A Phase 1/2 Open-Label, Dose Escalation Study Investigating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ASP2215 in Patients with Relapsed or Refractory Acute Myeloid Leukemia

ISN/Protocol 2215-CL-0101

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Sponsor: Astellas Pharma Global Development (APGD), Inc.

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Northbrook, IL 60062

STATISTICAL ANALYSIS PLAN

Version 3 (Amendment 3), dated 20-Sep 2017

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APGD	Astellas Pharma Global Development
aPTT	Activated Partial Thromboplastin Time
ASCM	Analysis Set Classification Meeting
ASP2215	Astellas Compound code for 2215
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area Under the plasma concentration - time Curve
AUC_{24}	Area under the concentration-time curve from the time of dosing to 24 hours after dosing
AUC_{inf}	Area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{last}	Area under the concentration-time curve from the time of dosing to the last measurable concentration (Clast)
AUC_{tau}	Area under the concentration-time curve from the time of dosing to the start of the next dosing interval
BMI	Body Mass Index
BQL	Blow Quantification Limit
BUN	Blood Urea Nitrogen
Ca	Calcium
CI	Confidence Intervals
CK	Creatine Phosphokinase
Cl	Chloride
CL	Total systemic clearance after intravenous dosing
CL/F	Apparent total systemic clearance after single or multiple extra-vascular dosing
C_{last}	Concentration corresponding to the time of the last measurable concentration

Abbreviations	Description of abbreviations
C_{max}	Maximum Concentration
Cr	Creatinine
CR	Complete Remission
CRc	Composite Complete Remission
CRi	Complete Remission with incomplete hematological recovery
CRp	Complete Remission with incomplete platelet recovery
CRF	Case Report Form
CS	Classification Specifications
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{tau}	Concentration at time tau
C_{trough}	Minimum Concentration
CV	Coefficient of Variation
CYP3A4	Cytochrome P450-isozyme3A4
DBP	Diastolic Blood Pressure
DDI	Drug-drug Interaction
DLT	Dose Limiting Toxicity
DN	Dose Normalized
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
EFS	Event-Free Survival
FAB	French-American-British
FAS	Full Analysis Set
FLT3	FMS-like TyrosineKkinase
GD	Global Development
Gl	Glucose
H	High
hCG	Human Chorionic Gonadotropin
Hct	Hematocrit
HCO_3	Bicarbonate
Hgb	Hemoglobin
HSCT	Hematopoietic Stem Cell Transplant
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Abbreviations	Description of abbreviations
IND	Investigational New Drug
INR	International Normalization Ratio
IRT	Interactive Response Technology
ISN	International Study Number
ITD	Internal Tandem Duplication
IU/L	International units/liter
IV	Intravenous
K	Potassium
KIT	Cell surface receptor tyrosine kinase that binds to stem cell factor
L	Liter
L	Low
LDH	Lactate Dehydrogenase
LFS	Leukemia-Free Survival
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
Mg	Magnesium
Min	Minute
mL	Milliliter
mmHg	millimeters of mercury
MRD	Minimum Residual Disease
msec	milliseconds
MTD	Maximum Tolerated Dose
MUGA	Multigated acquisition scan
N	Number
N	Normal
Na	Sodium
NCI	National Cancer Institute
NR	No Response
NYHA	New York Heart Association
OS	Overall Survival
pAXL	Phosphorylated AXL
pAXLn	Phosphorylated AXL Normalized to Total AXL
PD	Pharmacodynamic
PD	Protocol Deviation
PDAS	Pharmacodynamic Analysis Set

Abbreviations	Description of abbreviations
pFLT3	Phosphorylated FLT3
pFLT3n	Phosphorylated FLT3 Normalized to Total FLT3
PGx	Pharmacogenomics
PK	Pharmacokinetic
Pi	Phosphate
PIA	Plasma Inhibitory Assay
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	Partial Remission
pS6	Phosporylated S6
PT	Prothrombin Time
PT	Preferred Term
PTT	Partial Thromboplastin Time
QD	quaque die, a Latin phrase meaning “every day”
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia’s factor
RBC	Red Blood Cell
RR	Interval between 2 consecutive r waves on an ECG
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SOC	System Organ Class
SOP	Standard Operating Procedure
$T_{1/2}$	Half-life
tAXL	Total AXL
TBL	Total Bilirubin
T Chol	Total Cholesterol
TdP	Torsade de pointes
TEAE	Treatment Emergent Adverse Event
tFLT3	Total FLT3
TK	Tyrosine Kinase
TLF	Tables, Listings and Figures
T_{max}	Time to observed C_{max}
T Prot	Total Protein
Trig	Triglycerides

Abbreviations	Description of abbreviations
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
V_z	Volume of distribution after intravenous dosing during the terminal elimination phase
V_z/F	Apparent volume of distribution during the terminal elimination phase after single extra-vascular dosing
WBC	White Blood Cell
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary
WOCBP	Women of childbearing potential

List of Key Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded as the starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock, interim analysis, or accumulation of substantial amount of data in an open-label study to ensure lack of bias. For operational efficiency an earlier time is usually targeted and wherever possible, the SAP should be developed in parallel with protocol finalization. For Phase 2-4 studies the SAP should be developed and approved before First Subject In (FSI). If the expected interval between FSI and soft-lock is less than 12 weeks, then the SAP should be approved by 12 weeks prior to the planned date of soft-lock. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

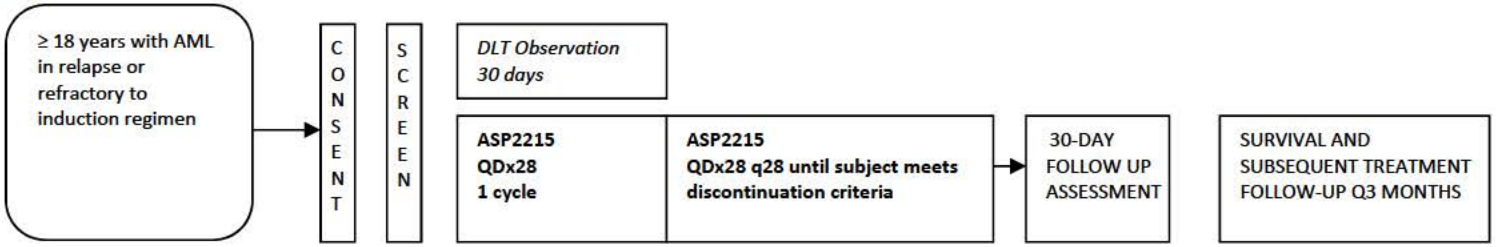
This statistical analysis is coordinated by the responsible biostatistician of GD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

Flow Chart

Cohort 1 (Escalation Cohort)



Cohort 2 (Expansion Cohort)

Expansion cohorts will start with 1st CR or one above the dose level with target inhibition

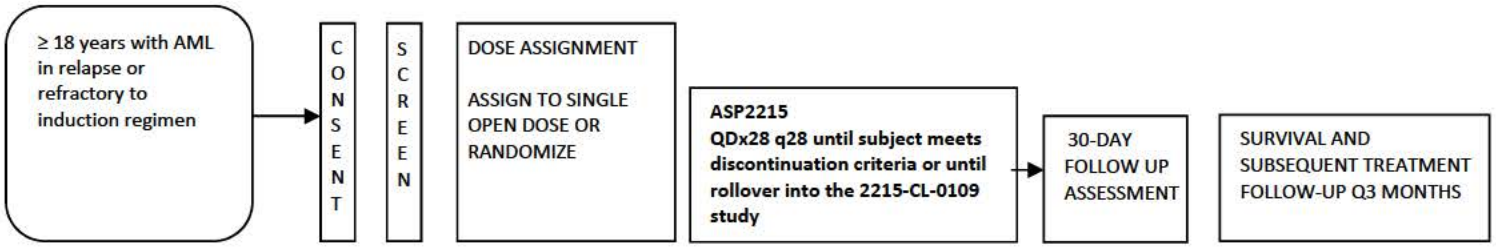


Table 1A Schedule of Assessments for Dose Escalation Phase (Cohort 1)

Activity	Screening (Day -14 to -3)	Day -2	Day -1	Cycle 1						Cycle 2		Subsequent Cycles
				D 1[r]	D 4±1	D 8±1	D 15	D 16	D 22±1	D 1 ±3	D 15 ±1	D 1±3
Signed ICF	X											
Medical and Disease History	X											
Physical Examination (incl. height and weight)[n]	X[n]	X[a]	X	X[n]	X	X	X		X	X[n]	X	X[n]
Vital Signs	X	X[a]	X	X	X	X	X		X	X	X	X
ECOG Performance	X			X			X			X	X	X
Prior and Concomitant Medications	X[b]	X	X	X	X	X	X		X	X	X	X
Pregnancy Test for WOCBP	X[f]			X						X		X
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	X											
Chest X-ray (or CT of chest)[t]	X											
12-lead ECG[d]	X[d]	X[d]	X[d]	X[d]		X[d]	X[d]	X[d]	X[d]	X[d]		X[d]
Ophthalmologic Assessment[m]	X						X			X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[p]	X[o]	X[a]	X	X[a]	X[a]	X[a]	X[a]		X[a]	X[a]	X[a]	X[a]
Thyroid Function Tests	X											X[q]
MUGA or ECHO[c]	X											
FLT3, C-CBL, AXL Mutation Status[j] (bone marrow aspirate or whole blood)	X											
Bone Marrow Aspiration and Biopsy	X[g]									X[g]		X[g]
AE/SAE Assessment	X	X	X	X	X	X	X		X	X	X	X
PK (whole blood samples for plasma PK)		X[e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]		X[e]
PIA (whole blood samples for plasma inhibitory assay)		X[l]	X[l]	X[l]		X[l]	X[l]	X[l]		X[l]		
PGx[h]	X											
Phosphorylation of FLT-3, S6 and AXL[k] (whole blood)		X	X			X	X					
ASP2215 Dosing at the Clinic[i]		X		X		X	X	X	X	X	X	X
IRT Transaction Required[s]	X	X				X	X		X	X	X	X
ASP2215 Dispensing for Subject Take Home				X		X		X	X	X	X	X

Table footnotes appear on next page

a. Obtained predose.
b. Includes medications taken within 28 days prior to screening.
c. MUGA scans are to be performed at Screening for subjects with history of congestive heart failure NYHA Class 3 or 4 (unless MUGA scans performed either within 3 months prior revealed LVEF ≥45%).
d. Screening ECGs are required. ECG assessment will be evaluated at D-2 and C1D15 at pre-dose, 2, 4, 6, and 24 hours post-dose. Pre-dose ECG assessment will also be evaluated on C1D1, C1D8, C1D22, and D1 of each subsequent cycle. 24 hr post-dose ECG assessment will be performed on D-1 and D16 respectively. All efforts should be made to conduct ECG monitoring in triplicate between 7:00 am and 3:00 pm at all assessment time points. Pre-dose assessments should be taken within 0.5 hours before drug administration. In addition, 2, 4, 6, and 24 hour post-dose assessments should be performed within ± 0.5 hours of nominal time. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs 10 minutes resting prior to first ECG and at least 5 minutes apart per time-point) and transmitted electronically for central reading. See Section 5.4.5 of the protocol amendment 10.
e. PK samples will be collected at D-2 and C1D15 at pre-dose (0.5 hours before drug administration), 0.5 (±10 minutes), 1 (±10 minutes), 2 (±10 minutes), 4 (±20 minutes), 6 (±20 minutes), and 24 hours (±90 minutes) post dose (the 24 hour sample will be collected on Day -1 and before the next dose of ASP2215 on Day 16 respectively). Samples will also be collected on C1D1, C1D8, and C1D22 pre-dose (0.5 hours before drug administration) and 2 hours (±10 minutes) post dose. Thereafter PK samples will be collected pre-dose (0.5 hours before drug administration) on Day 1 of each cycle. See Section 5.6.1 of the protocol amendment 10.
f. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study treatment.
g. Bone marrow samples are required during Screening, Cycle 2 Day 1 and Cycle 3 Day 1. Screening samples may be collected up to 21 days prior to C1D1. For subjects who do not achieve a complete remission (CR, CRp, or CRi), the bone marrow assessments will be repeated at Day 1 of every 2 subsequent cycles. For subjects who achieve a complete remission (CR, CRp, or CRi), bone marrow will be repeated on one month after the date of remission and every 3 subsequent cycles for up to 1 year from Cycle 1 Day 1 and after that only if there is suspicion of relapse in the peripheral blood. Bone marrow samples are also required at the Early Termination/End-of Study Visit, and as clinically indicated. If bone marrow aspirate is unobtainable (i.e., dry tap), an additional EDTA tube of peripheral blood should be collected instead.
h. Buccal swab collected at Screening for optional pharmacogenomic study.
i. ASP2215 is taken daily without food at home except on clinic days when it will be taken at the clinic and Day -1 when no ASP2215 will be taken. Subjects will be instructed to take the daily dose with water as close to the same time each morning as possible.
j. FLT3, C-CBL and AXL mutation status will be assessed from bone marrow sample taken at the Screening Visit. If bone marrow sample is unavailable (e.g., dry tap), the whole blood sample taken at the Screening Visit will be used.
k. Predose and 2 hours (±10 minutes) post dose on Day -2. Predose Day -1 (no dose on this day), Day 8, and Day 15 for determination of phosphorylation of FLT3, S6 and AXL. Day -1 sample will be taken in proximity to 24 hour PK sample following Day -2 dose administration.
l. PIA samples will be collected at D-2 and C1D15 at pre-dose (0.5 hours before drug administration), 2 (±10 minutes), 6 (±20 minutes), and 24 hours (±90 minutes) post dose (the 24 hour sample must be collected on Day -1 and before the next dose of ASP2215 on D 16). Samples will also be collected on C1D1, C1D8, and C2D1 pre-dose (0.5 hours before drug administration) and 2 hours (±10 minutes) post dose.
m. Ophthalmologic assessment to be performed by visual acuity measurement, ophthalmoscopy, slit lamp biomicroscopy, visual fields and optical coherence tomography (OCT) at Screening (within 12 days prior to dosing), 15th Day of Cycle 1 (± 3 days), 1st Day of Cycle 2 (± 3 days), Cycle 3 (± 3 days), and every 2 cycles thereafter (± 3 days), at the end of treatment, and when clinically indicated.
n. Height measurement performed only at Screening. Weight measurement should be performed on D1 of each Cycle.
o. Subjects may be screened from local labs only. However, screening samples must be submitted for central read.
p. Additional laboratory tests should be performed according to institutional standard of care.
q. Thyroids function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1 etc.).
r. For scheduling and logistical purposes, up to 3 days are allowed between Day -1 and Cycle 1 Day 1.
s. For the purposes of drug preparation and dispensing activities, IRT Transactions may be done prior to the visit and do not need to fall within the protocol visit windows.
t. Chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of Screening.

Table 1B Schedule of Assessments for Expansion Phase with CYP3A4 Inhibitor Voriconazole Study (Cohort 2, Starting Dose Level)

			Cycle 1					Cycle 2			Subsequent Cycles
Activity	**Screening (Day -14 to -1)**	**D 1**	**D 4±1**	**D 8±1**	**D 15**	**D 16**	**D 22+1**	**D 1 ±2**	**D 2**	**D 15 ±1**	**D 1±3**
Signed ICF	X										
Medical and Disease History	X										
Physical Examination [o]	X [o]	X [o a]	X	X	X		X	X [o]		X	X [o]
Vital Signs	X	X [a]	X	X	X		X	X		X	X
ECOG Performance	X	X [a]			X			X		X	X
Prior and Concomitant Medications	X [b]	X	X	X	X		X	X		X	X
Pregnancy Test for WOCBP	X [f]	X						X			X
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	X										
Chest X-ray (or CT of chest) [t]	X										
12-lead ECG [d]	X	X		X	X [d]	X	X	X [d]	X		X [d]
Ophthalmologic Assessment [m]	X				X			X			X [m]
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis) [q]	X [p]	X [a]	X [a]	X [a]	X [a]		X [a]	X [a]		X [a]	X [a]
Thyroid Function Tests	X										X [r]
MUGA or ECHO [c]	X										
FLT3, C-CBL,AXL Mutation Status [j] (bone marrow aspiration or whole blood)	X										
Bone Marrow Aspiration and Biopsy	X [g]							X [g]			X [g]
AE/SAE Assessment	X	X	X	X	X		X	X		X	X
PK (whole blood samples for plasma PK)		X [e]		X [e]	X [e]	X [e]	X [e]	X [e]	X [e]		X [e]
PIA (whole blood samples for plasma inhibitory assay)		X [l]		X [l]	X [l]			X [l]			
PGx [h]	X										
Phosphorylation of FLT-3, S6 and AXL [k] (whole blood)		X		X	X						
ASP2215 Dosing at the Clinic [i]		X		X	X	X	X	X	X	X	X
IRT Transaction Required [s]	X	X		X	X		X	X		X	X
ASP2215 Dispensing for Subject Take Home		X		X		X	X		X	X	X
Voriconazole (CYP3A4 Inhibitor) dosing						X [n]	X [n]	X [n]			

Table footnotes appear on next page

a. Obtained predose.
b. Includes medications taken within 28 days prior to screening.
c. MUGA scans are to be performed at Screening for subjects with history of congestive heart failure NYHA Class 3 or 4 (unless MUGA scans performed either within 3 months prior revealed LVEF ≥45%).
d. Screening ECG is required. ECG assessment will be evaluated at C1D15 and C2D1 at pre-dose, 2, 4, 6, and 24 hours post-dose. 24 hr post-dose ECG assessment will be performed on D16 and C2D2 respectively. Pre-dose ECG assessment will also be evaluated on C1D1, C1D8, C1D22, and D1 of each subsequent cycle. All efforts should be made to conduct ECG monitoring in triplicate between 7:00 am and 3:00 pm at all assessment time points. Pre-dose assessments should be taken within 0.5 hours before drug administration. In addition, 2, 4, 6, and 24 hour post-dose assessments should be performed within ± 0.5 hours of nominal time. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. See Section 5.4.5 of the protocol amendment 10.
e. PK samples for ASP2215 will be collected at C1D15, and C2D1 at pre-dose (0.5 hours before drug administration), 0.5(±10 minutes), 1 (±10 minutes), 2 (±10 minutes), 4 (±20 minutes), 6 (±20 minutes), and 24 hours (±90 minutes) post dose. 24 hr post-dose PK assessment will be performed on D16 and C2D2 respectively. Predose (0.5 hours before drug administration) PK samples will also be collected on C1D1, C1D8, C1D22, and on Day 1 of each cycle starting at Cycle 3. A predose (0.5 hours before drug administration) PK sample for CYP3A4 inhibitor will be taken on C2D1. See Section 5.6.1 of the protocol amendment 10.
f. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study treatment.
g. Bone marrow samples are required during Screening, Cycle 2 Day 1 and Cycle 3 Day 1. Screening samples may be collected up to 21 days prior to C1D1. For subjects who do not achieve a complete remission (CR, CRp, or CRi), the bone marrow assessments will be repeated at Day 1 of every 2 subsequent cycles. For subjects who achieve a complete remission (CR, CRp, or CRi), bone marrow will be repeated on one month after the date of remission and every 3 subsequent cycles for up to 1 year from Cycle 1 Day 1 and after that onlyif there is suspicion of relapse in the peripheral blood. Bone marrow samples are also required at the Early Termination/End-of Study Visit, and as clinically indicated. If bone marrow aspirate is unobtainable (i.e., dry tap), an additional EDTA tube of peripheral blood should be collected instead.
h. Buccal swab collected at Screening for optional pharmacogenomic study.
i. ASP2215 is taken daily without food at home except for clinic days when it will be taken at the clinic. Subjects will be instructed to take the daily dose with water as close to the same time each morning as possible.
j. FLT3, C-CBL and AXL mutation status will be assessed from bone marrow sample taken at the Screening Visit. If bone marrow sample is unavailable (e.g., dry tap), the whole blood sample taken at the Screening Visit will be used.
k. Predose and 2 hours (±10 minutes) post dose on Day 1, Day 8, and Day 15 for determination of phosphorylation of FLT3, S6 and AXL.
l. PIA samples will be collected at C1D1, C1D8, C1D15 and C2D1 at pre-dose (0.5 hours before drug administration) and 2 hours (±10 minutes) post dose.
m. Ophthalmologic assessment to be performed by visual acuity measurement, ophthalmoscopy and slit lamp biomicroscopy, visual fields and optical coherence tomography (OCT) at Screening (within 12 days prior to dosing), 15th Day of Cycle 1 (± 3 days), 1st Day of Cycle 2 (± 3 days), Cycle 3 (± 3 days), and every 2 cycles thereafter (± 3 days), at the end of treatment, and when clinically indicated.
n. Voriconazole (CYP3A4 inhibitor) will be administered at 200 mg every 12 hours starting on C1D16 through C2D1.
o. Height measurement performed only at Screening. Weight measurement should be performed on D1 of each Cycle.
p. Subjects may be screened from local labs only. However, samples must be submitted for central read.
q. Additional laboratory tests should be performed according to institutional standard of care.
r. Thyroids function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1 etc.).
s. For the purposes of drug preparation and dispensing activities, IRT Transactions may be done prior to the visit and do not need to fall within the protocol visit windows.
t. Chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of Screening.

