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

ClinicalTrials.gov Identifier: NCT02014558

Date of Protocol Version 12.0: 02 June 2017

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

1 Astellas Way

Northbrook, IL 60062

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Protocol for Phase 1/2 Study of ASP2215

ISN/Protocol 2215-CL-0101

Version 12.0

Incorporating Substantial Amendment 11 [See Attachment 1]

02 June 2017

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

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Version 2.0 Incorporating Substantial Amendment 1 [16Jul2013]
Version 1.0 Original [23Apr2013]

Table of Contents

List of In-text Tables

List of In-text Figures

I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors, etc.) are located in Section 14. Sponsor's Signatures; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

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

Version 12.0 / Incorporating Substantial Amendment 11

02 June 2017

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ----------

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	[redacted] **Astellas Pharma Global Development, Inc.** **Mobile:** [redacted] **Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Global Pharmacovigilance** **North America Fax Number: 888-396-3750** **(North America Alternate Fax: 847-317-1241)** **International Fax Number: +44 800 471 5263** **Email: safety-us@astellas.com**
Medical Monitor/ Medical Expert:	[redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
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III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APGD	Astellas Pharma Global Development, Inc.
APL	Acute promyelocytic leukemia
aPTT	Activated partial thromboplastin time
ASP2215	Compound code for study drug
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the plasma concentration time curve
BCL-ABL	Chronic myelogenous leukemia in blast crisis
BCVA	Best-corrected visual acuity
Ca	Calcium
C_{max}	Maximum concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CR	Complete remission
CRc	Composite complete remission
CRi	Complete remission with incomplete hematologic recovery
CRO	Contract research organization
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Minimum concentration
CV	Coefficient of variation
CYP3A4	Cytochrome P450-isozyme3A4
DDI	Drug-drug interaction
DFS	Disease-free survival
DIC	Disseminated intravascular coagulation
DL	Dose level
DLI	Donor lymphocytes infusion
dL	Deciliter
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviations	Description of abbreviations
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVHD	Graft-versus-host disease
hCG	Human chorionic gonadotropin
hERG	Human ether-a-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HSCT	Hematopoietic stem cell transplant
HNSTD	Highest non-severely toxic dose
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalization ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ISN	International study number
ITD	Internal tandem duplication
IUD	Intrauterine device
IU	International unit
IUS	Intrauterine system
K	Potassium
kg	Kilogram
L	Liter
LA-CRF	Liver abnormality case report form
LFT	Liver function test
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
MATE1	Multidrug and toxin extrusion 1
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mmHG	Millimeters mercury

Abbreviations	Description of abbreviations
ms	Millisecond
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCE	New chemical entity
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	No observed adverse effect level
NPM1	Nucleophosmin-1 gene
NYHA	New York Heart Association
OCT	Optical coherence tomography
OS	Overall survival
PAF	Platelet activating factor
PD	Pharmacodynamic
PDAS	Pharmacodynamic analysis set
PGx	Pharmacogenomics
PIA	Plasma inhibitory assay
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PR	Partial remission
PTT	Partial thromboplastin time
QTc	QT interval corrected
QTcF	Fridericia-corrected QT interval
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SOC	System organ class
SOP	Standard operating procedure
STD_{10}	Severely toxic dose in 10% of animals
TBL	Total bilirubin
TK	Tyrosine kinase
t_{max}	Time to attain C_{max}
ULN	Upper limit of normal
VA	Visual acuity
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential

Definition of Key Study 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.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	02 June 2017 / Version 12.0
Sponsor: Astellas Pharma Global Development Inc (APGD)	**Protocol Number:** 2215-CL-0101
Name of Study Drug: ASP2215	**Phase of Development:** Phase 1/2

Title of Study:
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 (AML)

Planned Study Period:
From 4Q2013 to 3Q2017

Study Objective(s):
The primary objectives of this study are to:

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

The secondary objectives of this study are to:

- 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.

Planned Total Number of Study Centers and Location(s):
Approximately 35 centers
United States, Italy, France and Germany

Study Population:
Patients with AML who relapsed after or are refractory to induction or salvage treatment.

Number of Subjects to be Enrolled/Randomized:
Up to 40 subjects in dose escalation cohort and up to 250 subjects in dose expansion cohort.

Study Design Overview:
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.

Study Design Overview continued**:**

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

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

Cohort 1

Cohort 1 will comprise the initial dose escalation cohort with up to 10 dose levels (Table 1). 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 1). 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 by the investigator to be related (e.g., possibly, probably, or definitely) 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 1 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 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 the dose escalation cohort (Cohort 1) may participate in the dose expansion cohort (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 C1 D1.
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 CR, 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 escalation 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 with FLT3 mutations will be enrolled in dose levels selected for further expansion (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 2B) 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 2D) will be evaluated. After completion of the CYP3A4 inhibition expansion (Schedule 2B) and until MTD is determined, Cohort 2 subjects will participate without the drug-drug interaction (DDI) component (Schedule 2C). DDI studies (Schedules 2B, 2D and 2E) will be conducted in the United States only. European sites whose patients are randomized to the DDI arms of the study will follow Schedule 2C 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 2C even if patients are randomized to Schedule 2B or 2D.

Patients who have a contraindication to voriconazole or midazolam can participate in the trial without the DDI component (Schedule 2C) 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 2B to evaluate the effect of CYP3A4 inhibition for strong inhibitor voriconazole.

To further evaluate DDI, a sub-study with a MATE1 substrate will be conducted [Table 2E]. 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 2E) 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.

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 one 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 evaluations [Section 5.1.2].

Continuation of Subjects in open label roll over study:

Should the Sponsor make the decision to end the study after primary analysis, all subjects receiving ASP2215 may be enrolled in an ASP2215 rollover study (2215-CL-0109). Subjects must not meet any discontinuation criteria for this study and must meet the entry criteria for the rollover study prior to being enrolled.

Subjects who choose not to participate or are not eligible for Study 2215-CL-0109 will complete their participation in Study 2215-CL-0101 by completing the End of Treatment follow up visit upon activation of Study 2215-CL-0109 at the institution.

Subjects, who are being followed for Long-term Follow-up at the time of study closure, will be discontinued.

Figure 1: Optimal Dose Escalation and Expansion

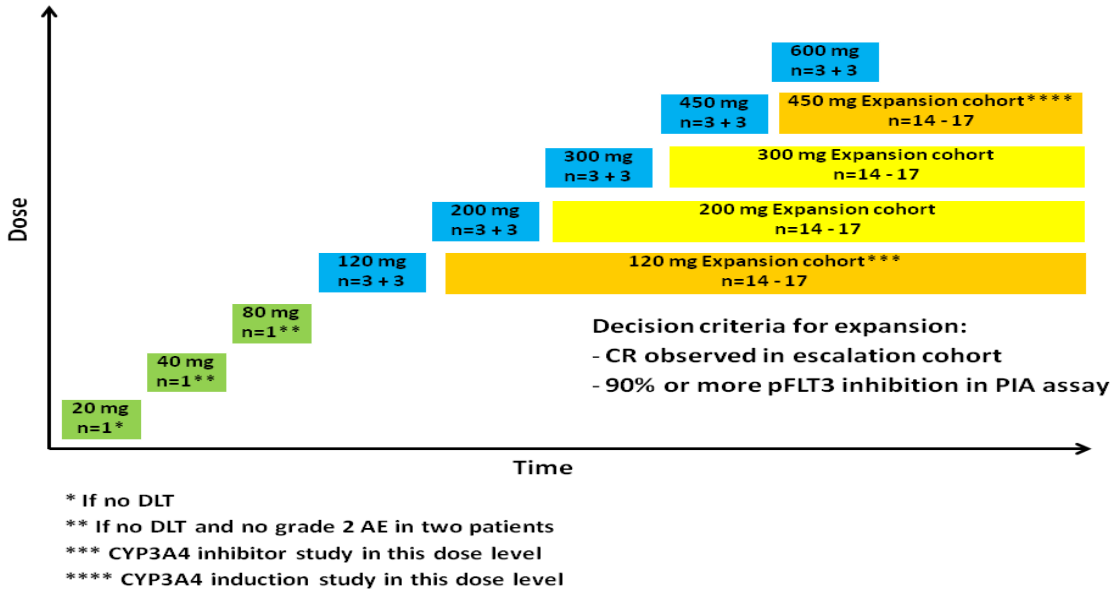
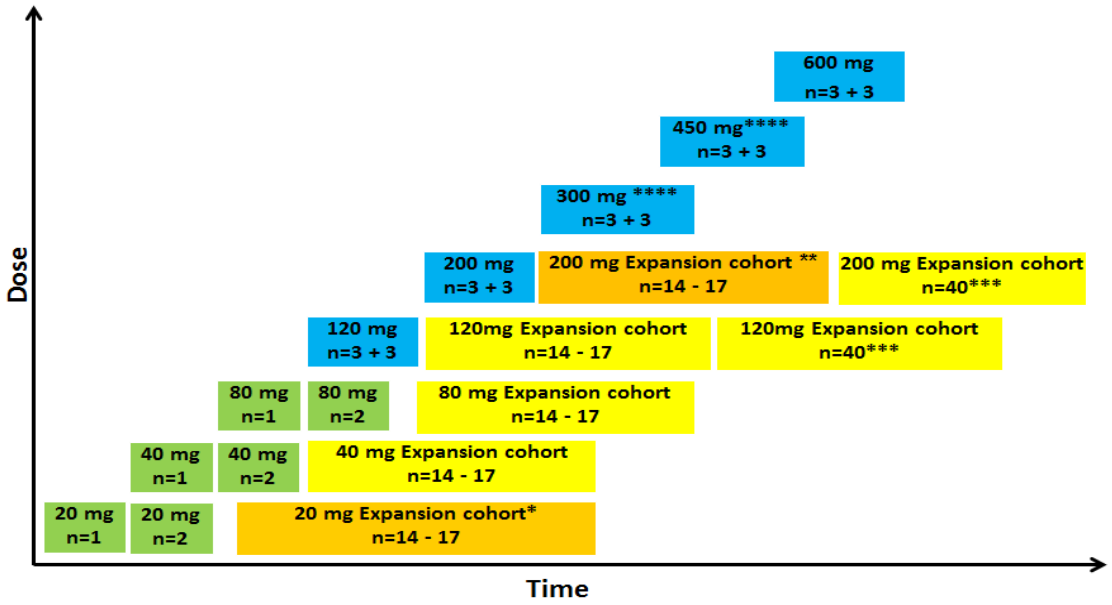


Figure 2: Optimal Efficacy Expansion of Cohort 2



* 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

Inclusion/Exclusion Criteria:

Waivers to the inclusion criteria will NOT be allowed.

Inclusion:

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is ≥18 years of age at the time of obtaining informed consent.
3. Subject is defined as morphologically documented primary or secondary AML by the World Health Organization (WHO) criteria (2008) and fulfills one of the following:
   - Refractory to at least 1 cycle of induction chemotherapy
   - Relapsed after achieving remission with a prior therapy
4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
5. Subject's interval from prior treatment to time of study drug administration is at least 2 weeks for cytotoxic agents (except hydroxyurea given for controlling blast cells), or at least 5 half-lives for prior experimental agents or noncytotoxic agents.
6. Subject must meet the following criteria as indicated on the clinical laboratory tests*:
   - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × institutional upper limit normal (ULN)
   - Total serum bilirubin ≤ 1.5 × institutional ULN
   - Serum creatinine ≤ 1.5 × institutional ULN or an estimated glomerular filtration rate (eGFR) of > 50 ml/min as calculated by the Modification of Diet in Renal Disease (MDRD)

equation.

7. Subject is suitable for oral administration of study drug.
8. Female subject must be either:
   - Of non child bearing potential:
     - post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
     - documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening)
   - Or, if of childbearing potential,
     - must have a negative urine pregnancy test at Screening*, and
     - must use two forms of birth control** (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 180 days after the final study drug administration.
9. Female subject must not be breastfeeding at Screening or during the study period, and for 60 days after the final study drug administration.
10. Female subject must not donate ova starting at Screening and throughout the study period, and for 180 days after the final study drug administration.
11. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control** (one of which must be a barrier method) starting at Screening and continue throughout the study period and for 120 days after the final study drug administration.
12. Male subject must not donate sperm starting at Screening and throughout the study period and for 120 days after the final study drug administration.
13. Subject agrees not to participate in another interventional study while on treatment.

<u>MATE1 Sub-study (Schedule 2E) Subjects Only</u>:

14. Subject has documented FLT3 mutation positive AML (ITD and/or activating point mutations)

*Screening labs and diagnostic tests may be performed by local laboratories to determine eligibility; however, samples will also be submitted for central read.

** Acceptable forms of birth control include:
- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Exclusion:

Waivers to the exclusion criteria will NOT be allowed.

Subject will be excluded from participation if any of the following apply:

1. Subject was diagnosed as acute promyelocytic leukemia (APL).
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has active malignant tumors other than AML or Myelodysplastic Syndrome (MDS).
4. Subject has persistent non-hematological toxicities of ≥ Grade 2 (CTC AE v4), with symptoms and objective findings, from prior AML treatment (including chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation, or surgery).
5. Subject has had hematopoietic stem cell transplant (HSCT) and meets any of the following:
   - Is within 2 months of transplant from C1D1

- Has clinically significant graft-versus-host disease requiring treatment
- Has ≥ Grade 2 persistent non-hematological toxicity related to the transplant

Donor lymphocytes infusion (DLI) is not permitted ≤ 30 days prior to study registration or during the first cycle of treatment on the study in Cohort 1 and first two cycles of the treatment in Cohort 2.

6. Subject has clinically active central nervous system leukemia.
7. Subject has disseminated intravascular coagulation abnormality (DIC).*
8. Subject has had major surgery within 4 weeks prior to the first study dose.
9. Subject has had radiation therapy within 4 weeks prior to the first study dose.
10. Subject has congestive heart failure NYHA class 3 or 4, or subject with a history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram performed within 3 months prior to study entry results in a left ventricular ejection fraction that is ≥ 45%.
11. Subject with mean Fridericia-corrected QT interval (QTcF) > 450 ms at Screening based on central reading.
12. Subject with Long corrected QT interval (QTc) Syndrome at Screening.
13. Subject with hypokalemia and hypomagnesemia at Screening (defined as values below lower limit of normal [LLN]).
14. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of CYP3A4 or of P-glycoprotein (P-gp) or substrates of multidrug and toxin extrusion 1 (MATE 1) with the exception of antibiotics, antifungals, and antivirals that are used as standard of care post-transplant or to prevent or treat infections and other such drugs that are considered absolutely essential for the care of the subject.
15. Subject requires treatment with concomitant drugs that target serotonin 5HT1R or 5HT2BR receptors or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject
16. Subject has an active uncontrolled infection.*
17. Subject is known to have human immunodeficiency virus infection.
18. Subject has active hepatitis B or C, or other active hepatic disorder.*
19. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation (e.g. ophthalmic conditions such as advanced cataracts, subject is unable to undergo a comprehensive ophthalmologic exam, inability to visualize the fundus).

<u>MATE1 Sub-study (Schedule 2E) Subjects Only:</u>

20. Subject has known severe allergy to penicillins or cephalosporins.
21. Subject was previously treated with ASP2215.

*Screening labs and diagnostic tests may be performed at local laboratories to determine eligibility; however, samples will also be submitted for central read.

Investigational Product(s):

ASP2215 tablets containing 10 mg, 40 mg or 100 mg of active ingredient.

Dose(s):

ASP2215 will be administered once daily in the following dose levels. However, not all dose levels will enroll, as described in the Study Design Overview.

Table 1: 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 2.2.1 Study Design.

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

Mode of Administration:

ASP2215 will be administered orally without food allowed for at least 2 hours before and 1 hour after dosing. Subjects will be instructed to take the daily dose with water as close to the same time each morning as possible.

Comparative Drug(s):

Not applicable.

Concomitant Medication Restrictions or Requirements:

Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited. Treatment with concomitant drugs that are strong inihibitors or inducers of P-gp, and concomitant drugs that target serotonin 5HT2BR receptors or signma nonspecific receptor should be avoided with the exception of drugs that are considered absolutely essential for the care of the subject. Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals, and antivirals that are used as standard to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjexts should be closely monitored for adverse events (AEs).

Precaution should be used in use of ASP2215 with concomitant drugs that are known to prolong QT or QTc intervals.

During the initial 15 days of treatment in expansion cohorts with DDI studies [Table 2B Schedule of Assessments with CYP3A4 Inhibitor Voriconazole, Table 2D Schedule of Assessments for Expansion Phase with CYP3A4 Induction, and Table 2E Schedule of Assessments for Expansion Phase with MATE1 Substrate Study], moderate or strong CYP3A4 inhibitors are prohibited, unless required for treatment of active infections. In addition, during the initial 15 days of treatment for subjects assigned to Schedule 2E, MATE1 substrates are prohibited. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215 with the following exceptions:

- Hydroxyurea up to 5 gm daily for up to 2 weeks to keep the absolute blast count below 50,000
- Hematopoietic Stem Cell Transplants (HSCT) for patients with CRc or PR

- Intrathecal Chemotherapy used as prophylaxis

Please see Section 5.1.4 for additional information on HSCT.

Duration of Treatment:

One dose daily in 28 day cycles until a discontinuation criterion is metor until rollover into the 2215-CL-0109 study.

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.

Discontinuation Criteria

Subjects who meet any of the following criteria during the study will be withdrawn from study treatment:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is non-compliant with protocol based on the Investigator or Medical Monitor assessment.
- Subject is found to have significantly deviated from any one of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit and no DLT may be kept in the study after discussion with the medical monitor).
- Subject develops an unacceptable study drug-related toxicity (DLT) or SAE requiring discontinuation of treatment.
- Subject will be taken off treatment if there is no PR or CRc and the subject, in the opinion of the Investigator, is no longer deriving clinical benefit after 2 cycles of therapy.
- ASP2215 dose is interrupted for greater than 15 days. Subjects may be allowed to continue treatment after discussions with the medical monitor if the interruption was not due to an ASP2215 related adverse event.
- Investigator/sub-investigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- Death

The subject will be discontinued from the post-treatment period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- More than 3 years has passed from the End Of Treatment Visit.

