Name of Sponsor/Company: Astellas Pharma Global Development Inc		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: Gilteritinib (ASP2215)		

SYNOPSIS

Title of Study: A Phase 1b/2 Study of ASP2215 in Combination with Erlotinib in Subjects with EGFR Activating Mutation-Positive (EGFRm+) Advanced NSCLC Who Have Acquired Resistance to an EGFR Tyrosine Kinase Inhibitor (TKI)

Investigators/Coordinating Investigator: [redacted], MD

Study Centers: 4 centers in Japan

Publication Based on the Study: No publications based on the results of this study were available at the time this original report was approved.

Study Period: 11.5 Months, Sep 2015 through Sep 2016

Study Initiation Date (Date of First Enrollment): 08 Sep 2015

Study Completion Date (Date of Last Evaluation): 28 Sep 2016

Phase of Development: Phase 1b/2

Objectives: The primary objective of the phase 1b portion of the clinical study was to evaluate the safety and tolerability of ASP2215 in combination with erlotinib and to determine the recommended phase 2 dose (RP2D) of ASP2215.

The primary objective of the phase 2 portion of the clinical study was to evaluate the objective response rate (ORR) of the RP2D of ASP2215 in combination with erlotinib.

The secondary objectives of the phase 1b portion of the clinical study were to determine the pharmacokinetic profiles of ASP2215 and erlotinib and to evaluate the ORR of ASP2215 in combination with erlotinib.

The secondary objectives of the phase 2 portion of the clinical study were to evaluate progression-free survival (PFS), duration of response (DOR) and disease control rate (DCR) of ASP2215 in combination with erlotinib. In addition, other secondary endpoints were to evaluate safety and tolerability of ASP2215 in combination with erlotinib and to determine the pharmacokinetic profiles of ASP2215 and erlotinib.

Methodology: This was an open-label phase 1b/2 study of ASP2215 in combination with erlotinib in patients with EGFR activating mutation-positive (EGFRm+) advanced NSCLC who have acquired resistance to an EGFR TKI. Ten patients with NSCLC were enrolled into the phase 1b portion of the study located in 4 centers in Japan.

The phase 1b portion was to determine the RP2D for ASP2215 in combination with erlotinib 150 mg (Regimen A). If the ASP2215 RP2D for Regimen A was determined to be 80 mg or 120 mg, then additional cohorts were to be enrolled to escalate ASP2215 in combination with erlotinib 100 mg (Regimen B).

Dosing Cohorts and Dose Escalation Meetings:

At least 3, and no more than 12, dose-limiting toxicity (DLT)-evaluable patients were to be enrolled in a given dose cohort. Three or 4 patients were to be enrolled in the initial cohort for each dose level. A dose escalation meeting was to be held with the sponsor and investigators (Dose Escalation Committee) once the cohort completed cycle 1 and the data were available for review. Dose escalation, cohort expansion or de-escalation decisions were to be guided by a modified toxicity probability interval (mTPI) design that provided dose assignment rules based on a posterior estimate of the DLT rate in cycle 1 when the target DLT rate is 30%. The committee could choose a more conservative dosing decision than what was outlined in the algorithm, based on the totality of safety (e.g., DLTs in cycle ≥ 2) and available pharmacokinetic data. Based on the outcome of the dose escalation meeting, an additional 3 or 4 patients could have been enrolled to either the same dose (expansion cohort) or another dose level (initial cohort or a de-escalation cohort). The dose escalation decision process was to be repeated as needed up to 12 DLT-evaluable patients in a given dose level. In order for a dose level to be declared the RP2D, 12 DLT-evaluable patients must have been treated at that dose level in the respective regimen.

Regimen A:

The ASP2215 starting dose was to be 120 mg. The subsequent dose levels are outlined in the table below.

Phase 1b: Regimen A		
Dose Level	**ASP2215 (mg)**	**Erlotinib (mg)**
-2	40 (1 × 40 mg tablet)	150 (1 × 150 mg tablet)
-1	80 (2 × 40 mg tablets)	150 (1 × 150 mg tablet)
1 (starting dose)	120 (3 × 40 mg tablets)	150 (1 × 150 mg tablet)
2	200 (5 × 40 mg tablets)	150 (1 × 150 mg tablet)
3	320 (8 × 40 mg tablets)	150 (1 × 150 mg tablet)

Regimen B:

If the Regimen A ASP2215 RP2D was determined to be 80 mg or 120 mg, then Regimen B was to be evaluated.