Table 1C Schedule of Assessments for Expansion Phase without DDI Studies (Cohort 2, Intermediate Dose Levels)

Activity	Screening (Day -14 to -1)	Cycle 1					Cycle 2		Subsequent Cycles
		D 1	D 4±1	D 8±1	D 15±1	D 22±1	D 1 ±3	D 15 ±1	D 1±3
Signed ICF	X								
Medical and Disease History	X								
Physical Examination [n]	X [n]	X [n a]	X	X	X	X	X [n]	X	X [n]
Vital Signs	X	X [a]	X	X	X	X	X	X	X
ECOG Performance	X	X [a]			X		X	X	X
Prior and Concomitant Medications	X [b]	X	X	X	X	X	X	X	X
Pregnancy Test for WOCBP	X [f]	X					X		X
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	X								
Chest X-ray (or CT of chest) [s]	X								
12-lead ECG [d]	X	X [d]		X	X [d]	X	X [d]		X [d]
Ophthalmologic Assessment [m]	X				X		X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis) [p]	X [o]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]
Thyroid function tests	X								X [q]
MUGA or ECHO [c]	X								
FLT3, C-CBL,AXL Mutation Status [j] (bone marrow aspirate or whole blood)	X								
Bone Marrow Aspiration and Biopsy	X [g]						X [g]		X [g]
AE/SAE Assessment	X	X	X	X	X	X	X	X	X
PK (whole blood samples for plasma PK)		X [e]		X [e]	X [e]	X [e]	X [e]		X [e]
PIA (whole blood samples for plasma inhibitory assay)		X [l]		X [l]	X [l]		X [l]		
PGx [h]	X								
Phosphorylation of FLT-3, S6 and AXL [k] (whole blood)		X		X	X				
ASP2215 Dosing at the Clinic [i]		X		X	X	X	X	X	X
IRT Transaction Required [r]	X	X		X	X	X	X	X	X
ASP2215 Dispensing for Subject Take Home		X		X	X	X	X	X	X

Table footnotes appear on next page

a. Obtained predose.

b. Includes medications taken within 28 days prior to screening.

c. MUGA scans are to be performed at Screening for subjects with history of congestive heart failure NYHA Class 3 or 4 (unless MUGA scans performed either within 3 months prior revealed LVEF ≥45%).

d. Screening ECG is required. ECG assessment will be evaluated at C1D1 and C1D15 at pre-dose, and 2 hours post-dose. Pre-dose ECG assessment will also be evaluated on C1D8, C1D22 and D1 of each subsequent cycle. All efforts should be made to conduct ECG monitoring in triplicate between 7:00 am and 3:00 pm at all assessment time points. Pre-dose assessments should be taken within 0.5 hours before drug administration. In addition, 2 hour post-dose assessment should be performed within ± 0.5 hours of nominal time. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. See Section 5.4.5 of the protocol amendment 10.

e. PK samples for ASP2215 will be collected at C1D1 and C1D15 at pre-dose (0.5 hours before drug administration), 2, hours (±10 minutes) post dose. ASP2215 pre-dose (0.5 hours before drug administration) PK samples will also be collected on C1D8, C1D22 and on Day 1 of each cycle starting at Cycle 2. See Section 5.6.1 of the protocol amendment 10.

f. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 72 hours prior to the start of study treatment.

g. Bone marrow samples are required during Screening, Cycle 2 Day 1 and Cycle 3 Day. Screening samples may be collected up to 21 days prior to C1D1. For subjects who do not achieve a complete remission (CR, CRp, or CRi), the bone marrow assessments will be repeated at Day 1 of every 2 subsequent cycles. For subjects who achieve a complete remission (CR, CRp, or CRi), bone marrow will be repeated on one month after the date of remission and every 3 subsequent cycles for up to 1 year from Cycle 1 Day 1 and after that only if there is suspicion of relapse in the peripheral blood. Bone marrow samples are also required at the Early Termination/End-of Study Visit, and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of peripheral blood should be collected instead. For France and Germany Only: Bone marrow aspirate is required. Collection of both the bone marrow aspirate and bone marrow biopsy is preferred, but biopsy samples are only required in case of inadequate aspirate.

h. Buccal swab collected at Screening for optional pharmacogenomic study.

i. ASP2215 is taken daily at home except for clinic days when it will be taken at the clinic.

j. FLT3 and C-CBL and AXL mutation status will be assessed from bone marrow sample taken at the Screening Visit. If bone marrow sample is unavailable (e.g., dry tap), the whole blood sample taken at the Screening Visit will be used.

k. Pre-dose and 2 hours (±10 minutes) post dose on Day 1. Pre-dose on Day 8 and Day 15 for determination of phosphorylation of FLT3, S6 and AXL.

l. PIA samples will be collected at C1D1, C1D8, C1D15, and C2D1 at pre-dose (0.5 hours before drug administration) and 2 hours (±10 minutes) post dose.

m. Ophthalmologic assessment to be performed by visual acuity measurement, ophthalmoscopy and slit lamp biomicroscopy, visual fields and optical coherence tomography (OCT) at Screening (within 12 days prior to dosing), 15th Day of Cycle 1 (± 3 days), 1st Day of Cycle 2 (± 3 days), Cycle 3 (± 3 days), and every 2 cycles thereafter (± 3 days), at the end of treatment, and when clinically indicated.

n. Height measurement performed only at Screening. Weight measurement should be performed on D1 of each Cycle.

o. Subjects may be screened from local labs only. However, samples must be submitted for central read.

p. Additional laboratory tests should be performed according to institutional standard of care.

q. Thyroids function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1 etc.).

r. For the purposes of drug preparation and dispensing activities, IRT Transactions may be done prior to the visit and do not need to fall within the protocol visit windows.

s. Chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of Screening.

Table 1D Schedule of Assessments for Expansion Phase with CYP3A4 Induction Study (Cohort 2, MTD Level)

Activity	Screening (Day -14 to -2)	D -1	Cycle 1 D 1	Cycle 1 D4±1	Cycle 1 D8±1	Cycle 1 D 15	Cycle 1 D 16	Cycle 1 D 22±1	Cycle 2 D 1 ±3	Cycle 2 D 15 ±1	Subsequent Cycles D 1±3
Signed ICF	X										
Medical and Disease History	X										
Physical Examination [n]	X [n]	X	X [n a]	X [n]	X	X		X	X [n]	X	X [n]
Vital Signs	X	X	X [a]	X	X	X		X	X	X	X
ECOG Performance	X	X	X [a]			X			X	X	X
Prior and Concomitant Medications	X [b]	X	X	X	X	X		X	X	X	X
Pregnancy Test for WOCBP	X [f]		X						X		X
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	X										
Chest X-ray (or CT of Chest) [s]	X										
12-lead ECG [d]	X	X [d]	X		X [d]	X	X	X	X		X [d]
Ophthalmologic Assessment [m]	X [m]					X			X		X [m]
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis) [p]	X [o]	X [a]	X [a]	X [a]	X	X [a]		X [a]	X [a]	X [a]	X [a]
Thyroid Function Tests	X										X [q]
MUGA or ECHO [c]	X										
FLT3, C-CBL, AXL Mutation Status [j] (bone marrow aspirate or whole blood)	X										
Bone Marrow Aspiration and Biopsy	X [g]								X [g]		X [g]
AE/SAE Assessment	X	X	X	X	X	X		X	X	X	X
PK (Whole blood Samples for plasma PK)		X [e]	X [e]		X [e]	X [e]	X [e]	X [e]	X [e]		X [e]
PIA (whole blood samples for plasma inhibitory assay)			X [l]		X [l]	X [l]			X [l]		
PGx [h]	X										
Phosphorylation of FLT-3, S6 and AXL [k] (whole blood)			X		X	X					
ASP2215 Dosing at the Clinic [i]			X		X	X	X	X	X	X	X
IRT Transaction Required [r]	X		X		X	X		X	X	X	X
ASP2215 Dispensing for Subject Take Home			X		X		X	X	X	X	X
Midazolam Dosing [e]		X [e]				X [e]					

Table footnotes appear on next page

a. Obtained predose.
b. Includes medications taken within 28 days prior to screening.
c. MUGA scans are to be performed at Screening for subjects with history of congestive heart failure NYHA Class 3 or 4 (unless MUGA scans performed either within 3 months prior revealed LVEF ≥45%).
d. Screening ECGs are required. ECG assessment will be evaluated at D-1 and C1D15 at pre-dose, 2, 4, 6, and 24 hours post-dose. 24 hr post-dose ECG assessment will be performed on C1D1 and C1D16 respectively. Pre-dose ECG assessment will also be evaluated on C1D1, C1D8, C1D22 and D1 of each subsequent cycle. All efforts should be made to conduct ECG monitoring in triplicate between 7:00 am and 3:00 pm at all assessment time points. Pre-dose assessments should be taken within 0.5 hours before drug administration. In addition, 2, 4, 6, and 24hour post-dose assessments should be performed within ± 0.5 hours of nominal time. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. See Section 5.4.5 of the protocol amendment 10.
e. Midazolam (2 mg of syrup (1.0 ml) by mouth) will be administered as a single dose on Days -1 and C1D15. For all Midazolam PK timepoints, Vital Signs including respiratory rate are to be done. Midazolam PK samples will be collected at D-1 and C1D15 at pre-dose (0.5 hours before drug administration), 0.5 (±10 minutes), 1 (±10 minutes), 2 (±10 minutes), 4 (±20 minutes), 6 (±20 minutes), and 24 hours (±90 minutes) post dose (the 24 hour sample must be collected before the dose of ASP2215). 24 hr post-Midazolam dose assessment will be performed on C1D1 and D16 respectively. PK samples for ASP2215 will be collected at C1D1, C1D8, C1D15, and C1D22 at pre-dose (0.5 hours before drug administration), and 2 hours (±10 minutes) post dose. ASP2215 pre-dose (0.5 hours before drug administration) PK samples will also be collected on Day 1 of each cycle starting at Cycle 2. See protocol amendment 10 Sec 5.6.1.
f. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 72 hours prior to the start of study treatment.
g. Bone marrow samples are required during Screening, Cycle 2 Day 1 and Cycle 3 Day 1. Screening samples may be collected up to 21 days prior to C1D1. For subjects who do not achieve a complete remission (CR, CRp, or CRi), the bone marrow assessments will be repeated at Day 1 of every 2 subsequent cycles. For subjects who achieve a complete remission (CR, CRp, or CRi), bone marrow will be repeated on one month after the date of remission and every 3 subsequent cycles for up to 1 year from Cycle 1 Day 1 and after that only if there is suspicion of relapse in the peripheral blood. Bone marrow samples are also required at the Early Termination/End-of Study Visit, and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of peripheral blood should be collected instead.
h. Buccal swab collected at Screening for optional pharmacogenomic study.
i. ASP2215 is taken daily without food at home except for clinic days when it will be taken at the clinic. Subjects will be instructed to take the daily dose with water as close to the same time each morning as possible.
j. FLT3, C-CBL and AXL mutation status will be assessed from bone marrow sample taken at the Screening Visit. If bone marrow sample is unavailable (e.g., dry tap), the whole blood sample taken at the Screening Visit will be used.
k. Predose and 2 hours (±10 minutes) post dose on C1D1. Pre dose on C1D8 and C1D15 for determination of phosphorylation of FLT3, S6 and AXL.
l. PIA samples will be collected at C1D1, C1D8, C1D15 and C2D1 pre-dose (0.5 hours before drug administration) and 2 hours (±10 minutes) post dose.
m. Ophthalmologic assessment to be performed by visual acuity measurement, ophthalmoscopy and slit lamp biomicroscopy, visual fields and optical coherence tomography (OCT) at Screening (within 12 days prior to dosing), 15th Day of Cycle 1 (± 3 days), 1st Day of Cycle 2 (± 3 days), Cycle 3 (± 3 days), and every 2 cycles thereafter (± 3 days), at the end of treatment, and when clinically indicated.
n. Height measurement performed only at Screening. Weight measurement should be performed on D1 of each Cycle.
o. Subjects may be screened from local labs only. However, samples must be submitted for central read.
p. Additional laboratory tests should be performed according to institutional standard of care.
q. Thyroids function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1 etc.).
r. For the purposes of drug preparation and dispensing activities, IRT Transactions may be done prior to the visit and do not need to fall within the protocol visit windows.
s. Chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of Screening.

Table 1E Schedule of Assessments for Expansion Phase with MATE1 Substrate Study (Cohort 2, MATE1 Sub-study)

Activity	Screening (Day -14 to -2)	D -1	Cycle 1							Cycle 2		Subsequent Cycles
			D 1	D 4±1	D 8±1	D 9	D 15	D 16	D 22±1	D 1 ±3	D 15 ±1	D 1±3
Signed ICF	X											
Medical and Disease History	X											
Physical Examination [l]	X [l]	X	X [l a]	X	X		X		X	X [l]	X	X [l]
Vital Signs	X	X	X [a]	X	X		X		X	X	X	X
ECOG Performance	X	X	X [a]				X			X	X	X
Prior and Concomitant Medications	X [b]	X	X	X	X		X		X	X	X	X
Pregnancy Test for WOCBP	X [f]		X							X		X
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	X											
Chest X-ray (or CT of Chest) [q]	X											
12-lead ECG [d]	X	X	X		X	X [s]	X	X	X	X		X
Ophthalmologic Assessment [k]	X [k]						X			X		X [k]
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis) [n]	X [m]	X [a]	X [a]	X [a]	X [a]		X [a]		X [a]	X [a]	X [a]	X [a]
Thyroid Function Tests	X											X [o]
MUGA or ECHO [c]	X											
FLT3, C-CBL, AXL Mutation Status [j] (bone marrow aspirate or whole blood)	X											
Bone Marrow Aspiration and Biopsy	X [g]									X [g]		X [g]
AE/SAE Assessment	X	X	X	X	X		X		X	X	X	X
ASP2215 PK (Whole blood Samples)			X [e]		X [e]		X [e]	X [e]	X [e]	X [e]		X [e]
PGx [h]	X											
ASP2215 Dosing at the Clinic [i]			X		X		X	X	X	X	X	X
Cephalexin Dosing and PK Collection [r]		X [r]	X				X [r]	X				
IRT Transaction Required [p]	X	X	X		X		X		X	X	X	X
ASP2215 Dispensing for Subject Take Home			X		X			X	X	X	X	X

a. Obtained predose.

b. Includes medications taken within 28 days prior to screening.

c. MUGA scans are to be performed at Screening for subjects with history of congestive heart failure NYHA Class 3 or 4 (unless MUGA scans performed either within 3 months prior revealed LVEF ≥45%).

Table footnotes continued on next page

d. Screening ECGs are required. ECG assessment will be evaluated at D-1 and C1D15 at pre-dose, 2 hours post, and 24 hours post dose. 24 hr post-dose ECG assessment will be performed on C1D1 and C1D16 respectively. Pre-dose ECG assessment will also be evaluated on C1D1, C1D8, C1D22 and D1 of each subsequent cycle. All efforts should be made to conduct ECG monitoring in triplicate between 7:00 am and 3:00 pm at all assessment time points. Pre-dose assessments should be taken within 0.5 hours before drug administration. In addition, 2 and 24 hour post-dose assessments should be performed within ± 0.5 hours of nominal time. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. See Section 5.4.5 of protocol amendment 10. If the QTcF for a subject from Day 1 to Day 8 has increased > 30 ms with no other known etiology, a confirmatory ECG should be performed on Day 9 and a dose reduction considered. See Section 5.1.2 of protocol amendment 10 and footnote s. The mean QTcF of the triplicate ECG tracings based on central reading will be used for all treatment decisions.

e. Pre-dose (0.5 hours before drug administration) PK samples will be collected at C1D1, C1D8, C1D16, C1D22 and on Day 1 of each cycle starting at Cycle 2. See Section 5.6.1 of protocol amendment 10. PK samples for ASP2215 will be collected on C1D15 at pre-dose (0.5 hours before drug administration), 1 (±10 minutes), 2 (±10 minutes), 4 (±20 minutes), 6 (±20 minutes).

f. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 72 hours prior to the start of study treatment.

g. Bone marrow samples are required during Screening, Cycle 2 Day 1 and Cycle 3 Day 1. Screening samples may be collected up to 21 days prior to C1D1. For subjects who do not achieve a complete remission (CR, CRp, or CRi), the bone marrow assessments will be repeated at Day 1 of every 2 subsequent cycles. For subjects who achieve a complete remission (CR, CRp, or CRi), bone marrow will be repeated on one month after the date of remission and every 3 subsequent cycles for up to 1 year from Cycle 1 Day 1 and after that only if there is suspicion of relapse in the peripheral blood. Bone marrow samples are also required at the Early Termination/ End-of Study Visit, and as clinically indicated. If bone marrow aspirate is unobtainable (i.e., dry tap), an additional EDTA tube of peripheral blood should be collected instead.

h. Buccal swab collected at Screening for optional pharmacogenomic study.

i. ASP2215 is taken daily without food at home except for clinic days when it will be taken at the clinic. Subjects will be instructed to take the daily dose with water as close to the same time each morning as possible.

j. FLT3, C-CBL and AXL mutation status will be assessed from bone marrow sample taken at the Screening Visit. If bone marrow sample is unavailable (i.e., dry tap), the whole blood sample taken at the Screening Visit will be used.

k. Ophthalmologic assessment to be performed by visual acuity measurement, ophthalmoscopy and slit lamp biomicroscopy, visual fields and optical coherence tomography (OCT) at Screening (within 12 days prior to dosing), 15th Day of Cycle 1 (± 3 days), 1st Day of Cycle 2 (± 3 days), Cycle 3 (± 3 days), and every 2 cycles thereafter (± 3 days), at the end of treatment, and when clinically indicated.

l. Height measurement performed only at Screening. Weight measurement should be performed on D1 of each Cycle.

m. Subjects may be screened from local labs only. However, samples must also be submitted for central read.

n. Additional laboratory tests should be performed according to institutional standard of care.

o. Thyroids function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1 etc.).

p. For the purposes of drug preparation and dispensing activities, IRT Transactions may be done prior to the visit and do not need to fall within the protocol visit windows.

q. Chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of Screening.

r. Cephalexin (Total daily dose 500 mg via oral tablet or capsule) will be administered as a single dose on Days -1 and C1D15. Cephalexin plasma PK samples will be collected at D-1 and C1D15 at pre-dose (0.5 hours before drug administration), 0.5 (±10 minutes), 1 (±10 minutes), 1.5 (±10 minutes), 2 (±10 minutes), 3 (±10 minutes), 4 (±20 minutes), 6 (±20 minutes), and 24 hours (±90 minutes) post dose (the 24 hour sample must be collected before the dose of ASP2215). 24 hr post-Cephalexin dose assessment will be performed on C1D1 and D16 respectively. Urine samples for cephalexin PK will be collected on Day -1 and C1D15 at 0-3 hours, 3-6 hours and 6-24 hours post dose with urine volume recorded and a sample from each timepoint collected.

s. A Cycle 1 Day 8 ECG will be taken and the central read results will be provided to the site 24 hours after receipt of the tracing. A confirmatory ECG should be performed on Cycle 1 Day 9 if the mean QTcF from the central read ECG for Cycle 1 Day 1 to Cycle 1 Day 8 has increased > 30 ms with no other known etiology. On Cycle 1 Day 8, it is recommended that the ECG is taken as early as possible in the morning and transmitted immediately. In addition, it is recommended that the Cycle 1 Day 9 visit is scheduled later in the day in order to allow for receipt and assessment of the Cycle 1 Day 8 central read ECG. This also allows for a subject to be contacted if the Cycle 1 Day 9 ECG is no longer required. If the Cycle 1 Day 9 ECG is still required, the result of the central read ECG will be received on Cycle 1 Day 10, in which the investigator should assess if the ASP2215 dose modification should occur as per the dose interruption or reduction guideline in Section 5.1.2 of protocol amendment 10.

Table 1F Post-Treatment Schedule of Assessments

Activity	End of Treatment Visit [a]	30-Day Follow-Up[i]	Long-term Follow-Up[j]
Physical Examination	X [b]		
Vital Signs	X [b]		
ECOG Performance	X [b]		
Concomitant Medications	X		
Pregnancy Test for WOCBP	X		
12-lead ECG	X [c]		
Ophthalmologic Assessment	X [b]		
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	X [b]		
Bone Marrow Aspiration and Biopsy	X [h]		
FLT3 , AXL and C-CBL Mutations [g] (bone marrow aspirate or whole blood)	X		
AE/SAE Assessment	X [d]	X [e]	
IRT Transaction Required	X		
Survival and Subsequent Anti-leukemic Treatments and Their Outcomes		X [e]	X [f]

a. End of Treatment Visit is to be performed within 7 days of last dose.
b. Does not need to be repeated if collected at a regularly scheduled visit within 3 days of the End of Treatment Visit.
c. ECG monitoring should be between 7:00 am and 3:00 pm, if possible.
d. If the subject undergoes HSCT, SAE data will only be collected for 7 days after End of Treatment Visit.
e. Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.
f. Telephone contact every 3 months after the 30-Day follow up.
g. FLT3, AXL and C-CBL mutation analysis will be performed for relapsed subjects.
h. Does not need to be repeated if collected within 2 weeks of the End of Treatment Visit.
i. The 30-day follow-up visit and long term follow-up visits will not be performed if subject is enrolled into the roll-over study (2215-CL-0109).
j. Long-term follow-up will be discontinued upon termination of the study by the Sponsor.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objectives

- Assess the safety and tolerability, including determination of the maximum tolerated dose (MTD) of oral ASP2215 in subjects with relapsed or treatment-refractory AML.
- Determine the pharmacokinetic (PK) parameters of ASP2215.