- Death

Endpoints for Evaluation:

Primary:

- Safety and Tolerability (Determine MTD and AEs)
- Pharmacokinetics (ASP2215)

Secondary:

- Efficacy of ASP2215 in AML
  - CR rate
  - Composite CR rate (CR + CRp + CRi)
  - Best response rate (CRc + partial remission [PR])
  - Duration of response
  - Overall survival
  - Event free survival
  - Leukemia free survival
- Pharmacokinetics of ASP2215, effect of strong or moderate CYP3A4 inhibitors
- Pharmacokinetics of midazolam, potential induction of CYP3A4 by ASP2215
- Pharmacokinetics of cephalexin, MATE1 inhibition by ASP2215

Exploratory:

Statistical Methods:

Sample Size Justification:

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

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 cohort as described in the Study Design Overview section. A 2-parameter Bayesian logistic regression will be used to model the dose-toxicity relationship on DLT. Subjects in either dose escalation cohort or dose expansion cohorts 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 procedures 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.

Subject Assignment in Cohort 2 Dose Expansion Cohort:

As a dose level is decided to be expanded, up to 17 subjects will be enrolled for the dose level in the dose expansion cohort (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 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.

If 10 subjects without FLT3 mutations (ITD or activating point mutations) are enrolled into 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.

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

Subject Assignment in Cohort 2 MATE1 Sub-study Dose Expansion Cohort:

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 and 40 mg tablets will be used.

Further Expansion for Efficacy Evaluation

To improve guidance for Recommended Phase 2 Dose, 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. A minimum of 42 evaluable (receive 2 cycles of treatment or discontinue for progressive disease) FLT3 mutated patients will be enrolled.

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
34	10
37	11

Safety Analyses:

Safety analyses will consist of data summaries of AEs, DLTs, and other safety parameters. The number and percent of subjects experiencing 1 or more AE(s) will be summarized by cohort and dose level. The relationship to study drug, time of onset, and severity of AE will also be summarized. AEs will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

descriptive statistics.

Efficacy Analyses:

Complete remission (CR) rate, composite complete remission rate, overall response rate duration of confirmed response, disease-free survival (DFS),overall survival (OS), event free survival (EFS) and leukemia free survival, will be summarized using descriptive statistics. The survival curve and median for time-to-event variables will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval.

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

Pharmacokinetics Analyses:

Plasma concentrations and PK parameters will be summarized by cohort using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) of the mean and geometric mean). Time-course of drug concentrations will be plotted as appropriate.

Subjects with sufficient PK samples will have PK parameter estimates for ASP2215 including calculation of AUC_{24}, C_{max}, C_{trough} and t_{max} using standard NCA.

Pharmacodynamics:

Percent inhibition of phosphorylation of FLT3, S6 and AXL as compared to baseline sampling will be summarized by cohort (except for Schedule 2E).

Other Exploratory Analyses:

[redacted]

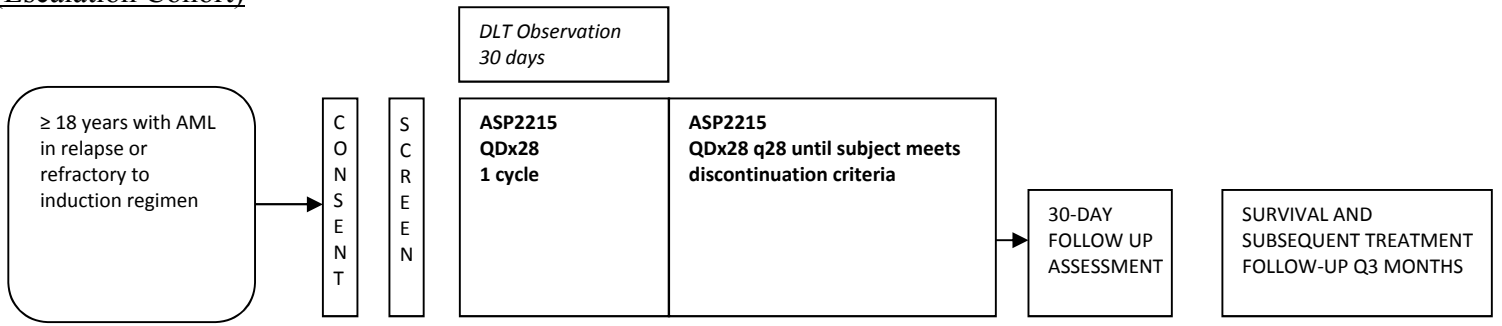
Interim Analyses:

No interim analysis is planned.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Figure 1 Study 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

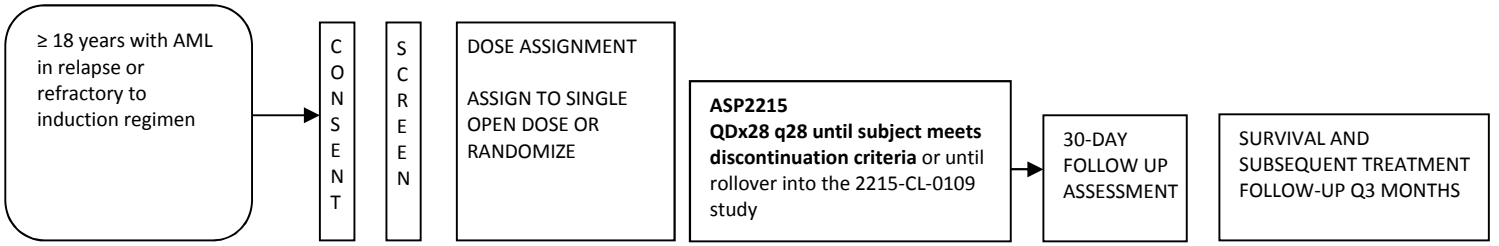


Table 2A Schedule of Assessments for Dose Escalation Phase (Cohort 1)

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[m]
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

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. 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
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 must be collected on Day -1 and before the next dose of ASP2215 on Day 16). 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
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 (i.e., 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 D16). 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 also 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 2B Schedule of Assessments for Expansion Phase with CYP3A4 Inhibitor Voriconazole Study (Cohort 2, Starting Dose Level)

Activity	Screening (Day -14 to -1)	Cycle 1						Cycle 2			Subsequent Cycles
		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]			

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. 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 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

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

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 (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. 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. 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 also 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 2C Schedule of Assessments for Expansion Cohort 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 [m]
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

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. 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
e. PK samples for ASP2215 will be collected at C1D1 and C1D15 at pre-dose (0.5 hours before drug administration) and 2 hours (±10 minutes) post dose. ASP2215 predose (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
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. 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 (i.e., 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. 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 also 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 2D Schedule of Assessments for Expansion Phase with CYP3A4 Induction Study (Cohort 2, MTD Level)

Activity	Screening (Day -14 to -2)	D-1	Cycle 1						Cycle 2		Subsequent Cycles
			D 1	D4±1	D8±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 [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 [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
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]		
PGxh	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]					

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. 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
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 predose (0.5 hours before drug administration) PK samples will also be collected on Day 1 of each cycle starting at Cycle 2. See Section 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 (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 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 also 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 2E 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.

Footnotes continued on next page

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 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. 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 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. 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.

Table 2F 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 and does not resume ASP2215, 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

1 INTRODUCTION

1.1 Background

AML accounts for approximately 80% of acute leukemias diagnosed in adults. The median age at diagnosis is 66 years. It is estimated that 13,780 people (7,350 men and 6,430 women) will be diagnosed with AML, and 10,200 will die from the disease in 2012 in the United States. [Howlader, 2011]. While 60% to 80% of younger patients achieve a complete remission with standard therapy, only about 20% to 30% of the overall patient population has long-term disease-free survival. Outcomes are worse for patients aged 60 years or over, with complete remission rates in the range of 40% to 55% and poor long-term survival rates.

Along with age, remission rates and overall survival depend on a number of other factors, including cytogenetics, previous bone marrow disorders (such as myelodysplastic syndromes) and co-morbidities. Currently, there is no effective cure for the disease.

FLT3 is a member of the class III receptor tyrosine kinase family that is normally expressed on the surface of hematopoietic progenitor cells. FLT3 and its ligand play an important role in proliferation, survival, and differentiation of multipotent stem cells. FLT3 is over expressed in the majority of AML cases. In addition, activated FLT3 with internal tandem duplication (ITD) at juxtamembrane domain and tyrosine kinase domain (TKD) mutations at around D835 in the activation loop are present in 25% to 30% and 5% to 10% of AML cases, respectively [Schlenk, 2009]. These activated mutations in FLT3 are oncogenic, and show transforming activity in cells [Yamamoto, 2001]. Furthermore, patients with these activated FLT3 show poor prognosis [Yanada, 2005].

Axl is a member of TAM family (Tyro-3, Axl, and Mer) receptor tyrosine kinases and is normally expressed in cells of mesenchymal origin, such as osteoblasts, fibroblasts, and blood cells. Axl has been reported to be overexpressed or activated in many cancers, including acute myeloid leukemia (AML) [Linger 2008]. Axl overexpression in AML confers drug resistance [Hong 2008] and is associated with adverse prognosis [Rochlitz 1999 and Ben-Batalla 2013]. Axl inhibition suppresses the growth of human FLT3-positive AML in vivo [Park 2013]. Finally, Axl inhibition is also active in FLT3-negative (but Axl expressing) AML in vivo [Ben-Batalla 2013].

ASP2215 hemifumarate is a new chemical entity (NCE) discovered by Astellas Pharma Inc. in collaboration with [redacted] ASP2215 has an inhibitory effect on tyrosine kinases, mainly FLT3, Axl and ALK. ASP2215 demonstrated favorable efficacy in a non-clinical AML model, which means complete regression of tumors in the xenograft model mice transplanted with MV4-11, human AML cell line expressing FLT3-ITD, by repeated oral doses. In addition, ASP2215 inhibited the growth of cells expressing either wild type FLT3, FLT3-ITD, FLT3-D835Y, or FLT3-ITD-D835Y.

1.2 Non-clinical and Clinical Data

1.2.1 Non-clinical Studies

1.2.1.1 Nonclinical Pharmacology

Primary Pharmacodynamic Studies

Inhibitory activity of ASP2215 on various tyrosine kinases [2215-PH-0006]

The inhibitory activity of ASP2215 against 79 tyrosine kinases and the IC_{50} values against FLT3 and KIT kinases were evaluated.

Among 79 tyrosine kinases tested, ASP2215 inhibited activities of FLT3, NPM-ALK, LTK, ALK and AXL kinases at 1 nmol/L, and TRKA, ROS, RET and MER kinases at 5 nmol/L by over 50% [Table 1]. IC_{50} values against FLT3 and KIT kinase activities were 0.291 and 229 nmol/L, respectively.

Table 1 Inhibitory Effect of ASP2215 on Various Tyrosine Kinases

Kinase	% Inhibition	
	ASP2215 (nmol/L)	
	1	5
FLT3	86.8	96.4
NPM1-ALK	82.2	99.5
LTK	81.8	97.5
ALK	76.1	97.6
AXL	54.3	85.5
TRKA	38.3	74.9
ROS	35.0	71.7
RET	26.0	65.5
MER	21.5	55.7

Affinity of ASP2215 to various receptors, ion channels, transporters and effect of ASP2215 on enzyme reactions [2215-PH-0007]

The affinity of ASP2215 to 20 receptors, 3 ion channels, 2 transporters and the inhibitory effect of ASP2215 on 3 enzyme reactions were evaluated. ASP2215 at 10 mcmol/L showed > 50% inhibition against each radioligand binding to Serotonin 5HT2B (human) receptor, Sigma (non-selective, guinea pig) receptor, Serotonin 5HT1 (non-selective, rat) receptor, and Adenosine A1 (rat) receptor, with respective IC_{50} values of 0.190, 0.615, 4.90 and 4.57 mcmol/L. Each radioligand binding to all other receptors, ion channels, and tested enzyme reactions were not inhibited by >50% by ASP2215 at 10 mcmol/L [Table 2 and Table 3].

Table 2 Inhibition Effect of ASP2215 on Radioligand Binding to Various Receptors, Ion Channels and Transporters

Assay name	Inhibition (%)		
	ASP2215	Positive substance	
K Channel KATP (Rat)	4.79	99.15	(Glybenclamide)
K Channel SkCa (Rat)	20.31	99.17	(Apamin)
Leukotriene B4 (Guinea pig)	0.00	98.35	(Leukotriene B4)
Leukotriene D4 (Guinea pig)	30.22	100.00	(Leukotriene D4)
Melatonin MT1 (Human)	6.53	99.86	(Melatonin)
Muscarinic (Non-selective) (Rat)	11.73	100.00	(Atropine)
Muscarinic M1 (Human)	31.45	100.00	(Atropine)
Muscarinic M2 (Human)	3.94	100.00	(Atropine)
Na Channel Site 2 (Rat)	35.38	100.00	(Dibucaine)
Neurokinin NK1 (Human)	40.97	99.59	(L-703,606)
Neurokinin NK2 (Human)	18.52	100.00	(Neurokinin A)
Neurokinin NK3 (Human)	16.62	99.23	(Senktide)
Norepinephrine Transporter (Human)	1.86	100.00	(Desipramine)
Nicotinic (Neuronal) (Rat)	25.87	100.00	([±]-Nicotine)
Opiate (Non-selective) (Rat)	23.44	100.00	(Naloxone)
Opiate μ (Human)	6.49	96.41	(DAMGO)
Oxytocin (Rat)	2.95	99.95	(Oxytocin)
PAF (Rabbit)	3.17	98.07	(PAF)
Serotonin 5HT1 (Non-selective) (Rat)	54.61	97.91	(Serotonin)
Serotonin 5HT2B (Human)	100.00	99.98	(Serotonin)
Serotonin Transporter (Human)	0.35	100.00	(Imipramine)
Sigma (Non-selective) (Guinea pig)	92.39	100.00	(Haloperidol)
Testosterone (Human)	0.00	99.60	(Testosterone)
Vasopressin V1 (Rat)	3.09	96.95	([Arg8]-Vasopressin)
VIP 1 (Human)	0.00	99.88	(VIP)

DAMGO: Dermorphin, endomorphin, morphiceptin, nociceptin, and octreotide; PAF: platelet-activating factor
Test substance concentration: 10 mcmol/L, Positive substance concentration: 1 mcmol/L for leukotriene B4, leukotriene D4 and VIP, or 10 mcmol/L for the others. Data are expressed as the mean values of duplicate samples.

Table 3 Inhibition Effect of ASP2215 on Various Enzymes

Assay name	Inhibition (%)		
	ASP2215	Positive substance	
Acetylcholinesterase (Human)	0.00	99.28	(Eserine)
MAO-A (Rat)	11.36	97.18	(Clorgyline)
MAO-B (Rat)	0.00	93.14	(Ro 16-6491)

MAO-A: monoamine oxidase A; MAO-B: monoamine oxidase B Test substance concentration: 10 mcmol/L, Positive substance concentration: 100 mcmol/L for Ro 16-6491, or 10 mcmol/L for the others. Data are expressed as the mean values of duplicate samples.

<u>Effect of ASP2215 on the growth of Ba/F3 cells expressing FLT3 (wt, ITD, D835Y, and ITD-D835Y) [2215-PH-0009]</u>

The inhibitory effect of ASP2215 on proliferation of Ba/F3 cells expressing either FLT3-wt, FLT3-ITD, FLT3-D835Y, or FLT3-ITD-D835Y was evaluated. Inhibition of cell growth was assessed by a luminescent cell viability assay (CellTiter-Glo™), where Ba/F3 cells were

exposed to ASP2215 for 2 days. ASP2215 inhibited the cell growth of Ba/F3 cells expressing FLT3-wt, FLT3ITD, FLT3-D835Y, and FLT3-ITD-D835Y with IC_{50} values of 0.92, 1.8, 1.6, and 2.1 nmol/L, respectively.

Effect of ASP2215 on the growth of MV4-11 cells [2215-PH0008]

The inhibitory effect of ASP2215 on proliferation of MV4-11 cells, AML cells endogenously expressing FLT3-ITD, was evaluated. Inhibition of cell growth was assessed by a luminescent cell viability assay (CellTiter-Glo™), where MV4-11 cells were exposed to ASP2215 for 5 days.

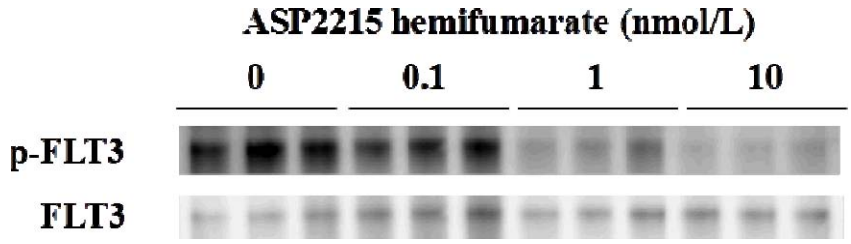
ASP2215 inhibited the growth of MV4-11 cells with an IC_{50} value of 0.92 nmol/L.

Inhibitory effect of ASP2215 on phosphorylation of FLT3 in MV4-11 cells [2215-PH-0010]

The inhibitory effect of ASP2215 on phosphorylation of FLT3 in MV4-11 cells was evaluated. ASP2215 was added to the wells containing MV4-11 cells to achieve final concentrations of 0, 0.1, 1, and 10 nmol/L. At 2 hours after addition of ASP2215, the amount of phosphorylated FLT3 was analyzed by immunoprecipitation and western-blotting. Signals for FLT3 and phosphorylated FLT3 were detected using a CCD camera and quantified using ImageQuant TL software. The signals for phosphorylated FLT3 were normalized using those for FLT3. The mean percentage of phosphorylated FLT3 relative to control was calculated.

