Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not available		
Name of Active Ingredient: Gilteritinib (ASP2215)		

SYNOPSIS

Title of Study: A Phase 1 Open-label, Dose-escalation Study Investigating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ASP2215 in Japanese Patients With Relapsed or Refractory Acute Myeloid Leukemia

Coordinating Investigator: [redacted], MD, PhD

Study Centers: Study 2215-CL-0102 was conducted at 5 sites in Japan.

Publication Based on the Study: Not applicable.

Study Period: 16 Jun 2014 to 27 Jun 2016

Study Initiation Date (Date of First Informed Consent Signed): 16 Jun 2014

Study Completion Date (Date of Last Evaluation): 27 Jun 2016

Phase of Development: Phase 1

Objectives:

The primary objectives of the study were to assess the safety and tolerability of ASP2215, determine the maximum tolerated dose (MTD) based on the onset of dose-limiting toxicity (DLT) and/or determine the recommended dose (RD) of ASP2215 for the next phase.

The secondary objectives of the study were to assess the antileukemic activity of various doses of ASP2215 and determine the pharmacokinetic parameters of ASP2215.
The exploratory objective of the study was to assess the pharmacodynamic parameters of ASP2215.

Methodology:

This study was an open-label, dose-escalation study of single and repeated oral once daily dosing of ASP2215 in patients with relapsed or treatment-refractory acute myeloid leukemia (AML).

Each dose level had a single-dose period (cycle 0, which consisted of 2 days) and a repeated-dose period (cycle 1 and the subsequent cycles, each cycle consisting of 28 days). The enrolled patients orally received their assigned single dose in cycle 0 (day -2), followed by a 2-day observation period (dosing day inclusive). From cycle 1 onwards, the patients received oral ASP2215 once daily in 28-day cycles until one of the discontinuation criteria was met. The DLT observation period was 30 days starting with the first dose in cycle 0 (day -2) and including cycle 1 (the first 28-day treatment cycle).

The starting dose level was 20 mg daily. ASP2215 was to be administered in at least 1 patient at the 20-mg dose level and at least 3 patients at the subsequent dose levels (40, 80, 120, 200 and 300 mg). Patients who had received ASP2215 in a certain dose level were not assigned to another dose level.

Bayesian-continual reassessment method (Bayesian-CRM) was used to calculate the recommended dose level for the subsequent cohort based on DLT incidence. The dose escalation meetings were held with the sponsor, the investigators and the medical expert at minimum after the all patients in each cohort completed cycle 1. Dose levels were determined based on the recommended dose level calculated from Bayesian-CRM and the available safety information. If the next Bayesian-CRM-recommended dose level already had 6 patients, patient enrollment and DLT assessment were to be stopped.

The MTD was defined as the highest dose level at which the posterior mean DLT rate was estimated to be closest to 33% by using Bayesian-CRM based on DLT incidence. The sponsor determined the RD by comprehensively assessing the data obtained from the study including the MTD, safety, pharmacokinetics and efficacy of ASP2215, after the discussion with the medical expert, the investigators and the statistical advisor.

Number of Patients (Planned, Enrolled and Analyzed):

A total of 36 patients were planned (DLT evaluable patients: 1 to 6 patients at Dose Level 1 and 3 to 6 patients at the other dose levels; for the entire trial: maximum of 36 patients in total).

Twenty-seven patients were enrolled in the study and 24 patients received the study drug. All 24 patients receiving the study drug were included in the safety analysis set (SAF) and pharmacokinetic analysis set (PKAS). Of the 24 patients, 19 patients were included in the full analysis set (FAS), 18 patients in the dose-determining analysis set (DDAS).

Diagnosis and Main Criteria for Inclusion:

Male or female patients ≥ 18 years of age, inclusive, at the time of obtaining informed consent, who provided written informed consent and to whom all the inclusive and none of the exclusion criteria applied, were eligible for inclusion in this study. Patients had to be defined as morphologically documented primary or secondary AML by the WHO criteria (2008) and fulfilled one of the following: refractory to a prior induction chemotherapy or relapsed after achieving remission with a prior therapy.

Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. Patients' interval from prior treatment to time of study drug administration was at least 14 days for antineoplastic agents other than ASP2215 (except hydroxyurea given for controlling blast cells), or at least 5 half-lives for prior other investigational products or drugs used for immunosuppressive therapy post hematopoietic stem cell transplantation. Patients must have been suitable for oral administration of study drug.

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

ASP2215 was available either as 10 or 100 mg tablets contained within 30 count bottles. The study centers were provided with bottles containing 30 tablets of ASP2215 10 or 100 mg. The lot numbers for ASP2215 10 mg tablets were [redacted] and [redacted]; the lot number for ASP2215 100 mg tablets was [redacted].

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

ASP2215 was administered as a single dose in cycle 0 (day -2), followed by a 2-day observation period (dosing day inclusive). From cycle 1 onwards, ASP2215 was administered once daily in a 28-day cycle until one of the discontinuation criteria was met.

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

Criteria for Evaluation:

Efficacy:

Antitumor response was assessed on the days of bone marrow sampling based on the bone marrow findings and peripheral blast count, neutrophil count and platelet count. Antitumor response was defined per modified Cheson criteria (2003). Best response was defined as the best assessment (complete remission [CR], CR with incomplete platelet recovery [CRp], CR with incomplete hematologic recovery [CRi] or partial remission [PR]) obtained at each efficacy assessment time point after the start of treatment. Duration of response was defined as the period from the first day of achieving CR, CRp, CRi or PR to the first day of confirmed relapse.

Pharmacokinetics:

The following plasma pharmacokinetic parameters of ASP2215 were estimated:

- Single-dose period: AUC_{inf}, AUC_{last}, AUC_{24}, AUC_{48}, C_{max}, C_{24}, CL/F, Lambda z, t_{max}, $t_{1/2}$, V_z/F
- Repeated-dose period: AUC_{tau}, C_{max}, C_{trough}, C_{24}, CL/F, t_{max}, PTR, R_{ac} (AUC), R_{ac} (C_{max}) and R_{ac} derived $t_{1/2}$

The following urine pharmacokinetic parameters were estimated:

- Single-dose period: Ae_{24}, Ae_{48}, Ae_{24}%, Ae_{48}%, CL_R
- Repeated-dose period: Ae_{tau}, Ae_{tau}%, CL_R

Pharmacodynamics:

Blood FMS-like tyrosine kinase-3 (FLT3) and AXL phosphorylation were to be evaluated to assess inhibitory effect of ASP2215 on phosphorylation. However, analyses of blood FLT3 and AXL phosphorylation were not performed, because sufficient evaluable measurements could not be obtained from the collected samples and the results were deemed not interpretable.