The Regimen B ASP2215 starting dose was to be at least 80 mg, based on the toxicities observed. The ASP2215 dose was to be further escalated if indicated by the mTPI algorithm after at least 6 patients had been evaluated at the starting dose.

Number of Patients (Planned, Enrolled and Analyzed): Approximately 30 patients were to be enrolled in the phase 1b portion of the clinical study, depending on DLT incidence. Approximately 60 patients were to be enrolled in the phase 2 portion of the study. A total of 10 patients were enrolled and analyzed in the phase 1b portion of the study. A decision was made to terminate the study due to the occurrence of grade 3 and 4 ALT and AST increases at the initial and reduced dose levels of ASP2215 (120 mg and 80 mg) with erlotinib 150 mg in the phase 1b portion of the clinical study.

Diagnosis and Main Criteria for Inclusion: Male or female patients, ≥ 18 years of age, with histologically or cytologically confirmed metastatic or locally advanced, unresectable NSCLC with a documented exon 19

deletion or exon 21 L858R EGFR activating mutation as well as prior treatment with any EGFR tyrosine kinase inhibitor were eligible for enrollment into the phase 1b portion of the study. Female patients must have been of nonchildbearing potential or using 2 forms of highly effective birth control; male patients and their female spouse/partners who were of childbearing potential must have also been using 2 forms of highly effective birth control. Patients may not have had prolonged QT interval nor have received medications known to prolong the QT interval. Patients may not have received strong or moderate inhibitors or strong inducers of cytochrome P450 3A4, inhibitors and inducers of P-glycoprotein, substrates of multidrug and toxin extrusion 1 or drugs that target serotonin 5-hydroxytryptamine receptor 1 or 5-hydroxytryptamine 2B receptor within 1 week prior to dosing or used any inducer of metabolism. Patients must have received prior treatment with an EGFR TKI and had to have an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2 at screening. Patients must have been able to provide written informed consent and meet all the inclusion criteria and have none of the exclusion criteria.

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

Each patient received 120 mg (3 tablets of 40 mg each) or 80 mg (2 tablets of 40 mg each) of ASP2215 in combination with 150 mg (1 tablet of 150 mg) of erlotinib orally once daily.

ASP2215 lot numbers were 14071H (expiration Jan 2017), 14072G (expiration Jan 2017), 14094E (expiration Feb 2017) and 14095E (expiration Sep 2017).

Erlotinib lot numbers were 15079A (expiration Aug 2018), 15077A (expiration Dec 2018) and 15078A (expiration Dec 2018).

ASP2215 and erlotinib were to be administered together orally once daily with water on an empty stomach defined as at least 1 hour before or 2 hours after the ingestion of food. ASP2215 and erlotinib were to be taken together as close to the same time each morning as possible.

Duration of Treatment (or Duration of Study, if applicable):

ASP2215 was intended to be administered in combination with erlotinib orally once daily in the form of tablets for a 28 day treatment cycle until a discontinuation criterion was met. AE collection continued for 30 days following the last dose of study drug and patients were contacted 30-day posttreatment regarding this data.

Criteria for Evaluation:

The safety variables assessed included: the frequency, severity, seriousness, and relationship to study drug of treatment-emergent adverse events (TEAEs); DLT events; clinical laboratory variables (hematology, coagulation, biochemistry including thyroid function, liver enzymes and total bilirubin and urinalysis); vital signs (systolic and diastolic blood pressure, pulse oximetry, temperature and pulse rate); 12-lead electrocardiogram (ECG); and ophthalmologic examination including examinations for visual acuity, biomicroscopy, visual fields and optical coherence tomography

The pharmacokinetic variables assessed included: the evaluation of plasma concentration data of ASP2215, erlotinib and the metabolite of erlotinib, OSI-420 and using standard noncompartmental analysis, AUC_{24}, C_{max}, C_{trough} and t_{max} were estimated for ASP2215, erlotinib and the metabolite of erlotinib, OSI-420.

The biomarker variables assessed included: the effect of ASP2215 [redacted]

[redacted]

The efficacy variable assessed was best overall response, which was derived based on the time point response information on the case report form (CRF) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

Statistical Methods:

Four populations were used for the analyses: the safety analysis set (SAF), the dose-limiting toxicity evaluable set (DES), the pharmacokinetic analysis set (PKAS) and the biomarker analysis set (BMAS). The allocation of patients to analysis sets was determined prior to database hard lock.