In MV4-11 cells, ASP2215 at 0, 0.1, 1, and 10 nmol/L resulted in FLT3 phosphorylation of 100%, 86%, 19%, and 7%, respectively [Figure 2].

Figure 2 Inhibitory Effect of ASP2215 on FLT3 Phosphorylation in MV4-11 Cells



p-FLT3: phosphorylated FLT3

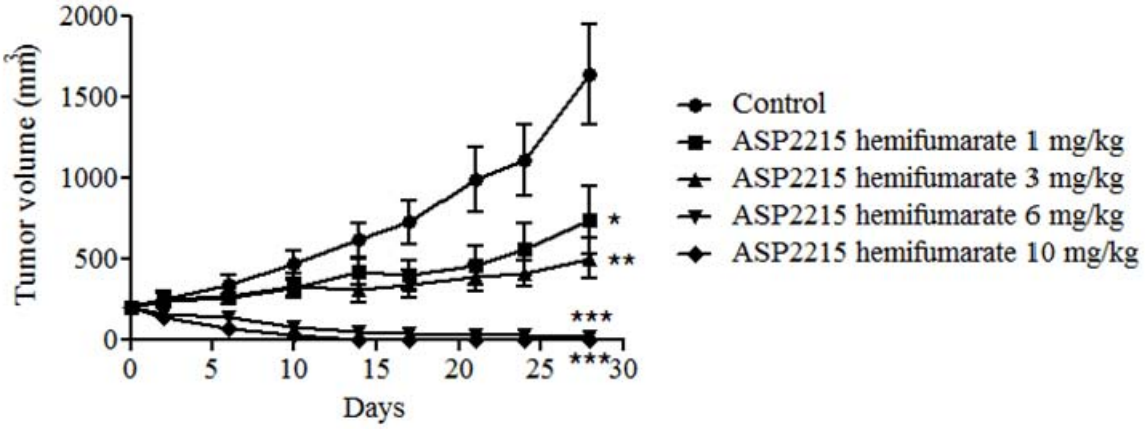
Antitumor activity of once-daily oral administration of ASP2215 in an MV4-11 xenograft model [2215-PH-0011]

The antitumor effect of ASP2215 at 1 to 10 mg/kg per day for 28 days in mice xenografted with human AML derived MV4-11 cells was evaluated. Nude mice were subcutaneously inoculated with MV4-11 cells. Mice were orally treated with either vehicle (0.5% methylcellulose solution; Control group) or ASP2215 at 1, 3, 6, or 10 mg/kg/day, once daily for 28 days. Antitumor activity was expressed as percent inhibition of tumor growth and percent regression of tumor. Tumor volume and body weight on Day 28 in ASP2215 treated groups were compared with those in the control group.

ASP2215 induced significant growth inhibition of MV4-11 tumors and tumor regression [Figure 3]. Further, ASP2215 at 6 and 10 mg/kg/day induced complete tumor regression for

4 and 6 out of 6 mice, respectively [Table 4]. Body weight of the mice treated with ASP2215 was not affected at any tested doses.

Figure 3 Antitumor Effect of ASP2215 in an MV4-11 Xenograft Model



Mice were treated with ASP2215 from Days 0 to 27. Each point represents the mean ± SEM (N=6). Data on Day −1 were utilized as those on Day 0. Statistical analysis was performed for the values on Day 28. *: P<0.05, **: P<0.01 and ***: P<0.001 compared with the control group (Dunnett's test).

Table 4 Effect of Once-daily Oral Administration of ASP2215 on Tumor Growth and Regression in an MV4-11 Xenograft Model

		Percent inhibition of tumor growth (%)	Percent regression of tumor (%)	Animal number with complete regression
ASP2215	1 mg/kg	63	--	--
	3 mg/kg	80	--	--
	6 mg/kg	>100	93	4/6
	10 mg/kg	>100	100	6/6

Nonclinical Safety Pharmacology Studies

In vitro Effects on hERG Current [2215-PT-0001]

ASP2215 hemifumarate showed a concentration-dependent suppression effect on the hERG current in hERG transfected HEK293 cells at concentrations of 3×10^{-6}, 1×10^{-5}, and 3×10^{-5} mol/L with compensated suppression rates of 18.1%, 32.8%, and 70.7%, respectively, and did not at 1×10^{-6} mol/L. The IC_{50} was 1.6×10^{-5} mol/L.

In vivo Effects on Central Nervous System in Rats [2215-PT-0003]

ASP2215 hemifumarate showed no effects on the central nervous system in rats at 10 mg/kg. At 30 mg/kg and higher, decreased urination was noted. In addition, at 100 mg/kg, decreased defecation was noted.

In vivo Effects on Central Nervous, Cardiovascular and Respiratory Systems in Dogs [2215-PT-0002]

ASP2215 hemifumarate did not show any effect on the cardiovascular or respiratory system in dogs up to 100 mg/kg, or on the central nervous system at 1 mg/kg. At 3 mg/kg and higher, the following signs were noted: retching at 3 mg/kg, vomiting and positive fecal occult blood at 10 mg/kg and higher, a decrease in the blood Ca concentration at 30 mg/kg, and salivation and an increase followed by a decrease in the blood Ca concentration at 100 mg/kg. All of the findings recovered.

1.2.1.2 Nonclinical Pharmacokinetics

In vitro metabolic activity of ASP2215 in recombinant human cytochrome P450 Enzymes [2215-ME-0001]

In vitro metabolism studies using recombinant human CYP-expressing microsomes indicated that the main CYP isozyme involved in the metabolism of ASP2215 was estimated to be CYP3A4.

In vitro metabolic fingerprinting of ASP2215 [2215-ME-0002]

In vitro metabolic fingerprinting of ASP2215 in pooled liver microsomes and cryopreserved hepatocytes using [^{14}C]ASP2215 hemifumarate indicated that all metabolite peaks of [^{14}C]ASP2215-derived radioactivity detected in human liver microsomes and hepatocytes were also found in those of at least one other species, suggesting that no human-specific ASP2215 metabolites were formed by liver microsomes or hepatocytes.

In vitro plasma protein binding of ASP2215 in mice, rats, rabbits, dogs, monkeys, and humans [2215-ME-0010]

The plasma protein binding ratios of ASP2215 at concentrations of 0.1, 1, and 10 mcg/mL as free base of [^{14}C]ASP2215 hemifumarate were 85.1% to 89.6% in normal mice; 75.4% to 84.2% in pharmacological model mice; 77.7% to 79.2% in rats; 75.5% to 78.7% in rabbits; 78.0% to 80.7% in dogs; 81.3% to 82.4% in monkeys; and 90.2% to 90.5% in humans. The major binding protein in human plasma was human serum albumin.

Inhibitory effect of ASP2215 on the MDR1-mediated transport, and transcellular transport of ASP2215 in human MDR1 expressing cells [2215-ME-0011]

ASP2215 is a substrate for P-gp. Although ASP2215 has the potential of P-gp inhibition, its potential was not so strong and the IC_{50} was more than 30 mcmol/L.

Inhibitory effect of ASP2215 on the human MATE1- and MATE2-K-mediated transport [2215-ME-0020]

ASP2215 showed inhibitory effect on MATE1-mediated [^{14}C] metformin transport and MATE2-K-mediated [^{14}C]metformin transport in a concentration dependent manner. The IC50 values of ASP2215 were calculated to be 0.0543 μmol/L and 47.7 μmol/L, respectively.

1.2.1.3 Nonclinical Toxicology

Single dose toxicity study [2215-TX-0001]

In the single oral dose toxicity study in rats, the approximate lethal dose level was 300 mg/kg for males and females. The major change was a gastrointestinal hemorrhagic disorder at 100 and 300 mg/kg. Reversibility of the changes noted in the surviving animals was seen.

Repeated dose toxicity studies [2215-TX-3004, 2215-TX-0002, 2215-TX-0003]

In the 1-week oral repeated dose toxicity study in rats, interstitial pneumonia in the lung and vacuolar change in the rod-cone layer of the retina were observed in a male at 30 mg/kg. In the 13-week oral repeated dose toxicity study in rats, deaths occurred at 20 mg/kg/day in both sexes. Target organ toxicity was identified in the gastrointestinal tract, immune system, bone marrow, eye, lung, kidney, and liver. The no observed adverse effect level (NOAEL) was lower than 2.5 mg/kg/day for males and females because low body weight was noted in males and effects on the immune system (low lymphocytes and serum gamma-globulin ratio, and low spleen weight) were noted in females. The changes noted during the dosing period recovered or tended to recover during the 4-week recovery period. The severely toxic dose in 10% of the animals (STD_{10}) in rats was considered to be 20 mg/kg/day. In the 4-week oral repeated dose study in dogs, deaths or moribund sacrifices occurred in males at 10 mg/kg/day (1 out of 4 animals), 100 mg/kg/day (all 7 animals), and 1000 mg/kg/day (6 out of 7 animals). Target organ toxicity was identified in the gastrointestinal tract, immune system, bone marrow, eye, kidney, and liver. The NOAEL was 1 mg/kg/day for males and females since decreased body weight, increased aspartate aminotransferase (AST) and thymic atrophy in males, lymphocyte necrosis in the mesenteric lymph node in females, and a positive fecal occult blood reaction and increased alkaline phosphatase (ALP) in both sexes were observed at 2.5 mg/kg/day and higher. Reversibility of the test article-related changes was indicated at the end of the 4-week recovery period. The highest non-severely toxic dose (HNSTD) in dogs was considered to be 5 mg/kg/day.

Genotoxicity studies [2215-TX-3008, 2215-TX-3009, 2215-TX-3010, 2215-TX-3011, 2215-TX-0004, 2215-TX-0005]

ASP2215 induced gene mutation in bacteria in the screening *in vitro* reversion test but the extent of the increase in the number of revertant colonies was marginal and the dose-relationship was unclear. On the other hand, ASP2215 did not induce gene mutation in the definitive *in vitro* reversion test in bacteria. Therefore, it was concluded that ASP2215 does not have a potential to induce gene mutation. Although ASP2215 induced micronuclei in the screening *in vitro* micronucleus test, it did not induce chromosomal aberrations in the definitive *in vitro* chromosomal aberration test in mammalian cells. The positive results in the screening test were obtained only at concentrations where evaluation could not be done due to cytotoxicity in the definitive study. It was concluded that ASP2215 does not have potential to induce chromosomal aberrations *in vitro*. The screening *in vivo* micronucleus test showed that ASP2215 has a potential to induce chromosomal aberrations in mice. Based on the results of the battery of genotoxicity studies above, it was concluded that ASP2215 has a potential to induce genotoxicity *in vivo*.

Phototoxicity study [2215-TX-0006]

ASP2215 hemifumarate showed no potential to induce phototoxicity to cultured mammalian cells (Balb/c 3T3 cells) under the conditions of this study.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Pre-Clinical Data

ASP2215 hemifumarate showed a concentration-dependent suppression effect on the hERG current in HEK293 cells at concentrations of $3x10^{-6}$, $1x10^{-5}$, and $3x10^{-5}$ mol/L with compensated suppression rates of 18.1%, 32.8%, and 70.7%, respectively, and did not at $1x10^{-6}$ mol/L. The IC_{50} was $1.6x10^{-5}$ mol/L.

ASP2215 hemifumarate showed no effects on the central nervous system in rats at 10 mg/kg. At 30 mg/kg and higher, decreased urination was noted. In addition, at 100 mg/kg, decreased defecation was noted.

ASP2215 hemifumarate did not show any effect on the cardiovascular or respiratory system in dogs up to 100 mg/kg, or on the central nervous system at 1 mg/kg. At 3 mg/kg and higher, the following signs were noted: retching at 3 mg/kg, vomiting and positive fecal occult blood at 10 mg/kg and higher, a decrease in the blood Ca^{+2} concentration at 30 mg/kg, and salivation and an increase followed by a decrease in the blood Ca^{+2} concentration at 100 mg/kg. All of the findings recovered.

In the single oral dose toxicity study in rats, the approximate lethal dose level was 300 mg/kg for males and females. The major change was a gastrointestinal hemorrhagic disorder at 100 and 300 mg/kg. Reversibility of the changes noted in the surviving animals was seen. No single oral dose toxicity study in dogs was conducted. In the 4-week toxicity study in dogs, a dose of 1000 mg/kg/day caused deaths and moribund sacrifices on Day 2. The cause of death and moribundity was considered to be deterioration of general condition caused by gastrointestinal hemorrhage. The MTD was 5 mg/kg/day.

In the 1-week oral repeated dose toxicity study in rats, interstitial pneumonia in the lung and vacuolar change in the rod-cone layer of the retina were observed in a male at 30 mg/kg. In the 13-week oral repeated dose toxicity study in rats, deaths occurred at 20 mg/kg/day in both sexes. Target organ toxicity was identified in the gastrointestinal tract, immune system, bone marrow, eye, lung, kidney, and liver. The NOAEL was lower than 2.5 mg/kg/day for males and females because low body weight was noted in males and effects on the immune system (low lymphocytes and serum gamma-globulin ratio, and low spleen weight) were noted in females. The changes noted during the dosing period recovered or tended to recover during the 4-week recovery period. STD_{10} in rats was considered to be 19 mg/kg/day. In the 4-week oral repeated dose study in dogs, deaths occurred at 10 mg/kg/day or more. Target organ toxicity was identified in the gastrointestinal tract, immune system, bone marrow, eye, kidney, and liver. The NOAEL was 1 mg/kg/day for males and females since decreased body weight, increased AST and thymic atrophy in males, lymphocyte necrosis in the mesenteric lymph node in females, and a positive fecal occult blood reaction and increased ALP in both

sexes were observed at 2.5 mg/kg/day or higher. Reversibility of the test article related changes was indicated at the end of the 4-week recovery period. The HNSTD in dogs was considered to be 5 mg/kg/day. The first human dose is 20 mg/day based on the STD_{10}.

Ocular toxicities (lens opacity, inflammation in the uvea and conjunctiva, and vacuolation in the rod-cone layer in the retina in rats, and dark discoloration of the ocular fundus in dogs) were observed. The lens opacity and inflammatory changes were reversible. In addition, the changes were observed only at the highest dose level in each study which was MTD or beyond MTD with low incidence. Therefore, these changes would not indicate a significant risk in clinical studies. In dogs, at the highest dose level of 5 mg/kg/day, abnormal fundus finding and OCT change were observed in some animals without any histopathological changes in the eye and these findings were reversible after the 4-week withdrawal period.

ASP2215 induced gene mutation in bacteria in the screening in vitro reversion test but the extent of the increase in the number of revertant colonies was marginal and the dose relationship was unclear. On the other hand, ASP2215 did not induce gene mutation in the definitive in vitro reversion test in bacteria. Therefore, it was concluded that ASP2215 does not have a potential to induce gene mutation. Although ASP2215 induced micronuclei in the screening in vitro micronucleus test, it did not induce chromosomal aberrations in the definitive in vitro chromosomal aberration test in mammalian cells. The positive results in the screening test were obtained only at concentrations where evaluation could not be done due to cytotoxicity in the definitive study. It was concluded that ASP2215 does not have a potential to induce chromosomal aberrations in vitro. The screening in vivo micronucleus test showed that ASP2215 has a potential to induce chromosomal aberrations in mice. Based on the results of the battery of genotoxicity studies above, it was concluded that ASP2215 has a potential to induce genotoxicity in vivo.

ASP2215 hemifumarate showed no potential to induce phototoxicity to cultured mammalian cells (Balb/c 3T3 cells) under the conditions of this study.

1.3.2 ASP2215 Clinical Data

Of the first 154 patients that received ASP2215, 147 (95.5%) developed at least one Treatment Emergent Adverse Event (TEAE) during the study. Overall, the most frequently reported TEAEs (occurring in at least 10% of patients) include febrile neutropenia (34.4%), anemia (27.9%), fatigue (26.6%), diarrhea (26.0%), peripheral edema (20.8%), increased AST (19.5%), dyspnea (18.2%), dizziness (16.9%), epistaxis (16.2%), constipation (15.6%), pyrexia, increased ALT and cough (14.9% each), nausea, sepsis and hypotension (14.3% each), vomiting (13.6%), increased blood creatinine and hypokalemia (13.0% each), decreased platelet count and hypocalcemia (12.3% each), hypomagnesemia (11.7%), hyponatremia (11.0%), thrombocytopenia, pneumonia and increased blood alkaline phosphatase (10.4% each). A total of 102 (66.2%) patients experienced at least 1 TEAE considered by the Investigator to be at least possibly related to study drug. Common drug-related TEAEs (occurring in at least 5% of patients) include fatigue (13.6%), diarrhea (10.4%), anemia, constipation (9.1% each), increased AST (8.4%), nausea, peripheral edema, decreased platelet

count (7.8% each), dizziness (7.1%), thrombocytopenia, vomiting (6.5% each) and increased ALT (5.8%).

A total of 112 (72.7%) of the patients developed at least one serious TEAE. The most commonly reported serious TEAE (occurring in at least 5% of patients) include febrile neutropenia (27.3%), sepsis (13.0%), AML (9.7%), pneumonia (6.5%), hypotension (5.8%), and diarrhea (5.2%). Of the serious TEAEs, 31 (20.1%) patients had serious TEAEs that were considered by the Investigators to be at least possibly related to ASP2215. Drug-related serious TEAEs that occurred in 2 more patients include febrile neutropenia (1.9%), diarrhea and abnormal liver function test (1.3% each). The most commonly reported drug-related serious TEAEs occurred in the MedDRA System Organ Class of Infections and infestations (bacteraemia, diverticulitis, sepsis, and urosepsis) and Blood and lymphatic system disorders (anemia, febrile neutropenia, hemolytic anemia).

After the data cutoff, 1 patient in the 200 mg dose group developed altered mental status and 1 episode of seizure with MRI results consistent with posterior reversible encephalopathy syndrome (PRES). ASP2215 was discontinued and the patient's symptoms resolved. Additionally, 1 case of rhabdomyolysis with associated CK elevations was reported in a patient in the 300 mg dose group. Both SAEs were considered DLTs.

