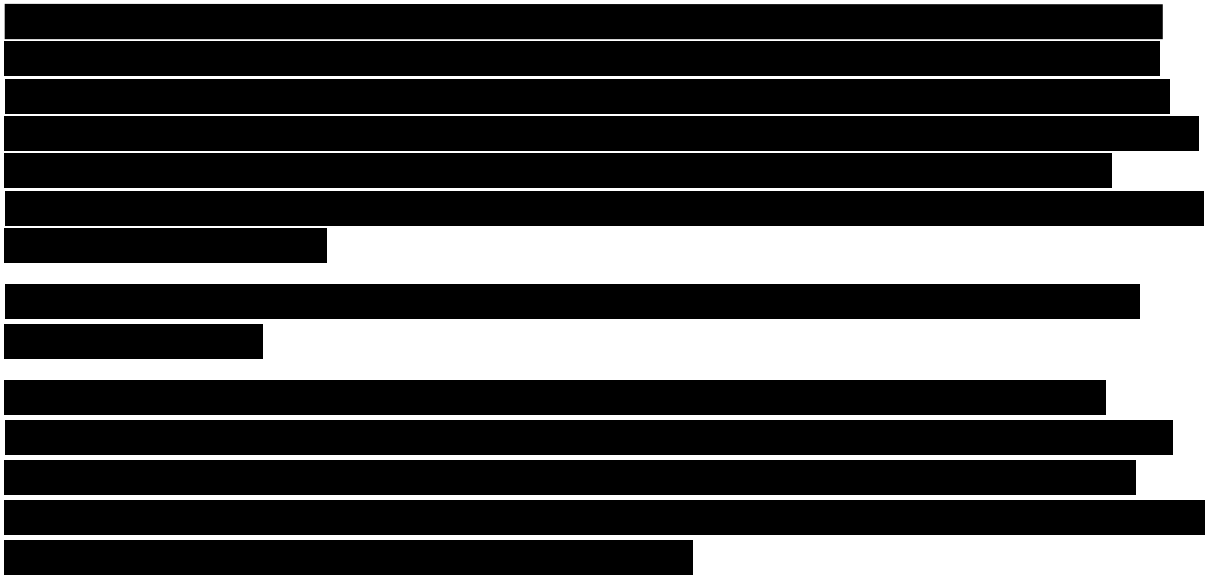
Source: Table 12.4.4.4.

For the Exon 20 cohort, median $AUC_{24}$, $AUC_{last}$, $C_{max}$, $t_{max}$ and $t_{last}$ values for the 300-mg dose level were 29000 h•ng/mL, 23900 h•ng /mL, 2360 ng/mL, 2.00 h, and 23.76 h, respectively, on cycle 2 day 1.

Dose proportionality was assessed for the 100- through 500-mg dose groups in the dose escalation and response expansion cohorts using power models. The 90% CI of the slope estimates for pharmacokinetic parameters after single dose ($AUC_{inf}$ and $AUC_{24}$) and multiple dose ($C_{max}$ and $AUC_{24}$) were within the prespecified limits of (0.569, 1.431). The 90% CI of the slope estimate for $C_{max}$ after single-dose ASP8273 was slightly outside of the prespecified limits. Overall, these results indicate that ASP8273 exposure is dose proportional in the dose range of 100 mg through 500 mg.

The accumulation indexes, based on the ratio of $AUC_{24}$ on cycle 2 day 1 to cycle 0 day 1 in the dose escalation cohort or on cycle 2 day 1 to cycle 1 day 1 in the response expansion cohort, do not show consistent accumulation with increasing doses of ASP8273.

Time to steady-state of ASP8273 plasma concentrations was assessed by comparing trough concentrations on cycle 1 day 8, cycle 1 day 15, cycle 2 day 1 and cycle 3 day 1. After once-daily dosing, steady-state ASP8723 was achieved by cycle 1 day 8 based on similar trough concentrations from cycle 1 day 8 through cycle 3 day 1 for all patients receiving ASP8273 300 mg.



**Safety Results:**

*DLTs:* A total of 4 of 110 patients experienced a DLT during the study including 1 patient (1.6%) in the 300-mg dose group and 3 patients (23.1%) in the 400-mg dose group [Table 8].

**Table 8 Description of DLTs (SAF)**

| ASP8273 Initial/Onset Dose Levels | DLT PT/ Reported Term | Onset/ End Day | Last Dose Day | Serious ?/ NCI-CTCAE Grade | Relationship to Study Drug |
|---|---|---|---|---|---|
| 300 mg/300 mg | Hyponatraemia/hyponatremia | 15/20 | 14 | No/ Grade 3 | Possible |
| 400 mg/400 mg | Appetite decreased/worsening anorexia | 9/14 | 257 | No/ Grade 3 | Possible |
| 400 mg/400 mg | Diarrhoea/diarrhea | 9/9 | 17 | No/ Grade 3 | Probable |
| 400 mg/400 mg | Hyponatraemia/hyponatremia | 16/28 | 29 | No/ Grade 3 | Possible |

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

DLT: dose limiting toxicity; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; SAF: safety analysis set.

Source: Appendices 13.2.7.1 and 13.2.7.6.