3.1.2 Secondary Objectives

- Investigate the anti-leukemic activity of various doses of ASP2215 in subjects with AML.
- Evaluate the effect of strong or moderate cytochrome P450-isozyme3A4 (CYP3A4) inhibitors on the PK of ASP2215.
- Evaluate the potential induction of CYP3A4 by ASP2215 by assessment of midazolam PK.
- Evaluate the effect of ASP2215 on MATE1 substrates by assessment of cephalexin PK.

3.2 Study Design

3.2.1 Study Design

This study is an open-label, dose escalation, first-in-human study in subjects with relapsed or refractory AML, with concomitant expansion cohort for multiple doses. One cycle is defined as 28 days and the subject will receive oral ASP2215 daily. The study treatment will continue until one of the discontinuation criteria is met or until rollover into the 2215-CL-0109 study.

The starting dose level of ASP2215 is 20 mg daily and the decision to dose escalate to the next dose level will be made based on the assessment of safety variables including occurrence of grade 2 adverse events (AE) or DLTs.

This study will have two cohorts of subjects (Figure 1 and Figure 2):

- Cohort 1: Dose escalation cohort
- Cohort 2: Dose expansion cohort

Cohort 1

Cohort 1 will comprise the initial dose escalation cohort with up to 10 dose levels (Table 2). This cohort will be run at approximately 5 centers which will only participate in the dose expansion cohort (Cohort 2) if the enrollment in the dose escalation cohort (Cohort 1) is on a pause (i.e., dose level being tested at the time is fully enrolled and the one higher dose level has not yet been opened). Subjects will be treated daily in 28 day cycles (with the exception of Cycle 1 where subjects will receive 29 doses). The DLT observation period is 30 days starting with the first dose taken on Day -2, and including the first 28 day treatment cycle. Subjects in Cycle 1 will have PK sampling performed prior to start of the first cycle and after receiving a single dose of the study drug on Day -2.

This study will follow an accelerated titration design. Dose levels are set at around 50% increments. One subject will be treated at the starting dose level of 20 mg. If no DLT is identified, the next subject will be enrolled at double the dose level, i.e. dose level 3 (40 mg see Table 2). This dose escalation approach will continue wherein only odd numbered dose levels (1, 3, 5) are tested until the first instance of a DLT or second instance (observed in two subjects at any of these dose levels) of a grade 2 AE judged related (e.g., possibly, probably, or definitely) by the investigator to be related to study drug (except for hematologic toxicities) occur.

When a DLT or second instance (observed in two subjects) of grade 2 AE related to study drug is observed in a subject, the dose escalation schedule will stop the double-dose level method and follow the next consecutive dose level in Table 2 utilizing the modified 3+3 design. Modified 3+3 design testing each consecutive dose level may also be followed if recommended by dose escalation committee based on the review of pharmacokinetics data. After dose level 5 (80 mg), each subsequent dose level (6-10) will be tested using the 3+3 design. In this phase, 3 subjects will be treated at each dose level. If no DLTs are observed, the subsequent subjects will be treated at the next dose level. If one DLT is observed in a dose level, 3 more subjects will be enrolled at that dose level. If the 3 additional subjects do not experience a DLT, the next dose level will be initiated. If 2 or more DLTs occur in a dose level, DLT will be established. The next lower dose level will be declared the maximum tolerated dose (MTD).

Subject replacement in the dose escalation cohort (Cohort 1)

A subject that receives less than 80% of the intended dose during Cycle 1 (e.g., misses 6 daily doses or leaves the study for reasons other than a DLT), will not be evaluable for DLT and will be replaced by another subject in the dose level. In addition, if after enrollment any subject is found not to fulfill any inclusion/exclusion criteria that would adversely affect safety or efficacy evaluation of that subject, they may be replaced after discussion between the Principal Investigator and Medical Monitor.

Cohort 2

Cohort 2 is the dose expansion cohort. This cohort will be conducted at approximately 35 additional centers that will not participate in the dose escalation cohort (Cohort 1). However, those centers participating in Cohort 1 may participate in Cohort 2 after the completion of the dose escalation phase (Cohort 1). Cohort 1 centers may also enroll patients in Cohort 2 if the enrollment in Cohort 1 is on a pause (i.e. dose level being tested at the time is fully enrolled and the one higher dose level has not yet been opened). Subjects will be treated daily in 28 day cycles. The DLT observation period is based on one completed cycle starting with the first dose taken on C1D1.

In the dose expansion phase (Cohort 2), a dose level may be expanded as follows:

- If one subject in the dose escalation cohort (Cohort 1) at any dose level achieves complete remission (CR), complete remission with low platelets (CRp) or complete remission with incomplete hematologic recovery (CRi) then this dose level will continue to enroll a

minimum of 3 subjects. After the decision is made to escalate to the next dose level (0/3 or 1/6 DLTs observed), the dose level will be expanded to enroll up to 17 additional subjects. All subsequent dose levels will also be expanded following a dose escalation decision for the dose level in the dose escalation cohort (Cohort 1). When more than one dose levels are expanded in the dose expansion cohort (Cohort 2), the newly enrolled patients will be randomized to all open expanded dose levels.

- In the absence of a CRc, if the median decrease of FMS-like tyrosine kinase (FLT3) phosphorylation in plasma inhibitory assay (PIA) is equal or greater than 90% in a dose level with at least 3 subjects, then this dose level and the subsequent levels will be expanded following a dose escalation decision for the dose level (0/3 or 1/6 DLTs observed) in the dose escalation cohort (Cohort 1).

Subjects will be assigned in the dose escalation cohort (Cohort 1) or randomized in the dose expansion cohort (Cohort 2) to one of the open dose levels as defined in the statistical methodology section (Section 7). At least 10 subjects with FLT3 mutations (internal tandem duplication (ITD) or activating point mutations) will be enrolled to each expanded dose level (including the subjects in the dose escalation cohort).

Dose levels at and above 120 mg will be further expanded (when found to be tolerable in Cohort 1) based on the efficacy results observed in escalation and expansion cohorts as described in the Statistical section. At least 42 evaluable subjects (receive 2 cycles of treatment or discontinue for progressive disease) with FLT3 mutations will be enrolled in dose levels selected for further expansion (See Figure 2). The safety in the dose expansion cohort (Cohort 2) will be monitored using Bayesian logistic regression modeling, as described in Section 7, based on the DLT rate observed in subjects from both the dose escalation and expansion cohorts. In the dose expansion cohort (Cohort 2), and for the first dose level only, the effect of CYP3A4 inhibition for strong inhibitor voriconazole (Schedule 1B) will be evaluated in all subjects in the dose level. In the dose expansion cohort (Cohort 2), and at the highest dose level of ASP2215 (MTD or one level below MTD), the effect of ASP2215 on midazolam pharmacokinetics (Schedule 1D) will be evaluated. After completion of the CYP3A4 inhibition expansion (Schedule 1B) and until MTD is determined, Cohort 2 subjects will participate without the DDI component (Schedule 1C). DDI studies (Schedule 1B, 1D, and 1E) will be conducted in the United States only. European sites whose patients are randomized to the DDI arms of the study will follow Schedule 1C and will not administer their patients these medications. In addition, US sites approved by the sponsor to join the trial who cannot conduct the DDI portion of the trial will also be allowed to follow Schedule 1C even if patients are randomized to Schedule 1B or 1D. Patients who have a contraindication to voriconazole or midazolam can participate in the trial without the DDI component (Schedule 1C) after discussion with the medical monitor.

If the first dose level closes prior to 12 patients completing the DDI component with voriconazole, the next lowest dose level open for enrollment will participate according to Schedule 1B to evaluate the effect of CYP3A4 inhibition for strong inhibitor voriconazole.

To further evaluate drug-drug interaction (DDI), a sub-study with a MATE1 substrate will be conducted [Table 1E]. This cohort will have approximately 20 subjects and will be enrolled at 200 mg. The goal of this sub-study is to evaluate the effect of ASP2215 on the MATE1 transporter. The pharmacokinetics of 500 mg cephalexin will be investigated prior to initiation of ASP2215 treatment at Cycle 1 Day -1 and at Day 15 of Cycle 1. This DDI sub-study (Schedule 1E) will be conducted in the United States only. Subjects who have severe allergies to penicillins or cephalosporins cannot participate in this sub-study cohort.

Safety Information: Summary safety tables from the Dose escalation cohort (Cohort 1) meetings will be shared with all investigators participating in both cohorts (escalation and expansion). These tables include severe and non-severe AEs.

Re-Enrollment into the trial will be permissible for subjects who discontinue treatment for reasons other than toxicity or disease progression as long as they fulfill all Inclusion and Exclusion Criteria. All subjects that re-enroll will enroll into Cohort 2 and will follow the assigned Schedule of Assessments as if they are a new subject.

Intra-subject dose escalation for Cohorts 1 and 2:

In the dose escalation cohort (Cohort 1), if the subjects on 20 mg and 40 mg dose levels do not achieve a composite CR (CRc), defined as either of CR, CRp or CRi, after 1 cycle of treatment and did not have DLT, they may dose escalate to the next dose level.

In the dose expansion cohort (Cohort 2), subjects who do not achieve a CRc may dose escalate to the next dose level, if the next dose level has opened up for expansion (i.e., a decision has been made to escalate to next higher dosing level).

Subjects who dose escalate will revert to more frequent safety evaluation (Refer to Section 3.2.3).

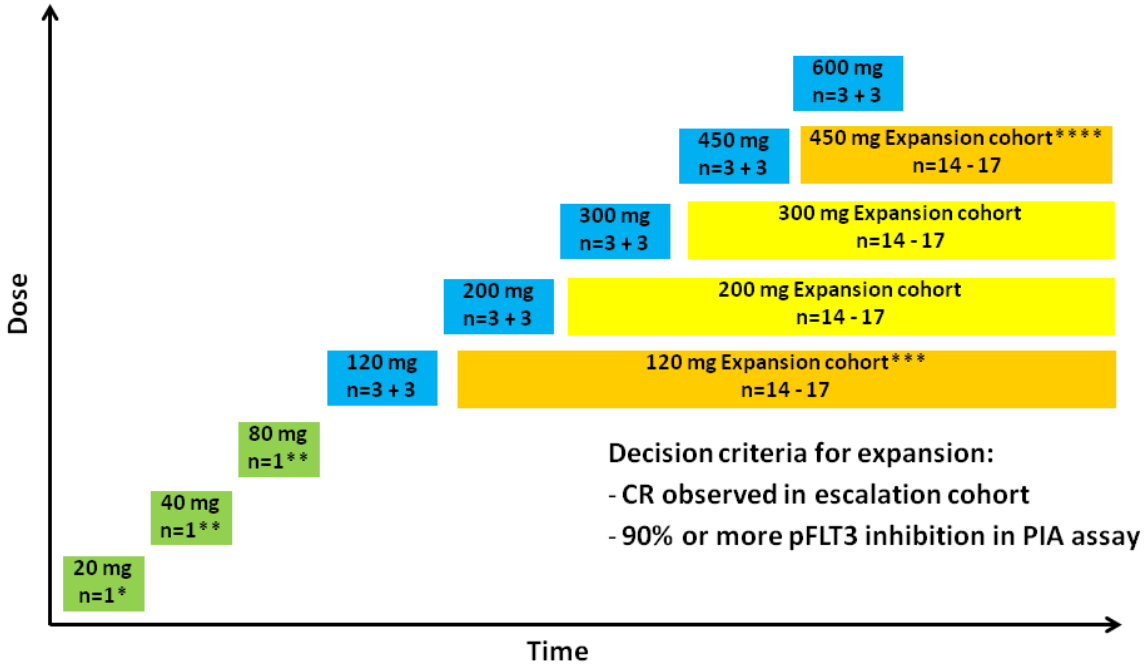
Table 2 Dose Levels

Dose Level	ASP2215 Dose
DL1	20 mg
DL2*	30 mg
DL3	40 mg
DL4*	60 mg
DL5	80 mg
DL6	120 mg
DL7	200 mg
DL8**	300 mg
DL9	450 mg
DL10	600 mg

* These dose levels may be omitted as described in Section 3.2.1 Study Design.

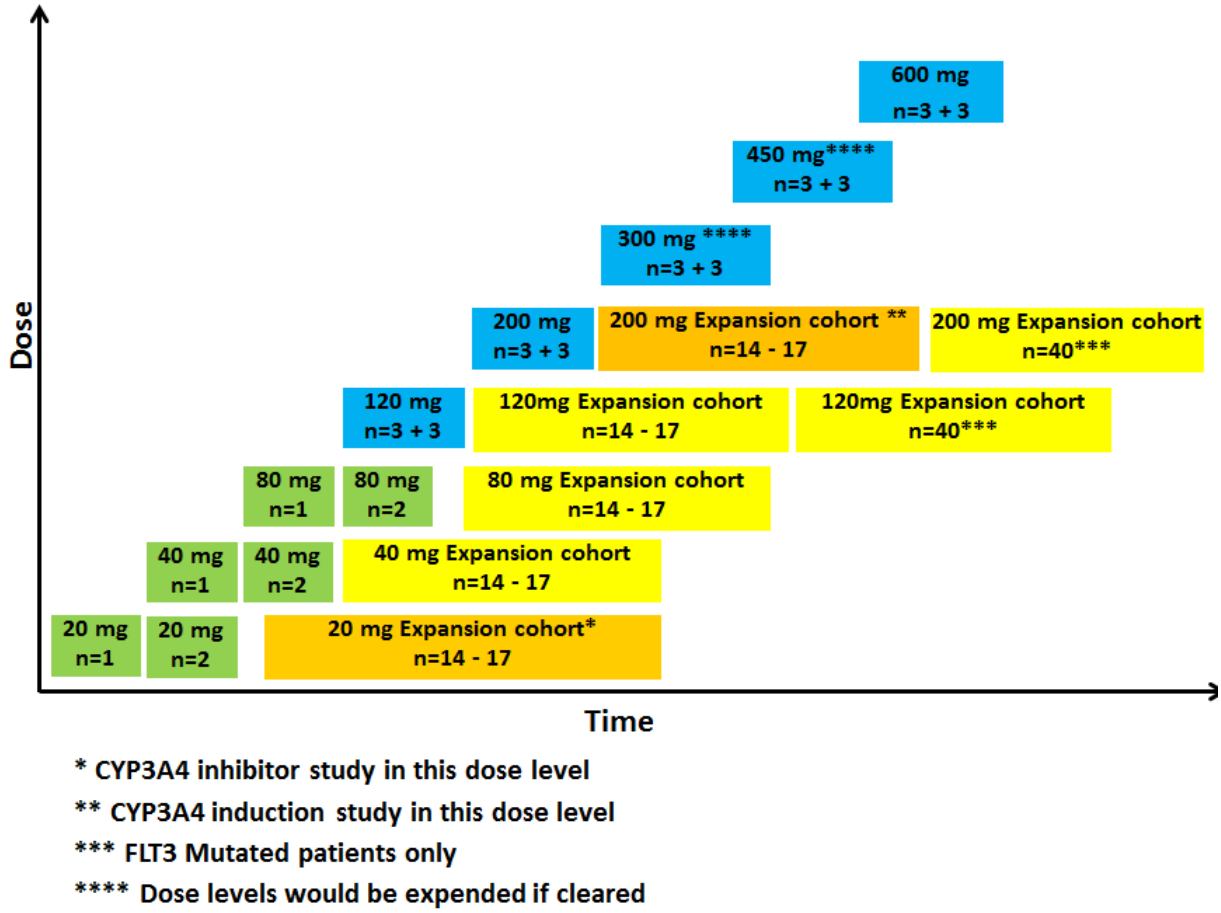
** For patients being treated with 40 mg tablets, dose escalations to 280 mg will be permitted

Figure 1 Optimal Dose Escalation and Expansion



* If no DLT
** If no DLT and no grade 2 AE in two patients
*** CYP3A4 inhibitor study in this dose level
**** CYP3A4 induction study in this dose level

Figure 2 Optimal Efficacy Expansion of Cohort 2

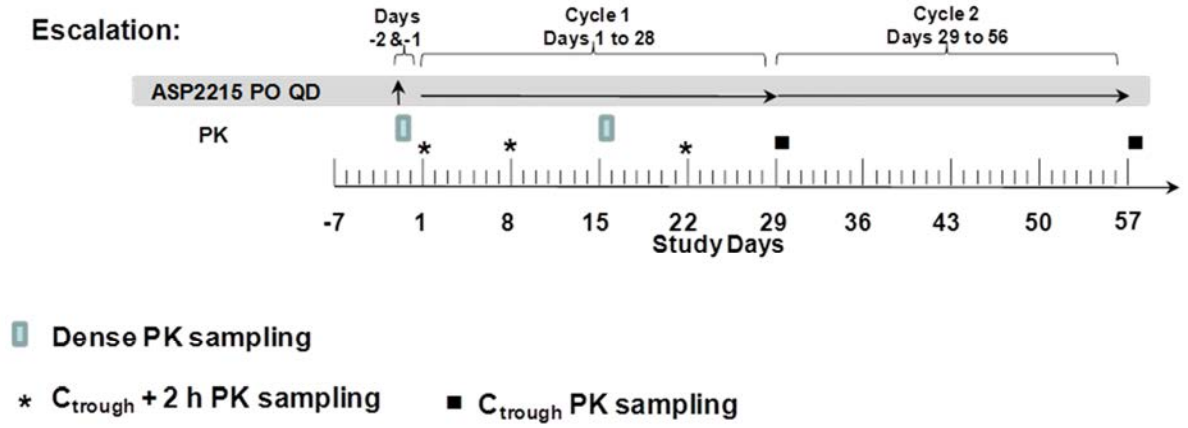


* CYP3A4 inhibitor study in this dose level
** CYP3A4 induction study in this dose level
*** FLT3 Mutated patients only
**** Dose levels would be expended if cleared

3.2.2 Dose/Dose Regimen and Administration Period

3.2.2.1 Dose Escalation Phase (Cohort 1)

ASP2215 will be administered on Day -2 to evaluate pharmacokinetics following a single dose through 48 hours. Starting on Day 1 of Cycle 1 ASP2215 will be administered QD for 28 additional doses until disease progression or patient discontinuation.



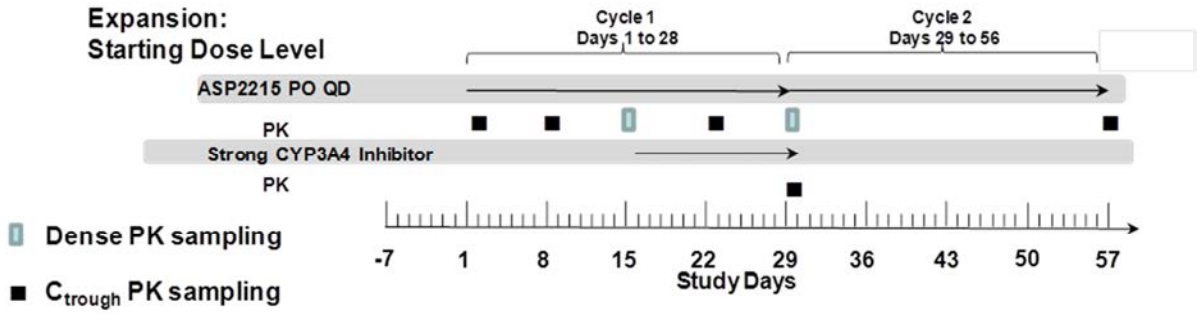
See [Table 1A]: Schedule of Assessments for Dose Escalation Phase (Cohort 1)

3.2.2.2 Expansion Phase (Cohort 2)

During the initial 15 days of treatment in the expansion cohorts with DDI studies (Schedule 1B, 1D and 1E), moderate or strong CYP3A4 inhibitors are prohibited, unless required for treatment of active infections. DDI studies (Schedule 1B, 1D and 1E) will be conducted in the United States only. European sites whose patients are randomized to the DDI arms of the study will follow schedule 1C and will not administer their patients these medications. In addition, US sites approved by the sponsor to join the trial who cannot conduct the DDI portion of the trial will also be allowed to follow schedule 1C even if patients are randomized to schedule 1B or 1D.