At doses of 120 mg/day and higher, moderate increases (grade 2) in creatinine kinase were seen in 10 of 59 patients (17%). One patient (1.6%) had severe (grade 3) elevation in creatinine kinase. For CK, 21 (13.6%) of patients experienced a shift of 2 grades or higher, and these shifts appeared to increase with increasing dose. For ALT, 19 (12.3%) patients experienced a shift of 2 grades or higher. For AST, 19 (12.3%) patients experienced a shift of 2 grades or higher.

1.4 Risk-Benefit Assessment

Approximately 30% of adult AML patients are refractory to induction therapy. Furthermore, of those who achieve CR, approximately 75% will relapse. Generally, there is no established standard for these patients and less than 20% will achieve CR with subsequent treatment. The response duration for patients who achieve CR with subsequent treatment is limited and most of the patients relapse. Patients who are in 2nd relapse or refractory to 1st salvage have an extremely poor prognosis, with survival measured in weeks.

Some of the issues with other FLT3 inhibitor compounds are their short duration of disease control due to point mutations, prolonged myelosupression and corrected QT interval (QTc) prolongation.

ASP2215 inhibits FLT3-ITD and FLT3 point mutations (D835). FLT3 is over-expressed in the majority of AML cases. There are activating FLT3 mutations in approximately 35% of AML cases. These mutations increase the transforming activity and decrease the prognosis for AML patients.

ASP2215 showed no significant findings in the safety pharmacology studies. In the repeated dose toxicity studies with rats and dogs, mortality was shown and all major findings were

reversible and monitorable. ASP2215 has the potential to induce chromosomal aberrations *in vivo*. However, this potential will not interfere with human clinical studies recruiting AML patients, considering its potential benefit against the risk.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 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.

2.1.2 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.

2.2 Study Design and Dose Rationale

2.2.1 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 4 and Figure 5]:

- 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 5]. 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 5). 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 5 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 (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 with FLT3 mutations will be enrolled in dose levels selected for further expansion [Figure 5]. 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 2B) 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 2D) will be evaluated. After completion of the CYP3A4 inhibition expansion (Schedule 2B) and until MTD is determined, Cohort 2 subjects will participate without the DDI component (Schedule 2C). DDI studies (Schedules 2B, 2D and 2E) will be conducted in the United States only. European sites whose patients are randomized to the DDI arms of the study will follow Schedule 2C 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 2C even if patients are randomized to Schedule 2B or 2D.

Patients who have a contraindication to voriconazole or midazolam can participate in the trial without the DDI component (Schedule 2C) 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 2B 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 2E]. 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 2E) 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.

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 evaluations [Section 5.1.2].

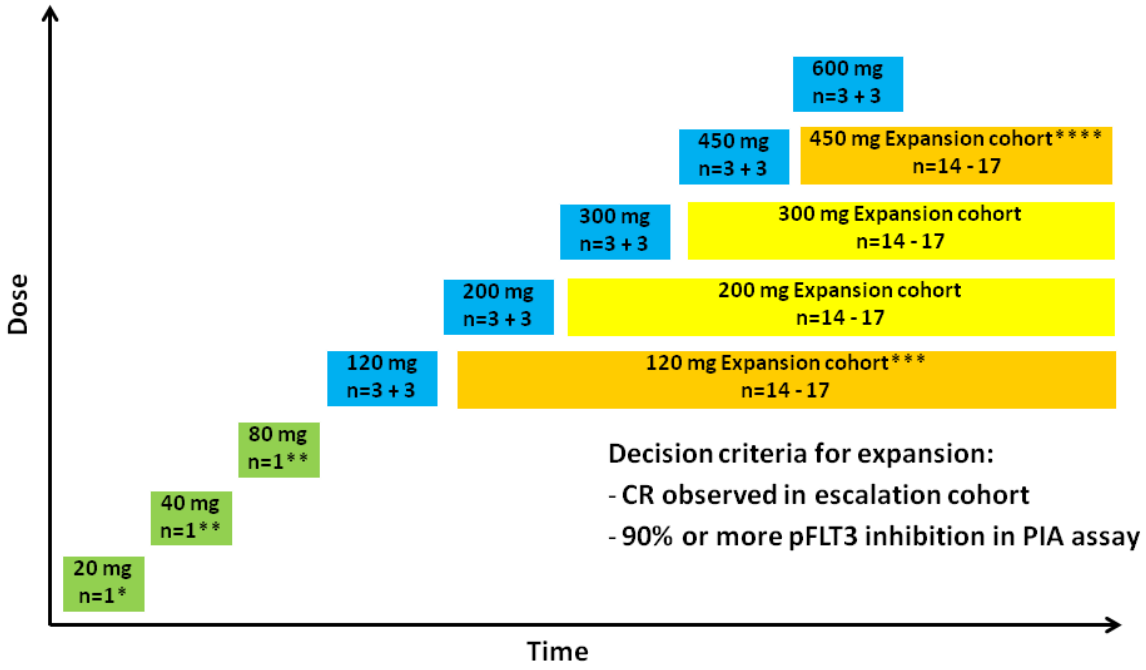
Continuation of Subjects in open label roll over study:

Should the Sponsor make the decision to end the study after primary analysis, all subjects receiving ASP2215 may be enrolled in an ASP2215 rollover study (2215-CL-0109). Subjects must not meet any discontinuation criteria for this study and must meet the entry criteria for the rollover study prior to being enrolled.

Subjects who choose not to participate or are not eligible for Study 2215-CL-0109 will complete their participation in Study 2215-CL-0101 by completing the End of Treatment follow up visit upon activation of Study 2215-CL-0109 at the institution.

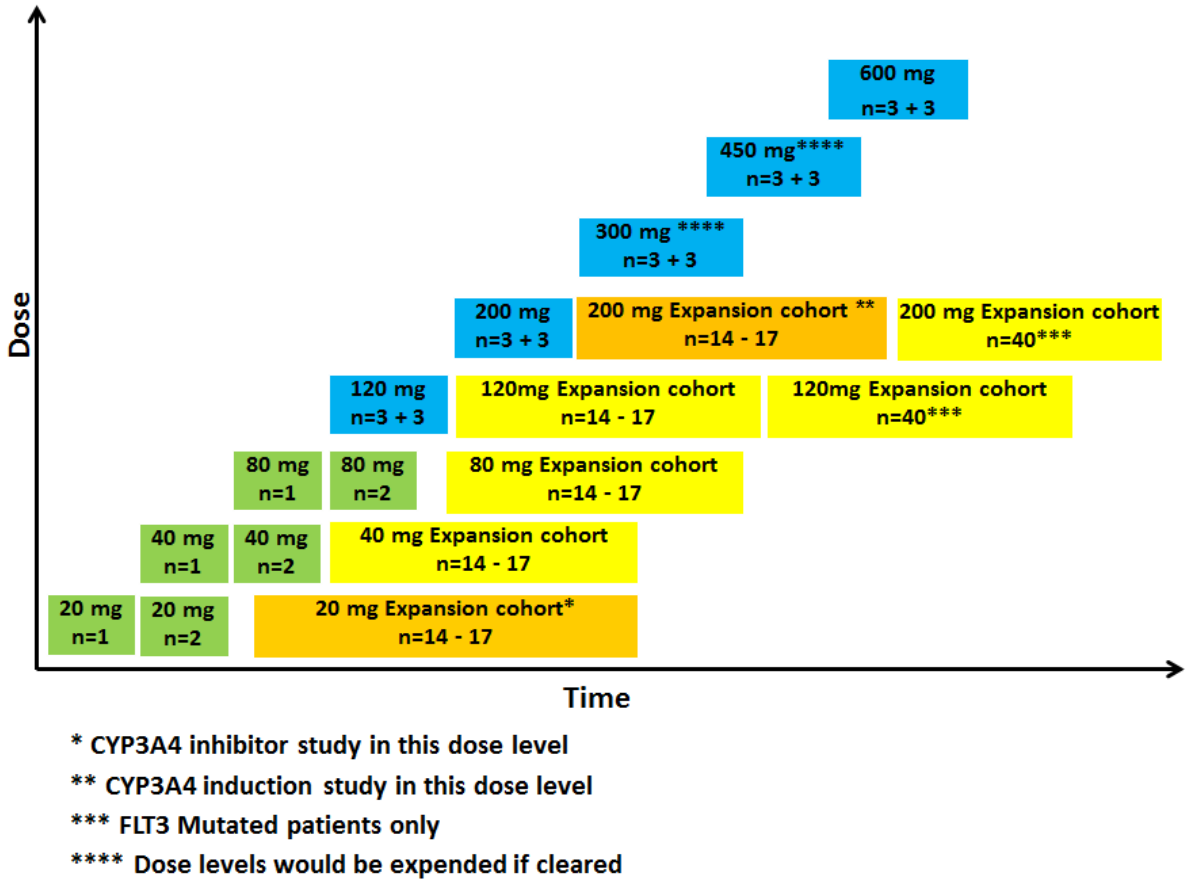
Subjects, who are being followed for Long-term Follow-up at the time of study closure, will be discontinued.

Figure 4 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 5 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

Table 5 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 2.2.1 Study Design.

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

2.2.2 Dose Rationale

ASP2215 has been tested in numerous pre-clinical studies. In the repeated dose toxicity studies, deaths due to deteriorated general conditions occurred at 20 and 10 mg/kg/day in rats and dogs, respectively. Target organs were the gastrointestinal tract, immune system, eye, liver, kidney, lung and/or bone marrow in rats and dogs at ASP2215 doses at 2.5 mg/kg/day or more. All major findings were reversible and monitorable. STD_{10} and HNSTD were 20 and 5 mg/kg/day in rats and dogs, respectively. Human equivalent doses based on body surface area conversion (factor: 0.162 for rat, 0.541 for dog) of the STD10 in rats and the HNSTD in dogs are 3.2 mg/kg and 2.7 mg/kg, respectively. One tenth of the rat STD10 is 19 mg for a person of 60 kg body weight (3.2 mg/kg x 1/10 x 60 kg) and one sixth of the dog HNSTD is 27 mg for a person of 60 kg body weight (2.7 mg/kg × 1/6 × 60 kg). The first human dose is 20 mg/day based on the rat STD_{10}.

2.3 Endpoints

2.3.1 Primary Endpoints

- Safety and Tolerability (Determine MTD)
- Pharmacokinetics (ASP2215)

2.3.1.1 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 or probably 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.

2.3.2 Secondary Endpoints

- Efficacy of ASP2215 in AML
    - CR rate
    - CRc rate (CR + CRp + CRi)
    - Best response rate (CRc + partial remission [PR])
    - Duration of response

  - Overall survival
  - Event free survival
  - Leukemia free survival

- Pharmacokinetics of ASP2215, effect of strong or moderate CYP3A4 inhibitors
- Pharmacokinetics of midazolam, potential induction of CYP3A4 by ASP2215
- Pharmacokinetics of cephalexin, MATE1 inhibition by ASP2215

2.3.3 Exploratory Endpoints

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects with AML who relapsed after or are refractory to induction or salvage treatment will be selected for this study. **Re-Screening is allowed, with a limit of two re-screenings for any potential subject.**

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.

3.2 Inclusion Criteria

Waivers to the inclusion criteria will NOT be allowed.

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is ≥ 18 years of age at the time of obtaining informed consent.

3. Subject is defined as morphologically documented primary or secondary AML by the World Health Organization (WHO) criteria (2008) and fulfills one of the following:
    - Refractory to at least 1 cycle of induction chemotherapy
    - Relapsed after achieving remission with a prior therapy
4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
5. Subject's interval from prior treatment to time of study drug administration is at least 2 weeks for cytotoxic agents (except hydroxyurea given for controlling blast cells), or at least 5 half-lives for prior experimental agents or noncytotoxic agents.
6. Subject must meet the following criteria as indicated on the clinical laboratory tests*:
    - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × institutional upper limit normal (ULN)
    - Total serum bilirubin ≤ 1.5 × institutional ULN
    - Serum creatinine ≤ 1.5 × institutional ULN or an estimated glomerular filtration rate (eGFR) of > 50 ml/min as calculated by the Modification of Diet in Renal Disease (MDRD) equation.
7. Subject is suitable for oral administration of study drug.
8. Female subject must be either:
    - Of non child bearing potential:
        - post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
        - documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening)
    - Or, if of childbearing potential,
        - must have a negative urine pregnancy test at Screening*, and
        - must use two forms of birth control** (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 180 days after the final study drug administration.
9. Female subject must not be breastfeeding at Screening or during the study period, and for 180 days after the final study drug administration.
10. Female subject must not donate ova starting at Screening and throughout the study period, and for 180 days after the final study drug administration.
11. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control** (one of which must be a barrier method) starting at Screening and continue throughout the study period and for 120 days after the final study drug administration.
12. Male subject must not donate sperm starting at Screening and throughout the study period and for 120 days after the final study drug administration.
13. Subject agrees not to participate in another interventional study while on treatment.

MATE1 Sub-study (Schedule 2E) Subjects Only:

14. Subject has documented FLT3 mutation positive AML (ITD and/or activating point mutations)

*Screening labs and diagnostic tests may be performed at local laboratories to determine eligibility. However, samples will also be submitted for central read.

**Acceptable forms of birth control include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

3.3 Exclusion Criteria

Waivers to the exclusion criteria will NOT be allowed.

Subject will be excluded from participation if any of the following apply:

1. Subject was diagnosed as acute promyelocytic leukemia (APL).
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has active malignant tumors other than AML or Myelodysplastic syndrome (MDS).
4. Subject has persistent nonhematological toxicities of ≥ Grade 2 (CTC AE v4), with symptoms and objective findings, from prior AML treatment (including chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation, or surgery).
5. Subject has had hematopoietic stem cell transplant (HSCT) and meets any of the following:
   - Is within 2 months of transplant from C1D1
   - Has clinically significant graft-versus-host disease requiring treatment
   - Has ≥ Grade 2 persistent non-hematological toxicity related to the transplant

   Donor lymphocytes infusion (DLI) is not permitted ≤ 30 days prior to study registration or during the first cycle of treatment on the study in Cohort 1 and first two cycles of the treatment in Cohort 2.
6. Subject has clinically active central nervous system leukemia.
7. Subject has disseminated intravascular coagulation abnormality (DIC)*.
8. Subject has had major surgery within 4 weeks prior to the first study dose.
9. Subject has had radiation therapy within 4 weeks prior to the first study dose.
10. Subject has congestive heart failure NYHA class 3 or 4, or subject with a history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram performed within 3 months prior to study entry results in a left ventricular ejection fraction that is ≥ 45%*.

11. Subject with mean Fridericia-corrected QT interval (QTcF) > 450 ms at Screening based on central reading.
12. Subject with Long QTc Syndrome at Screening.
13. Subject with hypokalemia and hypomagnesemia at Screening (defined as values below lower limit of normal [LLN]).
14. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of CYP3A4 or of P-glycoprotein (P-gp) or substrates of multidrug and toxin extrusion 1 (MATE 1) with the exception of antibiotics, antifungals, and antivirals that are used as standard of care post-transplant or to prevent or treat infections and other such drugs that are considered absolutely essential for the care of the subject.
15. Subject required treatment with concomitant drugs that target serotonin 5HT1R or 5HT2BR receptors or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
16. Subject has an active uncontrolled infection*.
17. Subject is known to have human immunodeficiency virus infection.
18. Subject has active hepatitis B or C, or other active hepatic disorder*.
19. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation (e.g., ophthalmic conditions such as advanced cataracts, subject is unable to undergo a comprehensive ophthalmologic exam, inability to visualize the fundus).

MATE1 Sub-study (Schedule 2E) Subjects Only:

20. Subject has known severe allergy to penicillins or cephalosporins.
21. Subject was previously treated with ASP2215.

*Screening labs and diagnostic tests may be performed at local laboratories to determine eligibility. However, samples will also be submitted for central read.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

ASP2215 is an oral tablet that is available in a 10 mg tablet or a 100 mg tablet. The tablets are contained within blister cards.

There will be a total of 140 tablets per carton (10 cards per carton and 14 tablets per card). The study site personnel will fill out the sub carton dispensing label to indicate the subject's ASP2215 dose and the corresponding number of tablets that need to be taken each day.

ASP2215 is also available in a 10 mg tablet, 40 mg tablet, and 100 mg tablet. The tablets are contained within 30 count bottles.

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at APGD-AUST or Sponsor's designee in accordance with APGD-AUST or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each blister pack and bottle will bear a label conforming to regulatory guidelines, GMP and local laws and regulations which identifies the contents as investigational drug.

The study centers will be provided cartons containing 10- 2x7 blisters cards. Blistered ASP2215 should be stored between (2°C to 8°C) and protected from light, with excursions in the temperature permitted from (0°C to 15°C). Temperature logs are to be maintained by the site with the storage temperatures recorded daily (at minimum).

Study centers will be provided bottles containing 30 tablets of ASP2215 10 mg, 40 mg or 100 mg. Bottled ASP2215 should be stored at room temperature between 20°C and 25°C (68°F and 77°F) and protected from light in a tight container, with excursions in temperature permitted between 15°C and 30°C (59°F and 86°F).

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator/or designee and

- that such deliveries are recorded,
- that study drug is handled and stored according to labeled storage conditions,
- that study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- that any unused study drug is returned to the Sponsor or destroyed according to Institutional SOPs.

Drug inventory and accountability records for the study drugs will be kept by the investigator/ or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.

- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the Sponsor or designee at the end of the study or upon expiration or destroyed according to Institutional SOPs.

4.4 Blinding

This section is not applicable as this is an open label study.