*TEAEs:* Overall, 96.9% (126/130) of patients in the SAF reported at least one TEAE including 95.2% (79/83) of patients in the 300-mg dose group and 100% of patients in all of the remaining dose groups [Table 9].

**Table 9 Overview of TEAEs**

| | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 12) | 200 mg (n = 12) | 300 mg (n = 83) | 400 mg (n = 13) | 500 mg (n = 7) | Total (N = 130) |
|---|---|---|---|---|---|---|---|---|
| TEAEs | 1 (100) | 2 (100) | 12 (100) | 12 (100) | 79 (95.2) | 13 (100) | 7 (100) | 126 (96.9) |
| Drug-related† TEAEs | 0 | 1 (50.0) | 10 (83.3) | 10 (83.3) | 71 (85.5) | 12 (92.3) | 7 (100) | 111 (85.4) |
| Deaths | 0 | 0 | 1 (8.3) | 3 (25.0) | 9 (10.8) | 1 (7.7) | 0 | 14 (10.8) § |
| Serious TEAEs‡ | 1 (100) | 0 | 4 (33.3) | 6 (50.0) | 37 (44.6) | 6 (46.2) | 3 (42.9) | 57 (43.8) |
| Drug-related† Serious TEAEs‡ | 0 | 0 | 1 (8.3) | 1 (8.3) | 7 (8.4) | 3 (23.1) | 2 (28.6) | 14 ( 10.8) |
| TEAEs Leading to Permanent Discontinuation of Study Drug | 0 | 0 | 2 (16.7) | 4 (33.3) | 17 (20.5) | 3 (23.1) | 3 (42.9) | 29 (22.3) |
| Drug-related† TEAEs Leading to Permanent Discontinuation of Study Drug | 0 | 0 | 0 | 1 (8.3) | 9 (10.8) | 2 (15.4) | 2 (28.6) | 14 (10.8) |
| TEAEs Leading to Dose Reduction | 0 | 0 | 1 (8.3) | 0 | 8 (9.6) | 6 (46.2) | 2 (28.6) | 17 (13.1) |
| Drug-related† TEAEs Leading to Dose Reduction | 0 | 0 | 1 (8.3) | 0 | 8 (9.6) | 5 (38.5) | 2 (28.6) | 16 (12.3) |
| Grade 3 or Higher TEAEs | 1 (100) | 0 | 8 (66.7) | 6 (50.0) | 50 (60.2) | 9 (69.2) | 6 (85.7) | 80 (61.5) |

All patients who received at least 1 dose of study drug (SAF).

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

TEAEs are counted based on the patient's assigned initial assigned dose.

AE: adverse event; SAE: serious adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

† Possible or probable, as assessed by the investigator, or records where relationship was missing.

‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms.

*Footnotes continued on next page*

§ Two patients (1 each in the 300-mg and 400-mg dose groups) died more than 28 days after the last dose of study drug and are not counted here.

Source: Table 12.6.1.2.

The most common TEAEs occurring in ≥ 10% of patients in the ASP8273 300-mg dose group were diarrhea (51.8%), nausea (34.9%), fatigue (26.5%), constipation (25.3%), cough (22.9%), dizziness (22.9%), vomiting (21.7%), decreased appetite (20.5%), hyponatremia (20.5%), blood creatine phosphokinase increased (19.3%), dyspnea (19.3%), headache (19.3%), urinary tract infection (19.3%), paresthesia (18.1%), dry mouth (16.9%), alanine aminotransferase increased (15.7%), anemia (15.7%), peripheral sensory neuropathy (15.7%), aspartate aminotransferase increased (13.3%), muscular weakness (12.0%), back pain (10.8%), gastroesophageal reflux disease (10.8%), muscle spasms (10.8%), oedema peripheral (10.8%), platelet count decreased (10.8%) and vision blurred (10.8%) [Table 10].