Safety:

The safety and tolerability of ASP2215 were assessed by evaluation of the following variables: DLT, adverse events (AEs), clinical laboratory variables (hematology, biochemistry and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, arterial oxygen saturation and body weight), 12-lead electrocardiogram (ECG), ophthalmologic examinations and ECOG PS.

Statistical Methods:

Efficacy:

The FAS consisted of all patients who received at least 1 dose of the study drug and who were assessed for at least 1 posttreatment efficacy variable. The primary efficacy analysis was performed on the FAS. The following classifications according to the modified Cheson criteria (2003) were summarized by frequency: CR,

CRp, CRi, PR, no response (NR), not evaluable (NE), composite CR (CRc) defined as CR + CRp + CRi and overall response rate defined as CRc + PR. Descriptive statistics were calculated for the duration of response.

Pharmacokinetics:

The PKAS consisted of all patients who received the study drug, from whom samples for drug concentration measurement were collected for at least 1 posttreatment time point, and from whom drug concentration data were available. The pharmacokinetic analysis was performed on the PKAS. Plasma or urine concentrations and pharmacokinetic parameters of ASP2215 were summarized by dose group using descriptive statistics, including number of patients, mean, SD, minimum, median, maximum, geometric mean and coefficient of variation (%CV) of the mean and geometric mean.

Dose proportionality of ASP2215 was assessed for AUC_{last}, AUC_{tau} and C_{max} using the power model. The estimates of the slope of the regression line and its 95% confidence interval (CI) were shown. No dose proportionality was declared if the 95% CI did not contain 1.

To visually assess the steady state, mean C_{trough} from cycle 1 day 8, 15, 22, 28 and 29 were plotted.

Accumulation was assessed for C_{max} and AUC_{tau} using the analysis variance with day as a fixed effect and patients as a random effect.

Safety:

The DDAS consisted of all patients who did not meet any of the following criteria: (1) patients who received less than 80% of the intended doses of ASP2215 during cycle 1 for other reasons than interruption or discontinuation of the study treatment due to DLTs; and/or (2) patients whose safety could not be assessed adequately in cycle 0 and cycle 1, such as due to a lack of the required safety assessment(s). The number and percentage of patients with a DLT were summarized by dose level for the DDAS to calculate DLT rate. The posterior mean of the DLT rate at each dose level was estimated from the Bayesian-CRM and the posterior density plot was presented.

The SAF consisted of all patients who received at least 1 dose of the study drug and was used for analyses of all safety analyses except the DLT assessment. The number and percentage of patients experiencing 1 or more AEs was summarized by dose level. All AEs were coded to system organ class (SOC) and preferred term (PT) using MedDRA version 16.1. The severity of all AEs was graded by the investigator based on National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Laboratory parameters were summarized by dose level using descriptive statistics, shifts in change from baseline and data listings of clinically significant abnormalities. Vital signs and ECG parameters and their changes from baseline were summarized by dose level using descriptive statistics.

Summary of Results/Conclusions:

Twenty-seven patients were enrolled in the study. Of these, 24 received the study drug and 3 discontinued before the start of study drug [Table 1]. All 24 patients discontinued study treatment; the primary reasons for discontinuation were other including progressive disease (15 patients), AE (6 patients), withdrawal by patient (2 patients) and lack of efficacy (1 patient).

The majority of patients within the SAF were male (62.5%, 15/24) and ≥ 65 years of age (83.3%, 20/24). Patient demographics were generally similar between patients that were FLT3 mutation-positive versus FLT3

mutation-negative except for ECOG PS (a numerically higher percentage of patients with ECOG PS of 0 in FLT3 mutation-negative patients than FLT3 mutation-positive patients) [Table 2].

Efficacy Results:

Based on the response at end of treatment, 7 patients achieved CRc for a CRc rate of 36.8% (95% CI: 16.3%, 61.6%) and the response rate was 47.4% (95% CI: 24.4%, 71.1%) [Table 3]. Patients in the 200-mg dose group had the highest CRc rate and response rate in ≥ 80-mg dose groups: the CRc rate and the response rate were 57.1% (95%CI: 18.4%, 90.1%) at end of treatment.

At end of treatment, in the FLT3 mutation-positive patients, 3 patients achieved CRc for a CRc rate of 60.0% (95% CI: 14.7%, 94.7%) and the response rate was 80.0% (95% CI: 28.4%, 99.5%) [Table 4]. Anti-leukemic activity of ASP2215 was demonstrated by CRc rate in patients between the 20-mg and 200-mg dose groups.

Across all dose groups, the median duration of CRc was 86.5 days and the median duration of remission was 113.5 days [Table 5].

Pharmacokinetic Results:

ASP2215 exhibits linear, dose-proportional pharmacokinetics in patients with relapsed or treatment-refractory AML at doses ranging from 20 to 300 mg administered once daily [Figure 1 and Figure 2]. Median t_{max} was observed between 3 and 7 hours following single and multiple dosing [Table 6 and Table 7]. The estimated $t_{1/2}$ ranged from 84 to 126 hours. Given the long half-life, extensive accumulation was observed with ASP2215 concentrations increasing by up to approximately 8-fold after multiple dose administration. Steady-state ASP2215 concentrations were achieved by day 15 after multiple doses.

Safety Results:

Within the 24 DLT evaluable patients, 3 patients experienced a DLT during cycle 0 and cycle 1, including 1 patient (25.0%) in the 120-mg dose group and 2 patients (100.0%) in the 300-mg dose group [Table 8].

Overall, all patients receiving the study drug experienced at least 1 AE and 91.7% (22/24) of the patients experienced a drug-related AE [Table 9]. The common AEs occurring in ≥ 20% of all patients were hepatic function abnormal and blood creatine phosphokinase increased (37.5%, 9/24), blood lactate dehydrogenase increased (33.3%, 8/24), diarrhea and pyrexia (29.2%, 7/24) and febrile neutropenia, stomatitis, renal impairment and hypertension (20.8%, 5/24) [Table 10]. Of these common AEs, hepatic function abnormal, blood creatine phosphokinase increased and diarrhea appeared to have increased incidence with increasing doses. The majority of the common AEs including hepatic function abnormal, blood creatine phosphokinase increased and diarrhea were considered by the investigator to be related to study drug. Overall, 66.7% (16/24) of all patients experienced AEs with maximum NCI-CTCAE grade 3 or higher. NCI-CTCAE grade 3 or higher AEs reported in ≥ 10% of all patients were platelet count decreased (16.7%, 4/24) and disseminated intravascular coagulation, febrile neutropenia, pneumonia and blood creatine phosphokinase increased (12.5%, 3/24).