For continuous variables, descriptive statistics included the number of patients (n), mean, standard deviation, median, minimum and maximum. When needed, other percentiles (e.g., 10%, 25%, 75% and 90%) were used. In addition, for continuous pharmacokinetic parameters, the coefficient of variation was calculated and for C_{max}, C_{trough} and AUC; the geometric mean was also calculated. Frequencies and percentages were displayed for categorical data. AEs, TEAEs and medical history were coded in the Medical Dictionary for Regulatory Activities (MedDRA) (version 17.1); events were graded by NCI CTCAE Grade (version 4.03) and were summarized by system organ class (SOC) and preferred term (PT) as well as by PT alone, by treatment group for the SAF.

All analyses of safety were presented by treatment group for SAF, unless specified otherwise. DLT events were summarized by dose level using DES. All AEs were listed and evaluated by incidence including serious adverse events, deaths and discontinuation due to adverse events; severity, investigator-attributed relationship to study drug, duration, and outcome of the events were also recorded.

The pharmacokinetic parameters were calculated using a noncompartmental method. Patients with sufficient pharmacokinetic samples had pharmacokinetic parameter estimates for ASP2215 and erlotinib (and its metabolite), including calculation of AUC_{24}, C_{max}, C_{trough} and t_{max}, using standard noncompartmental analysis. For the AUC determinations, linear up and log down analysis was used.

Summary of Results/Conclusions:

Population

Ten patients were enrolled in the clinical study and 10 patients (100%) received at least 1 dose of study drug [Table 1]. One patient was excluded from the DES because they were only on study drug treatment for 11 days and did not experience a DLT. Of the 10 patients enrolled in this clinical study, the majority were female (60%), ≤ 65 years (60%) and all patients were Asian. Patients had a mean age of 64.1 years, a mean weight of 60 kg, a mean height of 160.6 cm and a mean BMI of 23.2 kg/m^2 [Table 2].

Efficacy Results:

For the patients in the ASP2215 120 mg + erlotinib 150 mg dose group, 1 patient had a best overall response of stable disease and 2 patients had a best overall response of progressive disease (PD). For the patients in the ASP2215 80 mg + erlotinib 150 mg dose group, 3 patients had a best overall response of stable disease and

3 patients had a best overall response of PD; 1 patient's response was not evaluable as the only on treatment assessment was conducted on day 17.

In summary, no response was observed for the 10 patients enrolled. The small number of patients in the study, with only 2 patients receiving more than 2 cycles of study treatment, did not provide enough data to allow for meaningful conclusions regarding the efficacy of this combination regimen.

Pharmacokinetic Results:

ASP2215 was rapidly absorbed with t_{max} observed between approximately 2 and 6 hours. After multiple dose administration, ASP2215 exhibited moderate to extensive accumulation Table 3. Erlotinib was rapidly absorbed with t_{max} observed between approximately 2 and 4 hours. Its major pharmacologically-active metabolite, OSI-420, was rapidly formed with median t_{max} observed at 2 hours Table 4.

[redacted]

Safety Results:

The mTPI algorithm required de-escalation of ASP2215 from 120 mg to 80 mg due to 2 of 3 patients experiencing DLT in cycle 1. Among the 6 DLT-evaluable patients treated at the de-escalated dose level of ASP2215 80 mg in combination with erlotinib 150 mg, 2 patients experienced DLT in cycle 1 and an additional patient experienced DLT in cycle 2. Although the mTPI algorithm (based on cycle 1 DLT) allowed more patients to be enrolled at this dose level, the sponsor, in accordance with the recommendation of the Dose Escalation Committee, terminated the study due to grade ≥3 ALT and/or AST increases that were observed at both the initial ASP2215 dose level of 120 mg and the de-escalated ASP2215 dose level of 80 mg in combination with erlotinib 150 mg.

Of the 10 patients enrolled in the study, 9 were DLT evaluable. A total of 5 DLT-evaluable patients experienced a DLT during the study, including 2 (66.7%) of the 3 patients in the ASP2215 120 mg + erlotinib 150 mg dose group and 3 (50%) of the 6 DLT-evaluable patients in the ASP2215 80 mg + erlotinib 150 mg dose group. The DLTs in cycle 1 were enteritis (grade 3), AST increased (grade 4) and ALT increased (grade 3 and grade 4); the DLTs in cycle ≥ 2 were grade 3 and grade 2 hypoalbuminemia. Five DLTs of grade ≥ 3 ALT and/or AST increased were observed in 4 of the 9 DLT-evaluable patients Table 5. All 5 patients with DLTs had the administration of the study drugs interrupted or withdrawn due to DLTs.