**Table 10 Most Common (≥ 10% in Any Dose Level) TEAEs by Dose Group and Total (SAF)**

| MedDRA v16.1 SOC PT, n (%) | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 12) | 200 mg (n = 12) | 300 mg (n = 83) | 400 mg (n = 13) | 500 mg (n = 7) | Total (n = 130) |
|---|---|---|---|---|---|---|---|---|
| **All Systems** | | | | | | | | |
| Any TEAE | 1 (100) | 2 (100) | 12 (100) | 12 (100) | 79 (95.2) | 13 (100) | 7 (100) | 126 (96.9) |
| **Blood and Lymphatic System Disorders** | | | | | | | | |
| Anaemia | 1 (100) | 0 | 2 (16.7) | 2 (16.7) | 13 (15.7) | 1 (7.7) | 0 | 19 (14.6) |
| Thrombocytopenia | 0 | 0 | 0 | 0 | 6 (7.2) | 0 | 2 (28.6) | 8 (6.2) |
| **Cardiac Disorders** | | | | | | | | |
| Atrial fibrillation | 0 | 1 (50.0) | 0 | 0 | 4 (4.8) | 0 | 0 | 5 (3.8) |
| **Eye Disorders** | | | | | | | | |
| Vision blurred | 0 | 0 | 1 (8.3) | 0 | 9 (10.8) | 2 (15.4) | 1 (14.3) | 13 (10.0) |
| Dry eye | 0 | 0 | 2 (16.7) | 0 | 8 (9.6) | 0 | 1 (14.3) | 11 (8.5) |
| Cataract | 0 | 0 | 0 | 1 (8.3) | 3 (3.6) | 0 | 1 (14.3) | 5 (3.8) |
| Visual impairment | 0 | 1 (50.0) | 0 | 0 | 2 (2.4) | 0 | 0 | 3 (2.3) |
| Diabetic retinopathy | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Ocular hypertension | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| **Gastrointestinal Disorders** | | | | | | | | |
| Diarrhoea | 0 | 1 (50.0) | 2 (16.7) | 3 (25.0) | 43 (51.8) | 8 (61.5) | 6 (85.7) | 63 (48.5) |
| Nausea | 0 | 1 (50.0) | 3 (25.0) | 7 (58.3) | 29 (34.9) | 7 (53.8) | 4 (57.1) | 51 (39.2) |
| Constipation | 0 | 1 (50.0) | 2 (16.7) | 4 (33.3) | 21 (25.3) | 6 (46.2) | 4 (57.1) | 38 (29.2) |
| Vomiting | 0 | 1 (50.0) | 1 (8.3) | 3 (25.0) | 18 (21.7) | 4 (30.8) | 2 (28.6) | 29 (22.3) |
| Dry mouth | 0 | 0 | 0 | 2 (16.7) | 14 (16.9) | 4 (30.8) | 3 (42.9) | 23 (17.7) |
| Abdominal pain | 0 | 0 | 1 (8.3) | 0 | 7 (8.4) | 2 (15.4) | 1 (14.3) | 11 (8.5) |
| Gastrooesophageal reflux disease | 0 | 0 | 1 (8.3) | 0 | 9 (10.8) | 1 (7.7) | 0 | 11 (8.5) |
| Abdominal distension | 0 | 0 | 0 | 0 | 1 (1.2) | 1 (7.7) | 1 (14.3) | 3 (2.3) |
| Retching | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| **General Disorders and Administration Site Conditions** | | | | | | | | |
| Fatigue | 0 | 0 | 5 (41.7) | 3 (25.0) | 22 (26.5) | 10 (76.9) | 4 (57.1) | 44 (33.8) |
| Oedema peripheral | 1 (100) | 0 | 2 (16.7) | 3 (25.0) | 9 (10.8) | 1 (7.7) | 1 (14.3) | 17 (13.1) |
| Pain | 1 (100) | 0 | 1 (8.3) | 1 (8.3) | 2 (2.4) | 1 (7.7) | 0 | 6 (4.6) |
| Pyrexia | 0 | 0 | 0 | 0 | 3 (3.6) | 2 (15.4) | 0 | 5 (3.8) |
| Non-cardiac chest pain | 0 | 0 | 0 | 0 | 2 (2.4) | 0 | 2 (28.6) | 4 (3.1) |
| Chills | 0 | 0 | 0 | 0 | 3 (3.6) | 0 | 1 (14.3) | 4 (3.1) |
| Chest discomfort | 0 | 0 | 0 | 0 | 0 | 1 (7.7) | 2 (28.6) | 3 (2.3) |
| Malaise | 0 | 0 | 0 | 0 | 1 (1.2) | 2 (15.4) | 0 | 3 (2.3) |

