Phase 3 Open-label, Multicenter, Randomized Study of ASP2215 versus Salvage Chemotherapy in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) with FLT3 Mutation

Protocol for Phase 3 Study of ASP2215

ISN/Protocol 2215-CL-0303

Version 7.0

Incorporating Substantial Amendment 3

05 June 2023

Sponsor:

Astellas Pharma Inc.

Protocol History:

Version 1.0 [13Feb2017]
Version 2.0 [29Jun2017]
Version 3.0 [08Aug2018]
Version 4.0 [10Oct2019]
Version 5.0 [25Mar2020]
Version 6.0 [18Feb2021]

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

Required signatures (e.g., protocol authors, Sponsor's reviewers and contributors, etc.) are located in [Section 13 Sponsor's Signatures]; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

Phase 3 Open-label, Multicenter, Randomized Study of ASP2215 versus Salvage Chemotherapy in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) with FLT3 Mutation

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Version 7.0/ 05 June 2023

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: .....

.....

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Substantial Amendment 3 (Version 7.0)	05 Jun 2023
Substantial Amendment 2 (Version 6.0)	18 Feb 2021
Nonsubstantial Amendment 3 (Version 5.0)	25 Mar 2020
Nonsubstantial Amendment 2 (Version 4.0)	10 Oct 2019
Nonsubstantial Amendment 1 (Version 3.0)	08 Aug 2018
Substantial Amendment 1 (Version 2.0)	29 Jun 2017
Original Protocol	13 Feb 2017

Amendment 3 [Substantial] 05 Jun 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament, the Council of the European Union and EU Clinical Trial Regulation.

Overall Rationale for the Amendment:

To provide access to study drug to subjects continuing to receive clinical benefit where applicable reimbursement of the marketed product cannot be established.

Summary of Changes

Substantial Changes

Section Number	Description of Change	Brief Rationale
IV, 2.2.1, 6, 6.1, 6.1.2, 7.5.1, 12.8	The study treatment continues until subjects meet the discontinuation criteria or applicable reimbursement becomes available in the country of residence.	To provide access to study drug to subjects continuing to receive clinical benefit in countries where applicable reimbursement of the marketed product cannot be established yet.
IV, V (Flow Chart and Table 5), 2.2.1, 5.1.2, 5.3.4, 5.3.5, 5.5.2, 5.5.6, 5.6.1, 7.5.1, 12.8	After the subjects' reconsent, the subject will be managed according to the local institution's standard of care. Only SAEs will be collected and reported until 30 days after the last dose of study treatment. No data will be collected in the eCRF.	To reduce subject's burden for the study procedures, considering the subjects' safety and efficacy.
5.5.2	Add important medical events to the list of events held by the Sponsor that may require additional information.	To bring protocol 2215-CL-0303 into alignment with other gilteritinib documents.

Non-substantial Changes

Section Number	Description of Change	Brief Rationale
II, 13	PPD as the Clinical Research Contacts. Astellas Pharma China, Inc. is replaced by Astellas (China) Investment Co., Ltd.	To provide corrected personnel information.
II, 5.5.6	Change the 24 h-Contact for Serious Adverse Events (SAEs) from Quintiles East Asia Pte Ltd (Singapore) to IQVIA RDS East Asia Pte Ltd.	To update the safety reporting information.
IV,2.2.1, 12.7, 12.7.1	Update language to indicate the COE has been implemented.	To bring protocol language up to date.
IV, 7.1	The planned sample size with EFS event is updated from 230 to 250.	To correct an error aligning the latest SAP.
12.1	Add substrates of P-gp, BCRP and OCT1 to the list of excluded and cautionary concomitant medications.	To bring protocol 2215-CL-0303 into alignment with latest IB.
Throughout	Minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol.	To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24 h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.6**	PPD Development Medical Department/ Development Division Astellas (China) Investment Co., Ltd. 27th floor, Beijing IFC Tower, No.8 Jianguomenwai Avenue, Chaoyang District, Beijing 100022, P.R.C PPD Please email the SAE Worksheet to: IQVIA Lifecycle Safety Department IQVIA RDS East Asia Pte. Ltd. Email address: QLS_ASP2215@iqvia.com For more information, please refer to the SAE worksheet completion guideline.
Medical Monitor/Medical Expert	PPD Development Medical Department/ Development Division Astellas (China) Investment Co., Ltd. 27th floor, Beijing IFC Tower, No.8 Jianguomenwai Avenue, Chaoyang District, Beijing 100022, P.R.C PPD
Clinical Research Contacts	PPD Development Clinical Department/ Development Division Astellas (China) Investment Co., Ltd. 27th floor, Beijing IFC Tower, No.8 Jianguomenwai Avenue, Chaoyang District, Beijing 100022, P.R.C PPD