3.2.2.2.1 Expansion Cohort with CYP3A4 Inhibitor Study (Cohort 2 Starting Dose Level) (Evaluation of CYP3A4 inhibitor on ASP2215)

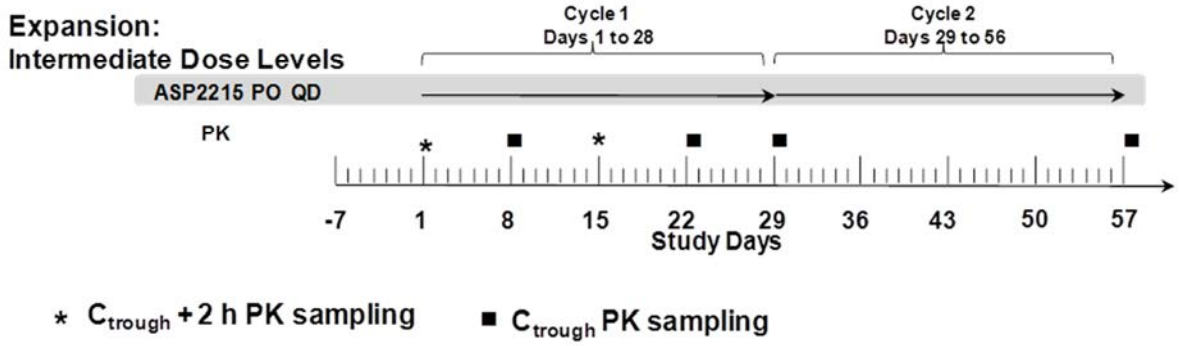
ASP2215 will be administered QD starting on Day 1 of Cycle 1. Starting on Day 16 a strong CYP3A4 inhibitor (voriconazole) will be administered daily at 200 mg every 12 hours through Day 1 of Cycle 2. Voriconazole for use in this trial will be provided by Astellas (15 day supply).



See [Table 1B]: Schedule of Assessments for Expansion Phase with CYP3A4 Inhibitor Study (Cohort 2, Starting Dose Level)

3.2.2.2.2 Expansion Cohort without DDI Studies (Cohort 2 Intermediate Dose Levels)

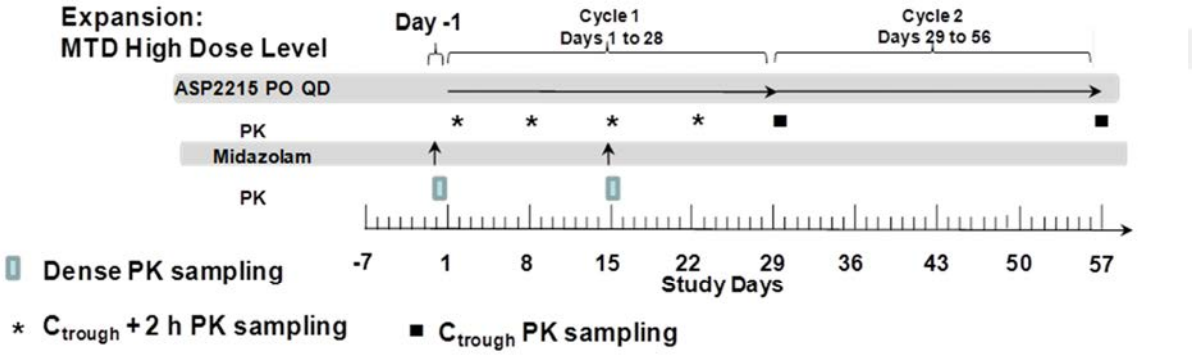
ASP2215 will be administered QD starting on Day 1 of Cycle 1.



See [Table 1C]: Schedule of Assessments for Expansion cohort without DDI Studies (Cohort 2, Intermediate Dose Levels)

3.2.2.2.3 Expansion Cohort with Induction Study (Cohort 2- MTD Level) (Evaluation of the effect of steady state ASP2215 on Midazolam)

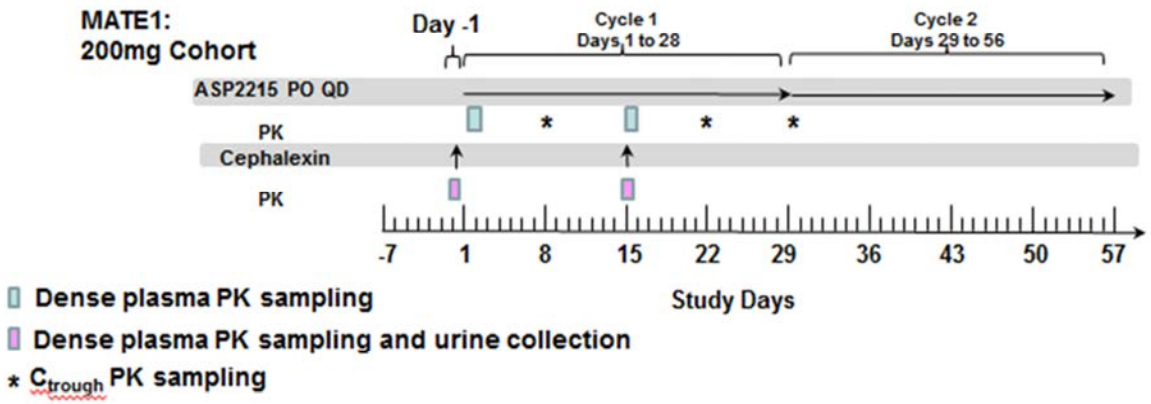
Midazolam (2 mg of syrup (1.0 ml) by mouth) will be administered as a single oral dose on Day -1 and Day 15 of Cycle 1. ASP2215 will be administered QD starting on Day 1 of Cycle 1. Midazolam for use in this trial will be provided by Astellas.



See [Table 1D]: Schedule of Assessments for Expansion Phase with CYP3A4 Induction Study (Cohort 2, MTD Level)

3.2.2.2.4 Expansion Cohort with MATE1 Substrate Study (Cohort 2 – MATE1 Sub-study) (Evaluation of the effect of steady state ASP2215 on Cephalexin)

Cephalexin (500 mg oral tablet or capsule) will be administered as a single oral dose on Day -1 and Day 15 of Cycle 1. ASP2215 200 mg will be administered QD starting on Day 1 of Cycle 1. Cephalexin for use in this trial will not be provided by Astellas.



See [Table 1E]: Schedule of Assessments for Expansion Phase with MATE1 Substrate Study (Cohort 2, MATE1 Sub-study)

3.2.3 Increase or Reduction in Dose of the Study Drug(s)

Guidelines for ASP2215 dose reduction are provided in Table 3

The ASP2215 dose may be reduced for subjects after Cycle 1 in the dose escalation phase (Cohort 1), and at any cycle in the dose expansion phase (Cohort 2). Dose reduction during Cycle 1 in the dose escalation phase (Cohort 1) is only allowed if the subject has already experienced clinical benefit and after discussion with the medical monitor. Note that dose reductions should occur in a step-wise manner, following the dose levels outlined in Table 2 After the initial dose reduction, additional dose reductions may occur unless stated otherwise. If no further dose reductions are available, study treatment will be discontinued.

Table 3 Guidelines for ASP2215 Dose Reduction Event

ASP2215 Dosing Instructions	
Event	
QTc Prolongation	If the mean QTcF from Cycle 1 Day 1 to Cycle 1 Day 8 has increased > 30 ms based on central read ECG without any other etiology, a confirmatory ECG will be performed on Day 9. If the Cycle 1 Day 9 central read ECG is confirmatory, a dose reduction should be considered. QTcF values based on central reading from triplicate ECGs should be used for this determination (i.e., Day 8 mean QTcF from triplicate ECGs at predose minus the Day 1 mean QTcF from triplicate ECGs at predose).
Retinopathy	
Grade 2	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.
Grade 3/4	Treatment will be discontinued.

Table continued on next page

Non-hematological Events	
Grade 3 related to ASP2215	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.
Grade 4 toxicity at least possibly due to study drug	Treatment will be discontinued
Myelosuppression	
CRp or CRi	Dose may be reduced without interruption if the following criteria are met: • Subject has received a minimum of 2 cycles of ASP2215 • Platelets < 25 x 10^9/L and/or ANC ≤ 0.5 x 10^9/L; • Marrow blasts < 5%; • No evidence of extramedullary disease; Further stepwise dose reduction is permitted if dosing 1 full cycle at the reduced dose has not resulted in the desired hematologic recovery.

Guidelines for dose escalation are provided in Table 4

In the dose escalation cohort (Cohort 1), if the subjects on 20 mg and 40 mg dose levels do not achieve a composite CR (CRc), defined as either of CR, CRp or CRi, after 1 cycle of treatment and did not have DLT, they may dose escalate to the next dose level. Only one dose escalation is allowed for lack of response.

In the dose expansion cohort (Cohort 2), subjects who do not achieve a CRc may dose escalate to the next dose level, if the next dose level has opened up for expansion (i.e., a decision has been made to escalate to next higher dosing level). After the initial dose escalation, additional dose escalations may occur following the dose levels in Table 2 if the next dose level has opened up for expansion (i.e., a decision has been made to escalate to next higher dosing level).

Table 4 Guidelines for ASP2215 Dose Escalation Event

Cohort 1 (Dose escalation cohort)	
No CRc (CR, CRp or CRi) after Cycle 1	Patients on 20 mg, 30mg or 40 mg can escalate one dose level
	Patients on 60-600 mg cannot escalate dose
Cohort 2 (Dose expansion cohort)	
No CRc (CR. CRp or CRi) after Cycle 1	Can dose escalate in a step wise manner following the dose levels in Table 2

If the dose escalated as per Table 4, the patients will revert to more frequent safety evaluations. The following tests will need to be done weekly (+/- 1 day) for one cycle. Resume regular monthly evaluation schedule as described in the Schedule of Assessments after the completion of the escalation cycle.

Weekly Assessments

Cohort 1 (Dose Escalation)	Cohort 2 (Dose Expansion)
Physical Exam Vital Signs ECG Clinical Laboratory Tests AE/SAE Evaluation In-Clinic Dosing Pre-Dose PK Serial PKs at Day of Escalation and 2 weeks post escalation • Pre-dose (0.5 hours before drug administration), 0.5 (±10 minutes), 1 (±10 minutes), 2 (±10 minutes), 4 (±20 minutes), 6 (±20 minutes), and 24 hours (±90 minutes) post dose Serial ECGs at Day of Escalation and 2 weeks post escalation • Pre-dose, 2, 4, 6, and 24 hours post	Physical Exam Vital Signs ECG Clinical Laboratory Tests AE/SAE Evaluation In-Clinic Dosing Pre-Dose PK

3.3 Randomization

Patient assignment will be performed manually until the availability of the Interactive Response Technology (IRT) during the Escalation phase (Cohort 1). Prior to the initiation of the study treatment, the site staff will complete and forward the subject registration form to the Astellas designee to receive the assigned treatment. Specific procedures for assignment are contained in the Regulatory Binder. After the IRT system becomes available, patients will be registered, enrolled and assigned treatment through IRT interactions. Specific procedures for randomization through the IRT are contained in the IWRS Manual in the Regulatory Binder.

Randomization will be performed via Interactive Response Technology (IRT) during Expansion phase (Cohort 2). Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomized treatment. Specific procedures for randomization through the IRT are contained in the IWRS Manual in the Regulatory Binder.

As a dose level is decided to be expanded, up to 17 subjects will be enrolled for the dose level in the dose expansion phase (to have a total of 20 subjects enrolled at a dose level including the subjects from dose escalation cohort). When more than one dose levels are expanded in the dose expansion phase (Cohort 2), the newly enrolled subjects will be randomized to one of the open expanded dose levels, based on the relative chance of (20 – n)

in each dose level, where n is the number of subjects already enrolled in the dose level, including both the dose escalation and expansion phases.

If 10 subjects without FLT3 mutations (internal tandem duplication (ITD) or activating point mutations) are enrolled an expanded dose level (including the subjects in the dose escalation cohort and dose expansion cohort), only subjects with FLT3 mutations can be enrolled to the dose level.

Dose levels at and above 120 mg will be further expanded (when found to be tolerable in Cohort 1) based on the efficacy results observed in escalation and expansion cohorts. Approximately 40 additional subjects will be enrolled at these dose levels to bring the total enrolled to approximately 60 patients at the dose level inclusive of Cohort 1 subjects.

Approximately 20 FLT3 mutation positive patients will be enrolled in the Expansion Phase with MATE1 Substrate Study (Schedule 2E). All patients will be assigned to ASP2215 200 mg dose level.

4 SAMPLE SIZE

The sample size is not based on statistical power calculation. It should provide adequate information for the objective of the study.

Up to 40 subjects are planned to be enrolled into up to 10 dose levels in the dose escalation phase depending on the number of dose levels studied. The dose expansion phase will enroll up to 250 subjects in the expansion cohort depending on the number of dose levels expanded. The total number of subjects estimated for enrollment is between 2 and 270 subjects. This excludes consideration of the replacement of subjects in the Dose Escalation Cohort (Cohort 1) that meet the replacement criteria, in which case the sample size would increase based on the number of subjects replaced.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock.

Safety Analysis Set (SAF) will be used for the analyses of safety and biomarker variables. Full Analysis Set (FAS), Safety Analysis Set (SAF) and Per Protocol Set (PPS) will be used for efficacy analysis. Pharmacokinetic Analysis Set (PKAS) will be used for pharmacokinetic analyses. Pharmacodynamic Analysis Set (PDAS) will be used for the analyses of pharmacodynamic data. The data from all patients who were randomized or allocated to treatment will be included in the data listings. All allocated/randomized subjects are those who signed the informed consent form, had a randomization/registration date, received a randomization number (for subjects in expansion phase only) and received drug assignment through either the Astellas clinical study manager or the IRT system.

5.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all subjects who were enrolled and received at least one dose of study drug and who have at least one post-treatment data point. Re-enrolled subjects will be excluded from FAS. All three subjects enrolled at site [redacted] will be excluded from FAS due to concerns with this site's compliance to good clinical practice as explained in the attached study communication memo (Appendix 10.2).

Specifically, the following will lead to a subject's exclusion from the FAS:

- No study drug taken
- No data post-treatment
- Previous enrolled into the study and discontinued the treatment and re-enrolled into the study
- Three subjects enrolled at site [redacted]

The selection of subjects for the FAS will be confirmed in the Analysis Set Classification Meeting (ASCM).

The FAS will be used for summaries of efficacy data, as well as selected demographic and baseline characteristics.

5.2 Per Protocol Set (PPS)

The Per-Protocol Set (PPS) includes all subjects of the FAS who do not meet criteria for exclusion from PPS listed in Section 5.2.1 of this SAP.

Final judgments on exclusion of subjects from the PPS are to be made at the ASCM, held prior to database hard lock.

The PPS will be used for sensitivity analyses of efficacy data. Also, selected demographic and baseline characteristics will be summarized for the PPS.

5.2.1 Reasons for Exclusion From PPS

The following reasons may lead to subject's exclusion from PPS:

- Entered into the study even though the subject violates the inclusion or exclusion criteria which may affect the assessment of the efficacy of the study drug
- Received wrong treatment or incorrect dose
- Administration of anti-leukemia treatment prohibited by protocol
- No post-baseline efficacy measurement

5.3 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all subjects who received at least one dose of study drug. Re-enrolled subjects will be excluded from SAF.

The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables. The SAF will also be used for sensitivity analyses of efficacy data.

5.4 Pharmacokinetics Analysis Set (PKAS)

The Pharmacokinetics Analysis Set (PKAS) consists of the subset of the SAF for which sufficient plasma concentration data are available to facilitate derivation of at least one PK parameter and for whom the time of dosing on the day of sampling is known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the Classification Specifications.

The PKAS is used for all tables and graphical summaries of the PK data.

5.5 Pharmacodynamic Analysis Set (PDAS)

The Pharmacodynamic Analysis Set (PDAS) will include the subjects from the SAF for whom sufficient pharmacodynamic measurements were collected. Any formal definitions for exclusion of subjects from the PDAS will be documented in the Classification Specifications.

The PDAS will be used for all analyses of pharmacodynamic data.

5.6 Re-Enrolled Analysis Set

Re-Enrolled Analysis Set includes subjects who discontinued treatment for reasons other than toxicity or disease progression and were re-enrolled into expansion phase and received at least one dose of study drug after re-enrollment.

5.7 Post-HSCT Analysis Set

Post-HSCT Analysis Set includes subjects who received at least one dose of study drug and meet either of the following criteria:

- Underwent on-study HSCT and resumed ASP2215 after HSCT
- Discontinued the treatment for HSCT and were re-enrolled into the study and received at least one dose of study drug after re-enrollment

Post-HSCT Analysis Set will be used for selected safety and efficacy summaries.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

Efficacy endpoints of ASP2215 in AML are secondary endpoints of the study.

6.1.1 Response Definition

Response to treatment will be defined per modified Cheson criteria [2003] as outlined below.

- Complete Remission (CR)

For subjects to be classified as being in CR at a post-baseline visit, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an absolute neutrophil count (ANC) > 1 x 10^9/L and platelet count ≥ 100 x 10^9/L, and normal marrow differential with < 5% blasts, and they will be red blood cell (RBC) and platelet transfusion independent (defined as 1 weeks without RBC transfusion

and 1 week without platelet transfusion). There must be no presence of Auer rods. There should be no evidence of extramedullary leukemia. The blast counts in peripheral blood must be ≤ 2%.

- Complete Remission with Incomplete Platelet Recovery (CRp)

For subjects to be classified as being in CRp at a post-baseline visit, they must achieve CR except for incomplete platelet recovery ($< 100 \times 10^9$/L).

- Complete Remission with Incomplete Hematological Recovery (CRi)

For subjects to be classified as being in CRi at a post-baseline visit, they must fulfill all the criteria for CR except for incomplete hematological recovery with residual neutropenia $< 1 \times 10^9$/L with or without complete platelet recovery. RBC and platelet transfusion independence is not required.

- Composite Complete Remission (CRc)

For subjects to be classified as being in CRc at a post-baseline visit, they must either achieve CR, CRp or CRi.

- Complete Remission with Partial Hematologic Recovery (CRh)

For subjects to be classified as being in CRh at a post-baseline visit, they cannot be classified as being in CR and must have bone marrow blasts < 5% and partial hematologic recovery ANC >= 0.5 x 10^9/L and platelets >= 50 x 10^9/L. There should be no evidence of extramedullary leukemia.

- Partial Remission (PR)

For subjects to be classified as being in PR at a post-baseline visit, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25%. A value of less or equal than 5% blasts is also considered a PR if Auer rods are present. There should be no evidence of extramedullary leukemia.

- Non-Responder (NR)/Not Evaluable (NE)

Subjects who do not achieve CR, or CRp, or CRi or PR will be considered non-responder. Except in the situation where no bone marrow assessments are formed and no blast from peripheral blood is observed (blast <= 2%), in which case a subject will be considered not evaluable.

- Relapse

Relapse after CR, CRh, CRp or CRi is defined as a reappearance of leukemic blasts in the peripheral blood (> 2%) or ≥ 5% blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

- Best Response

Best response is defined as the best measured response for all visits (in the order of CR, CRp, CRi, and PR) post-treatment. Subjects who achieve the best response of CR, CRp, CRi or PR will be classified as responders. Subjects who do not achieve at least PR will be considered non-responders.

Two best responses will be defined. Best response at the end of cycle 2 is defined as the best measured response (CR, CRp, CRi, PR) up to the end of 2 cycles of treatment. Best response at the end of treatment is defined as the best measured response (in the order of CR, CRp, CRi, PR) up to the End of Treatment Visit.

6.1.2 Efficacy Variables

Efficacy variables include:

- CR rate – Defined as the number of subjects with CR divided by the number of subjects in the analysis population. Subjects with unknown or missing response, or who provide no information on response at the end of study will be treated as non-responders and will be included in the denominator when calculating rates.
- CRp rate, CRi rate, PR rate – Defined similarly as CR rate.
- Composite complete remission (CRc) rate– Defined as the confirmed remission rate of all complete and incomplete CRs (i.e., CR+ CRp + CRi).
- Complete remission and complete remission with partial hematologic recovery (CR/CRh) rate - Defined as the number of subjects who achieve either CR or CRh at any of the post-baseline visits divided by the number of subjects in the analysis population.
- Complete remission with partial hematologic recovery (CRh) rate – Defined as the number of subjects who achieve CRh at any of the post-baseline visits and do not achieve best response of CR divided by the number of subjects in the analysis population.
- Best response rate – Defined as the number of subjects with CR or CRp or CRi or PR divided by the number of subjects in the analysis population (i.e., CR+ CRp + CRi + PR). Subjects with unknown or missing response, or who provide no information on response at the end of study will be treated as non-responders and will be included in the denominator when calculating rates.
- Overall survival (OS) – The time from the date of first dose of study drug until the date of death from any cause (death date – first dose date + 1). For a subject who is not known to have died by the end of study follow-up, OS is censored at the date of last contact (date of last contact – first dose date + 1).

  The date of last contact is the latest date the subject is known to be alive.

Subjects who discontinue the treatment and are re-enrolled into the study will be followed from first dose date before re-enrollment until the death or last contact after re-enrollment.

As sensitivity analysis, OS will be defined similarly as above, however, subject who undergo an allogeneic HSCT will be censored at the time of HSCT (HSCT date – first dose date +1).

- Event-free survival (EFS) – The time from the date of first dose of study drug until the date of documented relapse, treatment failure or death from any cause, whichever occurs first (relapse date or treatment failure date or death date – first dose date + 1). For a subject with none of these events, EFS is censored at the date of last relapse-free disease assessment (last relapse-free disease assessment date – first dose date +1). Subject without post-treatment disease assessment will be censored at randomization date.