One patient death occurred during the study from subdural hematoma that was considered to be related to study drug. Overall, 29.2% (7/24) of all patients experienced serious adverse events (SAEs) [Table 11]. The only SAE reported in ≥ 2 patients was subdural hematoma (8.3%, 2/24). The majority of SAEs were considered by the investigator to be related to study drug. Overall, 25.0% (6/24) of all patients experienced AEs resulting in permanent discontinuation of study drug. The only AE leading to discontinuation reported in ≥ 2 patients was

pneumonia (8.3%, 2/24). All the AEs resulting in discontinuation except for 1 event in the 200-mg dose group were considered by the investigator to be related to study drug.

In this study, AEs of special safety interest reported included diarrhea, lower gastrointestinal hemorrhage, gastroenteritis, blood creatine phosphokinase increased, electrocardiogram QT prolonged, blood creatinine increased, hypocalcemia, muscular weakness, syncope, coma hepatic, delirium and renal impairment. The most common AE of special interest was blood creatine phosphokinase increased (37.5%, 9/24), followed by diarrhea (29.2%, 7/24) and renal impairment (20.8%, 5/24).

For all hematology test parameters (hemoglobin, leukocytes and platelets), more than 1 patient had baseline values < NCI-CTCAE grade 3 that shifted to worst postbaseline values ≥ NCI-CTCAE grade 3. For the following chemistry test parameters, more than 1 patient had baseline values < NCI-CTCAE grade 3 that shifted to worst postbaseline values ≥ NCI-CTCAE grade 3: creatine kinase, albumin, phosphate and potassium. Although there were no patients with ALT and/or AST > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN across all dose groups, ASP2215 could be associated with increasing levels of ALT and AST with increasing doses.

Overall, mean changes in vital signs fluctuated and showed no particular change across dose groups during treatment. Few potentially clinically significant vital sign values were found.

The maximum postbaseline QT interval corrected using Fridericia's correction factor (QTcF) of > 450 msec was observed in 37.5% (9/24) of evaluable patients and the maximum QTcF change from baseline of > 30 msec was observed in 22.7% (5/22) of evaluable patients. One patient in the 20-mg dose group experienced a maximum postbaseline QTcF of > 480 msec and a maximum QTcF change from baseline of > 60 msec. The proportion of patients with changes in QTcF interval showed no particular trend with increasing doses.

CONCLUSIONS:

- ASP2215 was generally well tolerated at doses up to 200 mg in the study. Based on the DLT evaluation results, the MTD for the study in Japanese patients was determined to be 200 mg.
- Based on exposure, response and safety data, a starting dose of 120 mg is expected to result in adequate drug exposure for clinical efficacy for phase 3 studies in patients with FLT3 mutation-positive relapsed or treatment-refractory AML.
- ASP2215 exhibits linear, dose-proportional pharmacokinetics in patients with relapsed or treatment-refractory AML at doses ranging from 20 to 300 mg administered once daily.
- The CRc rate at end of treatment was 36.8% (7/19) of all patients. Anti-leukemic activity of ASP2215 was demonstrated by CRc rate in patients between the 20-mg and 200-mg dose groups.

Date of Report: 12 May 2017

Table 1 Patient Disposition

n (%)	20 mg	40 mg	80 mg	120 mg	200 mg	300 mg	Total
Informed consent	–	–	–	–	–	–	27
Received study drug	1	4	4	4	9	2	24
Discontinued before start of study drug	–	–	–	–	–	–	3
Treatment Discontinuation							
Yes	1 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	9 (100.0)	2 (100.0)	24 (100.0)
Primary Reason for Treatment Discontinuation †							
Withdrawal by Patient	0	0	0	1 (25.0)	1 (11.1)	0	2 (8.3)
Adverse Event	0	1 (25.0)	1 (25.0)	0	2 (22.2)	2 (100.0)	6 (25.0)
There is No PR, CR, CRp or CRi After 2 cycles Of Therapy	0	0	1 (25.0)	0	0	0	1 (4.2)
Other ‡	1 (100.0)	3 (75.0)	2 (50.0)	3 (75.0)	6 (66.7)	0	15 (62.5)
Study Discontinuation							
Yes	1 (100.0)	3 (75.0)	3 (75.0)	3 (75.0)	3 (33.3)	0	13 (54.2)
No	0	1 (25.0)	1 (25.0)	1 (25.0)	6 (66.7)	2 (100.0)	11 (45.8)
Primary Reason for Study Discontinuation †							
Progressive Disease	0	1 (33.3)	2 (66.7)	2 (66.7)	3 (100.0)	0	8 (61.5)
Withdrawal by Patient	0	0	0	1 (33.3)	0	0	1 (7.7)
Death	0	0	1 (33.3)	0	0	0	1 (7.7)
Other	1 (100.0)	2 (66.7)	0	0	0	0	3 (23.1)

CR: complete remission; CRi: complete remission with incomplete hematological recovery; CRp: complete remission with incomplete platelet recovery; PR: partial remission.

† Only the primary reason for discontinuation was collected.

‡ Other included progressive disease.

Source: Tables 12.1.1.1, 12.1.1.2, 12.1.1.3 and 12.1.1.4

Table 2 Demographic Characteristics by Central FLT3 Mutation Status – Safety Analysis Set

Characteristic		FLT3 Positive n = 5	FLT3 Negative n = 16	Total n = 24 †
Sex, n (%)	Male	3 (60.0)	10 (62.5)	15 (62.5)
	Female	2 (40.0)	6 (37.5)	9 (37.5)
Race, n (%)	Asian	5 (100.0)	16 (100.0)	24 (100.0)
Age (years)	Mean (SD)	72.0 (7.0)	71.4 (5.6)	70.7 (6.3)
	Min, Max	64, 81	63, 81	60, 81
Age Group, n (%)	< 65 years	1 (20.0)	1 (6.3)	4 (16.7)
	≥ 65 years	4 (80.0)	15 (93.8)	20 (83.3)
Height (cm)	Mean (SD)	159.62 (10.01)	160.09 (6.57)	160.53 (7.01)
	Min, Max	150.0, 176.3	151.7, 171.9	150.0, 176.3
Weight (kg)	Mean (SD)	48.46 (4.10)	54.76 (11.09)	53.65 (9.77)
	Min, Max	45.5, 55.5	36.0, 78.4	36.0, 78.4
Body Mass Index (kg/m^2)	Mean (SD)	19.22 (3.02)	21.39 (4.61)	20.87 (4.06)
	Min, Max	15.4, 23.1	14.9, 33.5	14.9, 33.5
ECOG Performance Status, n (%)	0	2 (40.0)	9 (56.3)	12 (50.0)
	1	3 (60.0)	6 (37.5)	11 (45.8)
	2	0	1 (6.3)	1 (4.2)
	3	0	0	0
	4	0	0	0

ECOG: Eastern Cooperative Oncology Group.