	PPD Astellas Pharma, Inc. 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-8411, JAPAN PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of Abbreviations
$5HT_1R$	5-hydroxytryptamine receptor 1
$5HT_{2B}R$	5-hydroxytryptamine receptor 2B
ΔQTcF	Fridericia-corrected QT interval change from baseline
ADR	Adverse Drug Reaction
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
API	Astellas Pharma Inc.
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AXL	AXL tyrosine kinase
BCRP	Breast cancer resistance protein
BFI	Brief Fatigue Inventory
Ca^{2+}	Calcium
CK	Creatine kinase
C_{max}	Maximum tissue concentration
CMH	Cochran-Mantel-Haenszel
COE	Crossover extension
CR	Complete remission
CRc	Composite complete remission
CRF	Case Report Form
CRi	Complete remission with incomplete hematologic recovery
CRO	Contract Research Organization
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Observed trough concentration
CYP	Cytochrome P450
DLT	Dose limiting toxicity
DTP	Direct-to-Participant
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
EGFR	Epidermal Growth Factor Receptor
EGFR m+	Epidermal Growth Factor Receptor Mutation positive
EQ-5D-5L	EuroQol Group-5 Dimension-5 Level Instrument
FACIT-Dys-SF	Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FAS	Full Analysis Set

Abbreviations	Description of Abbreviations
FLAG	Fludarabine, cytarabine and granulocyte colony-stimulating factor
FLT3	FMS-like tyrosine kinase
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
GVHD	Graft-versus-host disease
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplant
IAP	Interim Analysis Plan
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalization ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITD	Internal tandem duplication
ITT	Intention to Treatment Set
IV	Intravenous
LA-CRF	Liver Abnormality-Case Report Form
LFS	Leukemia-free survival
LFT	Liver function tests
LLN	Lower limit of normal
LoDAC	Low-dose cytarabine
LVEF	Left ventricular ejection fraction
MATE1	Multidrug and toxin extrusion protein 1
MDS	Myelodysplastic syndrome
MEC	Mitoxantrone, etoposide and intermediate-dose cytarabine
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NR	No response
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
OS	Overall survival
PD	Progressive disease
PD	Protocol deviation
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PIA	Plasma inhibitory assay

Abbreviations	Description of Abbreviations
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	Partial remission
PRO	Patient reported outcome
PT	Preferred term
PT	Prothrombin time
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RBC	Red blood cell
SAE	Serious adverse event
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOP	Standard Operating Procedure
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TK	Tyrosine kinase
TKD	Tyrosine kinase domain
TLFs	Tables, listings and figures
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization

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.
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.
Screen failure	Potential subject who signed consent but did not meet 1 or more criteria required for participation in a trial and did not randomize to the trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the randomization.
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:	05 Jun 2023/Version 7.0
Sponsor: Astellas Pharma Inc. (API)	**Protocol Number:** 2215-CL-0303
Name of Study Drug: ASP2215	**Phase of Development:** Phase 3
Title of Study: Phase 3 Open-Label, Multicenter, Randomized Study of ASP2215 versus Salvage Chemotherapy in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) with FLT3 Mutation	
Planned Study Period: From June 2017 until last subject discontinuation of study treatment under local standard of care.	
Study Objective(s): The primary objective is to: • Determine the clinical benefit of ASP2215 therapy in subjects with FMS-like tyrosine kinase (FLT3) mutated AML who are refractory to or have relapsed after first-line AML therapy as shown with overall survival (OS) compared to salvage chemotherapy. The key secondary objectives are to: • Determine the overall efficacy in event-free survival (EFS) of ASP2215 compared to salvage chemotherapy. • Determine the overall efficacy in complete remission (CR) rate of ASP2215 compared to salvage chemotherapy. The secondary objectives are to: Evaluate the safety and efficacy of ASP2215 therapy versus salvage chemotherapy in terms of: • leukemia-free survival (LFS) • duration of remission • composite complete remission (CRc) rate • transplantation rate • patient reported fatigue (Brief Fatigue Inventory [BFI]) • adverse events (AEs), safety labs, vital signs, electrocardiograms (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance scores • evaluate the PK of ASP2215 therapy in Chinese population	

The exploratory objectives are to:

Evaluate the safety and efficacy of ASP2215 therapy versus salvage chemotherapy in terms of:

- Pharmacogenomics (PGx)
- FLT3 gene mutation status
  - mutation types and frequency
  - relationship to efficacy and safety
- exploratory (predictive) biomarkers of ASP2215 activity
- resource utilization in this study population including hospitalization, blood transfusion, antibiotic iv infusions, medication for AEs and opioid usage
- patient reported dyspnea (Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms [FACIT-Dys-SF])
- patient reported signs, symptoms and impacts of AML (Functional Assessment of Cancer Therapy-Leukemia [FACT-Leu], dizziness and mouth sore items)
- EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L)

Planned Total Number of Study Centers and Location(s):

Approximately 50 centers:
China, Russia, Singapore, Thailand, and Malaysia

Two (or more) study sites in China will be designated as a "pharmacokinetic cohort site" (PK cohort site) which will collect PK samples after single and multiple doses in Chinese subjects. The first 20 subjects (10 male and 10 female) randomized into ASP2215 arm at PK cohort sites will participate in PK cohort.

Study Population:

FLT3-mutated subjects with relapsed or refractory AML after first-line therapy.

Number of Subjects to be Enrolled / Randomized:

318 subjects will be randomized

Among 318 subjects, approximately 20 Chinese subjects who are randomized into the ASP2215 arm will be allocated to the PK cohort.

Study Design Overview:

This is phase 3, open-label, multicenter, randomized study to compare the efficacy and safety of ASP2215 therapy to salvage chemotherapy in FLT3-mutated AML subjects who are refractory to or have relapsed after first-line AML therapy.

Three hundred eighteen subjects will be randomized in a 1:1 ratio to receive ASP2215 or salvage chemotherapy.

Among 318 subjects, approximately 20 Chinese subjects (10 male and 10 female subjects) who are randomized into the ASP2215 arm will be allocated to the PK cohort. Subjects in the PK cohort will be requested to be hospitalized from the date of randomization (Day 1) to at least the completion of all the assessments planned on Day 2. All subjects in the PK cohort will undergo blood sampling for PK measurement of ASP2215. Subjects in PK cohort will be administered the study drug in the same manner and undergo the same

efficacy and safety assessments as other subjects except for blood sampling for additional PK measurements.

Subjects will enter the screening period up to 14 days prior to the start of treatment. Prior to randomization, the investigator will preselect a salvage chemotherapy regimen for each subject; options will include low-dose cytarabine (LoDAC), mitoxantrone, etoposide and intermediate-dose cytarabine (MEC) or fludarabine, high-dose cytarabine and granulocyte colony-stimulating factor (FLAG). The randomization will be stratified by response to first-line therapy and preselected salvage chemotherapy. Subjects will be administered treatment over continuous 28-day cycles and per institutional guidelines for chemotherapy product preparation and administration. The dose and duration of study treatments are outlined in [Section 5.1.1 Dose/Dose Regimen and Administration Period] of the protocol.

For subjects taking ASP2215 or LoDAC, treatment should continue until the subject meets a treatment discontinuation criterion.

Subjects receiving MEC or FLAG will receive 1 cycle of therapy and will be assessed for response on or after day 15, per institutional guidelines. If the bone marrow cellularity is 20% or greater with at least a 50% reduction in blasts, the subject may receive a second cycle of the same chemotherapy. If bone cellularity is between 5% and 20%, the investigator should make the decision whether the subject should receive another treatment cycle or be observed for recovery. If marrow cellularity is 5% or less, the subject will be observed for recovery. Subjects achieving CR, complete remission with incomplete hematologic recovery (CRi) or complete remission with incomplete platelet recovery (CRp) may receive a second cycle of chemotherapy at the investigator's discretion. Subjects with no response (NR) or progressive disease will discontinue study treatment following cycle 1.

Dose adjustments for ASP2215 are described in [Section 5.1.2 Interruption, Reduction or Escalation in Dose of the Study Drug] of the protocol.

Subjects who have a donor identified and achieve a response allowing them to undergo hematopoietic stem cell transplant (HSCT) per each institution's assessment can undergo HSCT without leaving the study. However, ASP2215 should be stopped and a pre-HSCT 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 - 90 days post HSCT
- Subject has had successful engraftment as demonstrated by absolute neutrophil count (ANC) $\geq 500/mm^3$ and platelets $\geq 20000/mm^3$ without transfusions
- Subject does not have $\geq$ grade 2 acute graft-versus-host disease (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. Subjects who do not resume ASP2215 will be followed for primary endpoint.