  Treatment failure includes those subjects who discontinued the treatment due to "progressive disease" or "lack of efficacy" without a previous response of CR, CRp, CRi or PR.

  Treatment failure date refers to the start of new anti-leukemia therapy or the last treatment evaluation date when new anti-leukemia therapy date is not available.

  For subjects who are censored, last relapse-free disease assessment date refers to the subject's last disease assessment date.

- Leukemia-free survival (LFS) – The time from the date of first CRc until the date of documented relapse or death for subjects who achieve CRc (relapse date or death date – first CRc disease assessment date + 1). For a subject who is not known to have relapsed or died, LFS is censored on the date of last relapse-free disease assessment date (last relapse-free disease assessment date – first CRc disease assessment date + 1).
- Duration of remission – This includes duration of CRc (DCRc), duration of CR (DCR), duration of CRi (DCRi), duration of CRp (DCRp), duration of CR/CRh (DCRCRh), duration of CRh (DCRh), and duration of response (DR) (i.e., CRc + PR).
    - Duration of CRc – Duration of CRc is defined as the time from the date of first CRc until the date of documented relapse for subjects who achieved CRc (relapse date – first CRc disease assessment date + 1). Subjects who die without report of relapse are considered non-events and censored at their last relapse-free disease assessment date (last relapse-free disease assessment date – first CRc disease assessment date + 1). Other subjects who do not relapse on study are considered non-events and censored at the last relapse-free disease assessment date.
    - Duration of CR is defined similarly as duration of CRc for subjects who achieved CR.
    - Duration of CRp is defined similarly as duration of CRc for subjects who achieved CRp.

- Duration of CRi is defined similarly as duration of CRc for subjects who achieved CRi.
- Duration of CR/CRh is defined similarly as duration of CRc for subjects who achived either CR or CRh. For subjects who achieve both CR and CRh, the first CR date or CRh date, whichever occurs first, will be used.
- Duration of CRh is defined similarly as duration of CRc for subjects who achieved CRh but don't have best response of CR.
- Duration of response – Duration of response is defined as the time from the date of either first CRc or PR until the date of documented relapse of any type for subjects who achieved CRc or PR (relapse date – first CRc or PR disease assessment date + 1). Subjects who die without report of relapse are considered non-events and censored at their last relapse-free disease assessment date (last relapse-free disease assessment date – first CRc or PR disease assessment date + 1). Other subjects who do not relapse on study are considered non-events and censored at the last relapse-free assessment date.

- Time to remission – This includes time to CRc (TTCRc), time to CR (TTCR), time to CRi (TTCRi), time to CRp (TTCRp), time to first CR/CRh (TTFCRCRh), time to best CR/CRh (TTBCRCRH), time to response (TTR), and time to best response (TTBR).
  - Time to CRc is defined as the time from the first dose of study drug until the date of first CRc (first CRc disease assessment date – first dose date +1). TTCRc will only be evaluated for subjects who achieved CRc.
  - Time to CR is defined similarly as time to CRc for subjects who achieved CR.
  - Time to CRp is defined similarly as time to CRc for subjects who achieved CRp.
  - Time to CRi is defined similarly as time to CRc for subjects who achieved CRi.
  - Time to first CR/CRh is defined similarly as time to CRc for subjects who achieved either CR or CRh. For subjects who achieve both CR and CRh, the first CR date or CRh date, whichever occurs first, will be used.
  - Time to best CR/CRh is defined similarly as time to CRc for subjects who achieved either CRor CRh. For subjects who achieve both CR and CRh, the first CR date will be used.
  - Time to response is defined as the time from the first dose of study drug until the date of either first CRc or PR (first CRc or PR disease assessment date – first dose date +1). TTR will only be evaluated for subject who achieved CRc or PR.
  - Time to best response is defined as the time from the first dose of study drug until the first disease assessment date when subject achieved best response (first disease assessment date of best response – first dose date +1). TTR will only be evaluated in subjects who achieved best response of CR, or CRp, or CRi, or PR.

- Transfusion status (dependent vs. independent)

  For the purpose of defining transfusion conversion rate and transfusion maintenance rate, transfusion status (independent vs. dependent) at baseline period and post-baseline period are defined in the following for subjects who took at least one dose of study drug:

  Baseline transfusion status:

  - Baseline period is defined as the period from 28 days prior to first dose until 28 days after the first dose. For subjects who are on treatment <28 days, baseline period is from the 28 days prior to first dose until the end of treatment.
  - Subjects are considered baseline transfusion independent if there is no RBC or platelet transfusions within the baseline period; otherwise, the subject is baseline transfusion dependent.

  Post-baseline transfusion status:

  - Post-baseline period is defined as the period from 29 days after first dose date until last dose date.
  - For subjects who are on treatment >=84 days, subjects are considered post-baseline transfusion independent if there is one consecutive 56 days without any RBC or platelet transfusion within post-baseline period.
  - For subjects who are on treatment >28 days but <84 days, if there is no RBC or platelet transfusion within post-baseline period, post-baseline transfusion status is not evaluable.
  - For subjects who are on treatment <=28 days, post-baseline transfusion status is not evaluable.
  - Otherwise, the subject is considered post-baseline transfusion dependent.

- Transfusion conversion rate
  Transfusion conversion rate is defined for subjects who have evaluable post-baseline transfusion status. It is defined as the number of subjects who were transfusion dependent at baseline period but become transfusion independent at post-baseline period divided by the total number of subjects who are transfusion dependent at baseline period.
- Transfusion maintenance rate
  Transfusion maintenance rate is defined for subjects who have evaluable post-baseline transfusion status. It is defined as the number of subjects who were transfusion independent at baseline period and still maintain transfusion independent at post-baseline period divided by the total number of subjects who are transfusion independent at baseline period.

6.2 Safety Variables

Safety and tolerability (determine MTD) are the primary endpoints of the study.

6.2.1 Definition of DLT

A DLT is defined as any of the following events that occur within 30 days starting with the first dose taken on Day -2, and including the first treatment cycle in dose escalation cohort (Cohort 1) and that is considered to be possibly, probably or definitely related to study drug. In Cohort 2, DLT observation period is the first treatment cycle (28 days).

Any Grade ≥ 3 non-hematologic or extramedullary toxicity. The following exceptions are noted:

- Alopecia, anorexia, or fatigue.
- Grade 3 nausea and/or vomiting if not requiring tube feeding or TPN, or diarrhea if not requiring or prolonging hospitalization that can be managed to Grade ≤ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 7 days of onset.
- Grade 3 fever with neutropenia, with or without infection.
- Grade 3 infection.

Hematologic toxicity will not be considered as a DLT. However, prolonged myelosuppression defined as ANC <500 for more than 21 days off therapy in the absence of evidence of active leukemia in the marrow or blood will be considered as a DLT.

6.2.2 Definition of MTD

The MTD is defined as the highest dose associated with the occurrence of DLTs in less than 33% of the subjects in dose escalation cohort. If ≥ 2 out of 6 subjects in dose escalation cohort experience a DLT in a dose level, the next lower dose level will be declared the maximum tolerated dose (MTD). Please see details in Section 3.2.1

6.2.3 Other Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity grade, seriousness, and relationship to study drug)
    - TEAE is defined as an adverse event observed after starting administration of the study drug. If the adverse event occurs on Day -2 (dose escalation phase) or Cycle 1 Day 1 (dose expansion phase) and the onset check box is marked “Onset after first dose of study drug” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day -2 (dose escalation phase) or Cycle 1 Day 1 (dose expansion phase) and the onset check box is marked “Onset before first dose of study drug”, then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity

(i.e., it is reported with a new start date). All adverse events collected that begin within 30 days after taking the last dose of study drug will also be counted as TEAE, except for subjects that undergo HSCT without leaving the study and plan to resume ASP2215 treatment after HSCT. For these subjects, TEAE is defined as adverse events observed after starting administration of the study treatment until the last dose before on study HSCT plus 30 days, and adverse events that begin after resumption of ASP2215 and within 30 days after the last dose of ASP2215 will also be counted as TEAE. Any AEs with onset dates completely missing will be considered TEAEs in summaries. AEs with partially missing onset dates will be assumed TEAEs unless the available portion of the date indicates that the onset was strictly before start of study medication.

- A drug-related TEAE is defined as any TEAE with at least possible relationship (possibly or probably related) to study treatment as assessed by the investigator or with missing assessment of the causal relationship.
- Adverse event during HSCT period is defined as an adverse event observed on or after the on study HSCT until the day before resumption of ASP2215.

- Serious adverse events (SAEs) include adverse events that are flagged as serious by the investigator on eCRF, or upgraded by the Sponsor based on review of the Sponsor's list of Always Serious term.
- Adverse events of special safety interest (AESI) are defined in the Safety Review Plan for ASP2215. Targeted medical events are identified using MedDRA preferred terms, MedDRA Queries (SMQs), and laboratory filters. Details are provided in the table below.

Targeted Medical Event	**Search Strategy (MedDRA Preferred Terms, MedDRA SMQ, and/or Lab Filter)**
Gastrointestinal (GI) hemorrhage	Gastrointestinal haemorrhage SMQ (narrow), Gastrointestinal perforation SMQ (narrow), Gastrointestinal ulceration SMQ (narrow) and Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures SMQ (narrow)
Hepatotoxicity	Drug-related hepatic disorders comprehensive search SMQ (broad and narrow)
Renal toxicity	Acute renal failure SMQ (broad and narrow)
Ocular Toxicity	Retinal disorders SMQ (broad and narrow), corneal disorders SMQ (broad and narrow), conjunctival disorders SMQ (broad and narrow), lens disorder SMQ (broad and narrow), uveitis (PT)
Phospholipidosis	Beta-N-acetyl-Dglucosaminidase abnormal (PT), Beta-N-acetyl-D-glucosaminidase increased (PT), Niemann-Pick disease (PT) Lipidosis (PT) Eosinophilic pneumonia SMQ (broad and narrow)
Table continued on next page	

Targeted Medical Event	Search Strategy (MedDRA Preferred Terms, MedDRA SMQ, and/or Lab Filter)
Pulmonary edema/hemorrhage	Acute pulmonary oedema (PT), bronchial oedema (PT), pulmonary oedema (PT), non-cardiogenic pulmonary oedema (PT), pleural effusion (PT), pulmonary haemorrhage (PT), bronchial haemorrhage (PT), pulmonary alveolar haemorrhage (PT), respiratory tract haemorrhage (PT), Haemoptysis (PT), Haemothorax (PT), Pleural haemorrhage (PT), pulmonary haematoma (PT), thoracic haemorrhage (PT), Tracheal haemorrhage (PT)
Interstitial pneumonia	Eosinophilic pneumonia SMQ (broad and narrow)
Prolonged QT interval	Torsade de Pointes/QTprolongation SMQ (broad and narrow), Death and Sudden death HLT

- Clinical laboratory variables
  Hematology, chemistry including liver function test and thyroid function test, coagulation, urinalysis, and bone marrow will be collected during the conduct of the study as listed in the table below.

Panel/Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Hematology	3- mL into ethylenediamine-tetraacetic acid (EDTA) tube	White Blood Cell Count (WBC)* WBC Differential* Red Blood Cell Count (RBC) Hemoglobin (Hgb)* Hematocrit (Hct)* Mean Corpuscular Volume Platelet Count* MCHC MCH
Table continued on next page		

Panel/Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Chemistry	8.5 mL into Serum tube	Sodium (Na) Potassium (K) Chloride (Cl) Bicarbonate (HCO_3) Blood Urea Nitrogen (BUN) Creatinine (Cr) Glucose (Gl) Calcium (Ca) Phosphate (Pi) Magnesium (Mg) Albumin (Alb) Total Protein (T Prot) Alkaline Phosphatase (AlkP) Lactate Dehydrogenase (LDH) Creatine Phosphokinase (CK) Aldolase Triglycerides (Trig) Total Cholesterol (T Chol) Phospholipid Globulin Liver Function Tests including: • Bilirubin Total (TBL) • Alanine Aminotransferase (ALT) • Aspartate Aminotransferase (AST) Thyroid function tests including: • TSH • Free T4
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	2.5 mL into Na Citrate tube	INR (with PT if reported) aPTT Fibrinogen (Screening Only) D-Dimer (Screening Only)
Urinalysis	Dipstick	Color Appearance Specific Gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen

Table continued on next page

Panel/Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Bone Marrow	Aspirate 3 mL EDTA, 2-3 bedside smear slides, and biopsy (or peripheral blood in the event of a dry tap)	Blast count and cell counts* Flowcytometry for blasts FLT3 mutation status C-CBL mutation status AXL mutation status

*In addition to the central read of these values, local results will also be collected and entered into the eCRF.

- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature)
- 12-lead electrocardiogram (ECG)
- Ophthalmologic assessment (visual acuity measurement, ophthalmoscopy, slit lamp biomicroscopy, visual fields and optical coherence tomography)
- ECOG performance scores

6.3 Pharmacokinetics Variables

6.3.1 Pharmacokinetics for ASP2215

Pharmacokinetics for ASP2215 is one of the primary endpoints of the study.

Plasma concentration data of ASP2215 will be used in noncompartmental pharmacokinetic analysis. Plasma concentration of ASP2215 will be evaluated for the dose escalation and dose expansion phases as outlined in Table 5 below. For the expansion phase with MATE1 substrate, plasma and urine concentration of cephalexin will be evaluated as outlined in Table 5 below.

Table 5 PK Sampling Schedule

Dose Escalation Phase (Cohort 1)	
ASP2215	
Cycle 1: Days -2, -and 15	Pre-dose (0.5 hours before drug administration)
	0.50, 1 and 2 hours post dose (±10 minutes), 4 and 6 hours post dose (±20 minutes), and 24 hours (±90 minutes) post ASP2215 dosing
Cycle 1: Days 1, 8 and 22	Pre-dose (0.5 hours before drug administration)
	2 hours (±10 minutes) post ASP2215 dosing
Cycles 2 + : Day 1	Pre-dose (0.5 hours before drug administration)
Expansion Phase with CP3A4 Inhibitor Voriconazole Study (Cohort 2, Starting Dose Level)	
ASP2215	
Cycle 1: Day 15 and Cycle 2: Day 1	Pre-dose (0.5 hours before drug administration)
	0.50, 1 and 2 hours post dose (±10 minutes), 4 and 6 hours post dose (±20 minutes), and 24 hours (±90 minutes) post ASP2215 dosing
Cycle 1: Days 1, 8 and 22	Pre-dose (0.5 hours before drug administration)
Cycles 3 + : Day 1	Pre-dose (0.5 hours before drug administration)

Table continued on next page

CYP3A4 Inhibitor Voriconazole	
Cycle 2: Day 1	Pre-dose (0.5 hours before drug administration)
Expansion Phase without DDI Studies (Cohort 2, Intermediate Dose Levels)	
ASP2215	
Cycle 1: Days 1 and 15	Pre-dose (0.5 hours before drug administration)
	2 hours (±10 minutes) post ASP2215 dosing
Cycle 1: Days 8 and 22 and Cycle 2+ : Day 1	Pre-dose (0.5 hours before drug administration)
Expansion Phase with CYP3A4 Induction Study (Cohort 2, MTD Level)	
ASP2215	
Cycle 1: Days 1, 8, 15, and 22	Pre-dose (0.5 hours before drug administration)
	2 hours (±10 minutes) post ASP2215 dosing
Cycles 2 + : Day 1	Pre-dose (0.5 hours before drug administration)
Midazolam	
Cycle 1: Day -1 and Day 15	Pre-dose (0.5 hours before drug administration)
	0.50, 1 and 2 hours post dose (±10 minutes), 4 and 6 hours post dose (±20 minutes), and 24 hours (±90 minutes) post Midazolam dosing
Expansion Phase with MATE1 Substrate Study (Cohort 2, MATE1 Sub-study)	
ASP2215	
Cycle 1: Day 15	Pre-dose (0.5 hours before drug administration) 1 and 2 hours post dose (±10 minutes), 4 and 6 hours post dose (±20 minutes) 24 hours (±90 minutes) post ASP2215 dosing
Cycle 1: Days 1, 8 and 22	Pre-dose (0.5 hours before drug administration)
Cycles 2 +: Day 1	Pre-dose (0.5 hours before drug administration)
Cephalexin	
Cycle 1: Day -1 and Day 15	Plasma PK: Pre-dose (0.5 hours before drug administration) 0.5, 1, 1.5, 2 and 3 hours post dose (±10 minutes) 4 and 6 hours post dose (±20 minutes) and 24 hours (±90 minutes) post cephalexin dosing Urine PK: 0-3 hours, 3-6 hours and 6-24 hours post dose.

In subjects with sufficient PK samples on Day -2 and Cycle 1 Day 15 of dose escalation phase, Cycle 1 Day 15 and Cycle 2 Day 1 of dose expansion phase with CYP3A4 inhibitor study, the following PK parameters will be determined for ASP2215:

Dose Escalation Phase

- Day – 2: C_{max}, t_{max}, AUC_{last}, AUC_{24}
- Cycle 1 Day 15: C_{max}, t_{max}, $t_{1/2}$, AUC_{last}, AUC_{24}
- Accumulation ratio: AUC_{24} Cycle 1 Day 15/AUC_{24} Day -2

$t_{1/2}$ may be based on accumulation ratio if the interval for $t_{1/2}$ using log-linear regression is shorter than the calculated $t_{1/2}$ and linear pharmacokinetics are observed.

Dose Expansion Phase with CYP3A4 Inhibitor Voriconazole Study (Cohort 2, Starting Dose Level)

- Cycle 1 Day 15 and Cycle 2 Day 1: C_{max}, t_{max}, AUC_{last}, AUC_{24},
- Ratio: AUC_{24} Cycle 2 Day 1/AUC_{24} Cycle 1 Day 15

Dose Expansion Phase with MATE1 Substrate Study (Cohort 2, MATE1 Sub-study)

- Cycle 1 Day 15: C_{max}, t_{max}, AUC_{last}, AUC_{24}

WinNonlin calculates $C_{tau,}$ based on the terminal rate constant and extrapolates or interpolates to the appropriate timepoint if C_{last} is not at the scheduled time (e.g., 24 hours) and bases AUC_{24} on this value. If this calculation is not possible then AUC_{last} may be reported.

In addition, dose normalized plasma concentration and dose normalized PK parameter (C_{max}, AUC_{24}, AUC_{last}), will be derived as follows:

Dose normalized plasma concentration = plasma concentration / ASP2215 dose level taken at the corresponding timepoint.

Dose normalized PK parameter = PK parameter / ASP2215 dose level taken at the corresponding visit.

6.3.2 Pharmacokinetics for Midazolam and Midazolam Metabolite

Pharmacokinetics for Midazolam is secondary endpoint of the study.

Plasma concentration of Midazolam and 1-hydroxy Midazolam (Midazolam metabolite, if available) will be evaluated for the dose expansion phases as outlined in Table 5.

The following PK parameters will be determined for Midazolam and 1-hydroxy (if possible) in dose expansion phase with induction study.

- Day -1 and Cycle 1 Day 15: C_{max}, t_{max}, AUC_{last}, AUC_{24}

WinNonlin calculates $C_{tau,}$ based on the terminal rate constant and extrapolates or interpolates to the appropriate timepoint if C_{last} is not at the scheduled time (e.g., 24 hours) and bases AUC_{24} on this value. If this calculation is not possible then AUC_{last} may be reported for AUC_{24}

6.3.3 Pharmacokinetics for CYP3A4 Inhibitor Voriconazole

Plasma concentration of CYP3A4 inhibitor Voriconazole will be evaluated for the dose expansion phases as outlined in Table 5.

6.3.4 Pharmacokinetics for Cephalexin

Pharmacokinetics for Cephalexin is secondary endpoint of the study.

Plasma concentration of Cephalexin will be evaluated for the dose expansion phases MATE1 sub-study as outlined in Table 5.

The following PK parameters and urinary PK parameters will be determined for Cephalexin in dose expansion phase MATE1 sub-study.

- Day -1 and Cycle 1 Day 15: C_{max}, t_{max}, $t_{1/2}$, , AUC_{last}, AUC_{inf}, CL/F, and V_z/F
- Day -1 and Cycle 1 Day 15 urinary PK parameters: Ae (amount of drug excreted in urine), %Ae (fraction of drug excreted into urine in %), CL_R (renal clearance)

6.4 [redacted]

6.5 [redacted]

6.6 Other Variables

- Body Mass Index (BMI)
  BMI = weight (kg) / [height (m)]^2
- Duration of exposure
  Duration of exposure to a study drug will be calculated in days, using the following formula:

  Date of last dose of study drug – Date of first dose + 1 – number of days without drug administration in between.
  When the start or stop date is missing, then the exposure will be treated as missing.
- Planned duration of exposure
  Planned duration of exposure will be calculated in days, using the following formula:

  Date of last dose of study drug – Date of first dose + 1, when first dose is on Cycle 1 Day 1;

  Date of last dose of study drug – Date of first dose, when first dose is on Day -2.