*Table continued next page*

| MedDRA v16.1 SOC PT, n (%) | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 12) | 200 mg (n = 12) | 300 mg (n = 83) | 400 mg (n = 13) | 500 mg (n = 7) | Total (n = 130) |
|---|---|---|---|---|---|---|---|---|
| Influenza-like illness | 0 | 0 | 0 | 0 | 1 (1.2) | 2 (15.4) | 0 | 3 (2.3) |
| Extravasation | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| **Infections and Infestations** | | | | | | | | |
| Urinary tract infection | 0 | 0 | 1 (8.3) | 1 (8.3) | 16 (19.3) | 2 (15.4) | 0 | 20 (15.4) |
| Oral candidiasis | 0 | 0 | 0 | 0 | 4 (4.8) | 2 (15.4) | 0 | 6 (4.6) |
| Upper respiratory tract infection | 0 | 0 | 1 (8.3) | 0 | 2 (2.4) | 2 (15.4) | 0 | 5 (3.8) |
| Lung infection | 0 | 0 | 0 | 2 (16.7) | 2 (2.4) | 0 | 0 | 4 (3.1) |
| **Injury, Poisoning and Procedural Complications** | | | | | | | | |
| Fall | 0 | 0 | 0 | 2 (16.7) | 1 (1.2) | 0 | 1 (14.3) | 4 (3.1) |
| Radiation retinopathy | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Tooth fracture | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| **Investigations** | | | | | | | | |
| Blood creatine phosphokinase increased | 0 | 0 | 3 (25.0) | 1 (8.3) | 16 (19.3) | 2 (15.4) | 3 (42.9) | 25 (19.2) |
| Alanine aminotransferase increased | 0 | 0 | 0 | 0 | 13 (15.7) | 0 | 3 (42.9) | 16 (12.3) |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 0 | 11 (13.3) | 0 | 3 (42.9) | 14 (10.8) |
| Platelet count decreased | 0 | 0 | 1 (8.3) | 2 (16.7) | 9 (10.8) | 0 | 0 | 12 (9.2) |
| Blood creatinine increased | 0 | 0 | 1 (8.3) | 0 | 3 (3.6) | 2 (15.4) | 1 (14.3) | 7 (5.4) |
| Weight decreased | 0 | 0 | 0 | 0 | 3 (3.6) | 2 (15.4) | 0 | 5 (3.8) |
| Weight increased | 0 | 0 | 0 | 0 | 2 (2.4) | 0 | 1 (14.3) | 3 (2.3) |
| **Metabolism and Nutrition Disorders** | | | | | | | | |
| Hyponatraemia | 0 | 0 | 3 (25.0) | 3 (25.0) | 17 (20.5) | 2 (15.4) | 4 (57.1) | 29 (22.3) |
| Decreased appetite | 0 | 1 (50.0) | 0 | 3 (25.0) | 17 (20.5) | 5 (38.5) | 4 (57.1) | 30 (23.1) |
| Hypoalbuminaemia | 0 | 0 | 1 (8.3) | 2 (16.7) | 3 (3.6) | 0 | 2 (28.6) | 8 (6.2) |
| Hypocalcaemia | 0 | 0 | 0 | 1 (8.3) | 2 (2.4) | 1 (7.7) | 2 (28.6) | 6 (4.6) |
| Dehydration | 0 | 0 | 0 | 1 (8.3) | 4 (4.8) | 2 (15.4) | 1 (14.3) | 8 (6.2) |
| Hyperglycaemia | 0 | 0 | 2 (16.7) | 2 (16.7) | 2 (2.4) | 0 | 2 (28.6) | 8 (6.2) |
| Hyperphosphataemia | 0 | 0 | 0 | 0 | 2 (2.4) | 0 | 1 (14.3) | 3 (2.3) |
| Hypophosphataemia | 0 | 0 | 0 | 0 | 1 (1.2) | 1 (7.7) | 1 (14.3) | 3 (2.3) |
| **Musculoskeletal and Connective Tissue Disorders** | | | | | | | | |
| Back pain | 0 | 0 | 2 (16.7) | 2 (16.7) | 9 (10.8) | 1 (7.7) | 2 (28.6) | 16 (12.3) |
| Muscular weakness | 0 | 0 | 0 | 2 (16.7) | 10 (12.0) | 1 (7.7) | 3 (42.9) | 16 (12.3) |
| Arthralgia | 0 | 0 | 2 (16.7) | 2 (16.7) | 5 (6.0) | 1 (7.7) | 1 (14.3) | 11 (8.5) |
| Myalgia | 0 | 1 (50.0) | 1 (8.3) | 1 (8.3) | 5 (6.0) | 1 (7.7) | 0 | 9 (6.9) |
| Musculoskeletal chest pain | 0 | 0 | 2 (16.7) | 0 | 6 (7.2) | 0 | 0 | 8 (6.2) |
| Muscle spasms | 0 | 0 | 1 (8.3) | 1 (8.3) | 9 (10.8) | 1 (7.7) | 1 (14.3) | 13 (10.0) |