Overall, 10 patients (100%) experienced at least one TEAE and 5 (50%) patients experienced a serious TEAE. Ten patients (100%) had drug-related TEAEs and 4 patients (40%) had drug-related serious TEAEs, which led to the withdrawal of treatment. An overview of TEAEs is provided in [Table 6].

AEs observed in 2 or more patients included diarrhoea, constipation, nausea, stomatitis, increases in each of ALT, AST, creatine phosphokinase, alkaline phosphatase, creatinine, and lactate dehydrogenase; skin disorders such as drug eruption, dry skin, pruritus, and rash; hypoalbuminemia, decreased appetite, paronychia, dizziness, dysgeusia, peripheral sensory neuropathy, malaise, proteinuria and insomnia. Details on the incidence of TEAEs by SOC and PT are provided in [Table 7].

Ten patients (100%) experienced a drug-related TEAE. Drug-related TEAEs observed in 2 or more patients included diarrhoea, constipation, stomatitis, increases in each of ALT, AST, creatine phosphokinase, alkaline phosphatase, creatinine and lactate dehydrogenase; skin disorders such as drug eruption and dry skin; hypoalbuminemia, paronychia, dysgeusia and proteinuria.

Ten serious TEAEs occurred in 5 patients (50%) [Table 8]. There were 2 serious TEAEs that were not considered related to the study drug, 1 each in 2 patients in the ASP2215 80 mg + erlotinib 150 mg dose group: a fracture and pleural effusion. Study drug-related serious TEAEs occurred in 4 patients (40%): 2 patients in the ASP2215 120 mg + erlotinib 150 mg dose group and 2 patients in the ASP2215 80 mg + erlotinib 150 mg dose group. The majority of drug-related serious TEAEs were increases in ALT (in 4 patients) and increases in AST (in 3 patients); 1 patient experienced grade 2 acute renal failure.

Four patients (40%) had TEAEs that led to permanent discontinuation of the study drugs. Of these discontinued patients, 2 patients were in the ASP2215 120 mg + erlotinib 150 mg dose group and 2 patients were in the ASP2215 80 mg + erlotinib 150 mg dose group. All of the TEAEs that led to discontinuation were drug-related. The majority of these drug-related TEAEs that led to discontinuation of the study drugs were increases in AST (in 3 patients) and ALT (in 2 patients); 1 patient experienced hypoalbuminemia that did not recover to grade ≤ 1 within 14 days.

Regarding AEs of special interest, grade 3 blood CK increased was reported in 1 patient, 5 patients experienced grade ≥ 3 ALT increased, 3 patients had grade ≥ 3 AST increased, a TEAE of QT prolongation occurred in 1 patient (grade 1) and a TEAE of ALT increased occurred in 1 patient leading to dose reduction. No patient had a mean QTcF greater than 480 msec while on study and no patient had a > 60 msec increase in mean QTcF relative to baseline.

Regarding severe events, grade ≥ 3 TEAEs other than AST increased and ALT increased occurred in 1 patient each (diarrhea, blood CK increased, enteritis, fracture, hypoalbuminemia, and pleural effusion). The only grade 4 TEAEs were ALT and AST increases.

CONCLUSIONS:

Although the stopping criteria in the protocol were not met, the sponsor, in accordance with the recommendation of the Dose Escalation Committee, terminated the study due to grade ≥ 3 ALT and/or AST increases that were observed at both the initial ASP2215 dose level of 120 mg and the de-escalated ASP2215 dose level of 80 mg in combination with erlotinib 150 mg. No cases of increased ALT and/or AST met Hy's Law criteria, as no bilirubin elevations were observed. Despite the absence of bilirubin elevations, the co-administration of ASP2215 with erlotinib demonstrated an undesirable safety profile at the dose levels evaluated.

Stable disease was the best overall response observed in this study (in 4 patients). The small number of patients in the study, with only 2 patients receiving more than 2 cycles of study treatment, did not allow for meaningful conclusions regarding the efficacy of this combination regimen.

ASP2215 was rapidly absorbed with t_{max} observed between approximately 2 and 6 hours. After multiple dose administration, ASP2215 exhibited moderate to extensive accumulation. Erlotinib was rapidly absorbed with t_{max} observed between approximately 2 and 4 hours. Its major pharmacologically-active metabolite, OSI-420, was rapidly formed with median t_{max} observed at 2 hours.