4.5 Assignment and Allocation

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.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

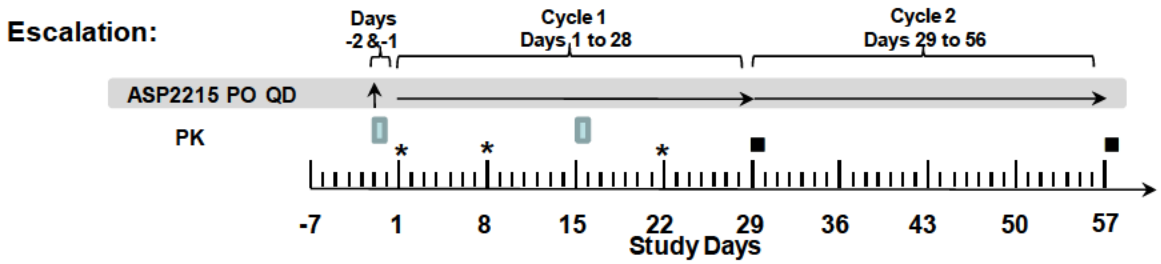
5.1.1 Dose/Dose Regimen and Administration Period

ASP2215 is an oral tablet that subjects will take once daily without food allowed for at least 2 hours before and 1 hour after dosing for continuous 28 day cycles. Subjects will be instructed to take the daily dose with water as close to the same time each morning as possible. ASP2215 will be self administered at home when subjects are not scheduled for clinic visits.

If a subject forgets to take a dose in the morning and it is before 1:00 p.m., they should be instructed to take their dose. If the subject forgets to take their daily dose and it is after 1:00 p.m., they should be instructed to wait for the next morning to dose. If vomiting occurs after dosing, the subject should not receive another dose, but just wait until the next morning to dose.

5.1.1.1 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 in 28 day cycles until disease progression or patient discontinuation.



Dense PK sampling

* C_{trough} + 2 h PK sampling ■ C_{trough} PK sampling

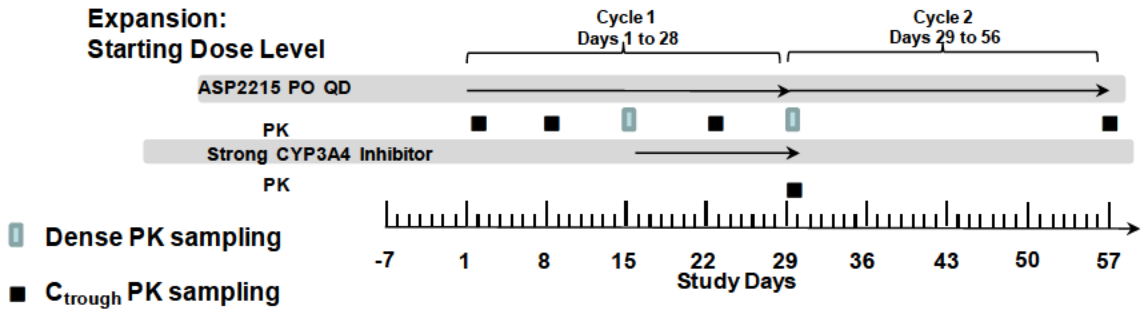
See [Table 2A]: Schedule of Assessments for Dose Escalation Phase (Cohort 1)

5.1.1.2 Expansion Phase (Cohort 2)

During the initial 15 days of treatment in the expansion cohorts with DDI studies [Table 2B Schedule of Assessments with CYP3A4 Inhibitor Voriconazole, Table 2D Schedule of Assessments for Expansion Phase with CYP3A4 Induction and Table 2E Schedule of Assessments for Expansion Phase with MATE1 Substrate Study], moderate or strong CYP3A4 inhibitors are prohibited, unless required for treatment of active infections. DDI studies (Schedules 2B, 2D and 2E) will be conducted in the United States only. European sites whose patients are randomized to the DDI arms of the study will follow Schedule 2C 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 2C even if patients are randomized to Schedule 2B or 2D.

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

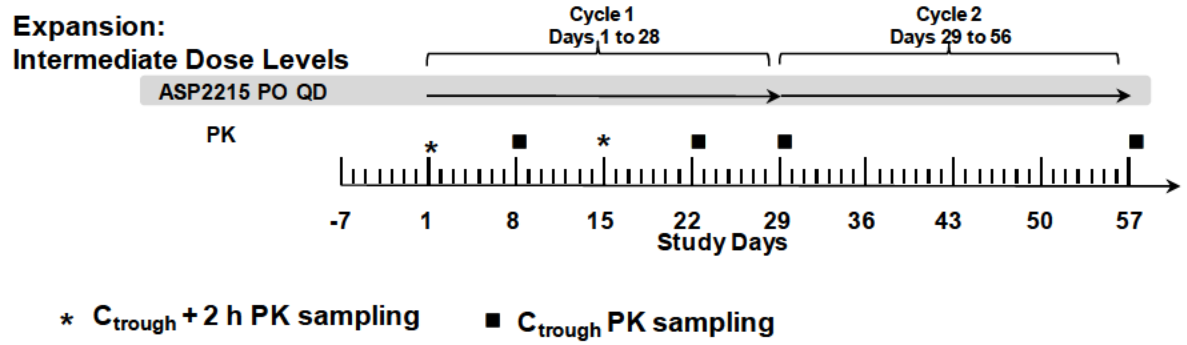
ASP2215 will be administered QD starting on Day 1 of Cycle 1. Starting on Day 16 a strong CYP3A4 inhibitor (voriconazole) will be administered daily at 200 mg every 12 hours through Day 1 of Cycle 2. Voriconazole for use in this trial will be provided by Astellas (15 day supply).



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

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

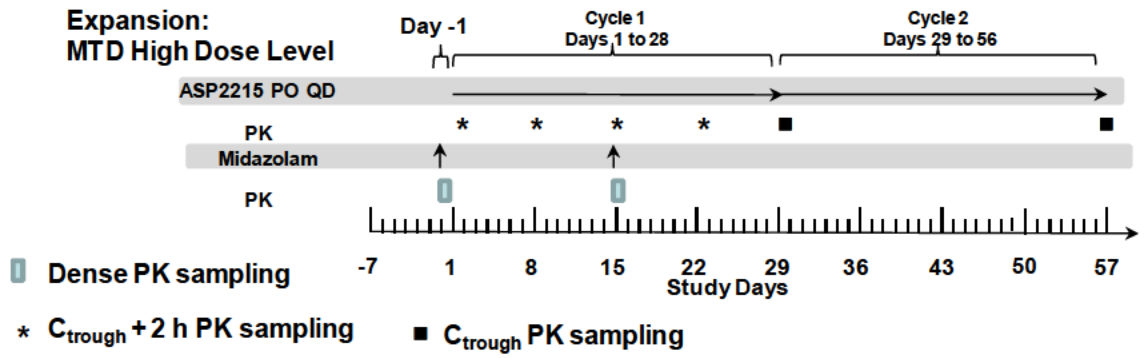
ASP2215 will be administered QD starting on Day 1 of Cycle 1.



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

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

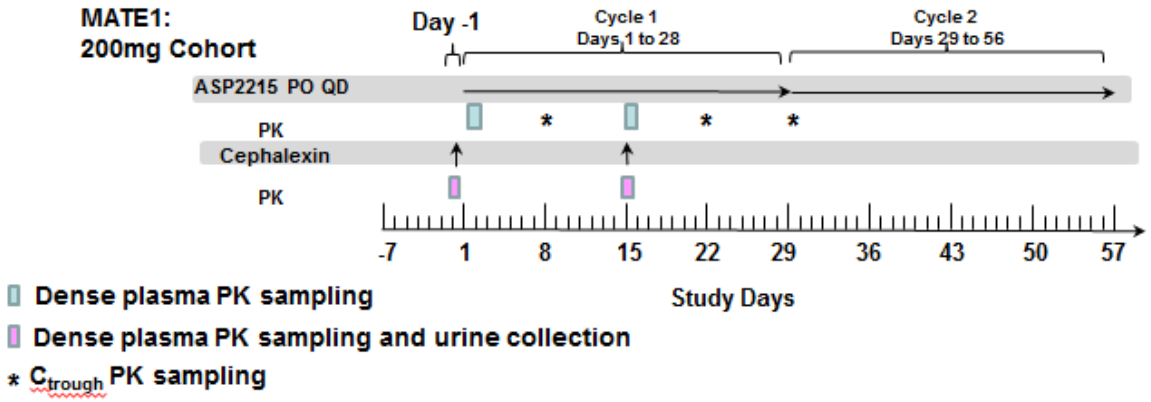
Midazolam (2 mg of syrup (1.0 ml) by mouth) will be administered as a single oral dose on Day -1 and Day 15 of Cycle 1. ASP2215 will be administered QD starting on Day 1 of Cycle 1. Midazolam for use in this trial will be provided by Astellas.



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

5.1.1.2.4 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 2E: Schedule of Assessments for Expansion Phase with MATE1 Substrate Study (Cohort 2, MATE1 Sub-study)

All subjects will be assessed for toxicities before being allowed to continue to subsequent cycles.

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

Guidelines for ASP2215 dose reduction are provided in Table 6

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 5 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 6 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.
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 7

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 5 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 7 Guidelines for ASP2215 Dose Escalation Event

Cohort 1 (Dose escalation cohort)	
No CRc (CR. CRp or CRi) after Cycle 1	Patients on 20 mg, 30 mg 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 5

If dose escalated as per Table 8, 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

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

All medications and concomitant treatments administered from 28 days prior to Cycle 1 Day 1 through the end of treatment visit must be recorded in the CRF. Documentation will include the medication name, indication, dose and dates of administration. Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited. Treatment with concomitant drugs that are strong inhibitors or inducers of P-gp and concomitant drugs that target serotonin $5HT_1R$ or $5HT_{2B}R$ or sigma nonspecific receptor are to be avoided with the exception of drugs

that are considered absolutely essential for the care of the subject. Treatment with concomitant drugs that are strong inhibotrs of CYP3A whould be avoided with with the exception of antibiotics, antifungals, and antivirals that are used as standard of care post-transplant or to prevent or treat infections. If CYP3A inhibitors are used comcomitantly, subjects should be closely monitored for AEs.

Precaution should be used in treatment of ASP2215 with concomitant drugs that are substrates of BCRP, since thetransporter has been shown to be inhibited by A2215 in *in vitro* studies.

Common CYP3A inhibitors, CYP3A inducers, drugs targeting the serotonin receptor P-gp inhibitors or inducers and drugs known to prolong QT or QTc intervals are listed [Appendix 12.1]. The investigator should consult individual labels for all drugs that the subject is taking to evaluate if they fall into any of the above named categories. For concomitant drugs that have the potential to prolong QT or QTc intervals, a cardiology consult should be obtained as medically indicated. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215 with the exception of hydroxyurea up to 5 g daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L, prophylactic intrathecal chemotherapy or cranial irradiation. Participation in another interventional study while on treatment is prohibited.

Refer to [Appendix 12.1 List of Excluded and Cautionary Concomitant Medications

During the initial 15 days of treatment in expansion cohorts with DDI studies [Table 2B Schedule of Assessments with CYP3A4 Inhibitor Voriconazole, Table 2D Schedule of Assessments for Expansion Phase with CYP3A4 Induction, and Table 2E Schedule of Assessments for Expansion Phase with MATE1 Substrate Study], moderate or strong CYP3A inhibitors are prohibited, unless required for treatment of active infections. Common CYP3A Inhibitors and CYP3A Inducers are listed in Appendix 12.1. In addition, during the initial 15 days of treatment for subjects assigned to Schedule 2E MATE1 substrates are prohibited. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215 with the the following exceptions:

- hydroxyurea up to 5 gm daily for up to 2 weeks to keep the absolute blast count below 50,000.
- HSCT for patients with CRc or PR
- Intrathecal Chemotherapy used as prophylaxis.

Please see Section 5.1.4 for additional information on HSCT.

5.1.4 Resumption of treatment after Hematopoietic Stem Cell Transplantation (HSCT)

Subjects who achieve a CRc or PR can undergo HSCT without leaving the study. However, ASP2215 should be stopped and an End of Treatment visit should be performed prior to starting the conditioning regimen for HSCT. ASP2215 can be resumed after stem cell transplantation if the following conditions are met:

- Subject is between 30 – 60 days post HSCT
- Subject has had successful engraftment as demonstrated by ANC $\geq 500/mm^3$ and platelets $\geq 20{,}000/mm^3$ without transfusions.
- Subject does not have Grade ≥ 2 acute GVHD
- Subject is in CRc

For subjects resuming treatment, subjects will follow the procedures listed under Subsequent Cycles Day 1 in the Schedule of Assessments.

5.1.5 Treatment Compliance

The dose and schedule of ASP2215 and CYP3A4 inhibitor administered to each subject will be recorded on the appropriate form at every cycle. Reasons for dose delay, reduction or omission will also be recorded. This information, plus tablet accountability for ASP2215 at every cycle will be used to assess compliance with the treatment.

Treatment compliance should be monitored closely and deviations in compliance should be reported to the Sponsor except in cases where directed by protocol or Principal Investigator (e.g., account for dose interruptions, adjustments, etc).

Any subjects that have been off treatment for more than 15 days other than for HSCT or study drug related AE, can only resume treatment after discussion with the medical monitor.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected for all subjects and will include initials, date of birth, sex, race and ethnicity.

5.2.2 Medical History

Medical history includes all significant medical conditions other than AML that have resolved prior to informed consent. Conditions that are ongoing at the time of consent will be collected on the Medical History eCRF. Details that will be collected include the onset date and recovery date and CTC grade, if applicable for ongoing conditions.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

AML diagnosis and studies related to AML subtype classification will be collected and will include date and method of diagnosis, bone marrow evaluations, histopathology, cytogenetics, immunophenotyping and cytochemistry, FLT3 mutation status performed using institutional assay, lumbar puncture results if performed (RBC, WBC and differential, cytospin results), and related genetic syndromes. Dates for diagnostic procedures will be collected.

5.2.4 Performance Status

The ECOG Scale [Oken, 1982] will be used to assess performance status.

Table 8 COG Performance Status

Grade	Description

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

5.3 Efficacy | Pharmacodynamics | Pharmacokinetics | Immunogenicity Assessment

5.3.1 Response Definitions

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

5.3.1.1 Composite Complete Remission Rate (CRc)

Defined as the confirmed remission rate of all complete and incomplete CRs (i.e., CR+ CRp + Cri).

5.3.1.2 Complete Remission (CR)

For subjects to be classified as being in CR, 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 week without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia.

5.3.1.3 Complete Remission with Incomplete Platelet Recovery (CRp)

For subjects to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery (< 100 × 10^9/L).

5.3.1.4 Complete Remission with Incomplete Hematological Recovery (CRi)

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

5.3.1.5 Partial Remission (PR)

For subjects to be classified as being in PR, 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%.

5.3.1.6 Relapse

Relapse after CR, CRp or CRi is defined as a reappearance of leukemic blasts in the peripheral blood 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.

5.3.1.7 Best Response

Best response is defined as the best measured response (CR, CRp, CRi, or PR) post-treatment.

Two best responses, up to the time of 2 cycles of treatment period and the End of Treatment Visit will be defined.

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), radial pulse rate (beats/minute), and temperature will be obtained and recorded at the times specified in the Schedule of Assessments. All vital sign measures will be obtained with the subject in the sitting or supine position.

If clinically significant vital sign changes from baseline (pretreatment) are noted, the changes will be documented as AEs on the Adverse Event page of the CRF. Clinical significance will be defined as a variation in vital signs, which has medical relevance that could result in an alteration in medical care. The Investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the baseline (pretreatment) value, or until the Investigator determines that follow up is no longer medically necessary.

5.4.2 Adverse Events

Adverse event collection will begin from time of informed consent and continue through the 30 Day Follow-Up visit. Adverse events will be documented at each clinic visit, but can be collected at any time. Any adverse event that meets the definition of an SAE will also be reported on a separate form to the Sponsor. See Section 5.5 Adverse Events and Other Safety Aspects for information regarding adverse event collection and data handling.

5.4.2.1 Adverse Events during HSCT

Adverse event collection will continue during HSCT for subjects who remain on study.

5.4.2.2 Adverse Events of Possible Hepatic Origin

See Appendix 12.2 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed centrally during the conduct of the study. Refer to the Schedule of Assessments for study visit collection dates.

Additional laboratory tests should be performed according to institutional standard of care. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/or delegated sub-investigator who is a qualified physician.

Panel/Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Hematology	3 mL into ethylenediaminetetraacetic 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
Chemistry	10 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
Chemistry	10 mL into Serum tube	Liver Function Tests including: • Bilirubin Total (TBL) • Alanine Aminotransferase (ALT) • Aspartate Aminotransferase (AST) Thyroid function tests including: • TSH • Free T4
Serum Pregnancy Test	1 mL Serum or urine**	HCG
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)
Table continued on next page		

Panel/Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Urinalysis	Dipstick	Color Appearance Specific Gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen
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
PK	4 mL into K2 EDTA	ASP2215 Cephalexin (MATE1 cohort)
PIA (except for Schedule 2E)	4 mL of heparinized plasma	FLT3 inhibition (PIA)
Phosphorylation of FLT3, S6 and AXL (except for Schedule 2E)	10 mL of heparinized whole blood	Phosphorylation of FLT3 Phosphorylation of AXL Phosphorylation of S6

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

**Please refer to Schedule of Assessments.

5.4.4 Physical Examination

Standard, full physical examinations will be performed to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, and lymphatic systems. Genitourinary and rectal system exam are to be performed only if clinically indicated. Physical examinations will be conducted at visits as outlined in the Schedule of Assessments. Each physical examination will include the observation and review of body system, weight at Screening and on D1 of each cycle, height is only required at Screening. If clinically significant worsening of findings from predose (Day 1) is noted at any study visit, the changes will be documented as AEs on the Adverse-Event page of the CRF. Clinical significance is defined as any variation in physical findings, which has medical relevance that could result in an alteration in medical care. The Investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the baseline (pretreatment) condition, or until the Investigator determines that follow up is no longer medically necessary.

5.4.5 Electrocardiogram (ECG)

ECGs will be conducted at visits as outlined in the Schedule of Assessments. 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 taken within ± 0.5 hours of nominal time. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs at least 5 minutes apart per timepoint) and transmitted electronically for central reading.