*Table continued next page.*

| MedDRA v16.1 SOC<br>PT, n (%) | 25 mg<br>(n = 1) | 50 mg<br>(n = 2) | 100 mg<br>(n = 12) | 200 mg<br>(n = 12) | 300 mg<br>(n = 83) | 400 mg<br>(n = 13) | 500 mg<br>(n = 7) | Total<br>(n = 130) |
|---|---|---|---|---|---|---|---|---|
| Musculoskeletal stiffness | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (14.3) | 2 (1.5) |
| Bone pain | 0 | 1 (50.0) | 0 | 0 | 0 | 0 | 0 | 1 (0.8) |
| Sensation of heaviness | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| **Nervous System Disorders** | | | | | | | | |
| Headache | 0 | 0 | 2 (16.7) | 5 (41.7) | 16 (19.3) | 2 (15.4) | 2 (28.6) | 27 (20.8) |
| Dizziness | 0 | 0 | 1 (8.3) | 4 (33.3) | 19 (22.9) | 1 (7.7) | 1 (14.3) | 26 (20.0) |
| Paraesthesia | 0 | 0 | 0 | 1 (8.3) | 15 (18.1) | 5 (38.5) | 0 | 21 (16.2) |
| Peripheral sensory neuropathy | 0 | 0 | 0 | 3 (25.0) | 13 (15.7) | 1 (7.7) | 1 (14.3) | 18 (13.8) |
| Neuropathy peripheral | 0 | 0 | 1 (8.3) | 1 (8.3) | 6 (7.2) | 2 (15.4) | 1 (14.3) | 11 (8.5) |
| Hypoaestheisa | 0 | 0 | 0 | 1 (8.3) | 4 (4.8) | 2 (15.4) | 1 (14.3) | 8 (6.2) |
| Dysgeusia | 0 | 0 | 1 (8.3) | 0 | 4 (4.8) | 1 (7.7) | 1 (14.3) | 7 (5.4) |
| Balance disorder | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (14.3) | 2 (1.5) |
| Cerebral haemorrhage | 0 | 0 | 0 | 1 (8.3) | 0 | 0 | 1 (14.3) | 2 (1.5) |
| Aphasia | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (14.3) | 2 (1.5) |
| Dizziness postural | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Peripheral motor neuropathy | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Sensory loss | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Slow speech | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| **Psychiatric Disorders** | | | | | | | | |
| Anxiety | 0 | 0 | 0 | 3 (25.0) | 6 (7.2) | 1 (7.7) | 2 (28.6) | 12 (9.2) |
| Insomnia | 0 | 1 (50.0) | 1 (8.3) | 1 (8.3) | 5 (6.0) | 1 (7.7) | 1 (14.3) | 10 (7.7) |
| Depression | 0 | 0 | 0 | 2 (16.7) | 6 (7.2) | 1 (7.7) | 1 (14.3) | 10 (7.7) |
| Confusional state | 0 | 0 | 0 | 2 (16.7) | 5 (6.0) | 0 | 0 | 7 (5.4) |
| Blunted affect | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Mental status changes | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (14.3) | 2 (1.5) |
| **Renal and Urinary Disorders** | | | | | | | | |
| Urinary Retention | 1 (100) | 0 | 0 | 0 | 6 (7.2) | 1 (7.7) | 1 (14.3) | 9 (6.9) |
| Urinary incontinence | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (14.3) | 2 (1.5) |
| Urinary tract disorder | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | | | | | |
| Dyspnoea | 0 | 1 (50.0) | 1 (8.3) | 4 (33.3) | 16 (19.3) | 5 (38.5) | 1 (14.3) | 28 (21.5) |
| Cough | 0 | 1 (50.0) | 1 (8.3) | 4 (33.3) | 19 (22.9) | 4 (30.8) | 1 (14.3) | 30 (23.1) |
| Dysphonia | 0 | 0 | 0 | 0 | 5 (6.0) | 1 (7.7) | 2 (28.6) | 8 (6.2) |
| Pleural effusion | 0 | 0 | 2 (16.7) | 1 (8.3) | 2 (2.4) | 2 (15.4) | 0 | 7 (5.4) |
| Upper-airway cough syndrome | 0 | 0 | 1 (8.3) | 3 (25.0) | 2 (2.4) | 1 (7.7) | 0 | 7 (5.4) |

*Table continued next page.*

| MedDRA v16.1 SOC<br>PT, n (%) | 25 mg<br>(n = 1) | 50 mg<br>(n = 2) | 100 mg<br>(n = 12) | 200 mg<br>(n = 12) | 300 mg<br>(n = 83) | 400 mg<br>(n = 13) | 500 mg<br>(n = 7) | Total<br>(n = 130) |
|---|---|---|---|---|---|---|---|---|
| Nasal congestion | 0 | 0 | 0 | 1 (8.3) | 2 (2.4) | 2 (15.4) | 1 (14.3) | 6 (4.6) |
| Productive cough | 0 | 0 | 0 | 0 | 4 (4.8) | 2 (15.4) | 0 | 6 (4.6) |
| Dyspnoea exertional | 0 | 0 | 0 | 0 | 3 (3.6) | 0 | 1 (14.3) | 4 (3.1) |
| Oropharyngeal pain | 0 | 0 | 0 | 2 (16.7) | 2 (2.4) | 0 | 0 | 4 (3.1) |
| Wheezing | 0 | 0 | 0 | 0 | 2 (2.4) | 0 | 1 (14.3) | 3 (2.3) |
| Throat irritation | 0 | 1 (50.0) | 0 | 0 | 0 | 0 | 0 | 1 (0.8) |
| **Skin and Subcutaneous Tissue Disorders** | | | | | | | | |
| Dry skin | 0 | 0 | 0 | 3 (25.0) | 8 (9.6) | 3 (23.1) | 0 | 14 (10.8) |
| Rash | 0 | 0 | 1 (8.3) | 2 (16.7) | 3 (3.6) | 0 | 1 (14.3) | 7 (5.4) |
| Pruritus | 0 | 0 | 0 | 2 (16.7) | 3 (3.6) | 1 (7.7) | 1 (14.3) | 7 (5.4) |
| Photodermatosis | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (14.3) | 2 (1.5) |
| Nail discolouration | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Rash maculo-papular | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (0.8) |
| Subcutaneous emphysema | 0 | 1 (50.0) | 0 | 0 | 0 | 0 | 0 | 1 (0.8) |
| **Vascular Disorders** | | | | | | | | |
| Hypotension | 0 | 1 (50.0) | 0 | 0 | 5 (6.0) | 1 (7.7) | 0 | 7 (5.4) |
| Hot flush | 0 | 0 | 0 | 1 (8.3) | 1 (1.2) | 1 (7.7) | 1 (14.3) | 4 (3.1) |

All patients who received at least 1 dose of study drug (SAF).

Within an SOC, a patient may have reported more than one type of adverse event.

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

TEAEs are counted based on the patient's assigned initial assigned dose.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.10.

Study drug-related TEAEs were experienced by 85.4% (111/130) of all patients including 85.5% (71/83) of patients in the 300-mg dose group, 92.3% (12/13) of patients in the 400-mg dose group and 100% (7/7) of patients in the 500-mg dose group [Table 11].