† Three patients who were categorized as “missing” or “invalid” were included in the total.

Source: Table 12.1.2.1.1b

Table 3 Response Assessment – Full Analysis Set

	20 mg n = 1	40 mg n = 3	80 mg n = 4	120 mg n = 2	200 mg n = 7	300 mg n = 2	Total n = 19
End of Cycle 2							
Best Overall Response, n (%) [95% CI] †							
n	1	3	3	2	5	1	15
CR	0 [0.0-97.5]	0 [0.0-70.8]	1 (33.3) [0.8-90.6]	0 [0.0-84.2]	0 [0.0-52.2]	0 [0.0-97.5]	1 (6.7) [0.2-31.9]
CRp	0 [0.0-97.5]	0 [0.0-70.8]	0 [0.0-70.8]	0 [0.0-84.2]	2 (40.0) [5.3-85.3]	0 [0.0-97.5]	2 (13.3) [1.7-40.5]
CRi	1 (100.0) [2.5-100.0]	0 [0.0-70.8]	0 [0.0-70.8]	1 (50.0) [1.3-98.7]	2 (40.0) [5.3-85.3]	0 [0.0-97.5]	4 (26.7) [7.8-55.1]
PR	0 [0.0-97.5]	1 (33.3) [0.8-90.6]	1 (33.3) [0.8-90.6]	0 [0.0-84.2]	0 [0.0-52.2]	0 [0.0-97.5]	2 (13.3) [1.7-40.5]
NR	0 [0.0-97.5]	2 (66.7) [9.4-99.2]	1 (33.3) [0.8-90.6]	1 (50.0) [1.3-98.7]	1 (20.0) [0.5-71.6]	1 (100.0) [2.5-100.0]	6 (40.0) [16.3-67.7]
NE	0 [0.0-97.5]	0 [0.0-70.8]	0 [0.0-70.8]	0 [0.0-84.2]	0 [0.0-52.2]	0 [0.0-97.5]	0 [0.0-21.8]
CRc Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	0 [0.0-70.8]	1 (33.3) [0.8-90.6]	1 (50.0) [1.3-98.7]	4 (80.0) [28.4-99.5]	0 [0.0-97.5]	7 (46.7) [21.3-73.4]
Response Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	1 (33.3) [0.8-90.6]	2 (66.7) [9.4-99.2]	1 (50.0) [1.3-98.7]	4 (80.0) [28.4-99.5]	0 [0.0-97.5]	9 (60.0) [32.3-83.7]
End of Treatment							
Best Overall Response, n (%) [95% CI] †							
n	1	3	4	2	7	2	19
CR	0 [0.0-97.5]	0 [0.0-70.8]	1 (25.0) [0.6-80.6]	0 [0.0-84.2]	0 [0.0-41.0]	0 [0.0-84.2]	1 (5.3) [0.1-26.0]
CRp	0 [0.0-97.5]	0 [0.0-70.8]	0 [0.0-60.2]	0 [0.0-84.2]	3 (42.9) [9.9-81.6]	0 [0.0-84.2]	3 (15.8) [3.4-39.6]
CRi	1 (100.0) [2.5-100.0]	0 [0.0-70.8]	0 [0.0-60.2]	1 (50.0) [1.3-98.7]	1 (14.3) [0.4-57.9]	0 [0.0-84.2]	3 (15.8) [3.4-39.6]
PR	0 [0.0-97.5]	1 (33.3) [0.8-90.6]	1 (25.0) [0.6-80.6]	0 [0.0-84.2]	0 [0.0-41.0]	0 [0.0-84.2]	2 (10.5) [1.3-33.1]
NR	0 [0.0-97.5]	2 (66.7) [9.4-99.2]	2 (50.0) [6.8-93.2]	1 (50.0) [1.3-98.7]	3 (42.9) [9.9-81.6]	2 (100.0) [15.8-100.0]	10 (52.6) [28.9-75.6]
NE	0 [0.0-97.5]	0 [0.0-70.8]	0 [0.0-60.2]	0 [0.0-84.2]	0 [0.0-41.0]	0 [0.0-84.2]	0 [0.0-17.6]
CRc Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	0 [0.0-70.8]	1 (25.0) [0.6-80.6]	1 (50.0) [1.3-98.7]	4 (57.1) [18.4-90.1]	0 [0.0-84.2]	7 (36.8) [16.3-61.6]
Response Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	1 (33.3) [0.8-90.6]	2 (50.0) [6.8-93.2]	1 (50.0) [1.3-98.7]	4 (57.1) [18.4-90.1]	0 [0.0-84.2]	9 (47.4) [24.4-71.1]

CR: complete remission; CRc: composite complete remission (CR + CRp + CRi); CRi: complete remission with incomplete hematological recovery; CRp: complete remission with incomplete platelet recovery; NE: not evaluable; NR: no response; PR: partial remission; response: CRc + PR.