In summary, this study demonstrated that ASP2215 in combination with erlotinib at the dose levels evaluated did not appear to have an acceptable safety profile due to ALT and AST increases. No further study of this combination is planned.

Date of Report: 17 Jul 2017

Table 1 Patient Disposition and Analysis Sets

Disposition and Analysis Sets	**Total (N = 10)**
Enrolled	10 (100%)
Treatment Discontinuation	10 (100%)
Study Discontinuation	1 (10%)
Analysis Sets	
Safety Analysis Set (SAF)	10 (100%)
DLT Evaluable Set (DES)	9 (90%)
Pharmacokinetic Analysis Set (PKAS)	10 (100%)
Biomarker Analysis Set (BMAS)	10 (100%)

SAF: Safety Analysis Set, which consisted of all patients who received at least one dose of study drugs; DES: DLT evaluable set, which is a subset of the SAF, and includes patients who were either administered at least 75% of planned dose during cycle 1 or experienced DLT during cycle 1; PKAS: pharmacokinetics analysis set, which consisted of the patients of the SAF for whom 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 is known; BMAS: biomarker analysis set, which consisted of the subset of patients of the SAF for whom biomarker data were available to facilitate derivation of at least one of the correlative biomarkers.

Source: End-of-Text Tables 12.1.1.2, 12.1.1.3 and 12.1.1.4

Table 2 Summary of Demographics and Baseline Characteristics for Patients in the Safety Analysis Set

Parameter Category/ Statistics	ASP2215 120 mg + Erlotinib 150 mg (N = 3)	ASP2215 80 mg + Erlotinib 150 mg (N = 7)	Total (N = 10)
Sex, n (%)			
Male	1 (33.3)	3 (42.9)	4 (40%)
Female	2 (66.7)	4 (57.1)	6 (60%)
Race, n (%)			
White	0	0	0
Black or African American	0	0	0
Asian	3 (100)	7 (100)	10 (100%)
American Indian or Alaska	0	0	0
Native	0	0	0
Native Hawaiian or other	0	0	0
Pacific Islander	0	0	0
Other	0	0	0
Ethnicity, n (%)			
Not Hispanic or Latino	3 (100)	7 (100)	10 (100%)
Hispanic or Latino	0	0	0
Age, years			
Mean (SD)	70.3 (8.4)	61.4 (5.9)	64.1 (7.5)
Median	66.0	64.0	65.0
Min - Max	65 – 80	55 – 68	55 – 80
Age Group			
≤ 65 years	1 (33.3)	5 (71.4)	6 (60%)
> 65 years	2 (66.7)	2 (28.6)	4 (40%)
Weight (kg)			
Mean (SD)	52.2 (3.8)	63.4 (9.8)	60.0 (9.8)
Median	53.6	65.8	60.5
Min - Max	48 – 55	44 – 73	44 – 73
Height (cm)			
Mean (SD)	158.2 (0.2)	161.6 (5.7)	160.6 (4.9)
Median	158.1	161.0	158.6
Min - Max	158 – 158	154 – 169	154 – 169
BMI (kg/m^2)			
Mean (SD)	20.9 (1.5)	24.2 (2.8)	23.2 (2.9)
Median	21.4	25.4	23.4
Min - Max	19 – 22	18 – 26	18 – 26

All patients who received at least 1 dose of the study drugs (Safety Analysis Set)
BMI: body mass index (weight [kg]/height [m^2]); Max: maximum; Min: minimum
Source: End-of-Text Table 12.1.2.1

Table 3 Plasma Pharmacokinetic Parameters of ASP2215 in Patients with NSCLC After Single and Multiple Dose Administration of ASP2215 80 mg + Erlotinib 150 mg - Pharmacokinetic Analysis Set

Parameter	ASP2215 80 mg + Erlotinib 150 mg Cycle 1 Day 1	ASP2215 80 mg + Erlotinib 150 mg Cycle 1 Day 28
AUC_{24} (h* ng/mL)	**N = 7**	**N = 3**
Mean (SD) %CV Median Min – Max GM	1890 (686) 36.4 1765 870 – 2736 1762	8342 (3023) 36.2 8501 5242 – 11283 7952
C_{max} (ng/mL)	**N = 7**	**N = 3**
Mean (SD) %CV Median Min – Max GM	119 (47.7) 40.0 116 47.7 – 186 110	408 (136.6) 33.5 402 275 – 548 393
t_{max} (h)	**N = 7**	**N = 3**
Median Min - Max	4.05 1.93 – 4.18	4.00 3.98 – 5.80