**Table 11 TEAEs by Relationship to Study Drug by Dose Level**

| Relationship, n (%)† | 25 mg (n = 1) | 50 mg (n = 2) | 100 mg (n = 12) | 200 mg (n = 12) | 300 mg (n = 63) | 400 mg (n = 13) | 500 mg (n = 7) |
|---|---|---|---|---|---|---|---|
| Not related | 1 (100) | 1 (50.0) | 3 (25.0) | 2 (16.7) | 2 (10.5) | 1 (7.7) | 0 |
| Possible | 0 | 1 (50.0) | 6 (50.0) | 8 (66.7) | 11 (57.9) | 7 (53.8) | 1 (14.3) |
| Probable | 0 | 0 | 3 (25.0) | 2 (16.7) | 6 (31.6) | 5 (38.5) | 6 (85.7) |
| Total | 1 (100) | 2 (100) | 12 (100) | 12 (100) | 19 (100) | 13 (100) | 7 (100) |

All patients who received at least 1 dose of study drug (Safety Analysis Set).
† If an adverse event changed in relationship, then the patient was counted only once with the highest degree of relationship.
SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 12.6.1.11.

Overall, the percentage of patients with maximum NCI-CTCAE Grade 3 or higher TEAEs was 61.5% (80/130) of patients across all dose groups including 100% (1/1) in the 25-mg dose group, no patient in the 50-mg dose group, 66.7% (8/12) in the 100-mg dose group, 50.0% (6/12) in the 200-mg dose group, 60.2% (50/83) in the 300-mg dose group, 69.2% (9/13) in the 400-mg dose group and 85.7% (6/7) in the 500-mg dose group. In the 300-mg dose group, the most common (occurring in 2 or more patients) TEAEs of maximum NCI-CTCAE Grade 3 or higher were hyponatremia (14.5%); aspartate aminotransferase increased (7.2%); alanine aminotransferase increased (6.0%); malignant neoplasm progression (6.0%); dyspnea (4.8%); anemia, back pain, atrial fibrillation and metastases to meninges (3.6% each); and abdominal pain, asthenia, embolism, hypoxia, pneumonia, pulmonary embolism and urinary tract infection (2.4%, each).

There were 14 patient deaths during the study period and 2 additional deaths that occurred > 28 days after the last dose of ASP8273 (1 patient each in the 300- and 400-mg dose groups). Deaths were reported in 1 of 12 (8.3%) patients in the 100-mg dose group, 3 of 12 (25.0%) patients in the 200-mg dose group, 9 of 83 (10.8%) patients in the 300-mg dose group and 1 of 13 (7.7%) patients in the 400-mg dose group. There were no patient deaths in the 25-, 50- and 500-mg dose groups. Including the deaths that occurred > 28 days after the last dose of ASP8273, the primary causes of death were malignant neoplasm progression (6 patients), respiratory failure (2 patients), confusional state/altered mental status (2 patients), depressed level of consciousness, multi-organ failure, metastases to CNS, metastases to meninges, cardiac failure and sepsis (1 patient each). None of the deaths in this study were considered by the investigator to be related to ASP8273.

[redacted]

SAEs were reported in 57 of 130 (43.8%) patients in the combined ASP8273 groups, including 1 of 1 (100%) patient in the 25-mg dose group, 4 of 12 (33.3%) of patients in the 100-mg dose group, 6 of 12 (50.0%) patients in the 200-mg dose group, 37 of 83 (44.6%) patients in the 300-mg dose group, 6 of 13 (46.2%) patients in the 400-mg dose group and 3 of 7 (42.9%) patients in the 500-mg dose group. No SAEs were reported in the 2 patients in the 50-mg dose group. The majority of SAEs were not considered by the investigator to be related to study drug.

Across all dose cohorts, 22.3% (29/130) of patients experienced a TEAE that resulted in permanent discontinuation of study drug including 16.7% (2/12) of patients in the 100-mg dose group, 33.3% (4/12) of patients in the 200-mg dose group, 20.5% (17/83) of patients in the 300-mg dose group, 23.1% (3/13) of patients in the 400-mg dose group and 42.9% (3/7) of patients in the 500-mg dose group. There was no patient in the 25- or 50-mg dose groups that had a TEAE that resulted in discontinuation. Of the 29 patients overall who experienced a TEAE resulting in permanent discontinuation of ASP8273, 14 (10.8%) patients had a TEAE resulting in permanent discontinuation of ASP8273 that was considered by the investigator to be related to study drug, including 9 (10.8%) patients in the 300-mg dose group.

TEAEs leading to dose reduction were reported in 8.3% (1/12) of patients in the 100-mg dose group, 9.6% (8/83) of patients in the 300-mg dose group, 46.2% (6/13) of patients in the 400-mg dose group and 28.6% (2/7) of patients in the 500-mg dose group. All of the TEAEs leading to dose reduction were considered study drug related with the exception of 2 events (nausea and vomiting) in a single patient in the 300-mg dose group and 1 event of colitis in the 400-mg dose group.

TEAES were evaluated for events of interest identified based on risks associated with the drug class and data available to date in studies of ASP8273. TEAEs of interest include hyponatremia, diarrhea, nausea, vomiting, LFT elevation, neuropathy, rash and interstitial lung disease. Regarding TEAEs of interest, only 1 patient experienced a TEAE of interest that was considered a DLT; a patient in the 400-mg dose group experienced Grade 3 diarrhea.