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

Source: Tables 12.3.1.1.1a and 12.3.1.1.1b

Table 4 Response Assessment by Central FLT3 Mutation Status – Full Analysis Set

	FLT3 Mutation					
	Positive					Negative
	20 mg n = 1	40 mg n = 1	80 mg n = 1	200 mg n = 2	Total n = 5	Total n = 11
End of Cycle 2						
Best Overall Response, n (%) [95% CI] †						
n	1	1	1	2	5	9
CR	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-84.2]	0 [0.0-52.2]	1 (11.1) [0.3-48.2]
CRp	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-97.5]	1 (50.0) [1.3-98.7]	1 (20.0) [0.5-71.6]	1 (11.1) [0.3-48.2]
CRi	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	0 [0.0-97.5]	1 (50.0) [1.3-98.7]	2 (40.0) [5.3-85.3]	1 (11.1) [0.3-48.2]
PR	0 [0.0-97.5]	0 [0.0-97.5]	1 (100.0) [2.5-100.0]	0 [0.0-84.2]	1 (20.0) [0.5-71.6]	1 (11.1) [0.3-48.2]
NR	0 [0.0-97.5]	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	0 [0.0-84.2]	1 (20.0) [0.5-71.6]	5 (55.6) [21.2-86.3]
NE	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-84.2]	0 [0.0-52.2]	0 [0.0-33.6]
CRc Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	0 [0.0-97.5]	2 (100.0) [15.8-100.0]	3 (60.0) [14.7-94.7]	3 (33.3) [7.5-70.1]
Response Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	1 (100.0) [2.5-100.0]	2 (100.0) [15.8-100.0]	4 (80.0) [28.4-99.5]	4 (44.4) [13.7-78.8]
End of Treatment						
Best Overall Response, n (%) [95% CI] †						
n	1	1	1	2	5	11
CR	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-84.2]	0 [0.0-52.2]	1 (9.1) [0.2-41.3]
CRp	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-97.5]	1 (50.0) [1.3-98.7]	1 (20.0) [0.5-71.6]	2 (18.2) [2.3-51.8]
CRi	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	0 [0.0-97.5]	1 (50.0) [1.3-98.7]	2 (40.0) [5.3-85.3]	0 [0.0-28.5]
PR	0 [0.0-97.5]	0 [0.0-97.5]	1 (100.0) [2.5-100.0]	0 [0.0-84.2]	1 (20.0) [0.5-71.6]	1 (9.1) [0.2-41.3]
NR	0 [0.0-97.5]	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	0 [0.0-84.2]	1 (20.0) [0.5-71.6]	7 (63.6) [30.8-89.1]
NE	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-97.5]	0 [0.0-84.2]	0 [0.0-52.2]	0 [0.0-28.5]
CRc Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	0 [0.0-97.5]	2 (100.0) [15.8-100.0]	3 (60.0) [14.7-94.7]	3 (27.3) [6.0-61.0]
Response Rate, n (%) [95% CI] †	1 (100.0) [2.5-100.0]	0 [0.0-97.5]	1 (100.0) [2.5-100.0]	2 (100.0) [15.8-100.0]	4 (80.0) [28.4-99.5]	4 (36.4) [10.9-69.2]

CR: complete remission; CRc: composite complete remission (CR + CRp + CRi); CRi: complete remission with incomplete hematological recovery; CRp: complete remission with incomplete platelet recovery; NE: not evaluable; NR: no response; PR: partial remission; response: CRc + PR.

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

Source: Tables 12.3.1.1.1c1, 12.3.1.1.1c2, 12.3.1.1.1.d1 and 12.3.1.1.1d2

Table 5 Duration of Remission – Full Analysis Set

	20 mg n = 1	40 mg n = 3	80 mg n = 4	120 mg n = 2	200 mg n = 7	300 mg n = 2	Total n = 19
Duration of CRc (Days)							
n †	1	0	1	1	4	0	7
Number of Events, (%)	1 (100.0)	0	1 (100.0)	1 (100.0)	3 (75.0)	0	6 (85.7)
Min, Max	30.0, 30.0	–	111.0, 111.0	110.0, 110.0	28.0, 116.0	–	28.0, 116.0
Median ‡	30.0	–	111.0	110.0	63.0	–	86.5
95% CI ‡	–	–	–	–	28.0, 116.0	–	28.0, 116.0
Duration of CR (Days)							
n †	0	0	1	0	0	0	1
Number of Events, (%)	0	0	1 (100.0)	0	0	0	1 (100.0)
Min, Max	–	–	111.0, 111.0	–	–	–	111.0, 111.0
Median ‡	–	–	111.0	–	–	–	111.0
95% CI ‡	–	–	–	–	–	–	–
Duration of CRp (Days)							
n †	0	0	0	0	3	0	3
Number of Events, (%)	0	0	0	0	2 (66.7)	0	2 (66.7)
Min, Max	–	–	–	–	28.0, 116.0	–	28.0, 116.0
Median ‡	–	–	–	–	72.0	–	72.0
95% CI ‡	–	–	–	–	28.0, 116.0	–	28.0, 116.0
Duration of CRi (Days)							
n †	1	0	0	1	2	0	4
Number of Events, (%)	1 (100.0)	0	0	1 (100.0)	1 (50.0)	0	3 (75.0)
Min, Max	30.0, 30.0	–	–	110.0, 110.0	63.0, 63.0	–	30.0, 110.0
Median ‡	30.0	–	–	110.0	63.0	–	63.0
95% CI ‡	–	–	–	–	–	–	30.0, 110.0
Duration of Remission (Days)							
n †	1	1	2	1	4	0	9
Number of Events, (%)	1 (100.0)	1 (100.0)	1 (50.0)	1 (100.0)	3 (75.0)	0	7 (77.8)
Min, Max	30.0, 30.0	127.0, 127.0	111.0, 111.0	139.0, 139.0	28.0, 116.0	–	28.0, 139.0
Median ‡	30.0	127.0	–	139.0	63.0	–	113.5
95% CI ‡	–	–	111.0, NE	–	28.0, 116.0	–	28.0, 139.0

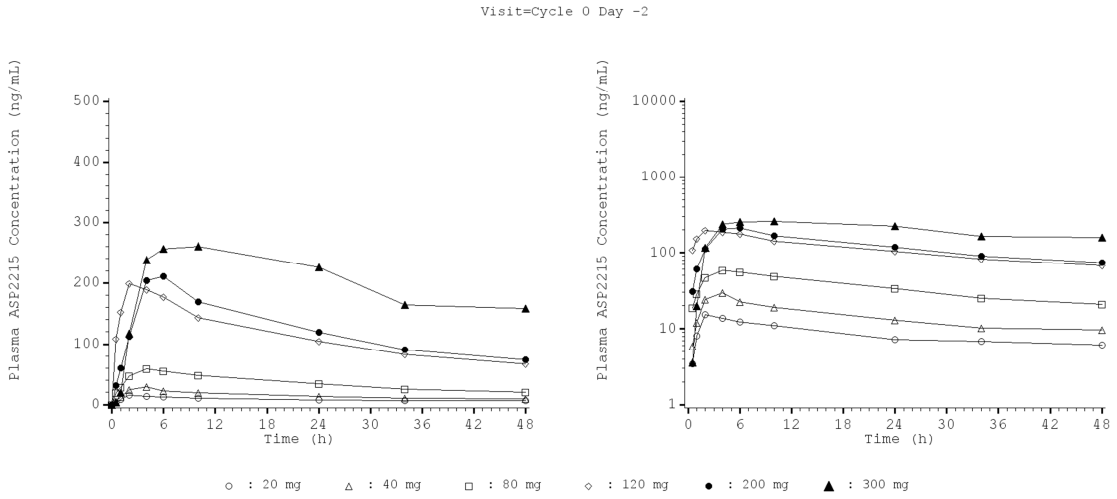
CR: complete remission; CRc: composite complete remission (CR + CRp + CRi); CRi: complete remission with incomplete hematological recovery; CRp: complete remission with incomplete platelet recovery; NE: not evaluable; Remission: CRc + PR.