All patients who received at least 1 dose of study drugs for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

AUC_{24}: area under the concentration-time curve at 24 hours; C_{max}: maximum concentration; %CV: percentage coefficient of variance; GM: geometric mean; Max: maximum; Min: minimum; t_{max}: time after dosing when C_{max} occurs

Source: End-of-Text Table 12.4.2.1

Table 4 Plasma Pharmacokinetic Parameters of Erlotinib and OSI-420 in Patients with NSCLC After Multiple (Cycle 1 Day 28) Dose Administration of ASP2215 80 mg + Erlotinib 150 mg - Pharmacokinetic Analysis Set

Parameter	Erlotinib	OSI-420
AUC_{24} (h*ng/mL)	**N = 3**	**N = 3**
Mean (SD) %CV Median Min – Max GM	54100 (23000) 42.5 42500 39200 – 80500 51200	12000 (9782) 81.7 7110 5581 – 23200 9735
C_{max} (ng/mL)	**N = 3**	**N = 3**
Mean (SD) %CV Median Min – Max GM	3160 (314) 9.90 3020 2940 – 3520 3150	611.3 (373) 61.0 433 361 – 1040 546
t_{max} (h)	**N = 3**	**N = 3**
Median Min - Max	2.00 1.90 – 4.00	2.00 1.90 – 24.0

Table footnotes appear on next page

All patients who received at least 1 dose of study drugs for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

AUC_{24}: area under the concentration-time curve at 24 hours; C_{max}: maximum concentration; %CV: percentage coefficient of variance; GM: geometric mean; Max: maximum; Min: minimum; t_{max}: time after dosing when C_{max} occurs

Source: End-of-Text Tables 12.4.2.2 and 12.4.2.3

Table 5 Dose-Limiting Toxicities - Safety Analysis Set

Patient Dose Group	DLT in Cycle 1?	DLT in Cycle ≥2?	DLT Description
Patient A ASP2215 120 mg + Erlotinib 150	Yes Yes	NA NA	Enteritis (Grade 3) AST increased (Grade 4)
Patient B ASP2215 120 mg + Erlotinib 150	Yes	NA	ALT increased (Grade 4)
Patient C ASP2215 80 mg + Erlotinib 150	No No No	Yes Yes Yes	Hypoalbuminaemia (Grade 3) Hypoalbuminaemia (Grade 2) Hypoalbuminaemia (Grade 3)
Patient D ASP2215 80 mg + Erlotinib 150	Yes	No	ALT increased (Grade 3)
Patient E ASP2215 80 mg + Erlotinib 150	Yes Yes	NA NA	AST increased (Grade 4) ALT increased (Grade 4)

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

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DLT: dose-limiting toxicity

Source: End-of-Text Appendix 13.2.7.6 and 13.2.1.2

Table 6 Overview of Adverse Events - Safety Analysis Set

	ASP2215 120 mg + Erlotinib 150 mg (N =3) n (%)	ASP2215 80 mg + Erlotinib 150 mg (N =7) n (%)	Total (N =10) n (%)
Any TEAE	3 (100%)	7 (100%)	10 (100%)
Drug-related† TEAEs	3 (100%)	7 (100%)	10 (100%)
Serious TEAEs‡	2 (66.7%)	3 (42.9%)	5 (50%)
Drug-related† Serious TEAEs‡	2 (66.7%)	2 (28.6%)	4 (40%)
TEAEs Leading to Withdrawal of Treatment	2 (66.7%)	2 (28.6%)	4 (40%)
Drug-related† TEAEs Leading to Withdrawal of Treatment	2 (66.7%)	2 (28.6%)	4 (40%)
Deaths§	0	0	0

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

A TEAE was a treatment-emergent adverse event, defined as an AE that began or worsened in severity on or after the date of the first dose of study drugs and within 30 days of the date of the last dose of study drugs. If the date of the last dose of study drugs was missing but first dose date was nonmissing, AEs that began after the first dose of study drugs were considered TEAEs. TEAEs also included any reported related AEs regardless of AE onset date.

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† Possibly or probably related to ASP2215 or erlotinib, 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, if any upgrade was done

§ All reported deaths after the first study drug administration until 30 days after the last dose of study medication.