Overall, 22.3% (29/130) of patients experienced TEAEs of hyponatremia including 25.0% (3/12) of patients in the 100-mg dose group, 25.0% (3/12) patients in the 200-mg dose group, 20.5% (17/83) of patients in the 300-mg dose group, 15.4% (2/13) patients in the 400-mg dose group, and 57.1% (4/7) patients in the 500-mg dose group. All of the hyponatremia events were considered to be related to study drug with the exception of 6 patients (2 patients each in the 100-mg, 200-mg and 300-mg dose groups). SAEs were reported for hyponatremia in 6 patients (1 patient in the 200-mg dose group, 3 patients in the 300-mg dose group and 2 patients in the 500-mg dose group). Hyponatremia was associated with dose reduction in 5 patients including 1 patient in the 300-mg dose group, 2 patients in the 400-mg dose group and 2 patients in the 500-mg dose group. Hyponatremia resulted in permanent discontinuation of study drug in 2 patients in the 300-mg dose group and 2 patients in the 500-mg dose group.

Across all dose groups, 48.5% (63/130) of patients experienced diarrhea, 39.2% (51/130) of patients experienced nausea and 22.3% (29/130) of patients experienced vomiting. Diarrhea was experienced by 51.8% (43/83) of patients in the 300-mg dose group, 61.5% (8/13) of patients in the 400-mg dose group and 85.7% (6/7) of patients in the 500-mg dose group. Nausea was experienced by 34.9% (29/83) of patients in the 300-mg dose group, 53.8% (7/13) of patients in the 400-mg dose group and 57.1% (4/7) of patients in the 500-mg dose group. Vomiting was experienced by 21.7% (18/83) of patients in the 300-mg dose group, 30.8% (4/13) of patients in the 400-mg dose group and 42.9% (3/7) of patients in the 500-mg dose group. There was no diarrhea, nausea or vomiting TEAEs with an NCI-CTCAE Grade 4 or higher. SAEs of nausea and/or vomiting were reported for 1 (8.3%) patient in the 100-mg dose group, 2 (2.4%) patients in the 300-mg dose group and 1 (7.7%) patient in the 400-mg dose group. Nausea led to discontinuation of study drug in 1 (8.3%) patient in the 100-mg dose group and 1 (7.7%) patient in the 400-mg dose group. Diarrhea led to dose reductions in 1 (1.2%) patient in the 300-mg dose group and 2 (15.4%) patients in the 400-mg dose group;

nausea led to dose reductions in 2 (2.4%) patients in the 300-mg dose group; and vomiting led to dose reductions in 1 (1.2%) patient in the 300-mg dose group.

TEAEs of alanine aminotransferase increased, aspartate aminotransferase increased and blood bilirubin increased were reported by 12.3% (16/130), 10.8% (14/130) and 3.1% (4/130) of all patients, respectively. Alanine aminotransferase increased was reported by 15.7% (13/83) of patients in the 300-mg dose group, no patients in the 400-mg dose group and 42.9% (3/7) of patients in the 500-mg dose group. Aspartate aminotransferase increased was reported by 13.3% (11/83) of patients in the 300-mg dose group, no patients in the 400-mg dose group and 42.9% (3/7) of patients in the 500-mg dose group. Blood bilirubin increased was reported by 8.3% (1/12) of patients in the 200-mg dose group, 2.4% (2/83) of patients in the 300-mg dose group, 7.7% (1/13) of patients in the 400-mg dose group and no patients in the 500-mg dose group. There were no TEAEs for alanine aminotransferase increased, aspartate aminotransferase increased or blood bilirubin increased that were Grade 4 or higher. The majority of the elevated LFTs were considered to be study drug related. No patient had an SAE for alanine aminotransferase increased or aspartate aminotransferase increased, but 1 (1.2%) patient in the 300-mg dose group had an SAE reported for blood bilirubin increased. One patient in the 300-mg dose group had an alanine aminotransferase increased TEAE that led to dose reduction. Two patients in the 300-mg dose group each had TEAEs of alanine aminotransferase increased and aspartate aminotransferase increased that led to permanent discontinuation of study drug.

One patient in the 300-mg dose group had an ALT and/or AST value > 3 x ULN and a total bilirubin value ≥ 2 x ULN on cycle 3 day 1 (visit day 42). The TEAEs reported for LFT increases in this patient were considered by the investigator to be not related to study drug [redacted] The patient was withdrawn from the study due to progressive disease on day 42 and died on day 57.

In all patients, TEAEs associated with neuropathies were reported including paresthesia (16.2%, 21/130), peripheral sensory neuropathy (13.8%, 18/130), muscular weakness (12.3%, 16/130), neuropathy peripheral (8.5%, 11/130), gait disturbance (5.4%, 7/130), peripheral motor neuropathy (0.8%, 1/130) and sensory loss (0.8%, 1/130). There was no neuropathy TEAE that was NCI-CTCAE Grade 4 or higher. There was 1 patient in the 300-mg dose group who had an SAE of Grade 3 muscular weakness with onset on day 141 (last dose on day 121); this SAE was considered by the investigator to be not related to study drug. There was 1 patient in the 400-mg dose group who had an SAE of Grade 3 muscular weakness with onset on day 59 (last dose on day 58); this SAE was considered by the investigator to have a possible relationship to study drug. One patient in the 300-mg dose group had a TEAE of Grade 2 peripheral sensory neuropathy that led to 2 dose reductions (300 mg to 100 mg) followed by permanent discontinuation of study drug (last dose on day 150). One patient in the 200-mg dose group also had a TEAE of Grade 2 peripheral sensory neuropathy that led to withdrawal of study drug (last dose on day 511).