† Duration of remission was calculated for patients who achieved at least 1 corresponding type of remissions. Patients with missing duration of remission were not included.

‡ Calculated using Kaplan-Meier estimate.

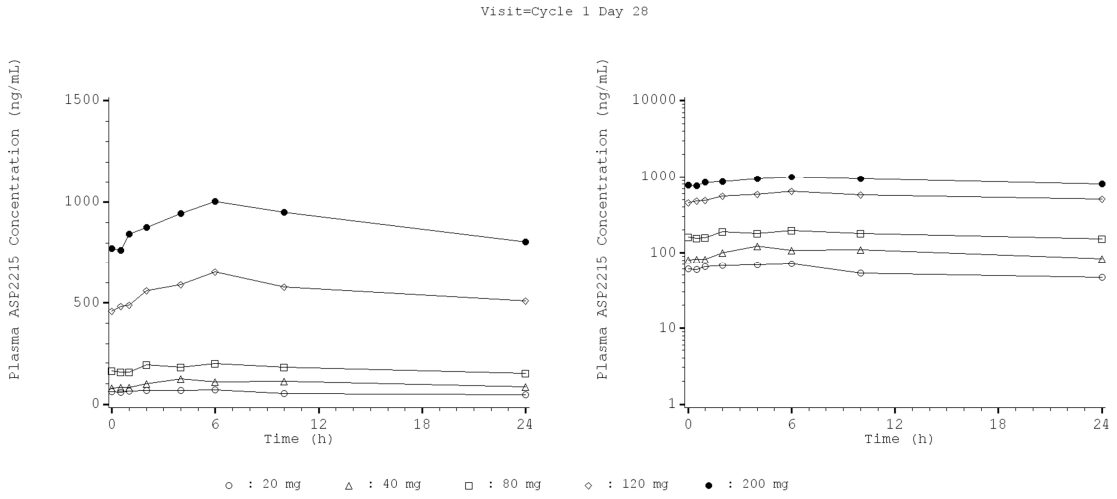
Source: Table 12.3.2.1

Figure 1 **Mean ASP2215 Plasma Concentration-time Profiles After Single Dose (Day -2) Administration (Linear and Semi-log Scale) - Pharmacokinetic Analysis Set**



Source: Figure 12.4.2.1

Figure 2 **Mean ASP2215 Plasma Concentration-time Profiles After Multiple Dose (Cycle 1 Day 28) Administration (Linear and Semi-log Scale) - Pharmacokinetic Analysis Set**



Source: Figure 12.4.2.2

Table 6 Plasma Pharmacokinetic Parameters of ASP2215 by Dose Group After Single Dose (Day -2) Administration – Pharmacokinetic Analysis Set

Parameter Statistic	20 mg (n = 1)	40 mg (n = 4)	80 mg (n = 4)	120 mg (n = 4)	200 mg (n = 9)	300 mg (n = 2)
C_{max} (ng/mL)						
Mean	15.32	29.81	67.07	216.38	221.22	292.49
(SD)	(NA)	(13.56)	(26.02)	(167.00)	(97.05)	(NA)
%CV	NA	45.5	38.8	77.2	43.9	NA
Median	NA	31.17	65.58	165.83	209.94	292.49
Min,	NA,	12.34,	44.47,	75.44,	91.62,	170.40,
Max	NA	44.56	92.64	458.44	403.11	414.58
AUC_{24} (ng·h/mL)						
Mean	241.65	435.59	1047.54	3340.23	3595.61	5367.62
(SD)	(NA)	(167.16)	(574.97)	(2353.76)	(1463.99)	(NA)
%CV	NA	38.4	54.9	70.5	40.7	NA
Median	NA	492.41	1036.55	2742.81	3616.03	5367.62
Min,	NA,	192.64,	438.43,	1183.55,	1776.16,	2810.75,
Max	NA	564.89	1678.61	6691.76	6701.00	7924.49
t_{max} (h)						
Median	NA	4.01	4.03	3.03	5.92	6.93
Min,	NA,	3.88,	2.00,	1.93,	3.85,	3.88,
Max	NA	4.08	9.93	6.17	10.00	9.98

NA: not applicable.

Source: Tables 12.4.2.1.1, 12.4.2.2.1, 12.4.2.3.1, 12.4.2.4.1, 12.4.2.5.1 and 12.4.2.6.1

Table 7 Plasma Pharmacokinetic Parameters of ASP2215 by Dose Group After Multiple Dose (Cycle 1 Day 28) Administration - Pharmacokinetic Analysis Set

Parameter Statistic	20 mg (n = 1)	40 mg (n = 3)	80 mg (n = 3)	120 mg (n = 2)	200 mg (n = 5)
C_{max} (ng/mL)					
Mean	70.53	122.96	205.90	680.23	1016.28
(SD)	(NA)	(66.06)	(36.78)	(NA)	(295.23)
%CV	NA	53.7	17.9	NA	29.0
Median	NA	158.24	215.76	680.23	886.50
Min,	NA,	46.75,	165.20,	668.89,	837.54,
Max	NA	163.88	236.75	691.57	1538.03
AUC_{tau} (ng·h/mL)					
Mean	1345.53	2411.97	4142.27	13463.35	21573.86
(SD)	(NA)	(1181.65)	(738.07)	(NA)	(6230.86)
%CV	NA	49.0	17.8	NA	28.9
Median	NA	3092.77	4510.94	13463.35	19400.24
Min,	NA,	1047.52,	3292.50,	13151.21,	16968.79,
Max	NA	3095.63	4623.37	13775.49	32181.53
t_{max} (h)					
Median	NA	3.92	6.08	5.06	6.00
Min,	NA,	2.05,	1.93,	4.03,	3.98,
Max	NA	3.95	6.12	6.08	10.00
R_{ac} (AUC)					
Mean	5.57	5.86	5.97	7.97	8.10
(SD)	(NA)	(0.70)	(4.08)	(NA)	(3.69)
%CV	NA	11.9	68.4	NA	45.6
Median	NA	5.48	4.68	7.97	8.83
Min,	NA,	5.44,	2.69,	4.83,	3.89,
Max	NA	6.67	10.55	11.11	12.18

NA: not applicable.