ECGs should be obtained after the subject has rested quietly and is awake in a fully supine position (or semi-recumbent, if supine not tolerated) for 10 minutes before the first ECG from a triplicate. Whenever a study procedure coincides with the scheduled timepoint for an ECG triplicate, the study activities will ideally be undertaken in a fixed sequence: ECG triplicate first, vital signs (blood pressure and heart rate) second, and any type of blood draw as the last assessment. This order of events can be changed if required in order to accommodate PK time points and is not mandatory.

The mean QTcF of the triplicate ECG tracings based on central reading will be used for all treatment decisions. 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 Cycle 1 Day 1 to Cycle 1 Day 8 has increased > 30 ms with no other known etiology, based on the central read ECG. 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 central read ECG will be received on 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

5.4.6 Ophthalmologic Exam

Ophthalmologic examinations will be conducted at visits as outlined in the Schedule of Assessments. The following tests and exams are required at every visit:

- Visual Acuity (VA): Best-corrected visual acuity (BCVA) as per ETDRS or Snellen charts
- Slit lamp examination
- Ophthalmoscopy
- Visual fields: Automated threshold visual fields, Humphrey 24-2. SITA Fast or Standard
- Optical coherence tomography (OCT)

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the (e)CRF accordingly.

5.5.2 Definition of Serious Adverse Events (SAEs)

An adverse event is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity,

should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

All of the events of interest noted above should be recorded on the (e)CRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' and the SAE worksheet.

The Sponsor has a list of events that they classify as "always serious" events. If an adverse event is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	**Criteria for causal relationship**
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.5.5 Reporting of Serious Adverse Events (SAEs)

SAE collection will begin from time of informed consent through 30 after last dose of study medication. In the case of a serious adverse event (SAE), the investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor/delegated CRO by fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel. Please fax or e-mail the SAE Worksheet to:

Astellas Pharma Global Development
Global Pharmacovigilance
North American Fax number: 888-396-3750
(North America Alternate Fax: 847-317-1241)
International Fax number: +44 800 471 5263
Email: safety-us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee [Section II Contact Details of Key Sponsor’s Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification.

Full details of the SAE should be recorded on the medical records and on the (e)CRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e., IND Safety Reports) to the regulatory agencies (i.e., FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e., EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor/delegated CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements of the IRB.

The heads of the study sites/investigators should provide written documentation of IRB notification for each report to the Sponsor.

The investigators should provide written documentation of IRB notification for each report to the Sponsor.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the adverse event progresses to an ″SAE″, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to Appendix 12.2 Liver Safety Monitoring and Assessment for detailed instructions on Drug Induced Liver Injury (DILI).

5.5.7 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in Appendix 12.3 Common Serious Adverse Events for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common serious adverse events” as specified in Appendix 12.3 Common Serious Adverse Events. The Sponsor will monitor these events throughout the course of the

study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.5.5 Reporting of Serious Adverse Events.

5.5.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 120 days from the discontinuation of dosing, the investigator should report the information to the Sponsor/delegated CRO as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the Sponsor as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected ASP2215 overdose, the subject should receive supportive care and monitoring. The Medical Monitor/Expert should be contacted as applicable.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

Plasma concentrations of ASP2215 will be evaluated for the escalation and expansion phases as outlined in Schedule of Assessments. For each sample 4 mL of blood will be collected and processed. For the expansion phase with CYP3A4 inhibitor (Cohort 2 initial starting dose level) plasma concentration of CYP3A4 inhibitor will be evaluated as outlined in the schedule of assessments (single 4 mL blood sample, predose Cycle 2 Day 1). For the expansion phase with Midazolam (Cohort 2 MTD) plasma concentration of Midazolam and 1-hydroxy midazolam (metabolite, if possible) will be evaluated as outlined in the Schedule of Assessments (4 mL blood sample collected at each time point). For the expansion phase with MATE1 substrate, plasma and urine concentration of cephalexin will be evaluated as outlined in the Schedule of Assessments [Table 2E] (4 mL blood sample and 6 mL urine sample collected at each time point).

Plasma samples may also be used for metabolite profiling of ASP2215. The reports for the metabolite profiling and identification will not be incorporated to the clinical study report.

Blood sampling, processing, storage and shipment instructions will be provided in the Lab manual. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory. Please refer to the Lab Manual for more detailed information on this topic.

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) 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, 1and 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 3 +: Day 1	Pre-dose (0.5 hours before drug administration)
CYP3A4 Inhibitor Voriconazole	
Cycle 2: Day 1	Pre-dose (0.5 hours before drug administration)
Table continued on next page	

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.

5.7 Other Measurements, Assessments or Methods

5.7.1 Pharmacodynamics

Excluding Schedule 2E, phosphorylation of FLT3, AXL and S6 will be evaluated to assess the percent inhibition of phosphorylation with samples collected as described in the Schedule of Assessments in the escalation and expansion phases (4 mL blood for each sample).

Excluding Schedule 2E, plasma inhibition assay (PIA) will be conducted from blood samples as described in the Schedule of Assessments in the escalation and expansion phases (4 mL blood for each sample).

Blood sampling, processing, storage and shipment instructions will be provided in the lab manual. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory. Please refer to the Lab Manual for more detailed information on this topic.

5.7.2 Samples for Exploratory Analyses

5.7.3 Sample for the Pharmacogenomics Sub-study (Optional)

An optional PGx research sub- study will be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. Germline DNA isolated from buccal swabs will be collected at screening and evaluated for genetic mechanisms underlying treatment response, pharmacokinetics, and safety endpoints. A sponsor-designated laboratory will perform the analyses.

Samples will be shipped to a Sponsor designated banking CRO.

Labels should uniquely identify each sample and contain at least:

- Protocol number 2215-CL-0101,
- Subject number, and
- Purpose and biological matrix (i.e., “biobanking”, “buccal swab”).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See Appendix 12.4, Retrospective PGx Sub-study for further details on the banking procedures.

5.8 Total Amount of Blood

The total amount of blood collected for study assessments for each subject will vary depending on how long they stay on treatment.

At any time during the study, if any laboratory abnormalities are found for a subject, for disease assessment, institutional monitoring for donor chimerism, and GVHD assessment, additional blood may be drawn for monitoring.

Additional blood beyond standard monitoring that will be drawn for this study will include draws for eligibility assessment, hematology, chemistry, coagulation, and pregnancy test at specific study defined time points, pharmacokinetics, and bioanalytical sampling.

The maximum amount of blood collected for study specific assessments within 24 hours is during the Dose Escalation Phase (Cohort 1) between Day -2 and Day -1 when approximately 64 mL of blood will be drawn.

The maximum amount of blood collected that is in addition to standard of care over any one month period is from Screening through Cycle 1 where approximately 272 mL will be drawn.

Total blood volumes (PK, pFLT+pAXL+pS6 and PIA) collected include:

- Table 2A Dose Escalation : Cycle 1 = 272 mL; Cycle 2 = 41 mL; additional cycles 19 mL/visit
- Table 2B Expansion CYP3A4 Inhibitor: Cycle 1 = 174 mL; ; Cycle 2 = 69 mL; additional cycles 19 mL/visit
- Table 2C Expansion without DDI: Cycle 1 = 158 mL; Cycle 2 = 41 mL; additional cycles 19 mL/visit
- Table 2D Expansion CYP3A4 Induction: Cycle 1 = 228 mL; Cycle 2 = 41 mL; additional cycles 19 mL/visit
- Table 2E Expansion MATE1 Substrate: Cycle 1 = 196 mL; Cycle 2 = 33 mL; additional cycles 19 mL/visit

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will

attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Discontinuation Criteria from Treatment for Individual Subjects:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is non-compliant with the protocol based on the Investigator or Medical Monitor assessment.
- Subject is found to have significantly deviated from any one of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit and no DLT may be kept in the study after discussion with the medical monitor).
- Subject develops an unacceptable study drug-related toxicity (DLT) or SAE requiring discontinuation of treatment.
- Subject will be taken off treatment if there is no PR or CRc and the subject, in the opinion of the Investigator, is no longer deriving clinical benefit after 2 cycles of therapy
- ASP2215 dose is interrupted for greater than 15 days. Subjects may be allowed to continue treatment after discussions with the medical monitor if the interruption was not due to an ASP2215 related adverse event.
- Investigator/sub-investigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- Death

The subject will be discontinued from the post treatment period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent).
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- More than 3 years has passed from the End of Treatment Visit.
- Death

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD-US. The Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be detailed in the Clinical Study Report (CSR).

Prior to Database 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 lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 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.

7.2 Analysis Set

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

7.2.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who are enrolled and receive at least one dose of study drug and who have at least one post-treatment data point. This will be the primary analysis set for efficacy analyses.

7.2.2 Per Protocol Set (PPS)

The per protocol set will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant non-adherence to the protocol and will be defined in the SAP. The PPS will be a secondary analysis set for efficacy analyses.

7.2.3 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who took at least one dose of study medication, and will be used for safety analyses.

7.2.4 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF population for which sufficient plasma concentration data is 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 in the Classification Specifications and determined the Classification Meeting.

7.2.5 Pharmacodynamic Analysis Set (PDAS)

The pharmacodynamic analysis set (PDAS) will include the subjects from the SAF population for whom sufficient pharmacodynamic measurements were collected The PDAS will be used for all analyses of pharmacodynamic data.

7.3 Demographics and Other Baseline Characteristics

7.3.1 Demographics

Demographics and other baseline characteristics will be summarized by cohort and dose for the SAF. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

7.3.2 Medical History

A detailed medical history for each subject will be obtained during screening period and will be summarized by cohort and dose levels for the SAF.

7.3.3 Disease History

Each subject's complete cancer history will be listed. The number and percentage of subjects will be used to summarize the AML subtype, FLT3, C-CBL, and AXL mutation status and allelic ratio.

7.3.4 Previous and Concomitant Medications

The frequency of concomitant medications (prescription, over-the-counter, and nutritional supplements) will be summarized by cohort, dose and preferred term for SAF. Medications will be coded using the WHO drug dictionary. Medications will be counted by the number of subjects who took each medication. A subject taking the same medication multiple times will only be counted once for that medication. Medications will be presented in decreasing order of frequency based on the total number of subjects who took each medication.

7.3.5 Subject Disposition

The number and percentage of all subjects during the study will be reported by cohort and dose for enrollment, study drug administration, subject completion, premature discontinuation, and major protocol violations.

7.3.6 Treatment Compliance

Treatment compliance is defined as the total number of study drug actually taken by the subject divided by the number of study drug expected to be taken during the study multiplied by 100. Descriptive statistics for study drug compliance will be presented by cohort and dose for the entire study period for the SAF by cohort and dose.

7.3.7 Extent of Exposure

Exposure to treatment, measured by the duration of treatment in number of days will be summarized by treatment on SAF. Duration of exposure to a study drug is defined as: (the last date that subject took study drug – the first dose date + 1). Any duration of dose interruptions will be excluded from the exposure. The total dose administered, number of dose reductions, number of dose escalations, number and proportion of subjects with dose reduction and dose escalation will be tabulated.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS in which FAS will be considered as primary and PPS as supportive.

7.4.1 Analysis of Efficacy Variables

Complete remission (CR) rate, composite complete remission rate, overall response rate, duration of confirmed response, disease-free survival (DFS), event free survival (EFS) and overall survival (OS), will be summarized using descriptive statistics. The survival curve and median for time-to-event variables will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval.

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

7.5 Analysis of Safety

Safety analyses will consist of data summaries of AEs, DLTs, and other safety parameters. Safety analyses will be performed on the SAF.

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 cohort as described in the Study Design Overview section [Section 2]. A 2-parameter Bayesian logistic regression will be used to model the dose-toxicity relationship on DLT. Subjects in either dose escalation cohort or dose expansion cohorts 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 procedures 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 Cohort 2 Dose Expansion Cohort

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 cohort (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 (ITD or activating point mutations) are enrolled into 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.

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

Further Expansion for Efficacy Evaluation

To improve guidance for Recommended Phase 2 Dose, 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 Cohort 2 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. A minimum of 42 evaluable (receive 2 cycles of treatment or discontinue for progressive disease) FLT3 mutated patients will be enrolled.

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
34	10
37	11

Subject Assignment in Cohort 2 MATE1 Sub-study Dose Expansion Cohort:

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 and 40 mg tablets will be used.

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 2.2.1. DLT will be summarized by cohort and dose for SAF.

7.5.4 Adverse Events

All adverse events recorded on treatment including within 30 days from the last study treatment will be summarized. AEs will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 14.1) and will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03.

The number and percent of subjects experiencing 1 or more AE(s) will be summarized by cohort, dose, SOC, and PT. The number and percentage of subjects with at least one Grade 3 or higher AE will be summarized by dose, SOC, and PT.

Distribution of the maximum severity (grade) and treatment-related AEs will be summarized by cohort, dose, SOC, and PT. Distribution of serious adverse events (SAEs), discontinuations due to AE, and deaths on study will be presented for each treatment.

Additional summary tables will be generated for the following population subsets: subjects with SAEs including deaths, subjects who discontinue due to AEs and investigator-attributed relationship to study drug for AEs and SAEs.

All summaries of AEs will include only treatment-emergent events unless otherwise stated. Listings of AEs, SAEs, deaths, and withdrawals due to adverse events will be presented.

AEs and SAEs reported during HSCT while off ASP2215 as well as before resumption of ASP2215 will be summarized and listed separately.

7.5.5 Laboratory Assessments

Clinical laboratory evaluations (including hematology, urinalysis, serum chemistry, and coagulation) and their changes from baseline will be summarized by treatment using descriptive statistics. Clinically significant abnormalities in laboratory values will be presented for each treatment. Shift tables will present shift from baseline to worst grade for selected variables using the NCI-CTCAE grade and lab reference range indicator. Frequency of subjects with laboratory values outside normal range will be generated in addition to tabulation of worst toxicity grade.

7.5.6 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by cohort and dose and time.

7.5.7 Physical Examination

Physical examinations will be listed by treatment group. All clinically significant abnormal findings will be recorded as medical history, baseline conditions, or adverse events and graded using NCI-CTCAE guidelines.

7.5.8 ECGs

The 12-lead ECG results will be summarized by treatment group and time point. Overall ECG interpretation will be summarized for each time point. A shift analysis table showing shifts from baseline in overall ECG (normal, abnormal not clinically significant, and abnormal clinically significant) will be provided. ECG parameters and their change from baseline will be summarized by cohort and dose using descriptive statistics.

7.5.9 Ophthalmologic Assessment

Ophthalmologic variables will be summarized by dose level at each visit for each eye.

7.6 Analysis of Pharmacokinetics

Plasma concentrations and PK parameters will be summarized by cohort using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) of the mean and geometric mean). Time-course of drug concentrations will be plotted as appropriate.

7.6.1 Estimation of Pharmacokinetic Parameters

Subjects with sufficient PK samples will have PK parameter estimates for ASP2215 including calculation of AUC_{24}, C_{max}, C_{trough} and t_{max} using standard NCA.

For subjects in the midazolam expansion cohort, those subjects with sufficient PK samples will have PK parameter estimates for midazolam (pre and post ASP2215 administration) and

1-hydroxy midazolam (metabolite, if possible) including calculation of AUC_{24}, C_{max}, C_{trough} and t_{max} using standard NCA.

For subjects in CYP3A4 inhibitor expansion group, the PK parameters for ASP2215 will be summarized by pre and post CYP3A4 inhibitor administration.

For subjects in the MATE1 expansion cohort, those subjects with sufficient PK samples will have PK parameter estimates for cephalexin (pre and post ASP2215 administration) including calculation of AUC, C_{max}, C_{trough} and t_{max} using standard NCA. In addition, urinary PK parameters of amount of drug excreted in urine (Ae), fraction of drug excreted into urine in % (Ae[%]) and renal clearance (CL_R) of cephalexin will be calculated.

7.6.2 Concentration-Response Relationship Analysis

Pharmacokinetic dose proportionality will be assessed.

7.7 Analysis of Pharmacodynamics

Percent inhibition of phosphorylation of FLT3, S6 and AXL as compared to baseline sampling will be summarized at each time point by cohort (except for Schedule 2E).

Plasma inhibitory assay as compared to baseline sampling will be summarized at each time point by cohort (except for Schedule 2E).

7.8 Protocol Deviations and Other Analyses

Protocol deviations as defined in Section 8.1.6. Protocol Deviations will be summarized for all randomized subjects by treatment group and total as well as by site. 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.

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

No formal interim analysis is planned.

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

Imputation methods for missing data, if applicable, and the definitions for windows to be used for analyses by visit will be outlined in the SAP.

7.11 Analysis of Re-Enrolled Subjects

The statistical handling of Re-Enrolled subjects will be defined in the Statistical Analysis Plan. Safety and efficacy information of the Re-Enrolled subjects will be summarized separately.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 10 days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at central laboratories. Laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

ECG results are performed at a central ECG reading, ERT. Central ECG read data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The central ECG laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and Adverse Events will be collected in the eCRF.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents

[Section 8.1.2] when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science of the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. (e)CRF completion will be described in the (e)CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding one year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies, or for APEB/APEL-sponsored studies within one year after last subject out (LSO) or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The Sponsor will notify the site/investigator if the NDA is approved or if the IND is discontinued. The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the CRFs supplied for each subject.

The investigator and sponsor will mutually agree upon the storage format for the retention of electronic data.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments.

Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Other Evaluation Committee(s)

Not applicable.

10.2 Other Study Organization- Dose Escalation Committee

The Dose Escalation Committee will be responsible for the review of safety data at specified time points in order to provide an assessment of whether dose escalation or reduction should occur within the next cohort and/or to determine when maximum tolerated dose has been reached in a given dose level. At each meeting, individual subject data will be reviewed for dose escalation decisions. Additional details regarding responsibilities and membership requirements will be included in the Subject Enrollment and Dose Escalation Plan.

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Yanada M, Matsuo K, Suzuki T, Kiyoi H, Naoe T. Prognostic significance of FLT3 internal tandem duplication and tyrosine kinase domain mutations for acute myeloid leukemia: a meta-analysis. Leukemia 2005;19(8):1345-9.