  When the start or stop date is missing, then the exposure will be treated as missing.
- Average daily dose
  Defined as total dose administered divided by planned duration of exposure.

- Relative dose intensity

  $$\frac{\text{Average daily dose}}{\text{Intial dose level actually taken}} \times 100\%$$

- Percent treatment compliance

  Treatment compliance for ASP2215 is defined as:

  $$\frac{\text{Total amount of study drug actually consumed}}{\text{Amount of study drug should have been taken}} \times 100\%$$

  Where, the amount of study drug that should have been taken depends on the duration of exposure and the actual dose level as recorded on the study drug dosing CRF page. It will be calculated as:

  Sum of [(stop date of study drug – start date of study drug + 1) * dose level]

  The amount of study drug actually consumed will be calculated as:

  (total number of 10 mg tablets dispensed – total number of 10 mg tablets returned) * 10 mg + (total number of 100mg tablets dispensed – total number of 100mg tablets returned) * 100 mg + (total number of 40 mg tablets dispensed – total number of 40 mg tablets returned) * 40 mg

- Duration of AML

  Duration of AML will be calculated in days using the following formula:

  (Registration/randomization date – date of initial diagnosis of AML) + 1

- Previous and concomitant medication

  Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug.

  Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

- Previous and concomitant transfusion

  Previous transfusion is defined as transfusion received before the date of first dose of study drug, i.e., transfusion completed before the date of first dose.

  Concomitant transfusion is defined as transfusion received between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

- CYP3A4 inhibitor types

  CYP3A4 inhibitor types are defined based on subject's consumption of the following medications while on the study according to concomitant medication and drug exposure information:

  Strong CYP3A4 inhibitor: voriconazole or posaconazole

  Moderate CYP3A4 inhibitor: fluconazole

  No CYP3A4 inhibitor: none of the above medication

- Baseline hepatic function group

  Baseline hepatic function group is defined per the NCI-ODWG criteria based on total bilirubin and AST at the baseline from central lab as follows:

  Normal: total bilirubin <= ULN and AST <= ULN

  Mild HD: ULN < total bilirubin < = 1.5 x ULN or AST > ULN

  Moderate HD: 1.5 x ULN < total bilirubin <= 3 x ULN, any AST

  Severe HD: 3 x ULN < total bilirubin <= 10 x ULN, any AST

- Baseline rental function group

  Baseline rental function group is defined using baseline eGFR (MDRD formula) as follows:

  Normal: eGFR >= 90

  Mild: 60 <= eGFR < 90

  Moderate: 30 <= eGFR < 60

  Severe: eGFR < 30

  eGFR is estimated by MDRD formula as follows:

  eGFR (mL/min/1.73 m^2) = 175 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

  Serum creatinine value from central lab need to be converted from micro moL/L to mg/dL (1 mg/dL = 88.4 micro mol/L)

7 STATISTICAL METHODOLOGY

7.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g., 10%, 25%, 75% and 90%) will be mentioned in the relevant section. In addition, for plasma concentrations and continuous PK parameters, the coefficient of variation and the geometric mean will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%. Kaplan-Meier survival curves will be displayed for time-to-event variables and median survival time will be estimated with 2-sided 95% confidence interval (CI).

Summaries based on FAS and PPS (e.g., disposition, baseline and efficacy data) will be presented by planned dose level, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented by actual dose level received. Pharmacokinetic summaries based on PKAS and pharmacodynamic summaries based on PDAS will be presented by actual dose level received. For subjects with dose increase/decrease, actual dose level refers to the initial dose level received before dose change.

All statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference, all alternative hypotheses will be two-sided, unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher on Unix. Specifications for table, figure, and data listing formats can be found in the TLF specifications for this study.

Baseline is defined as the last available measurement prior to the first dose of study drug. Unless otherwise specified, all summaries will be presented by cohort and dose level. Efficacy endpoints will also be stratified by FLT3 mutation status as detailed in Section 7.8

For the definition of subgroups of interest please refer to Section 7.8.

Laboratory results, vital signs, ECG, ECOG, and ophthalmologic assessments collected after on-study HSCT will be labeled as post-HSCT visits sequentially.

Re-enrolled subjects will not be included in summary statistics unless specifically stated otherwise. Information collected after re-enrollment will be listed.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number and percentage of subjects with informed consent, discontinued before allocation to treatment/randomization, allocated to treatment/randomized (overall only);
- Number and percentage of subjects allocated to treatment/randomized in each analysis set, by cohort, dose level and overall;
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation for allocated/randomized subjects, by cohort and dose level;
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation for allocated/randomized subjects and by cohort and dose level;
- Number and percentage of subjects completed and discontinued the post-study period, by primary reason for post-study period discontinuation for allocated/randomized subjects and by cohort and dose level; and
- Number and percentage of subjects excluded from PPS by reason for exclusion defined in Section 5.2.1, by cohort and dose level for FAS.

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all subjects randomized or allocated to treatment. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by cohort, dose level, and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than

one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics.

Number and percentage of subjects allocated to treatment in each country and site will be presented by cohort and dose level for the SAF.

Descriptive statistics for age, weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (defined in Section 7.8), race and baseline transfusion status will be presented. This will be done for the subjects not randomized/not allocated to treatment (screen failures), as well as for the SAF, FAS and PPS by cohort and dose level. Summary of demographic characteristics will be stratified by FLT3 mutation status from local assessment and central assessment.

Baseline hepatic function and renal function will be summarized using frequency tables by cohort and dose level for SAF.

Frequency tabulations for AML disease history including AML subtype as classified by World Health Organization (WHO) classification and French-American-British (FAB) classification, risk status, antecedent hematological disorder, central nervous system leukemia, local FLT3-ITD mutation status, local FLT3 point mutation status will be presented by cohort and dose level for the SAF.

Medical history other than AML and conditions existing at Baseline will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by cohort and dose level for the SAF. Baseline conditions are defined as those ongoing at the time of informed consent or arise following the time of informed consent and before the first dose of study drug. For ongoing medical conditions, Common Terminology Criteria for Adverse Events (CTCAE) grade will be provided in listing.

Frequency tabulations for prior transplant including number of transplant received, graft type, donor relatedness, match type and outcome of transplant will be presented by cohort and dose level for the SAF.

Results from lumbar puncture and MUGA scan, if performed, will be provided in listing.

Demographic information, AML disease history, medical history and prior transplant for re-enrolled subjects will be provided in listings.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by cohort and dose level for the SAF.

As with previous medication, concomitant medication will be summarized for each cohort and dose level by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Usage of concomitant medication and number of concomitant medication taken (grouped into categories as defined in Section 7.8) that prolong QT with known and possible risk of TdP will be summarized using frequency table by cohort and dose level for SAF. The list of medications are provided in Appendix 10.1

Previous and concomitant medications for re-enrolled subjects will be provided in listing.

7.2.5 Previous and Concomitant Transfusions

All transfusions received by subjects within 28 days prior to Day 1 of Cycle 1 through end of treatment will be recorded on the eCRF. Data will include the date, blood product, start and stop date, indication, and the number of units given.

Frequency tabulations of subjects received transfusions and blood product will be presented for previous transfusion and concomitant transfusion by cohort and dose level for SAF. Descriptive statistics will be presented for number of transfusion unit received per subject.

Previous and concomitant transfusions for re-enrolled subjects will be provided in listing.

7.2.6 Prior AML Chemotherapy

Frequency tabulations of subjects with prior AML chemotherapy, regimen, type of treatment, best response to prior AML therapy, lines of therapy received and subjects with prior TKI therapy will be presented by cohort and dose level for SAF. Descriptive statistics will be presented for duration of response to prior AML therapy.

Prior AML chemotherapy for re-enrolled subjects will be provided in listing.

7.2.7 Non-Medication Therapy

Frequency tabulations of subjects with non-medication therapy and reason for use will be presented by cohort and dose level for SAF. Number of non-medication therapy received per subject will be summarized using descriptive statistics.

Non-medication therapy for re-enrolled subjects will be provided in listing.

7.2.8 On-Study HSCT

For subjects undergo on-study HSCT, HSCT conditioning regimen and post-HSCT re-eligibility assessment for resuming study drug will be provided in listings.

7.3 Study Drugs

7.3.1 Exposure

The following information on ASP2215 drug exposure will be presented by cohort and dose level for the SAF:

- Descriptive statistics for cumulative amount of the drug subject was exposed to, average daily dose and relative dose intensity; and
- Number and percent of subject with dose increases, decreases or interruptions.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented by cohort and dose level.
- Exposure time will be categorized according to the following categories by cohort and dose level:
  - less than 14 days
  - at least 14 days, less than 28 days
  - at least 28 days, less than 56 days
  - at least 56 days, less than 84 days
  - 84 days or more
  - Unknown.

Counts and percentages of subjects in each of these categories will be summarized by cohort and dose level for the SAF.

Listing of subjects with dose reduction and dose escalation will also be provided.

Descriptive statistics for duration of exposure, cumulative amount of the drug subject was exposed to, average daily dose, and relative dose intensity will be presented for CYP3A4 inhibitor (Voriconazole), Midazolam, and Cephalexin by dose level for the SAF.

7.3.2 Treatment Compliance

Overall compliance with the ASP2215 dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by cohort and dose level.
- Percent compliance will be categorized according to the following categories by cohort and dose level:
  - less than 50%
  - at least 50%, less or equal to 80%
  - greater than 80%
  - Unknown.

Exposure and treatment compliance for re-enrolled subjects will be provided in listing.

7.4 Analysis of Efficacy

All analyses involving response will be carried out in two ways.

1. Derived response based on central assessment supplemented by local assessment: response will be derived based on the definitions in Section 6.1.1 using centrally evaluated myeloblast counts from bone marrow aspirate or biopsy assessments whichever is present (if both are present, both must qualify for the criteria) and centrally evaluated hematology results including ANC, platelet count and blast count in peripheral blood. If neither central bone marrow aspirate nor biopsy is available, myeloblast will be imputed with locally evaluated bone marrow aspirate/biopsy assessments (if both are present, both must qualify for the criteria). Missing central hematology results will be imputed with local hematology results as collected on the eCRF.
2. Investigator reported response: taken directly from the eCRF.

Derived response will be considered as primary and investigator reported response will be considered as supportive.

Efficacy analysis will be conducted on the FAS, SAF and PPS and stratified by FLT3 mutation status from local assessment and central assessment. Efficacy for re-enrolled subjects will be provided in listing.

- **Response Variables**

Best response after 2 cycles of treatment, and best response at the end of treatment will be summarized by dose level and FLT3 mutation status. The number and percentage of subjects in each category will be presented together with two-sided exact 95% CIs based on binomial distribution.

The number and percentage of subject with CRc, CRh, CR/CRh, and response (CRc + PR) will also be summarized by dose level and FLT3 mutation status along with two-sided exact 95% CI based on binomial distribution.

To explore the relationship between dose level and CR response, a dose-response logistic regression model will be fitted to the binary CR response with FLT3 mutation status, the first and second order of logarithm transformed dose as independent covariates for all subjects from the dose escalation phase and dose expansion phase. The CR response rate for each dose level will be estimated with two-sided 95% CI from this model.

The example SAS code for logistic regression and estimating model fitted CR rate and 95% CI is shown below:

```
proc logistic data=response;
class flt3;
model cr (event="1")= flt3 lndose lndose2/lackfit covb;
output out=predcr p=phat_cr lower=lcl_cr upper=ucl_cr /alpha=0.05;
run;
```

where *response* is the input dataset; *cr, flt3, lndose, lndose2* are variables for response, FLT3 mutation status, logarithm of dose and logarithm of dose square respectively; *predcr* is the output dataset, *phat_cr, lcl_cr, ucl_cr* are variables for predicted response rate, lower limit of confidence interval and upper limit of confidence interval respectively.

[redacted]

- **Time-to-Event Variables**

OS, EFS, LFS, and duration of remission will be summarized using descriptive statistics. The survival curve and the median will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% CIs.

The example SAS code used to produce median from Kaplan-Meier estimates and corresponding 95% CI is shown below:

```
proc lifetest data=adtte plots=(s) outsurv=surv;
time survtime*censor(0);
strata trt;
run;
```

where *adtte* is the input dataset, *surv* is the output dataset, *survtime, censor, trt* are variables for survival time, censoring, and dose respectively.

- **Transfusion Variables**

Transfuion conversion rate and transfusion maintenance rate will be summarized by dose level and FLT3 mutation status.

Shift table of transfusion status from baseline period to post-baseline period will be presented by dose level and FLT3 mutation status.

- **Further Expansion for Efficacy Evaluation and Stopping Rules**

To improve guidance for recommended phase 2 dose, dose levels at and above 120 mg will be further expanded as described in Section 3.2.1 The increased patient numbers will enable us to more accurately estimate the actual response rate (CRc) for a dose level based on the observed response rate. With approximately 42 evaluable FLT3 mutated subjects, the 90% 1-sided Confidence Interval is about 10% below the observed response rate for each dose level. If the estimated response rate is 50%, we would be 90% sure that the real response rate is higher than 40%. Response rate will be continuously monitored for each dose level and the enrollment will be stopped if the response rate for that dose level is at 90% significance level, less than 45% based on Wald's Sequential Probability Ratio Test with 25% as the unacceptable low response rate and 80% power. The following table will apply (e.g., if 7 or less subjects respond as 25 FLT3 mutated subjects complete 2 cycles of treatment in a dose level, the enrollment at the dose level will be stopped):

Enrolled Subjects	Number of CRc
14	3
17	4
20	5
23	6
25	7
28	8
31	9

Any dose level in the dose expansion cohort will be stopped if no CRc in more than 6 subjects who complete 2 treatment cycles or less than 2 CRc's in more than 12 subjects are achieved.

7.5 Analysis of Safety

All analysis of safety will be presented by cohort and dose level for SAF, unless specified otherwise.

7.5.1 Bayesian Logistic Regression Modeling in Dose Escalation and Expansion Phases

A modified 3+3 design with an accelerated titration is applied in the dose escalation phase as described in the Study Design section (Section 2). A 2-parameter Bayesian logistic regression will be used to model the dose-toxicity relationship on DLT. The relationship between the dose levels and the rate of DLT event is modeled as the following Bayesian logistic regression

$$logit\left(\frac{p_i}{1-p_i}\right) = \log(\alpha) + \beta\log(\frac{dose_i}{dose*})$$

Where p_i is the DLT rate at the *i*-th dose level, α and β are bivariately normally distributed with mean vector components μ_1 and μ_2 and variance-covariance matrix as shown below

$$\begin{pmatrix}\alpha\\ \beta\end{pmatrix} \sim N\left[\begin{pmatrix}\mu_1\\ \mu_2\end{pmatrix}, \begin{pmatrix}\sigma_1^2 & \rho\sigma_1\sigma_2\\ \rho\sigma_1\sigma_2 & \sigma_2^2\end{pmatrix}\right]$$

The bivariate normal non-informative prior for the parameter (α, β) is $\mu_1 = 2.27, \mu_2 = 0.26, \sigma_1 = 1.98, \sigma_2 = 0.40$ and $\rho = -0.16$, and the 1200mg dose level is used as the reference dose level *dose**.

Subjects in either dose escalation cohort or dose expansion cohort who complete at least one treatment cycle or experience DLTs will be included in the model-fitting process to provide the complete safety information. The estimated DLT rates based on the Bayesian logistic regression model for each dose level will be provided as references for dose escalation procedure in dose escalation cohort and safety monitoring in dose expansion cohort. If the DLT rate for an expanded dose level is equal or higher than 20% with a posterior probability of 80%, then the enrollment to the dose level will be paused and the safety will be reassessed.

7.5.2 Subject Assignment in Dose Expansion Phase

As a dose level is decided to be expanded, up to 17 subjects will be enrolled for the dose level in the dose expansion phase (to have a total of 20 subjects enrolled at a dose level including the subjects from dose escalation cohort). When more than one dose levels are expanded in the dose expansion phase (Cohort 2), the newly enrolled subjects will be randomized to one of the open expanded dose levels, based on the relative chance of (20 – n) in each dose level, where n is the number of subjects already enrolled in the dose level, including both the dose escalation and expansion phases. Randomization will be performed via Interactive Response Technology (IRT) during dose expansion phase (Cohort 2).

If 10 subjects without FLT3 mutations (internal tandem duplication (ITD) or activating point mutations) are enrolled an expanded dose level (including the subjects in the dose escalation cohort and dose expansion cohort), only subjects with FLT3 mutations can be enrolled to the dose level.

7.5.3 Determination of DLT and MTD

DLT review for dose escalation decisions and declaration of DLT and MTD will be performed for each dose level throughout the trial. Dose escalation decisions will be rule based as description in Study Design section (Section 3). The number and percentage of subjects with DLT, as classified by SOC and PT will be summarized for SAF.

7.5.4 Adverse Events

For the purpose of safety assessments in this study, events recorded during the pre-investigational period will be classified as Baseline Signs and Symptoms. All adverse event (AE) recorded on treatment including within 30 days from the last study treatment will be summarized.

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by SOC and PT. AEs will be graded using National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE).

An overview table will include the following details by cohort and dose level:

- Number and percentage of subjects with TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number and percentage of subjects with serious TEAEs and Astellas upgraded serious TEAE,
- Number and percentage of subjects with serious drug related TEAEs and Astellas upgraded serious drug related TEAE,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,

- Number and percentage of subjects with drug related TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with grade 3 or higher TEAE,
- Number of deaths,
- Number and percentage of subjects with AE during on-study HSCT period, and
- Number and percentage of subjects with SAE during on-study HSCT period.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by cohort and dose level. Summaries will be provided for:

- TEAEs
- drug related TEAEs,
- serious TEAEs and Astellas upgraded serious TEAE,
- drug related serious TEAEs and drug related Astellas upgraded serious TEAE,
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any dose level,
- common TEAEs that equal to or exceed a threshold of 5% in any dose level,
- AE during on study HSCT period, and
- SAE during on study HSCT period.

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized by cohort and dose level.

AE summary tables will include subject counts as opposed to AE counts. If a subject experiences more than one episode of a particular AE, that subject will be counted only once for that event. If a subject has more than one AE that code to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a body system, the subject will be counted only once in that body system.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by NCI-CTCAE severity grade and by relationship to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity grade or relationship, then the subject will be counted only once with the worst severity grade and highest degree of relationship, however, if any of the severity grade or relationship values are missing then the subject will be counted only once with missing severity grade or relationship.

The number and percentage of subjects with AESIs, as classified by PT, will be summarized by cohort and dose level.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by dose level for re-enrolled analysis set.

All AEs, deaths, SAEs, withdrawals due to adverse events, and AEs for re-enrolled subjects will be displayed in listings.

7.5.5 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study drug administration.

Quantitative clinical laboratory variables, i.e., hematology, biochemistry, coagulation and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median by cohort and dose level at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

The number and percentage of subjects below and above reference range will be summarized for each cohort and dose level at each visit.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by cohort and dose level at each visit.

For hematology and biochemistry two types of shift tables will be presented:

- Shift tables of reference range changes from baseline to each treatment visit (low, normal, high), and
- Summary shifts of reference range changes from baseline to each treatment visit (shift from normal or high to low, shift from normal or low to high, categorized increase [shift from low to normal, low to high, or from normal to high], categorized no change [value stays in the same reference range], categorized decrease [shift from high to normal, high to low, or from normal to low]).

Laboratory results will also be graded using NCI-CTCAE, where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same subject can be counted for both values if the subject has different laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of subjects for each visit. Shift tables of NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented. The number and percentage of subjects with grade 3 or 4 laboratory test results will be summarized by cohort and dose level and laboratory parameter (the name of the adverse event associated with the abnormal laboratory test result will be presented).

Laboratory results based on central assessment will be used for summaries as described above. Laboratory results based on local assessment and bone marrow results will be listed only.

7.5.5.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzymes and total bilirubin during the investigational period will be presented by cohort and dose level.

7.5.6 Vital Signs

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and body temperature) will be summarized using mean, standard deviation, minimum, maximum and median by cohort, dose level and visit. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by cohort, dose level and visit.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest value obtained during treatment for each subject for each cohort and dose level.

The following potentially clinically significant criteria are defined for each parameter:

Vital Sign Variable	Criteria
SBP	≥180 mmHg AND ≥20 mmHg change from baseline
DBP	≥105 mmHg AND ≥15 mmHg change from baseline
Pulse Rate	≥120 bpm AND ≥15 bpm change from baseline

7.5.7 Electrocardiograms (ECGs)

12-lead ECGs will be recorded in triplicate at the scheduled time points. Each ECG tracing will be taken 5 minutes apart. ECGs will be read at the site for clinical decision making and transmitted to a central reviewer. Data from the central reviewer will be used in summary presentations. The three values of each ECG parameter within a time point from the central reviewer will be averaged to determine time-specific parameter for a subject, and used in summaries.

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each cohort and dose level at each treatment visit and time point, including changes from baseline.

Number and percentage of subjects with normal and abnormal results as assessed by central review for the overall interpretation will be tabulated by cohort and dose level at each treatment visit and time point. A shift analysis table showing shift in overall ECG interpretation from baseline to each time point will be provided. The worst of the three overall ECG interpretations will be used as the time-specific overall ECG interpretation for a subject.