Source: Tables 12.4.2.1.2, 12.4.2.2.2, 12.4.2.3.2, 12.4.2.4.2 and 12.4.2.5.2

Table 8 Dose-limiting Toxicities by Dose Level – Safety Analysis Set

MedDRA ver. 16.1 SOC PT, n (%)	20 mg n = 1	40 mg n = 4	80 mg n = 4	120 mg n = 4	200 mg n = 9	300 mg n = 2	Total n = 24
Overall	0	0	0	1 (25.0)	0	2 (100.0)	3 (12.5)
Investigations	0	0	0	0	0	2 (100.0)	2 (8.3)
Amylase increased	0	0	0	0	0	1 (50.0)	1 (4.2)
Blood creatine phosphokinase increased	0	0	0	0	0	1 (50.0)	1 (4.2)
Blood lactate dehydrogenase increased	0	0	0	0	0	1 (50.0)	1 (4.2)
Metabolism and Nutrition Disorders	0	0	0	1 (25.0)	0	0	1 (4.2)
Tumour lysis syndrome	0	0	0	1 (25.0)	0	0	1 (4.2)
Nervous System Disorders	0	0	0	0	0	1 (50.0)	1 (4.2)
Syncope	0	0	0	0	0	1 (50.0)	1 (4.2)

Source: Table 12.6.1.1

Table 9 Overview of Adverse Events – Safety Analysis Set

n (%)	20 mg n = 1	40 mg n = 4	80 mg n = 4	120 mg n = 4	200 mg n = 9	300 mg n = 2	Total n = 24
AEs	1 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	9 (100.0)	2 (100.0)	24 (100.0)
Drug-related † AEs	1 (100.0)	3 (75.0)	3 (75.0)	4 (100.0)	9 (100.0)	2 (100.0)	22 (91.7)
Death	0	0	1 (25.0)	0	0	0	1 (4.2)
Serious AEs	0	1 (25.0)	1 (25.0)	0	5 (55.6)	0	7 (29.2)
Drug-related † Serious AEs	0	1 (25.0)	1 (25.0)	0	2 (22.2)	0	4 (16.7)
AEs Leading to Permanent Discontinuation of Study Drug	0	1 (25.0)	1 (25.0)	0	2 (22.2)	2 (100.0)	6 (25.0)
Drug-related † AEs Leading to Permanent Discontinuation of Study Drug	0	1 (25.0)	1 (25.0)	0	1 (11.1)	2 (100.0)	5 (20.8)
Grade 3 or Higher AEs	1 (100.0)	2 (50.0)	2 (50.0)	2 (50.0)	7 (77.8)	2 (100.0)	16 (66.7)
Drug-Related † Grade 3 or Higher AEs	0	1 (25.0)	1 (25.0)	1 (25.0)	4 (44.4)	2 (100.0)	9 (37.5)

AE: adverse event.

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

Source: Table 12.6.1.2

Table 10 Incidence of Adverse Events Reported in ≥ 2 Total Patients – Safety Analysis Set

MedDRA ver. 16.1 SOC PT, n (%)	20 mg n = 1	40 mg n = 4	80 mg n = 4	120 mg n = 4	200 mg n = 9	300 mg n = 2	Total n = 24
Overall	1 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	9 (100.0)	2 (100.0)	24 (100.0)
Blood and Lymphatic System Disorders	0	1 (25.0)	0	3 (75.0)	3 (33.3)	2 (100.0)	9 (37.5)
Febrile neutropenia	0	1 (25.0)	0	1 (25.0)	2 (22.2)	1 (50.0)	5 (20.8)
Disseminated intravascular coagulation	0	1 (25.0)	0	3 (75.0)	0	0	4 (16.7)
Anaemia	0	0	0	0	1 (11.1)	1 (50.0)	2 (8.3)
Eye Disorders	0	1 (25.0)	2 (50.0)	0	4 (44.4)	0	7 (29.2)
Corneal erosion	0	1 (25.0)	2 (50.0)	0	1 (11.1)	0	4 (16.7)
Gastrointestinal Disorders	0	1 (25.0)	4 (100.0)	1 (25.0)	7 (77.8)	2 (100.0)	15 (62.5)
Diarrhoea	0	1 (25.0)	0	0	4 (44.4)	2 (100.0)	7 (29.2)
Stomatitis	0	1 (25.0)	2 (50.0)	1 (25.0)	0	1 (50.0)	5 (20.8)
Constipation	0	0	2 (50.0)	0	2 (22.2)	0	4 (16.7)
Nausea	0	1 (25.0)	0	0	3 (33.3)	0	4 (16.7)
Vomiting	0	0	1 (25.0)	0	0	1 (50.0)	2 (8.3)
General Disorders and Administration Site Conditions	0	2 (50.0)	1 (25.0)	2 (50.0)	4 (44.4)	0	9 (37.5)
Pyrexia	0	0	1 (25.0)	2 (50.0)	4 (44.4)	0	7 (29.2)
Hepatobiliary Disorders	0	0	3 (75.0)	1 (25.0)	4 (44.4)	2 (100.0)	10 (41.7)
Hepatic function abnormal	0	0	2 (50.0)	1 (25.0)	4 (44.4)	2 (100.0)	9 (37.5)
Infections and Infestations	0	2 (50.0)	1 (25.0)	1 (25.0)	4 (44.4)	2 (100.0)	10 (41.7)
Pneumonia	0	2 (50.0)	0	0	1 (11.1)	1 (50.0)	4 (16.7)
Sepsis	0	0	1 (25.0)	0	0	1 (50.0)	2 (8.3)
Lung infection	0	1 (25.0)	0	0	0	1 (50.0)	2 (8.3)
Injury, Poisoning and Procedural Complications	0	2 (50.0)	1 (25.0)	1 (25.0)	1 (11.1)	0	5 (20.8)
Subdural haematoma	0	0	1 (25.0)	0	1 (11.1)	0	2 (8.3)
Investigations	1 (100.0)	1 (25.0)	1 (25.0)	4 (100.0)	7 (77.8)	2 (100.0)	16 (66.7)
Blood creatine phosphokinase increased	0	0	0	0	7 (77.8)	2 (100.0)	9 (37.5)
Blood lactate dehydrogenase increased	0	0	1 (25.0)	3 (75.0)	3 (33.3)	1 (50.0)	8 (33.3)
Platelet count decreased	0	0	0	0	3 (33.3)	1 (50.0)	4 (16.7)
Alanine aminotransferase increased	0	0	0	1 (25.0)	1 (11.1)	0	2 (8.3)
Amylase increased	0	0	0	1 (25.0)	0	1 (50.0)	2 (8.3)
Aspartate aminotransferase increased	0	0	0	1 (25.0)	1 (11.1)	0	2 (8.3)
Electrocardiogram QT prolonged	1 (100.0)	1 (25.0)	0	0	0	0	2 (8.3)
Metabolism and Nutrition Disorders	0	1 (25.0)	2 (50.0)	2 (50.0)	3 (33.3)	1 (50.0)	9 (37.5)
Hypokalaemia	0	0	0	1 (25.0)	2 (22.2)	0	3 (12.5)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (25.0)	0	4 (44.4)	0	5 (20.8)
Bone pain	0	0	0	0	2 (22.2)	0	2 (8.3)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	0	1 (25.0)	1 (25.0)	1 (25.0)	1 (11.1)	0	4 (16.7)