Yonezawa & Inui, 2011, Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacol. 2011 Dec; 164(7): 1817–1825.

12 APPENDICES

12.1 List of Excluded Concomitant Medications

The following lists describe medications and foods which are common inhibitors of CYP3A. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A.

CYP3A Inhibitors

Drug Type	Generic Drug Name
Human Immunodeficiency Virus Protease Inhibitors	Indinavir Nelfinavir Lopinavir/ritonavir Ritonavir Saquinavir
Food/Juice	grapefruit juice
Others	Boceprevir Clarithromycin Conivaptan Itraconazole Ketoconazole Nefazodone Posaconazole Telaprevir Telithromycin Voriconazole

The following lists describe medications and foods which are common strong inducers of CYP3A. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A.

CYP3A Inducers

Drug Type	Generic Drug Name
Antiepileptic, Anticonvulsant	Carbamazepine Phenytoin
Antibiotic	Rifampicin
Food/Juice Supplement	St. John's Wort

The following lists describe medications which target Serotonin Receptors. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound targets serotonin receptors.

Drugs Targeting Serotonin Receptor

Drug Type	**Generic Drug Name**
Affinity or function to 5HT2BR	Eletriptan Hydrobromide
Affinity or function to 5HT1R	**Drugs** Almotriptan Malate Aripiprazole Avitriptan Buspirone Hydrochloride Dihydroergotamine Mesylate Droperidol Eletriptan Hydrobromide Ergoloid Mesylates Ergonovine Maleate Ergotamine Tartrate Frovatriptan Succinate Haloperidol Decanoate Lesopitron Methylergonovine Maleate Methylergotamine Methysergide Maleate Naratriptan Hydrochloride Pizotifen Quetiapine Fumarate Rizatriptan Benzoate Sumatriptan Succinate Tegaserod Maleate Thioridazine Hydrochloride Ziprasidone Hydrochloride Ziprasidone Mesylate Zolmitriptan Zotepine

The following lists describe medications and foods which are common inhibitors or inducers of P-gp. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit or induce P-gp.

P-gp Inhibitors or Inducers

Transporter	Gene	Inhibitor	Inducer
P-gp	*ABCB1*	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir

Source: Table 12
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#major

The following list describes substrates of MATE1. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound is a substrate of MATE1.

MATE1 Substrate	
Transporter	**Substrate**
MATE1	cephalexin cephradine fexofenadine

MATE1: multidrug and toxin extrusion 1
Source: Yonezawa & Inui, 2011

Drugs targeting Sigma (nonspecific) Receptor (sigma R)

No list of drugs that target sigma nonspecific receptor is provided. Please consult individual drug labels for specific information on whether a compound targets sigma nonspecific receptors.

Drugs That May Prolong QT or QTc

The following list describes drugs that are known to prolong QT or QTc. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound is known to prolong QT or QTc.

Drug Type	**Generic Drug Name**
Class IA antiarrhythmics	Quinidine Procainamide Disopyramide
Class IC antiarrhythmics	Flecainide Propafenone Moricizine
Class III antiarrhythmics	Amiodarone Sotalol Bretylium Ibutilide Dofetilide
Antipsychotics	Thioridazine Mesoridazine Chlorpromazine Prochlorperazine Trifluoperazine Fluphenazine Perphenazine Pimozide Risperidone Ziprasadone Lithium Haloperidol
Tricyclic/tetracyclic antidepressants	Amitriptyline Desipramine Doxepin Dosulepin hydrochloride Imipramine Maprotiline
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) antidepressants	Venlafaxine
Macrolide antibiotics	Azithromycin Erythromycin Clarithromycin Dirithromycin Roxithromycin Tulathromycin
Fluoroquinolone antibiotics	Moxifloxacin Gatifloxacin
Table continued on next page	

Drug Type	**Generic Drug Name**
Azole antifungals	Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole
Antimalarials	Amodiaquine Atovaquone Chloroquine Doxycycline Halofantrine Mefloquine Proguanil Primaquine Pyrimethamine Quinine Sulphadoxine
Antiprotozoals	Pentamidine
Antiemetics	Droperidol Dolasetron Granisetron Ondansetron
Antiestrogens	Tamoxifen
Immunosuppressants	Tacrolimus

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases), or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN (in patients without liver metastases), > 5 x ULN (in patients with liver metastases)	or	> 2 x ULN
Severe*	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study or appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as a Serious Adverse Event (SAE). The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - acute viral hepatitis (A, B, C, D, E or other infectious agents).
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR, direct bilirubin
  - Consider gastroenterology or hepatology consultations.
  - Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, pre-existing or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in patients with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant)." The two "requirements" for Hy's Law are: 1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome.

References

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006:15:241-3.

12.3 Common Serious Adverse Events

The following is a list of serious adverse events that the Sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations or prevent the need to report an adverse event meeting the definition of an SAE as detailed in Section 5.5.2 Definition of Serious Adverse Event (SAE). The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". You are required to follow the requirements detailed in Section 5.5.5 Reporting of Serious Adverse Events (SAE).

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

Serious Adverse Events Caused by AML	**Grades usually observed with AML**
HEMATOLOGIC AE	
Anemia	0-4
Bone marrow hypocellular	0-4
CD4 lymphocytes decreased	0-4
Disseminated Intravascular Coagulation	0-3
Leukocytosis	0-4
Lymphocyte count decreased	0-4
Lymphocyte count increased	0-4
Neutropenia	0-4
Neutrophil count decreased	0-4
Platelet count decreased	0-4
Purpura	0-3
Thrombocytopenia	0-4
White blood cell decreased	0-4
INFECTION-RELATED AE	
Bacterial infection (regardless of organ-system involved or specific bacterial cause)	0-3
Chills	0-3
Cough	0-3
Febrile neutropenia (without infection)	0-4
Fever	0-5
Flu-like symptoms	0-3
Fungal infections (regardless of organ-system involved or fungal cause)	0-3
Mucositis	0-4
Periodontal disease	0-3
Pneumonia	0-5
Sepsis/septicemia/bacteremia (all causes)	0-5
Sinusitis	0-4
Sore throat	0-3
Table continued on next page	

Serious Adverse Events Caused by AML	**Grades usually observed with AML**
PSYCHIATRIC AND NERVOUS SYSTEM RELATED AE	
Anxiety	0-2
Cognitive disturbance	0-3
Confusion	0-5
Depressed level of consciousness	0-5
Depression	0-3
Libido decreased	0-2
Meningismus	0-5
Seizure	0-5
Somnolence	0-5
Syncope	3
OTHER AE	
Activated partial thromboplastin time prolonged	0-2
Alanine aminotransferase increased	0-2
Alkaline phosphatase increased	0-2
Anorexia	0-2
Aspartate aminotransferase increased	0-2
Blood bilirubin increased	0-2
Bone and/or joint pain	0-2
Bruising	0-2
Bleeding/hemorrhage	0-5
Diarrhea	0-2
Dyspnea	0-5
Fatigue	0-3
Flushing	0-2
Gamma-glutamyltransferase increased	0-1
GVHD - Acute and Chronic	0-2
Hypertrophied gums	0-1
Hyperuricemia	0-1
Hypokalemia	0-2
Hypotension	0-2
Hypoxia	0-3
INR increased	0-1
Lactate dehydrogenase increased	0-2
Malaise	0-2
Multi-organ failure	0-5
Nausea	0-2
Oral dysesthesia	0-2
Petichiae	0-2
Pruritus	0-3
Skin and subcutaneous tissue disorders	0-3
Transient ischemic attacks	0-2
Tumor Lysis Syndrome	3-5
Vasculitis	0-5
Vomiting	0-2
Weight loss	0-2

12.4 Retrospective PGx Sub-Study

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by one or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired buccal swab samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide separate written consent prior to providing any buccal swab samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide a buccal swab per vendor preparation instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

BANKING CRO STORAGE AND SAMPLE CODING

Once received at the banking CRO, the samples will be assigned a unique sample code (second code) and stored frozen. A table linking the subject number (first code) with the newly-assigned sample code (second code) will be kept by the banking CRO. PGx analysis will be conducted using the second code only.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and / or safety. Prior to initiating any analysis on the banked samples, the Astellas ethical committee (AREC) must approve the analysis plan.

DISPOSAL OF PGx SAMPLES / DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 11

I. The purpose of this amendment is:

Substantial Changes
1. Revise Study Design
DESCRIPTION OF CHANGE:
Subjects who are receiving ASP2215 treatment and have not met any 2215-CL-0101 discontinuation criteria may be eligible to continue to receive ASP2215 treatment in a rollover study, 2215-CL-0109. Subjects who choose not to participate or are not eligible for Study 2215-CL-0109 will complete their participation in Study 2215-CL-0101 by completing the End of Treatment follow-up visit upon activation of Study 2215-CL-0109 at the institution. Subjects in Study 2215-CL-0101 who are being followed for Long-term Follow-up at the time of study closure will be discontinued from any further follow-up.
RATIONALE:
The primary database lock and analyses for the 2215-CL-0101 study occurred on 17 June 2016 including data up to the cut-point of 24 November 2015. Astellas will close Study 2215-CL-0101 upon activation of Study 2215-CL-0109 at all participating institutions. Study 2215-CL-0109 provides access for eligible subjects to continue to receive ASP2215 treatment.
2. Update Concomitant Medication Guidelines
DESCRIPTION OF CHANGE:
Update concomitant drugs that strong inducers of cytochrome P450 (CYP) 3A, strong inhibitors or inducers of P-gp and drugs that target $5HT_1R$ and $5HT_{2B}R$ receptors are excluded. Drugs known to prolong QT or QTc intervals should be used with caution. Update list of excluded concomitant medications.
RATIONALE:
Text is revised based on data available from nonclinical (in vitro) studies and pharmacokinetic data from clinical studies of ASP2215, and for alignment with the current guidance to the investigator in the Investigator's Brochure.

Non-Substantial Changes
1. Update Contact Details of Key Sponsor's Personnel
DESCRIPTION OF CHANGE:
Update personnel changes.

RATIONALE:
Update the contact details based on changes to sponsor personnel.
2. Updated Planned Study Period
DESCRIPTION OF CHANGE:
Update the study period to current planned end date of 2017.
RATIONALE:
To reflect the most current information.
3. Update Pregnancy and Contraception Inclusion Criteria
DESCRIPTION OF CHANGE:
For female subjects the period after study participation during which the subject cannot become pregnant or donate ova is lengthened from 45 days to 180 days and for breastfeeding is lengthened from 45 days to 60 days. For male subjects the period after study participation during which the subject must use contraception and not donate sperm is lengthened from 105 days to 120 days. For female subjects and female partners of male subjects, pregnancy reporting is lengthened from 90 to 180 days from the discontinuation of dosing.
RATIONALE:
Increased reproductive restrictions to ensure maximum protection against potential embryofetal toxicity. Reporting period increased to clarify situation where female subject or partner of a male subject will be considered of non-child bearing potential. No new patients will be enrolled under this version of the protocol; however, patients are still receiving treatment with ASP2215 under the study. Therefore, post discontinuation requirements are provided.
4. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol.
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

II Contact Details of Key Sponsor's Personnel *Clinical Research Contact*	
WAS:	
Clinical Research Contact:	[redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
Clinical Research Contact:	[redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
IS AMENDED TO:	
Clinical Research Contact:	[redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
~~Clinical Research Contact:~~	[redacted] ~~Astellas Pharma Global Development, Inc.~~ ~~1 Astellas Way, Northbrook, Illinois 60062~~ [redacted]

IV Synopsis - Planned Study Period
WAS:
From 4Q2013 to 3Q2015
IS AMENDED TO:
From 4Q2013 to 3Q2017 ~~5~~

IV Synopsis – Study Design Overview and 2.2.1 Study Design
WAS:
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.
IS AMENDED TO:
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.**
ADDED:
<u>Continuation of Subjects in open label roll over study:</u> **Should the Sponsor make the decision to end the study after primary analysis, all subjects receiving ASP2215 may be enrolled in an ASP2215 rollover study (2215-CL-0109). Subjects must not meet any discontinuation criteria for this study and must meet the entry criteria for the rollover study prior to being enrolled.** **Subjects who choose not to participate or are not eligible for Study 2215-CL-0109 will complete their participation in Study 2215-CL-0101 by completing the End of Treatment follow-up visit upon activation of Study 2215-CL-0109 at the institution.** **Subjects, who are being followed for Long-term Follow-up at the time of study closure, will be discontinued.**

IV Synopsis - Inclusion Criteria and 3.2 Inclusion Criteria
WAS:
8. Female subject must be either: • Of non child bearing potential: • post-menopausal (defined as at least 1 year without any menses) prior to Screening, or • documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening) • Or, if of childbearing potential, • must have a negative urine pregnancy test at Screening*, and • must use two forms of birth control** (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 45 days after the final study drug administration. 9. Female subject must not be breastfeeding at Screening or during the study period, and for 45 days after the final study drug administration. 10. Female subject must not donate ova starting at Screening and throughout the study

period, and for 45 days after the final study drug administration. 11. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control** (one of which must be a barrier method) starting at Screening and continue throughout the study period and for 105 days after the final study drug administration. 12. Male subject must not donate sperm starting at Screening and throughout the study period and for 105 days after the final study drug administration.
IS AMENDED TO:
8. Female subject must be either: • Of non child bearing potential: • post-menopausal (defined as at least 1 year without any menses) prior to Screening, or • documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening) • Or, if of childbearing potential, • must have a negative urine pregnancy test at Screening*, and • must use two forms of birth control** (at least one of which must be a barrier method) starting at Screening and throughout the study period and for **180**~~45~~ days after the final study drug administration. 9. Female subject must not be breastfeeding at Screening or during the study period, and for **60**~~45~~ days after the final study drug administration. 10. Female subject must not donate ova starting at Screening and throughout the study period, and for **180**~~45~~ days after the final study drug administration. 11. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control** (one of which must be a barrier method) starting at Screening and continue throughout the study period and for **120**~~105~~ days after the final study drug administration. 12. Male subject must not donate sperm starting at Screening and throughout the study period and for **120**~~105~~ days after the final study drug administration.

IV Synopsis – Concomitant Medication Restrictions or Requirements
WAS:
Treatment with concomitant drugs that are strong inhibitors or inducers of CYP3A4 or of P-glycoprotein (P-gp), or substrates of multidrug and toxin extrusion 1 (MATE 1) should be avoided with the exception of antibiotics, antifungals, and antivirals that are used as standard of care post-transplant or to prevent or treat infections and other such drugs that are considered absolutely essential for the care of the subject.
IS AMENDED TO:
Treatment with concomitant drugs that are strong ~~inhibitors or~~ inducers of CYP3A4~~4~~ **are prohibited**. **Treatment with concomitant drugs that are strong inihibitors or inducers of** ~~or P-glycoprotein (~~P-gp~~)~~, **and concomitant drugs that target serotonin 5HT2BR**

receptors or signma nonspecific receptor ~~or substrates of multidrug and toxin extrusion 1 (MATE 1)~~ should be avoided **with the exception of drugs that are considered absolutely essential for the care of the subject. Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided** with the exception of antibiotics, antifungals, and antivirals that are used as standard ~~of care post transplant or~~ to prevent or treat infections ~~and other such drugs that are considered absolutely essential for the care of the subject~~. **If CYP3A inhibitors are used concomitantly, subjects should be closely monitored for adverse events (AEs).** **Precaution should be used in use of ASP2215 with concomitant drugs that are known to prolong QT or QTc intervals.**

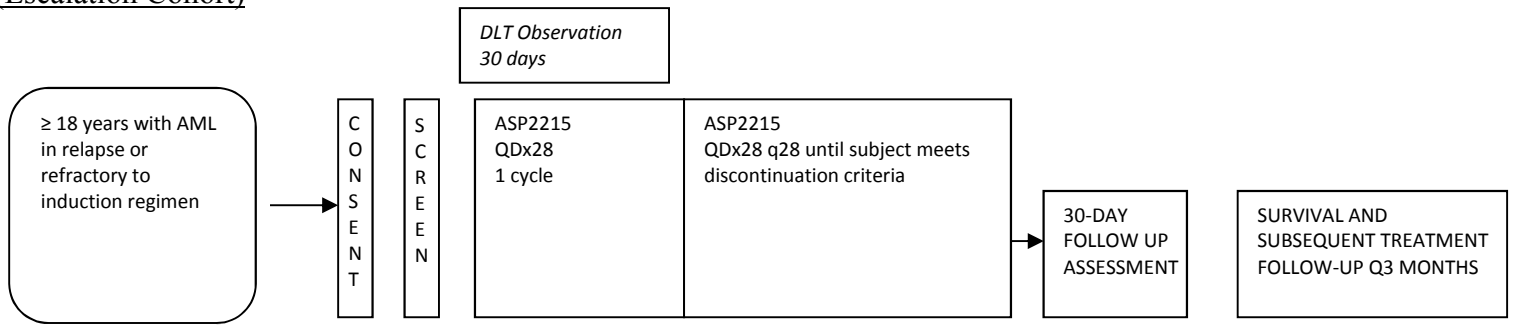
IV Synopsis – Duration of Treatment
WAS:
One dose daily in 28 day cycles until a discontinuation criterion is met.
IS AMENDED TO:
One dose daily in 28 day cycles until a discontinuation criterion is met or until rollover into the 2215-CL-0109 study.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

WAS:

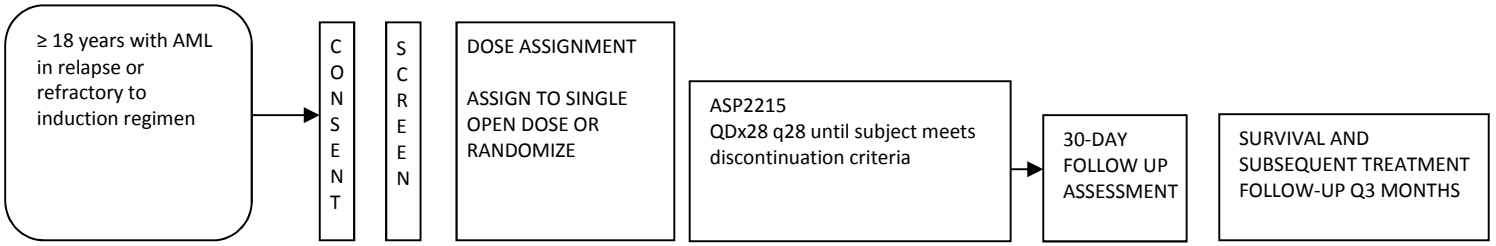
Figure 1 Study Flow Chart

Cohort 1 (Escalation Cohort)



Cohort 2 (Expansion Cohort)

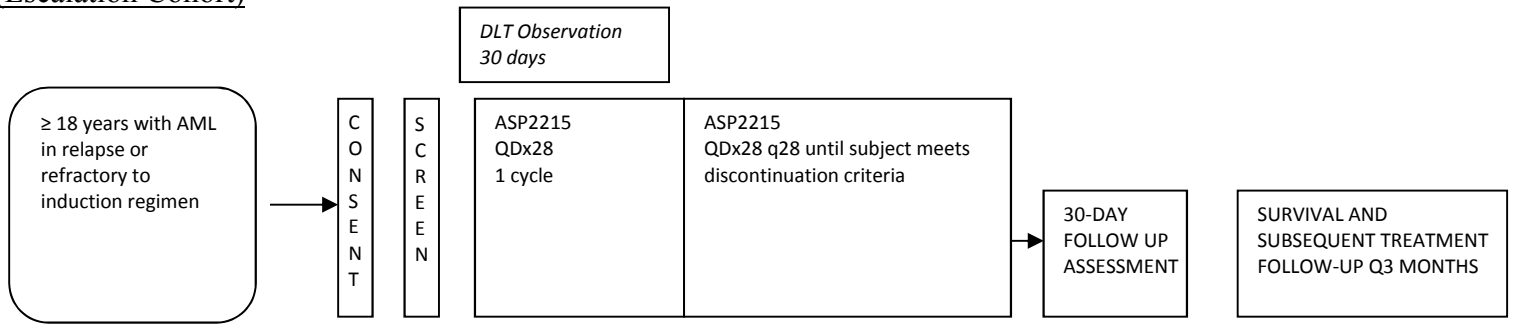
Expansion cohorts will start with 1st CR or one above the dose level with target inhibition



IS AMENDED TO:

Figure 1 Study 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

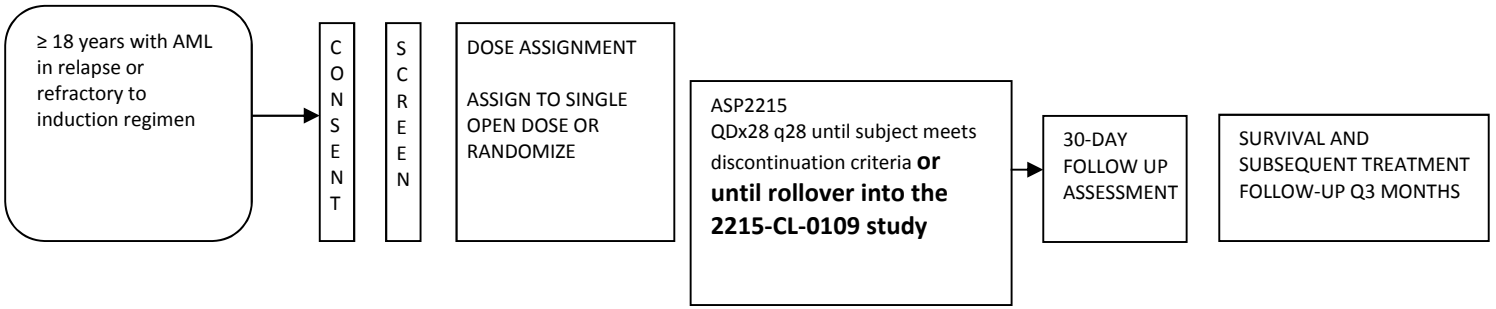


Table 2F – Post-Treatment Schedule of Assessments

WAS:

Activity	End of Treatment Visit [a]	30-Day Follow-Up	Long-term Follow-Up
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]

k. End of Treatment Visit is to be performed within 7 days of last dose.
l. Does not need to be repeated if collected at a regularly scheduled visit within 3 days of the End of Treatment Visit.
m. ECG monitoring should be between 7:00 am and 3:00 pm, if possible.
n. If the subject undergoes HSCT and does not resume ASP2215, SAE data will only be collected for 7 days after End of Treatment Visit
o. Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.
p. Telephone contact every 3 months after the 30-Day follow up.
q. FLT3, AXL and C-CBL mutation analysis will be performed for relapsed subjects.
r. Does not need to be repeated if collected within 2 weeks of the End of Treatment Visit.

IS AMENDED TO:

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 and does not resume ASP2215, 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.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

WAS:

All medications and concomitant treatments administered from 28 days prior to Cycle 1 Day 1 must be recorded in the CRF. Documentation will include the medication name, indication, dose and dates of administration. Treatment with concomitant drugs that are strong inhibitors or inducers of CYP3A4 or P-glycoprotein (P-gp) or substrates of multidrug and toxin extrusion 1 (MATE 1) should be avoided with the exception of antibiotics, antifungals, and antivirals that are used as standard of care post-transplant or to prevent or treat infections and other such drugs that are considered absolutely essential for the care of the subject.

Precaution should be used in treatment of ASP2215 with concomitant drugs that are substrates of CYP1A2, 2B6, 2C9, and 3A4/5; P-gp, and BCRP, since these enzymes or transporters have been shown to be inhibited (CYP 2C19, CYP3A4/5, P-gp, and BCRP) or induced (CYP1A2, 2B6, 2C9, 2C19, and 3A4/5) by A2215 in *in vitro* studies.

During the initial 15 days of treatment in expansion cohorts with DDI studies [Table 2B Schedule of Assessments with CYP3A4 Inhibitor Voriconazole, Table 2D Schedule of Assessments for Expansion Phase with CYP3A4 Induction, and Table 2E Schedule of Assessments for Expansion Phase with MATE1 Substrate Study], moderate or strong CYP3A4 inhibitors are prohibited, unless required for treatment of active infections. Common CYP3A4 Inhibitors and CYP3A4 Inducers are listed in Appendix 12.1. In addition, during the initial 15 days of treatment for subjects assigned to Schedule 2E MATE1 substrates are prohibited. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215 with the the following exceptions:

- hydroxyurea up to 5 gm daily for up to 2 weeks to keep the absolute blast count below 50,000.
- HSCT for patients with CRc or PR
- Intrathecal Chemotherapy used as prophylaxis.

Please see Section 5.1.4 for additional information on HSCT.

IS AMENDED TO:

All medications and concomitant treatments administered from 28 days prior to Cycle 1 Day 1 **through the end of treatment visit** must be recorded in the CRF. Documentation will include the medication name, indication, dose and dates of administration. Treatment with concomitant drugs that are strong ~~inhibitors or~~ inducers of CYP3A4**are prohibited. Treatment with concomitant drugs that are strong inhibitors or inducers of** ~~or P-glycoprotein (~~P-gp~~) or substrates of multidrug and toxin extrusion 1 (MATE 1) should be avoided~~**and concomitant drugs that target serotonin 5HT1R or 5HT2BR or sigma nonspecific receptor are to be avoided with the exception of drugs that are considered absolutely essential for the care of the subject. Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided** with the exception of antibiotics, antifungals, and antivirals that are used as standard of care post-transplant or to prevent or treat infections ~~and other such drugs that are considered absolutely essential for~~

~~the care of the subject~~. **If CYP3A inhibitors are used comcomitantly, subjects should be closely monitored for AEs.**

Precaution should be used in treatment of ASP2215 with concomitant drugs that are substrates of ~~CYP1A2, 2B6, 2C9, and 3A4/5; P-gp, and~~ BCRP, since the~~se enzymes or transporters have~~ **transporter has** been shown to be inhibited ~~(CYP 2C19, CYP3A4/5, P-gp, and BCRP) or induced (CYP1A2, 2B6, 2C9, 2C19, and 3A4/5)~~ by A2215 in *in vitro* studies.

Common CYP3A inhibitors, CYP3A inducers, drugs targeting the serotonin receptor P-gp inhibitors or inducers and drugs known to prolong QT or QTc intervals are listed [Appendix 12.1]. The investigator should consult individual labels for all drugs that the subject is taking to evaluate if they fall into any of the above named categories. For concomitant drugs that have the potential to prolong QT or QTc intervals, a cardiology consult should be obtained as medically indicated. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215 with the exception of hydroxyurea up to 5 g daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L, prophylactic intrathecal chemotherapy or cranial irradiation. Participation in another interventional study while on treatment is prohibited.

Refer to [Appendix 12.1, List of Excluded and Cautionary Concomitant Medications].

During the initial 15 days of treatment in expansion cohorts with DDI studies [Table 2B Schedule of Assessments with CYP3A4 Inhibitor Voriconazole, Table 2D Schedule of Assessments for Expansion Phase with CYP3A4 Induction, and Table 2E Schedule of Assessments for Expansion Phase with MATE1 Substrate Study], moderate or strong CYP3A4 inhibitors are prohibited, unless required for treatment of active infections. Common CYP3A4 Inhibitors and CYP3A4 Inducers are listed in Appendix 12.1. In addition, during the initial 15 days of treatment for subjects assigned to Schedule 2E MATE1 substrates are prohibited. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215 with ~~the~~ the following exceptions:

- hydroxyurea up to 5 gm daily for up to 2 weeks to keep the absolute blast count below 50,000.
- HSCT for patients with CRc or PR
- Intrathecal Chemotherapy used as prophylaxis.

Please see Section 5.1.4 for additional information on HSCT.

5.5.8 Procedure in Case of Pregnancy

WAS:

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 90 days from the discontinuation of dosing, the investigator should report the information to the Sponsor/delegated CRO as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this

information.

IS AMENDED TO:

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within **120** ~~90~~ days from the discontinuation of dosing, the investigator should report the information to the Sponsor/delegated CRO as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

12.1 List of Excluded Concomitant Mediations

WAS:

The following lists describe medications and foods which are common inhibitors of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

CYP3A4 Inhibitors

Drug Type	Generic Drug Name
Human Immunodeficiency Virus Protease Inhibitors	indinavir nelfinavir ritonavir saquinavir
Food/Juice	grapefruit/ grapefruit juice Seville oranges Star Fruit
Others	amiodarone cimetidine clarithromycin erythromycin fluoxetine fluvoxamine itraconazole ketoconazole mibefradil nefazodone troleandomycin verapamil

The following lists describe medications and foods which are common strong inducers of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A4.

CYP3A4 Inducers

Drug Type	Generic Drug Name
Anti-inflammatory	Dexamethasone
Antiepileptic, Anticonvulsant	Carbamazepine Phenytoin

Barbituate	Phenobarbital
Thiazolidinedione anti-hyperglycemic	Pioglitazone Troglitazone
Antibiotic	Rifabutin Rifampicin Rifapentine
Food/Juice Supplement	St. John's Wort

The following lists describe medications which target Serotonin Receptors. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound targets serotonin receptors.

Drugs Targeting Serotonin Receptor

Drug Type	Generic Drug Name
Affinity or function to 5HT2BR	Eletriptan Hydrobromide
Affinity or function to 5HT1R	Drugs Almotriptan Malate Aripiprazole Avitriptan Buspirone Hydrochloride Dihydroergotamine Mesylate Droperidol Eletriptan Hydrobromide Ergoloid Mesylates Ergonovine Maleate Ergotamine Tartrate Frovatriptan Succinate Haloperidol Decanoate Lesopitron Methylergonovine Maleate Methylergotamine Methysergide Maleate Naratriptan Hydrochloride Pizotifen Quetiapine Fumarate Rizatriptan Benzoate Sumatriptan Succinate Tegaserod Maleate Thioridazine Hydrochloride Ziprasidone Hydrochloride

	Ziprasidone Mesylate Zolmitriptan Zotepine

The following lists describe medications and foods which are common inhibitors or inducers of P-gp. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit or induce P-gp.

P-gp Inhibitors or Inducers

Transporter	Gene	Inhibitor	Inducer
P-gp	*ABCB1*	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir

Source: Table 12
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#major

The following list describes substrates of MATE1. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound is a substrate of MATE1.

MATE1 Substrate	
Transporter	Substrate
MATE1	cephalexin cephradine fexofenadine

MATE1: multidrug and toxin extrusion 1

Source: Yonezawa & Inui, 2011

Drugs targetting Sigma (nonspecific) Receptor (sigma R)

No list of drugs that target sigma nonspecific receptor is provided. Please consult individual drug labels for specific information on whether a compound targets sigma nonspecific receptors.

IS AMENDED TO:

The following lists describe medications and foods which are common inhibitors of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

CYP3A4 Inhibitors

Drug Type	Generic Drug Name
Human Immunodeficiency Virus Protease Inhibitors	**I~~i~~**ndinavir **N~~n~~**elfinavir **Lopinavir/ritonavir** **R~~r~~**itonavir **S~~s~~**aquinavir
Food/Juice	~~grapefruit/~~ grapefruit juice ~~Seville oranges~~ ~~Star Fruit~~
Others	~~amiodarone~~ ~~cimetidine~~ **Boceprevir** **C~~e~~**larithromycin ~~erythromycin~~ ~~fluoxetine~~ ~~fluvoxamine~~ **I~~i~~**traconazole **K~~k~~**etoconazole ~~mibefradil~~ **N~~n~~**efazodone **Posaconazole** **Telaprevir** **Telithromycin** **Voriconazole** ~~troleandomycin~~ ~~verapamil~~

The following lists describe medications and foods which are common strong inducers of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A4.

CYP3A4 Inducers

Drug Type	Generic Drug Name
~~Anti-inflammatory~~	~~Dexamethasone~~
Antiepileptic, Anticonvulsant	Carbamazepine Phenytoin
~~Barbituate~~	~~Phenobarbital~~
~~Thiazolidinedione anti-hyperglycemic~~	~~Pioglitazone~~ ~~Troglitazone~~
Antibiotic	~~Rifabutin~~ Rifampicin ~~Rifapentine~~
Food/Juice Supplement	St. John's Wort

The following lists describe medications which target Serotonin Receptors. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound targets serotonin receptors.

Drugs Targeting Serotonin Receptor

Drug Type	Generic Drug Name
Affinity or function to 5HT2BR	Eletriptan Hydrobromide
Affinity or function to 5HT1R	Drugs Almotriptan Malate Aripiprazole Avitriptan Buspirone Hydrochloride Dihydroergotamine Mesylate Droperidol Eletriptan Hydrobromide Ergoloid Mesylates Ergonovine Maleate Ergotamine Tartrate Frovatriptan Succinate Haloperidol Decanoate Lesopitron Methylergonovine Maleate Methylergotamine Methysergide Maleate Naratriptan Hydrochloride Pizotifen Quetiapine Fumarate Rizatriptan Benzoate Sumatriptan Succinate Tegaserod Maleate Thioridazine Hydrochloride Ziprasidone Hydrochloride Ziprasidone Mesylate Zolmitriptan Zotepine

The following lists describe medications and foods which are common inhibitors or inducers of P-gp. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit or induce P-gp.

P-gp Inhibitors or Inducers

Transporter	Gene	Inhibitor	Inducer

P-gp	*ABCB1*	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir

Source: Table 12
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#major

The following list describes substrates of MATE1. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound is a substrate of MATE1.

MATE1 Substrate	
Transporter	Substrate
MATE1	cephalexin cephradine fexofenadine

MATE1: multidrug and toxin extrusion 1

Source: Yonezawa & Inui, 2011

Drugs targetting Sigma (nonspecific) Receptor (sigma R)

No list of drugs that target sigma nonspecific receptor is provided. Please consult individual drug labels for specific information on whether a compound targets sigma nonspecific receptors.

Drugs That May Prolong QT or QTc

The following list describes drugs that are known to prolong QT or QTc. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound is known to prolong QT or QTc.

Drug Type	**Generic Drug Name**
Class IA antiarrhythmics	**Quinidine** **Procainamide** **Disopyramide**
Class IC antiarrhythmics	**Flecainide** **Propafenone** **Moricizine**
Class III antiarrhythmics	**Amiodarone** **Sotalol** **Bretylium** **Ibutilide**

	Dofetilide
Antipsychotics	**Thioridazine** **Mesoridazine** **Chlorpromazine** **Prochlorperazine** **Trifluoperazine** **Fluphenazine** **Perphenazine** **Pimozide** **Risperidone** **Ziprasadone** **Lithium** **Haloperidol**
Table continued on next page	
Tricyclic/tetracyclic antidepressants	**Amitriptyline** **Desipramine** **Doxepin** **Dosulepin hydrochloride** **Imipramine** **Maprotiline**
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) antidepressants	**Venlafaxine**
Macrolide antibiotics	**Azithromycin** **Erythromycin** **Clarithromycin** **Dirithromycin** **Roxithromycin** **Tulathromycin**
Fluoroquinolone antibiotics	**Moxifloxacin** **Gatifloxacin**
Azole antifungals	**Ketoconazole** **Fluconazole** **Itraconazole** **Posaconazole** **Voriconazole**
Antimalarials	**Amodiaquine** **Atovaquone** **Chloroquine** **Doxycycline** **Halofantrine** **Mefloquine** **Proguanil** **Primaquine** **Pyrimethamine** **Quinine** **Sulphadoxine**
Antiprotozoals	**Pentamidine**

Antiemetics	**Droperidol** **Dolasetron** **Granisetron** **Ondansetron**
Antiestrogens	**Tamoxifen**
Immunosuppressants	**Tacrolimus**

14 SPONSOR'S SIGNATURES

ELECTRONIC SIGNATURE PAGE

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