The QT interval corrected for heart rate by Fridericia's formula, QTcF, is defined as: $QTc\ (F) = QT/(RR)^{0.33}$, where RR interval is inversely proportional to heart rate (approximately RR = 60/heart rate).

The QTcF interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

	QTc Interval Criteria Value (msec)	
	Cumulative Category	**Interval Category**
Normal	≤ 450	≤ 450
Borderline	> 450	> 450 to ≤ 480
Prolonged	> 480	> 480 to ≤ 500
Clinically significant	> 500	> 500

The QTcF interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

	Change from Baseline	
Variable	**Cumulative Category**	**Interval Category**
QTc Interval (msec)	<0 ≥ 0 > 30 > 60	<0 ≥ 0 to ≤ 30 > 30 to ≤ 60 > 60

Number and percent of subjects with 12 lead ECG abnormalities as well as number and percent of subjects whose 12 lead ECG reading changed from normal at baseline to abnormal will be tabulated by cohort and dose level at each treatment visit and time point.

7.5.8 Pregnancies

A detailed listing of all pregnancies will be provided.

7.5.9 Eastern Cooperative Oncology Group (ECOG) Performance Scores

Number of percent of subjects for each category of the ECOG performance status at each assessment time will be provided. Negative change scores indicate an improvement and positive scores indicate a decline in performance.

ECOG will also be summarized using shift table from baseline to post-baseline score for each dose level by visit.

7.5.10 Ophthalmologic Assessment

Frequency tabulations of qualitative ophthalmologic variables (ophthalmoscopy, biomicroscopy – conjunctiva, biomicroscopy – cornea, biomicroscopy – anterior chamber, biomicroscopy – lens pathology, and optical coherence tomography) will be presented by cohort and dose level at each visit for each eye.

Quantitative ophthalmologic variables (logmar score for visual acuity, mean deviation for visual field) will be summarized using mean, standard deviation, minimum, maximum and median by cohort and dose level at each visit for each eye.

7.6 Analysis of PK

PK analysis will be conducted on the PKAS.

7.6.1 Estimation of PK Parameters

The PK parameter calculation will be performed using noncompartmental method in WinNonlin® ([redacted] USA, version 6.3 or higher) software. For AUC determination, linear up and log down analysis will be used.

7.6.2 Statistical Analysis

7.6.2.1 Plasma Concentrations and PK Parameters

Plasma concentrations and PK parameters (including urinary PK parameters) will be summarized by cohort and dose level and where appropriate by nominal time points using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV). Time-course of drug concentrations obtained from serial PK sampling will be plotted by cohort and dose level. For ASP2215, trough concentrations will also be plotted by cohort and dose level. To minimize the effect of dose modification on evaluation, ASP2215 plasma concentration data will be summarized and plotted by actual dose level excluding the data obtained at the visits within 15 days after the day of dose modification, ASP2215 plasma concentration data will also be summarized by initial dose level excluding all data obtained after dose modification.

Additional exploratory analyses may be performed after examination of the data.

7.6.2.2 Dose Proportionality

Dose proportionality over the dose range will be examined based on a combination of statistical analyses along with visual inspection of plots of parameters against doses. If non-proportionality is concluded or the results are inconclusive over the entire dose range, additional analyses may be performed on other dose ranges until a selected dose range is found for which dose proportionality is concluded.

Power model regression

Dose proportionality can be evaluated statistically by using the power model. The power model has the form:

$$\text{parameter} = a \times (\text{dose})^b \times \text{random error}$$

where parameter is PK parameter, a and b are the coefficient and exponent, respectively, of the power equation. The power model can be linearized by taking logarithms:

$$\ln(\text{parameter}) = \ln(a) + b \times \ln(\text{dose}) + \text{random error}$$

Proportionality will be concluded if the 90% confidence interval for b is entirely within the interval

$$\left(1 + \frac{\ln(0.5)}{\ln(r)}, 1 + \frac{\ln(2)}{\ln(r)}\right)$$

where r is the ratio of high dose to low dose.

7.6.2.3 Drug-Drug Interaction

- Strong CYP3A4 Inhibitor (Voriconazole):

A drug-drug interaction for the effect of voriconazole on ASP2215 will be examined by obtaining the Geometric LS Mean Ratio and 90% CI for ASP2215 for the following ratios:

  - C_{max} Cycle 2 Day 1 / C_{max} Cycle 1 Day 15
  - AUC_{24} Cycle 2 Day 1 / AUC_{24} Cycle 1 Day 15

- Induction by ASP2215

A drug-drug interaction for the effect of ASP2215 on Midazolam and 1-hydroxy Midazolam will be examined by obtaining the Geometric LS Mean Ratio and 90% CI for Midazolam and 1-hydroxy Midazolam for the following ratios:

  - C_{max} Cycle 1 Day 15 / C_{max} Cycle 1 Day -1
  - AUC_{24} Cycle 1 Day 15 / AUC_{24} Cycle 1 Day -1

- Effect of ASP2215 on MATE1 substrate

A drug-drug interaction for the effect of ASP2215 on Cephalexin will be examined by obtaining the Geometric LS Mean Ratio and 90% CI for Cephalexin for the following ratios:

  - C_{max} Cycle 1 Day 15 / C_{max} Cycle 1 Day -1
  - AUC_{last} Cycle 1 Day 15 / AUC_{last} Cycle 1 Day -1
  - AUC_{inf} Cycle 1 Day 15 / AUC_{inf} Cycle 1 Day -1
  - Ae Cycle 1 Day 15 / Ae Cycle 1 Day -1
  - CL/F Cycle 1 Day 15 / CL/F Cycle 1 Day -1
  - CLr Cycle 1 Day 15 / CLr Cycle 1 Day -1

The example SAS code used to produce Geometric LS Mean Ratio and 90% CI is shown below:

```
proc mixed alpha=0.1;
class visit;
by tmt;
model logpk = visit / ddfm=KR;
lsmeans visit/ diff=control('C1D15') CL alpha=0.1;
run;
```

where *visit, tmt, logpk* are variables for visit, dose, logarithm of PK parameter respectively.

- Potential of drug-drug interaction across cohorts

To explore the potential of drug-drug interaction with moderate or strong CYP3A4 inhibitors, dose-normalized PK parameters of ASP2215 (dose normalized C_{max}, dose normalized AUC_{24}, dose normalized AUC_{last}) will be summarized by cohort and CYP3A4 inhibitor type, and box-plot of these parameters will be presented, accordingly. In addition, the dose-normalized trough concentration will be summarized and plotted by CYP3A4 inhibitor use (no CYP3A4 inhibitor, moderate CYP3A4 inhibitor, strong CYP3A4 inhibitor). If possible, it will be further stratified by the presence of dose modification. To minimize the effect of dose modification on evaluation, the data from the visit within 15 days after the day of dose modification will be excluded. Analysis focusing on the entire use of CYP3A4 inhibitor (no CYP3A4 inhibitor use entirely, moderate CYP3A4 use entirely, strong CYP3A4 inhibitor use entirely) up to Cycle 2 Day 1 will also be conducted.

7.7 Analysis of PD

7.7.1 %pFLT3, %pAXL, and pS6

Baseline corrected phosphorylation of FLT3 (%pFLT3), and baseline corrected phosphorylation of AXL (%pAXL) will be summarized descriptively using mean, standard deviation, minimum, maximum and median by cohort and dose level at each visit. Phosphorylation of S6 (pS6) will be listed only.

Additional analysis may be conducted based on initial data assessment.

7.7.2 PIA

PIA will be summarized descriptively using mean, standard deviation, minimum, maximum and median by cohort and dose level at each visit.

Graphical assessment of percent inhibition vs. time will be evaluated.

Where time matched plasma concentration data are available, graphical assessment of percent inhibition vs. ASP2215 will be evaluated.

Additional analysis may be conducted based on initial data assessment.

7.8 Subgroups of Interest

7.8.1 FLT3 Mutation Status

Efficacy endpoints and demographics will be stratified by FLT3 mutation status (Positive, Negative, All Subjects) based on local assessment and central assessment. Demogrphics and response assessments will be further stratified by FLT3 mutations type (FLT3-ITD mutation vs. FLT3-Point mutation).

7.8.2 Demographic and Baseline Characteristics

Selected efficacy endpoints (response assessment, OS, EFS), safety endpoint (TEAE, drug-related TEAE, SAE, drug-related SAE) and demographics will be summarized for one or more subgroups defined on the basis of the categorized variables listed below:

Grouping variable	Subgroups
Age group	< 65 years
	>=65 years
Sex	Female
	Male
Prior TKI usage	Yes
	No
Prior HSCT status	Yes
	No
Prior lines of AML therapy	1 line of prior AML therapy
	2 lines of prior AML therapy
	>=3 lines of prior AML therapy

7.8.3 Subset Analysis for FLT3 Mutated Subjects in >=80mg Dose Levels

Subset analysis will be conducted on FLT3 mutated subjects in >=80mg dose levels, including treatment discontinuation, demographics, study drug exposure, response assessment, overall survival, duration of remission, drug-related TEAE, SAE, drug-related SAE, grade 3 or higher TEAE, TEAE with special safety interest, TEAE by NCI CTCAE grade, lab assessments, ECG, and ophthalmologic assessments.

The analyese will be based on local FLT3 mutation status, efficacy endpoints will also be analyzed using central FLT3 mutation status.

7.8.4 CYP3A4 Inhibitor Usage

CYP3A4 inhibitor types were defined in Section 6.6

To explore the impact of CYP3A4 inhibitor usage on safety and efficacy, TEAE, drug-related TEAE, SAE, drug-related SAE, as classified by SOC and PT, as well as response assessment will be summarized by cohort, dose level and subgroups defined below.

Grouping variable	Subgroups
CYP3A4 inhibitor usage	Yes
	No
CYP3A4 inhibitor type(*)	Strong CYP3A4 inhibitor
	Moderate CYP3A4 inhibitor
	No CYP3A4 inhibitor

(*) If a subject takes both strong CYP3A4 inhibitor and moderate CYP3A4 inhibitor, the subject isconsider as taking strong CYP3A4 inhibitor.

To explore the impact of CYP3A4 inhibitor usage on PK/PD, dose normalized PK parameters of ASP2215 as well as dose normalized trough concentration will be summarized by CYP3A4 inhibitor type as described in Section 7.6.2.3

7.8.5 Baseline Hepatic and Renal Function

Baseline hepatic function groups (normal, mild HD, moderate HD, severe HD) and baseline renal function groups (normal, mild, moderate, severe) were defined in Section 6.6.

To explore the impact of baseline hepatic function and baseline rental function on safety, TEAE, drug-related TEAE, SAE, drug related SAE, as classified by SOC and PT will be summarized by dose level and baseline hepatic function groups, and by dose level and baseline rental function groups for SAF in 120mg and 200mg dose levels.

Lab shift tables of NCI-CTCAE grade change from baseline to worst post-baseline grade will be summarized by baseline hepatic function groups and baseline rental function groups.

7.8.6 Drugs that Prolong QT with Known or Possible Risk of TdP

The list of medications that prolong QT with known or possible risk of TdP are provided in Appendix 10.1

To explore the impact of concomitant usage of QT prolongation drug on safety, TEAE, drug-related TEAE, SAE, drug related SAE as classified by SOC and PT will be summarized by cohort, dose level and subgroups defined below. QTcF interval will also be summarized by dose level and subgroups defined below.

Grouping variable	Subgroups
Usage of drug that prolong QT	Yes
	No
Number of drug taken that prolong QT	0-1
	2
	>=3

7.8.7 Post-HSCT Safety and Efficacy

Post HSCT safety and efficacy will be analyzed for subjects who undergo on-study HSCT and resume ASP2215 as well as subjects who come off treatment for HSCT and re-enroll into the study. TEAE, drug-related TEAE, SAE, drug-related SAE, and LFS within 2 months of restarting ASP2215 post HSCT will be summarized.

7.9 Other Analyses

7.9.1 [redacted]

[redacted]

7.9.2 PK-PD Analysis

7.9.2.1 dQTcF Exposure Relationship

Assessment of dQTcF versus ASP2215 plasma concentrations will be assessed graphically (plot with line and 95% CI) and by linear mixed effect modeling with ASP2215 as covariates. Other analyses may be explored.

7.9.2.2 [redacted]

[redacted]

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

Not applicable for this study.

7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.11.1 Missing Data

In general, missing PK data should not be imputed if an appropriate method for imputation is not provided prospectively. Missing samples should not be assigned concentration values and consequently should not be included in the pharmacokinetic analysis. It should be carefully considered if the missing data affects the estimation of individual pharmacokinetic parameters before further analysis.

Concentrations below the lower limit of quantification (BQL) should be treated as missing when the terminal elimination rate constant is evaluated. Otherwise BQL should be treated as zero in the estimation of individual pharmacokinetic parameters.

Imputation methods for other missing data, if applicable, are described in individual sections.

7.11.2 Outliers

Outliers of individual plasma concentrations can be identified by pharmacokinetic plausibility (e.g., concentration at pre-dose) or by appropriate statistical methods, and the dataset which excludes outliers can be used to calculate pharmacokinetic parameters for primary analysis. An additional analysis may be conducted as exploratory analysis using the original dataset before excluding the outliers may be performed and the differences between their results may be discussed if primary analysis is performed without outliers. A listing of outliers must be described in the pharmacokinetic analysis report along with the reasons for exclusion.

All values will be included in the non-PK analyses.

7.11.3 Visit Windows

Visit windows are allowed for certain visits per the schedule of assessments. Subject data will not be excluded from analyses due to the subject's failure to comply with the visit schedule. The visit windows for assessments are described in the following table.

CRF visit	Visit Window
Cycle 1 Day 4	C1D4 ± 1
Cycle 1 Day 8	C1D8 ± 1
Cycle 1 Day 22	C1D22 ± 1
Cycle 2 Day 1	C2D1 ± 3
Cycle 2 Day 15	C2D15 ± 1
Cycle X Day 1	CXD1 ± 3
End of Treatment Visit	Last dose date + 7

Scheduled visit will be calculated using number of days relative to the first dose date based on the fact that ASP2215 will be administered over continuous 28-day cycles. In the case of multiple observations at a specific visit, the observation which is closest to the target date will be used. If the observations have the same distance to the target visit, the latest one will be used.

In PK analysis, actual sampling times should be used in all calculations for individual pharmacokinetic parameters if an appropriate allowance of the deviation between actual and scheduled sampling times cannot be defined prospectively.

For ease of summarization, scheduled sampling times can be used to present results in tables, listings, and figures. Allowance of plasma concentrations for calculation of summary parameters will be based on sample time point:

- Pre-dose – Within 30 minutes before drug administration
- Post dose 0.5, 1, 1.5, 2 and 3 hours – Within ± 10 minutes of nominal time
- Post dose 4 and 6 hours – Within ±20 minutes of nominal time
- Post dose 24 hours – Within ±90 minutes of nominal time

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	06-Nov-2013	NA	Document finalized based on protocol amendment 1 dated 16-Jul-2013
2.0 (Amendment 1)	12-Sept-2014	Updated Schedule of Assessment and footnote	Updated due to protocol amendment 2 dated 21-Jan-2013, amendment 4 dated 19-May-2014, amendment 5 dated 07-Jul-2014
		Remove PD analysis from secondary objectives.	Updated due to protocol amendment 2 dated 21-Jan-2013
		Updated Study Design section to 1. allow changing to modified 3+3 design and testing all dose levels based on recommendation of dose escalation committee; 2. add subject replacement guidance; 3. allow subjects that have contraindication to voricaonzole and/or midazolam to participate without the DDI component; 4. allow voriconazole DDI study to be conducted at the next lowest dose level if the original dose level is closed before 12 subjects participated in the DDI study; 5. restrict DDI study participation to US only; 6. further expand selected dose levels for efficacy evaluation; 7. modification of re-screening language.	Updated due to protocol amendment 2 dated 21-Jan-2013, amendment 4 dated 19-May-2014, amendment 5 dated 07-Jul-2014
		Updated Dose/Dose Regimen and Administration Period section to 1. clarify dose and route of voriconazole and midazolam; 2. limit DDI study participation to US.	Updated due to protocol amendment 2 dated 21-Jan-2013, amendment 4 dated 19-May-2014,
		Updated Increase or Reduction in Dose of Study Drugs section to clarify required assessments and frequency of assessment after a subject dose escalation event.	Updated due to protocol amendment 2 dated 21-Jan-2013, amendment 4 dated 19-May-2014

Version	Date	Changes	Comment/rationale for change
		Updated Randomization section to 1. add instruction for use of IRT system; 2. further expand selected dose levels for efficacy evaluation.	Updated due to protocol amendment 2 dated 21-Jan-2013, amendment 5 dated 07-Jul-2014
		Incased sample size to approximately 170 subjects in the expansion cohort.	Updated due to protocol amendment 5 dated 07-Jul-2014
		Clarified "All allocated/randomized subjects" in Analysis Sets section	To provide additional guidance for programming.
		Added definition for AESI in Other Safety Variables section and AESI analysis in Analysis of Safety section	AESI analysis was added to provide additional safety summaries for targeted medical events.
		Updated laboratory assessment table in Other Safety Variables section	Updated due to protocol amendment 2 dated 21-Jan-2013
		Add allowable collection windows for PK samples in Pharmacokinetic Variables section	Updated due to protocol amendment 2 dated 21-Jan-2013.
		Clarified derivation of selected PK parameters and PK parameter symbols in Pharmacokinetic Variables section	Due to recent updates from pharmacokineticist
		Changed PD parameters from Secondary endpoints to Exploratory endpoints.	Updated due to protocol amendment 2 dated 21-Jan-2013.
		Added BMI derivation and clarified duration of exposure derivation in Other Variables section	To provide additional guidance for programming.
		Added further expansion for efficacy evaluation and stopping rules in Analysis of Efficacy section	Updated due to protocol amendment 5 dated 07-Jul-2014
		Added detailed formula for Bayesian logistic regression in Analysis of Safety section	To provide additional information for modeling.
		Updated power model regression in Dose Proportionality section	Due to recent updates from phase I statistics group
		Moved PK data handling from Analysis of PK section to Handing of Missing Data, Outliers, Visit Windows, and Other Information section	Move the text to the appropriate SAP section
		Add subgroup analysis to stratify all efficacy endpoints by FLT3 mutation status.	Due to increased interest in FLT3 mutated subjects in protocol amendment 5.

Version	Date	Changes	Comment/rationale for change
		Updated list of abbreviation	To add additional abbreviations for completeness
		Update section 1 about timing of SAP development	Updated to comply with version 3 SAP template dated 02-Jul-2014
		Updated Adverse Event section to include standard text relating to Always Serious AEs and clarify the summary for TEAE by severity grade and relationship	Updated to comply with version 3 SAP template dated 02-Jul-2014
		Updated clinical important QTc interval criteria and change from baseline criteria in ECG section.	Updated to comply with version 3 SAP template dated 02-Jul-2014
		Updated Appendix 10.1 Key contributors and approvers	Updated to comply with version 3 SAP template dated 02-Jul-2014
		Added explanation of variables in example SAS code	To provide additional clarification for programming
		Add peripheral blast <=2% criterion in section 6.1.1	To clarify the response definition
		Clarified imputation of central bone marrow aspirate/biopsy in section 7.4	To provide additional clarification for programming
3.0 (Amendment 2)	31-Aug-2015	Updated Schedule of Assessment and footnote	Updated due to protocol amendment 8 dated 16-Apr-2015, amendment 9 dated 26-May-2015
		Added secondary objective for MATE1 sub-study	Updated due to protocol amendment 9 dated 26-May-2015
		Updated study design (Section 3.2) to allow for re-enrolled subjects and add MATE1 sub-study	Updated due to protocol amendment 6 dated 23-Sep-2014, amendment 9 dated 26-May-2015
		Updated guidelines for dose reduction and dose escalation.	Updated due to protocol amendment 7 dated 15-Dec-2014, Amendment 10 dated 18-Aug-2014.
		Updated randomization (Section 3.3) and sample size (3.4) to incorporate MATE1 sub-study	Updated due to protocol amendment 9 dated 26-May-2015
		Added Re-enrolled Analysis Set	Updated due to protocol amendment 6 dated 23-Sep-2014
		In Section 6.1 (efficacy endpoint), clarified definitions for CRc, NR/NE, EFS. Added variable for time to remission.	To provide additional clarification for programming.
		In Section 6.2 (safety variables),	Updated due to protocol

Version	Date	Changes	Comment/rationale for change
		updated TEAE to take into consideration of on-study HSCT and added definitions for AE and SAE during on-study HSCT period.	amendment 7 dated 15-Dec-2014
		In Section 6.3 (PK variables), updated PK schedules and added PK variables related with MATE1 sub-study	Updated due to protocol amendment 9 dated 26-May-2015
		Updated Section 7 (Statistical Methodology) to: 1. Added analysis for re-enrolled subjects. 2. Added analysis based on central FLT3 mutation assessment. 3. Added analysis for AE/SAE during on-study HSCT period 4. Added analysis for QTc based on interval categories. 5. Added PK analysis for MATE1 sub-study.	Updated due to protocol amendment 6 dated 23-Sep-2014, amendment 7 dated 15-Dec-2014, amendment 9 dated 26-May-2015
	17-Sep-2015	Updated Section 7.8 (Subgroup of Interest) to: 1. Add subset analysis for FLT3 mutated subject in >=80mg dose level 2. Add subgroup analysis for CYP3A4 inhibitor usage 3. Add subgroup analysis for baseline hepatic and renal function 4. Add subgroup analysis for QT prolongation drug usage 5. Add subgroup analysis for post-HSCT safety and efficacy Updated Section 6.6 to add definitions for the corresponding subgroups of interest. Added Appendix 10.1	Updated due to protocol amendment 6 dated 23-Sep-2014, amendment 7 dated 15-Dec-2014, Added additional subgroup analysis due to new safety signals and address regulartory questions.
	23-Sep-2015	Update Section 6.3 and Section 7.6 to add definitions and analyses for dose normalized plasma concentration and dose normalized PK parameters, add additional DDI analysis with strong or moderate CYP3A4 inhibitor.	Add dose normalized analyses to adjust for within subject dose modifications.
	23-Sep-2015	Update Section 6.4 and Section 7.7 to clarify the definition and analyses for baseline corrected	To provide additional clarification for programming.