MedDRA ver. 16.1 SOC PT, n (%)	**20 mg n = 1**	**40 mg n = 4**	**80 mg n = 4**	**120 mg n = 4**	**200 mg n = 9**	**300 mg n = 2**	**Total n = 24**
Tumour associated fever	0	1 (25.0)	0	0	1 (11.1)	0	2 (8.3)
Nervous System Disorders	0	0	2 (50.0)	2 (50.0)	3 (33.3)	2 (100.0)	9 (37.5)
Headache	0	0	1 (25.0)	0	1 (11.1)	2 (100.0)	4 (16.7)
Somnolence	0	0	1 (25.0)	1 (25.0)	1 (11.1)	0	3 (12.5)
Dysaesthesia	0	0	0	0	1 (11.1)	1 (50.0)	2 (8.3)
Dysgeusia	0	0	0	1 (25.0)	0	1 (50.0)	2 (8.3)
Syncope	0	0	0	1 (25.0)	0	1 (50.0)	2 (8.3)
Psychiatric Disorders	0	0	1 (25.0)	0	2 (22.2)	0	3 (12.5)
Insomnia	0	0	1 (25.0)	0	1 (11.1)	0	2 (8.3)
Renal and Urinary Disorders	0	1 (25.0)	0	0	4 (44.4)	2 (100.0)	7 (29.2)
Renal impairment	0	1 (25.0)	0	0	2 (22.2)	2 (100.0)	5 (20.8)
Respiratory, Thoracic and Mediastinal Disorders	1 (100.0)	1 (25.0)	3 (75.0)	1 (25.0)	3 (33.3)	1 (50.0)	10 (41.7)
Cough	0	0	1 (25.0)	0	2 (22.2)	0	3 (12.5)
Pleural effusion	0	0	2 (50.0)	1 (25.0)	0	0	3 (12.5)
Epistaxis	0	0	2 (50.0)	0	0	0	2 (8.3)
Hypoxia	0	0	0	0	2 (22.2)	0	2 (8.3)
Skin and Subcutaneous Tissue Disorders	1 (100.0)	0	2 (50.0)	1 (25.0)	4 (44.4)	0	8 (33.3)
Rash	0	0	1 (25.0)	1 (25.0)	1 (11.1)	0	3 (12.5)
Vascular Disorders	1 (100.0)	0	0	1 (25.0)	4 (44.4)	2 (100.0)	8 (33.3)
Hypertension	1 (100.0)	0	0	0	2 (22.2)	2 (100.0)	5 (20.8)
Haematoma	0	0	0	1 (25.0)	1 (11.1)	0	2 (8.3)
Hypotension	0	0	0	0	2 (22.2)	0	2 (8.3)

Source: Table 12.6.1.3

Table 11 Incidence of Serious Adverse Events – Safety Analysis Set

MedDRA ver. 16.1 SOC PT, n (%)	20 mg n = 1	40 mg n = 4	80 mg n = 4	120 mg n = 4	200 mg n = 9	300 mg n = 2	Total n = 24
Overall	0	1 (25.0)	1 (25.0)	0	5 (55.6)	0	7 (29.2)
Blood and Lymphatic System Disorders	0	0	0	0	1 (11.1)	0	1 (4.2)
Febrile neutropenia	0	0	0	0	1 (11.1)	0	1 (4.2)
Cardiac Disorders	0	0	0	0	1 (11.1)	0	1 (4.2)
Cardiomyopathy	0	0	0	0	1 (11.1)	0	1 (4.2)
General Disorders and Administration Site Conditions	0	1 (25.0)	0	0	0	0	1 (4.2)
Oedema	0	1 (25.0)	0	0	0	0	1 (4.2)
Hepatobiliary Disorders	0	0	1 (25.0)	0	0	0	1 (4.2)
Cholangitis acute	0	0	1 (25.0)	0	0	0	1 (4.2)
Infections and Infestations	0	1 (25.0)	1 (25.0)	0	1 (11.1)	0	3 (12.5)
Bronchopneumonia	0	0	1 (25.0)	0	0	0	1 (4.2)
Bronchopulmonary aspergillosis	0	0	0	0	1 (11.1)	0	1 (4.2)
Pneumonia	0	1 (25.0)	0	0	0	0	1 (4.2)
Sepsis	0	0	1 (25.0)	0	0	0	1 (4.2)
Device related infection	0	1 (25.0)	0	0	0	0	1 (4.2)
Injury, Poisoning and Procedural Complications	0	0	1 (25.0)	0	1 (11.1)	0	2 (8.3)
Subdural haematoma	0	0	1 (25.0)	0	1 (11.1)	0	2 (8.3)
Investigations	0	0	0	0	1 (11.1)	0	1 (4.2)
Fibrin degradation products increased	0	0	0	0	1 (11.1)	0	1 (4.2)

Source: Table 12.6.1.5