Source: End-of-Text Table 12.6.1.1.2

Table 7 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term (MedDRA v17.1) - Safety Analysis Set

MedDRA v17.1 System Organ Class Preferred Term	ASP2215 120 mg + Erlotinib 150 mg (N =3) n (%)	ASP2215 80 mg + Erlotinib 150 mg (N =7) n (%)	Total (N =10) n (%)
Overall	**3 (100%)**	**7 (100%)**	**10 (100%)**
Gastrointestinal Disorders	3 (100%)	6 (85.7%)	9 (90%)
Diarrhoea	3 (100%)	4 (57.1%)	7 (70%)
Constipation	3 (100%)	2 (28.6%)	5 (50%)
Nausea	1 (33.3%)	1 (14.3%)	2 (20%)
Stomatitis	1 (33.3%)	1 (14.3%)	2 (20%)
Abdominal discomfort	1 (33.3%)	0	1 (10%)
Abdominal distension	0	1 (14.3%)	1 (10%)
Dyspepsia	0	1 (14.3%)	1 (10%)
Enteritis	1 (33.3%)	0	1 (10%)
Gastric Disorder	1 (33.3%)	0	1 (10%)
Haemorrhoids	1 (33.3%)	0	1 (10%)
Oral dysaethesia	0	1 (14.3%)	1 (10%)
Toothache	0	1 (14.3%)	1 (10%)
Vomiting	0	1 (14.3%)	1 (10%)
Investigations	3 (100%)	6 (85.7%)	9 (90%)
ALT increased	3 (100%)	5 (71.4%)	8 (80%)
AST increased	2 (66.7%)	6 (85.7%)	8 (80%)
Blood creatine phosphokinase increased	2 (66.7%)	3 (42.9%)	5 (50%)
Blood alkaline phosphatase increased	0	3 (42.9%)	3 (30%)
Blood creatinine increased	1 (33.3%)	1 (14.3%)	2 (20%)
Blood lactate dehydrogenase increased	0	2 (28.6%)	2 (20%)
Aldolase increased	0	1 (14.3%)	1 (10%)
Amylase increased	0	1 (14.3%)	1 (10%)
Electrocardiogram QT prolonged	1 (33.3%)	0	1 (10%)
Myoglobin blood increased	0	1 (14.3%)	1 (10%)
Platelet count decreased	1 (33.3%)	0	1 (10%)
Weight decreased	0	1 (14.3%)	1 (10%)
Skin and Subcutaneous Tissue Disorders	3 (100%)	6 (85.7%)	9 (90%)
Drug eruption	2 (66.7%)	6 (85.7%)	8 (80%)
Dry skin	2 (66.7%)	1 (14.3%)	3 (30%)
Pruritus	0	2 (28.6%)	2 (20%)
Rash	1 (33.3%)	1 (14.3%)	2 (20%)

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MedDRA v17.1 System Organ Class Preferred Term	ASP2215 120 mg + Erlotinib 150 mg (N =3) n (%)	ASP2215 80 mg + Erlotinib 150 mg (N =7) n (%)	Total (N =10) n (%)
Infections and Infestations	3 (100%)	3 (42.9%)	6 (60%)
Paronychia	1 (33.3%)	2 (28.6%)	3 (30%)
Acne pustular	0	1 (14.3%)	1 (10%)
Conjunctivitis	0	1 (14.3%)	1 (10%)
Cystitis	1 (33.3%)	0	1 (10%)
Gastroenteritis staphylococcal	1 (33.3%)	0	1 (10%)
Pharyngitis	1 (33.3%)	0	1 (10%)
Skin infection	0	1 (14.3%)	1 (10%)
Metabolism and Nutrition Disorders	2 (66.7%)	3 (42.9%)	5 (50%)
Hypoalbuminaemia	0	3 (42.9%)	3 (30%)
Decreased appetite	2 (66.7%)	0	2 (20%)
Hypophosphataemia	0	1 (14.3%)	1 (10%)
Nervous System Disorders	2 (66.7%)	2 (28.6%)	4 (40%)
Dizziness	0	2 (28.6%)	2 (20%)
Dysgeusia	1 (33.3%)	1 (14.3%)	2 (20%)
Peripheral sensory neuropathy	1 (33.3%)	1 (14.3%)	2 (20%)
Headache	0	1 (14.3%)	1 (10%)
Peripheral motor neuropathy	1 (33.3%)	0	1 (10%)
Respiratory, Thoracic and Mediastinal Disorders	0	4 (57.1%)	4 (40%)
Epistaxis	0	1 (14.3%)	1 (10%)
Haemoptysis	0	1 (14.3%)	1 (10%)
Hiccups	0	1 (14.3%)	1 (10%)
Pleural effusion	0	1 (14.3%)	1 (10%)
Pleurisy	0	1 (14.3%)	1 (10%)
General Disorders and Administration Site Conditions	2 (66.7%)	1 (14.3%)	3 (30%)
Malaise	2 (66.7%)	0	2 (20%)
Fatigue	0	1 (14.3%)	1 (10%)
Renal and Urinary Disorders	1 (33.3%)	2 (28.6%)	3 (30%)
Proteinuria	0	2 (28.6%)	2 (20%)
Renal failure acute	1 (33.3%)	0	1 (10%)
Cardiac Disorders	0	2 (28.6%)	2 (20%)
Atrial fibrillation	0	1 (14.3%)	1 (10%)
Sinus tachycardia	0	1 (14.3%)	1 (10%)
Musculoskeletal and Connective Tissue Disorders	1 (33.3%)	1 (14.3%)	2 (20%)
Arthralgia	0	1 (14.3%)	1 (10%)
Back pain	1 (33.3%)	0	1 (10%)
Myalgia	1 (33.3%)	0	1 (10%)
Pain in extremity	0	1 (14.3%)	1 (10%)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	1 (33.3%)	1 (14.3%)	2 (20%)
Cancer pain	0	1 (14.3%)	1 (10%)
Tumour pain	1 (33.3%)	0	1 (10%)
Psychiatric Disorders	0	2 (28.6%)	2 (20%)
Insomnia	0	2 (28.6%)	2 (20%)
Blood and Lymphatic System Disorders	0	1 (14.3%)	1 (10%)
Anemia	0	1 (14.3%)	1 (10%)