Version	Date	Changes	Comment/rationale for change
		phosphorylation of FLT3, AXL and S6.	
	14-Jan-2016	Update Section 5 to add Post-HSCT Analysis Set, and exclude subjects with legal findings from FAS	A new population was added to support the new subgroup analysis. FAS was updated to address the impact of subjects with legal findings on the analysis.
	14-Jan-2016	Update Section 6.6 and 7.3 to add definition and analysis for relative dose intensity.	Added to better evaluate the exposure to study drug.
	14-Jan-2016	Remove Section 7.6.2.3 (PK analysis for gender difference).	This is exploratory analysis, it will be conducted by PK group separately if needed.
	08-Feb-2016	Update Section 5.2.1 (reason for exclusion from PPS) to remove treatment compliance <80% criterion	Treatment compliance will be assessed for exclusion from PPS through ICH E3 criteria of incorrect treatment or wrong dose.
	02-Mar-2016	Update Section 6.3.1, 6.3.2, and 6.3.4 to update PK parameters to be estimated.	Clarified PK parameters which will be reported.
	02-Mar-2016	Update Section 7.6.2.3 to remove the language of the criteria based on 90%CI.	The criteria was removed because formal sample size calculation was not conducted.
	02-May-2016	Update Section 7.6.2.3 to update PK parameters for statistical analysis	Alignment of estimated PK parameters with statistical analysis of PK parameters for MATE1 cohort
4.0 (Amendment 3)	15-Aug-2017	Updated Flow chart and visit schedule, and Table 1F	Updated due to protocol amendment 11 dated 02-Jun-2017
	15-Aug-2017	Updated Response Definition in Section 6.1.1 to add definition for CRh, update PR definition, and clarify visit level response vs. subject level best response	Added CRh endpoint to support AA submission, added clarification to response definition
	15-Aug-2017	Update Section 6.1.2 to add efficacy endpoint for CR/CRh rate, CRh rate, duration of CR/CRh, duration of CRh, time to CRh, time to first CR/CRh, time to best CR/CRh, transfusion status, transfusion conversion rate and transfusion maintenance rate. Update Section 7.4 to add analyses for these endpoint.	Additional endpoint and analyses added to support AA submission.
	15-Aug-2017	Update Section 7.5.5 to add analysis for grade 3 or 4 laboratory	Additional endpoint and analyses added to support AA submission.

Version	Date	Changes	Comment/rationale for change
		results.	
	20-Sep-2017	Update last relapse-free disease assessment definition in Section 6.1.2 to include assessment with NE.	To be consistent with definitions in 2215-CL-0301
		Update duration of remission definition in Section 6.1.2 not to censor subject at HSCT	To be consistent with definitions in 2215-CL-0301
		Update Sections 6.5, 7.8.2, 7.9.1, to remove C-CBL mutation and AXL mutation.	3-gene analysis will be described in biomarker SAP

9 REFERENCES

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10 APPENDICES

10.1 Appendix 1: List of Medications that Prolong QT with Known or Possible Risk of TdP

CredibleMeds Filtered QTDrug List

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The last revision date: July 03, 2015 The

drug list below contains drugs from the categories: Known Risk of TdP

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral, injection
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia	Risk of TdP	oral
Arsenic trioxide	Trisenox®	Anti-cancer	Cancer (leukemia)	Risk of TdP	injection
Astemizole (Removed from US Market)	Hismanal®	Antihistamine	Allergic rhinitis	Risk of TdP	oral
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection
Bepridil (Removed from US Market)	Vascor®	Anti-anginal	Angina Pectoris (heart pain)	Risk of TdP	oral
Chloroquine	Aralen®	Anti-malarial	Malaria	Risk of TdP	oral
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Anti-psychotic / Anti-emetic	Schizophrenia, nausea, many others	Risk of TdP	oral, injection, suppository
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication	Risk of TdP	oral
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection
Cisapride (Removed from US Market)	Propulsid®	GI stimulant	Increase GI motility	Risk of TdP	oral
Citalopram	Celexa®, Cipramil®	Anti-depressant, SSRI	Depression	Risk of TdP	oral
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection	Risk of TdP	oral
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)	Risk of TdP	topical
Disopyramide	Norpace®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Dofetilide	Tikosyn®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Domperidone (On non US Market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Anti-nausea	Nausea, vomiting	Risk of TdP	oral, injection, suppository
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)	Risk of TdP	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Dronedarone	Multaq®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Anti-psychotic / Anti-emetic	Anesthesia (adjunct), nausea	Risk of TdP	injection
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection, increase GI motility	Risk of TdP	oral, injection
Escitalopram	Cipralex®, Lexapro®, Nexito®, [redacted]	Anti-depressant, SSRI	Depression (major), [redacted]	Risk of [redacted]	oral
	Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)				
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Fluconazole	Diflucan®, Trican®	Anti-fungal	Fungal infection	Risk of TdP	oral, injection
Grepafloxacin (Off market worldwide)	Raxar®	Antibiotic	Bacterial infection	Risk of TdP	oral
Halofantrine	Halfan®	Anti-malarial	Malaria	Risk of TdP	oral
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Anti-psychotic	Schizophrenia, agitation	Risk of TdP	oral, injection
Ibutilide	Corvert®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	injection
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection
Levomethadyl (Removed from US Market)	Orlaam®	Opiate	Narcotic dependence	Risk of TdP	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Mesoridazine (Removed from US Market)	Serentil®	Anti-psychotic	Schizophrenia	Risk of TdP	oral
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opiate	Narcotic dependence, pain	Risk of TdP	oral, injection
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Anti-emetic	Nausea, vomiting	Risk of TdP	oral, injection
Pentamidine	Pentam®	Antifungal	Fungal infection (Pneumocystis pneumonia)	Risk of TdP	injection
Pimozide	Orap®	Anti-psychotic	Tourette's Disorder	Risk of TdP	oral
Probucol (Removed from US Market)	Lorelco®	Antilipemic	Hypercholesterolemia	Risk of TdP	oral
Procainamide (Oral off US mkt)	Pronestyl®, Procan®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	injection
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia	Risk of TdP	injection
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral, injection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia	Risk of TdP	inhaled
Sotalol	Betapace®, Sotalex®, Sotacor®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Sparfloxacin (Removed from US Market)	Zagam®	Antibiotic	Bacterial infection	Risk of TdP	oral
Sulpiride (On non US Market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Anti-psychotic, atypical	Schizophrenia	Risk of TdP	oral
Terfenadine (Removed from US Market)	Seldane®	Antihistamine	Allergic rhinitis	Risk of TdP	oral
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Anti-psychotic	Schizophrenia	Risk of TdP	oral
Vandetanib	Caprelsa®	Anti-cancer	Cancer (thyroid)	Risk of TdP	oral

CredibleMeds Filtered QTDrug List

The last revision date: July 03, 2015 The

drug list below contains drugs from the categories: Possible Risk of TdP

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Alfuzosin	Uroxatral®	Alpha1-blocker	Benign prostatic hyperplasia	Possible Risk of TdP	oral
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	Dopamine agonist	Parkinson's disease	Possible Risk of TdP	injection
Aripiprazole	Abilify®, Aripiprex®	Anti-psychotic, atypical	Schizophrenia, depression (adjunct)	Possible Risk of TdP	oral, injection
Artenimol+piperaquine	Eurartesim®	Anti-malarial	Malaria	Possible Risk of TdP	oral
Atazanavir	Reyataz®	Anti-viral	Viral infection (HIV/AIDS)	Possible Risk of TdP	oral
Atomoxetine	Strattera®	Norepinephrine reuptake inhibitor	ADHD	Possible Risk of TdP	oral
Bedaquiline	Sirturo®	Antibiotic	Bacterial infection (Drug resistant tuberculosis)	Possible Risk of TdP	oral
Bortezomib	Velcade®, Bortecad®	Proteasome inhibitor	Cancer (multiple myeloma,lymphoma)	Possible Risk of TdP	injection
Bosutinib	Bosulif®	Tyrosine kinase inhibitor	Cancer (leukemia)	Possible Risk of TdP	oral
Ceritinib	Zykadia®	Kinase inhibitor	Cancer (Lung)	Possible Risk of TdP	oral
Clomipramine	Anafranil®	Anti-depressant, Tricyclic	Depression	Possible Risk of TdP	oral
Clozapine	Clozaril®, Fazaclo®, Versacloz®	Anti-psychotic, atypical	Schizophrenia	Possible Risk of TdP	oral
Crizotinib	Xalkori®	Kinase inhibitor	Cancer (Non-small cell lung cancer, metastatic)	Possible Risk of TdP	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Dabrafenib	Tafinlar®	Kinase inhibitor	Cancer (melanoma)	Possible Risk of TdP	oral
Dasatinib	Sprycel®	Tyrosine kinase inhibitor	Cancer (leukemia)	Possible Risk of TdP	oral
Degarelix	Firmagon®	Gonadotropin Releasing Hormone Agonist/antagonist	Cancer (prostate)	Possible Risk of TdP	injection
Desipramine	Pertofrane®, Norpramine®	Anti-depressant, Tricyclic	Depression	Possible Risk of TdP	oral
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	Sedative	Sedation	Possible Risk of TdP	injection
Dolasetron	Anzemet®	Anti-emetic	Nausea, vomiting	Possible Risk of TdP	oral, injection
Eribulin mesylate	Halaven®	Microtubule inhibitor	Cancer (breast, metastatic)	Possible Risk of TdP	injection
Famotidine	Pepcid®, Fluxid®, Quamatel®	H2-receptor antagonist	Gastric hyperacidity, GERD	Possible Risk of TdP	oral, injection
Felbamate	Felbatol®	Anti-convulsant	Epilepsy	Possible Risk of TdP	oral
Fingolimod	Gilenya®	Sphingosine phospate receptor modulator	Multiple Sclerosis	Possible Risk of TdP	oral
Foscarnet	Foscavir®	Anti-viral	Viral infection (HIV/AIDS)	Possible Risk of TdP	injection
Gatifloxacin (Removed from US Market)	Tequin®	Antibiotic	Bacterial infection	Possible Risk of TdP	oral, injection
Gemifloxacin	Factive®	Antibiotic	Bacterial infection	Possible Risk of TdP	oral
Granisetron	Kytril®, Sancuso®, Granisol®	Anti-emetic	Nausea, vomiting	Possible Risk of TdP	oral, injection, topical
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Anti-psychotic, atypical	Schizophrenia	Possible Risk of TdP	oral, injection
Imipramine (melipramine)	Tofranil®	Anti-depressant, Tricyclic	Depression	Possible Risk of TdP	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Isradipine	Dynaciro®	Anti-hypertensive	Hypertension	Possible Risk of TdP	oral
Lapatinib	Tykerb®, Tyverb®	Kinase inhibitor	Cancer (breast, metastatic)	Possible Risk of TdP	oral
Leuprolide (Leuprorelin)	Lupron®, Eligard®, Viadur®, Carcinil®, Enanton®, Leuplin®, Lucrin®, Procren®, Prostap® and others	Gonadotropin receptor agonist/antogist	Cancer (prostate)	Possible Risk of TdP	injection
Lithium	Eskalith®, Lithobid®	Anti-mania	Bipolar disorder	Possible Risk of TdP	oral, injection
Mifepristone	Korlym®, Mifeprex®	Progesterone antagonist	Pregnancy termination	Possible Risk of TdP	oral
Mirabegron	Myrbetriq®	Beta3 adrenergic antagonist	Bladder spasm	Possible Risk of TdP	oral
Mirtazapine	Remeron	Anti-depressant, Tetracyclic	Depression	Possible Risk of TdP	oral
Moexipril/HCTZ	Uniretic®, Univaso®	Anti-hypertensive	Hypertension	Possible Risk of TdP	oral
Nicardipine	Cardene®	Anti-hypertensive	Hypertension	Possible Risk of TdP	oral, injection
Nilotinib	Tasigna®	Kinase inhibitor	Cancer (leukemia)	Possible Risk of TdP	oral
Norfloxacin	Noroxin®, Ambigram®	Antibiotic	Bacterial infection	Possible Risk of TdP	oral
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	Anti-depressant, Tricyclic	Depression	Possible Risk of TdP	oral
Ofloxacin	Floxin®	Antibiotic	Bacterial infection	Possible Risk of TdP	oral, injection
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Anti-psychotic, atypical	Schizophrenia, bipolar disorder	Possible Risk of TdP	oral, injection
Oxytocin	Pitocin®, Syntocinon®	Oxytocic	Labor stimulation	Possible Risk of TdP	injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Isradipine	Dynacirc®	Anti-hypertensive	Hypertension	Possible Risk of TdP	oral
Lapatinib	Tykerb®, Tyverb®	Kinase inhibitor	Cancer (breast, metastatic)	Possible Risk of TdP	oral
Leuprolide (Leuprorelin)	Lupron®, Eligard®, Viadur®, Carcinil®, Enanton®, Leuplin®, Lucrin®, Procren®, Prostap® and others	Gonadotropin receptor agonist/antogist	Cancer (prostate)	Possible Risk of TdP	injection
Lithium	Eskalith®, Lithobid®	Anti-mania	Bipolar disorder	Possible Risk of TdP	oral, injection
Mifepristone	Korlym®, Mifeprex®	Progesterone antagonist	Pregnancy termination	Possible Risk of TdP	oral
Mirabegron	Myrbetriq®	Beta3 adrenergic antagonist	Bladder spasm	Possible Risk of TdP	oral
Mirtazapine	Remeron	Anti-depressant, Tetracyclic	Depression	Possible Risk of TdP	oral
Moexipril/HCTZ	Uniretic®, Univasc®	Anti-hypertensive	Hypertension	Possible Risk of TdP	oral
Nicardipine	Cardene®	Anti-hypertensive	Hypertension	Possible Risk of TdP	oral, injection
Nilotinib	Tasigna®	Kinase inhibitor	Cancer (leukemia)	Possible Risk of TdP	oral
Norfloxacin	Noroxin®, Ambigram®	Antibiotic	Bacterial infection	Possible Risk of TdP	oral
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	Anti-depressant, Tricyclic	Depression	Possible Risk of TdP	oral
Ofloxacin	Floxin®	Antibiotic	Bacterial infection	Possible Risk of TdP	oral, injection
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Anti-psychotic, atypical	Schizophrenia, bipolar disorder	Possible Risk of TdP	oral, injection
Oxytocin	Pitocin®, Syntocinon®	Oxytocic	Labor stimulation	Possible Risk of TdP	injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Sunitinib	Sutent®	Kinase inhibitor	Cancer (GIST, renal cell, pNET)	Possible Risk of TdP	oral
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	Immunosuppressant	Immune suppression	Possible Risk of TdP	oral, injection
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®	Anti-cancer	Cancer (breast)	Possible Risk of TdP	oral
Telavancin	Vibativ®	Antibiotic	Bacterial infection	Possible Risk of TdP	injection
Telithromycin	Ketek®	Antibiotic	Bacterial infection	Possible Risk of TdP	oral
Tetrabenazine (Orphan drug in US)	Nitoman®, Xenazine®	Monoamine Transporter Inhibitor	Chorea (Huntington's disease)	Possible Risk of TdP	oral
Tizanidine	Zanaflex®, Sirdalud®	Muscle relaxant	Muscle spasticity	Possible Risk of TdP	oral
Tolterodine	Detrol®, Detrusitol®	Muscle relaxant	Bladder spasm	Possible Risk of TdP	oral
Toremifene	Fareston®	Estrogen agonist/antagonist	Cancer (breast, metastatic)	Possible Risk of TdP	oral
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	Anti-depressant, Tricyclic	Depression	Possible Risk of TdP	oral, injection
Tropisetron (On non US Market)	Navoban®, Setrovel®	Anti-emetic	Nausea, vomiting	Possible Risk of TdP	oral, injection
Vardenafil	Levitra®	Phosphodiesterase 5 inhibitor	Erectile dysfunction	Possible Risk of TdP	oral
Vemurafenib	Zelboraf®	Kinase inhibitor	Cancer (melanoma)	Possible Risk of TdP	oral
Venlafaxine	Effexor®, Efexor®	Anti-depressant, SNRI	Depression	Possible Risk of TdP	oral
Vorinostat	Zolinza®	Histone deacetylase inhibitor	Cancer (lymphoma)	Possible Risk of TdP	oral
Ziprasidone	Geodon®, Zeldox®	Anti-psychotic, atypical	Schizophrenia	Possible Risk of TdP	oral, injection

10.2 Appendix 2: Study Communication Memo

astellas
Leading Light for Life

January 25, 2016

RE: 2215-CL-0101 Study Data Analyses Decision, Site [redacted] (PI: [redacted]

All three subjects enrolled at site [redacted] will be excluded from the study final efficacy analyses through means detailed in the study analysis plan and subject classification specifications. The efficacy exclusion is due to concerns with site [redacted] compliance with good clinical practice as outlined in the attached correspondence with the PI following an Astellas site audit. Astellas' concerns regarding this site's compliance have been reported to the site, ethics committee, FDA and BfArM regulatory bodies in November 2015.

All adverse event data for enrolled subjects at this site will be fully verified via hospital medical record documentation and will be included in the final safety analyses to ensure reporting of a comprehensive safety profile on the ASP2215 compound.

The patients at study site [redacted] are as follows:

[redacted]

[redacted]

[redacted]

Enclosure

Astellas Pharma Global Development, Inc.
1 Astellas Way, Northbrook, IL 60062
Tel: 224-205-8800

04 November 2015

[redacted]
Charite Universitätsmedizin Berlin
[redacted]

Protocol: 2215-CL-0101 - *A Phase 1/2 Open-Label, Dose Escalation Study Investigating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ASP2215 in Patients with Relapsed or Refractory Acute Myeloid Leukemia*

RE: [redacted] **Participation Notification in Astellas Sponsored Clinical Study 2215-CL-0101**

Dear [redacted]

This letter is formal written notification following the teleconference Astellas held with you on 03 November 2015 regarding Astellas action to end your participation as the Principal Investigator in the 2215-CL-0101 study due to the observation on subject [redacted] informed consents. Based on the implausibility of having a completed informed consent form (ICF) version that was released for use at your site post the date of death of subject [redacted] Astellas will close out your participation in the study and will communicate the observation and actions as applicable.

Astellas seeks to be in compliance with all applicable rules and regulations governing clinical research. Pursuant to the requirements of the US Code of Federal Regulations (CFR), title 21, Part 312.56(b) Astellas is ending your participation in the 2215-CL-0101 study and will notify your Central and Local Ethic Committees (EC), the U.S., Food and Drug Administration (FDA), and The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM).

The following is a summary of the observation that has prompted Astellas to end your participation in the study and report the observation to the regulatory authorities, Ethics Committees, and Institution:

Two versions of the main ICF for subject [redacted] (v4Deu3.0 and v6Deu5.0) had the same date for all signatures (01-Jun-2015). v6Deu5.0 was not released to the site for utilization until 15-Jul-2015 and the subject died [redacted] which was over a month prior to the new consent version availability at the site. An investigation of the observation by Astellas in conjunction with you and the Contract Research Organization (INC) did not provide any information to explain the chronology and plausibility for subject [redacted] having a signed consent post their death.

- The Investigator failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]
- The Investigator failed to maintain adequate and accurate case histories including signed and dated consent forms [21 CFR 312.62]

Your study monitor will be contacting you promptly to communicate the next steps regarding the final collection of subject data, including collection and final accountability of all clinical study drug and the steps to complete the close-out of your site. A copy of this letter will be provided to the central and local ethic committees. A correspondence to the FDA and BfArm on the Astellas observation and action is targeted for 03 November 2015.

Thank you for your continued collaboration in the investigation and next steps to close the study at your site. If you have any questions please contact your INC monitor or me at the contact information listed below.

Sincerely,

[redacted]

Astellas Pharma Development, Inc.
One Astellas Way, Northbrook IL 60062

[redacted]

Cc:
2215-CL-0101 Trial Master File

[redacted]

10.3 Appendix 3: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author (s)

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This Statistical Analysis Plan was approved by:

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[redacted]

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