In all patients, TEAEs were reported for rash including the following: rash (7, 5.4%), dermatitis acneiform (3, 2.3%), rash pustular (1, 0.8%), rash maculo-papular (1, 0.8%) and rash pruritic (1, 0.8%). Most of the TEAEs for rash were NCI-CTCAE Grade 1. There was no rash TEAE of ≥ Grade 4. One patient in the 300-mg dose group had an episode of Grade 3 dermatitis acneiform with first onset 103 days after ASP8273 300-mg treatment as Grade 1 that changed to Grade 3 on study day 128 and lessened in severity to Grade 1 on study day 134. This event, with possible relationship to study drug, led to dose interruption and then dose

reduction on study day 134. There were no SAEs reported for these rash events during the study and no rash TEAE led to discontinuation of study drug.

There were no TEAEs of interstitial lung disease reported in the study.

Few (< 2.3%) PCS vital sign values were observed during the study. Three patients experienced TEAEs of hypertension (PT) (i.e., 2 patients [2.4%] in the 300-mg dose group, and 1 patient [7.7%] in the 400-mg dose group) during the study.

Changes from baseline QTcF values ≥ 30 to < 60 msec (based on central review) were observed in 1 patient in the 100-mg dose group and 10 patients at multiple time points in the 300-mg dose group. Changes from baseline QTcF ≥ 60 msec (based on central review) in the 300-mg dose group were seen in 2 patients. There were no patients in the study who had absolute QTcF values > 480 msec based on central ECG review.

Baseline ECOG performance status was 1 for 65.1% (54/83) of patients in the 300-mg dose group, 69.2% (9/13) of patients in the 400-mg dose group and 85.7% (6/7) of patients in the 500-mg dose group. The median of the maximum changes from baseline in ECOG performance status was 0 for patients in the 300-, 400- and 500-mg dose groups. One patient (7.7%) in the 400-mg dose group had a maximum postbaseline ECOG performance status of 4. There were no patients who had an ECOG performance status of Grade 5 during the study.

Shifts from baseline to worst postbaseline ophthalmologic results showing worsening were seen in 2 patients in the ASP8273 300-mg dose group and 1 patient in the 500-mg dose group. Shifts from baseline to worst postbaseline ophthalmologic results showing improvement were seen in 1 patient in the 50-mg dose group and 2 patients in the 300-mg dose group. One TEAE of punctate keratitis occurred in the 300-mg dose group; no TEAEs of keratopathy were reported in the study.

**CONCLUSIONS:**

ASP8273 showed linear pharmacokinetics and demonstrated dose proportionality over the dose range of 100 mg to 500 mg. Oral absorption of ASP8273 was rapid with maximum concentrations achieved within 1 to 3 hours after a single dose and 1 to 4 hours at steady-state. Steady-state ASP8723 was achieved by day 8 after once-daily dosing. Median terminal elimination half-life of ASP8273 at 25 mg through 500 mg ranged approximately from 6 to 14 hours. A high-fat meal had no effect on the bioavailability of ASP8273. Coadministration of ASP8273 and midazolam did not alter ASP8273 exposure, but reduced midazolam and 1-hydroxy midazolam exposure ($AUC_{inf}$) by approximately 18% and 40%, respectively, compared with midazolam alone.

Tumor response was observed in patients enrolled in the 100-mg cohort or above. ASP8273 response assessments with confirmation for patients in the ASP8273 300-mg dose group were ORR of 34.9% (22/63; 95% CI: 23.3%, 48.0%) and DCR of 61.9% (39/63; 95% CI: 48.8%, 73.9%). For patients who were positive for T790M mutation at study entry in the ASP8273 300-mg dose group, ORR was 36.2% (21/58; 95% CI: 24.0%, 49.9%) and DCR was 63.8% (37/58; 95% CI: 50.1%, 76.0%) based on local testing. As of the data tabulations cut-off date of this report (28 Jul 2017), median DOR in the ASP8273 300-mg dose group was 8.6 months.

In the ASP8273 300-mg dose group, the median duration of PFS was 6.8 months and 53.8% of patients were progression free at 6 months. The median duration of PFS for patients in the 300-mg dose group who were positive for T790M mutation at study entry was 7.0 months and 55.0% of patients who were T790M mutation positive at study entry were progression free at 6 months based on local testing.

Overall, ASP8273 appears tolerated at doses up to 500 mg in this study and antitumor activity was observed at doses of 100 mg or greater in patients with NSCLC who have EGFR mutations. Based on data from both studies (8273-CL-0101 and 8273-CL-0102), 400 mg was declared the MTD and considering the balance between efficacy and long-term safety, the 300-mg dose was chosen as RP2D.

**Date of Report:** Reissued, 07 May 2019