Table continued on next page

MedDRA v17.1 System Organ Class Preferred Term	ASP2215 120 mg + Erlotinib 150 mg (N =3) n (%)	ASP2215 80 mg + Erlotinib 150 mg (N =7) n (%)	Total (N =10) n (%)
Injury, Poisoning and Procedural Complications	0	1 (14.3%)	1 (10%)
Fracture	0	1 (14.3%)	1 (10%)
Vascular Disorders	1 (33.3%)	0	1 (10%)
Hypertension	1 (33.3%)	0	1 (10%)

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

Within a system organ class, a patient may have reported more than 1 type of AE. For each preferred term, each patient was only counted once.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MedDRA: Medical Dictionary for Regulatory Activities

A TEAE was a treatment-emergent adverse event, defined as an AE that began or worsened in severity on or after the date of the first dose of study drugs and within 30 days of the date of the last dose of study drugs. If the date of the last dose of study drugs was missing but first dose date was non-missing, AEs that began after the first dose of study drugs were considered TEAEs. TEAEs also included any reported related AEs regardless of AE onset date.

Source: End-of-Text Table 12.6.1.2.2

Table 8 Patients with Serious Treatment-emergent Adverse Events (MedDRA v17.1) by System Organ Class and Preferred Term - Safety Analysis Set

MedDRA v17.1 System Organ Class Preferred Term	ASP2215 120 mg + Erlotinib 150 mg (N = 3) n (%)	ASP2215 80 mg + Erlotinib 150 mg (N = 7) n (%)	Total (N = 10) n (%)
Overall	**2 (66.7%)**	**3 (42.9%)**	**5 (50%)**
Investigations	**2 (66.7%)**	**2 (28.6%)**	**4 (40%)**
ALT increased	2 (66.7%)	2 (28.6%)	4 (40%)
AST increased	2 (66.7%)	1 (14.3%)	3 (30%)
Injury, Poisoning and Procedural Complications	**0**	**1 (14.3%)**	**1 (10%)**
Fracture	0	1 (14.3%)	1 (10%)
Renal and Urinary Disorders	**1 (33.3%)**	**0**	**1 (10%)**
Renal failure acute	1 (33.3%)	0	1 (10%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**1 (14.3%)**	1 (10%)
Pleural effusion	0	1 (14.3%)	1 (10%)

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

Within a system organ class, a patient may have reported more than one type of AE.

A TEAE was a treatment-emergent adverse event, defined as an AE that began or worsened in severity on or after the date of the first dose of study drugs and within 30 days of the date of the last dose of study drugs. If the date of the last dose of study drugs was missing but first dose date was nonmissing, AEs that began after the first dose of study drugs were considered TEAEs. TEAEs also included any reported related AEs regardless of AE onset date.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; MedDRA: Medical Dictionary for Regulatory Activities

Source: End-of-Text Table 12.6.1.3.3 and Appendix 13.2.7.4