After treatment discontinuation, subjects will have an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up, in which a telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs. After which the subjects will enter the long-term follow-up

period for collection of patient reported outcome (PRO) using EQ-5D-5L, subsequent AML treatment, remission status and survival (cause of death and date of death). The long-term follow-up will be every 3 months, for up to 3 years from the subject's end of treatment visit until the implementation and reconsent of the current protocol version 7.0, at which time they will discontinue from the study.

A formal interim analysis by an Independent Data Monitoring Committee (IDMC) will be done when approximately 50% of deaths by any cause have occurred. This analysis will be utilized to determine whether the study should be terminated earlier than planned if ASP2215 has more favorable or harmful outcome than the salvage chemotherapy group. If the interim analysis demonstrates a more favorable outcome for ASP2215, enrollment to the study may be stopped in advance. If it demonstrates a harmful outcome, the enrollment will be stopped. However, any subject continuing to derive clinical benefit from ASP2215 as assessed by the investigator will be allowed to continue treatment until they meet a discontinuation criterion as outlined in [Section 6 Discontinuation]or upon marketing authorization, commercial availability and applicable reimbursement of ASP2215 in the country of residence.

Subjects will be managed per the local institution's standard of care for safety and efficacy assessments while on study treatment after subjects reconsent under this protocol version 7.0. No data (including PK assessment) will be collected in the Electronic Case Report Forms after the subject reconsents under this protocol version 7.0. Only SAEs, as defined in [Section 5.5.2 Definition of Serious Adverse Events], will be collected and reported as outlined in [Section 5.5.6 Reporting of Serious Adverse Events]. SAE data will be reported in the safety database. SAE collection will continue until 30 days after last dose of study treatment. Once subjects receiving study treatment meet the study discontinuation criteria or upon marketing authorization and commercial availability and applicable reimbursement of ASP2215 in the country of residence, subjects will be discontinued from the study.

Subjects in long-term follow-up who are no longer receiving study treatment will be followed every 3 months for up to 3 years until implementation and reconsent of the current protocol version 7.0, at which time they will discontinue from the study.

The detailed assessments and procedures are presented in [Appendix 12.8 Continuation of Study Treatment with ASP2215].

The study planned interim analysis demonstrated superior OS outcome for the ASP2215 arm compared to the Salvage chemotherapy arm. The IDMC concluded that the primary endpoint of OS crossed the predefined efficacy stopping boundary and recommended that the study should stop for efficacy. According to IDMC's recommendation, the sponsor determined that no further screening/enrollment is required. In addition, the Crossover Extension (COE) is implemented to allow active salvage chemotherapy arm subjects and salvage chemotherapy arm subjects in follow to receive ASP2215 treatment on the study based on the investigators' discretion.

All eligible subjects must be evaluated and meet the eligibility criteria for COE.
Subjects on active salvage chemotherapy arm who are participating in COE, will have an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day

follow-up, in which a telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.

Day 1 of the COE will occur after COE informed consent form is signed and eligibility is confirmed.

In COE portion of the study, subjects will receive treatment with ASP2215 over continuous 28-day cycles. Subjects taking ASP2215 should continue until the subject meets a treatment discontinuation criterion. The subjects will have an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up, in which a telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs. Dose interruption and reduction due to adverse events related to ASP2215 must be followed [Table 9]

Study procedures during the COE will be limited to safety data collection including AE/SAE collection/assessment, clinical laboratory, ECGs, physical exams, vital signs and concomitant treatment as detailed in the schedule of assessment [Table 4 and Table 6].

Inclusion/Exclusion Criteria:

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 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 considered an adult according to local regulation (e.g., age ≥ 18 years old in China) at the time of signing informed consent.
3. Subject has a diagnosis of primary AML or AML secondary to myelodysplastic syndrome (MDS) according to World Health Organization classification [Swerdlow et al, 2008] as determined by pathology review at the treating institution.
4. Subject is refractory to or relapsed after first-line AML therapy (with or without HSCT) (see definition of line of therapy in Appendix 12.6).
   - Refractory to first-line AML therapy is defined as:
     a. Subject did not achieve CR/CRi/CRp under initial therapy. A subject eligible for standard therapy must receive at least 1 cycle of an anthracycline containing induction block in standard dose for the selected induction regimen. A subject not eligible for standard therapy must have received at least 1 complete block of induction therapy seen as the optimum choice of therapy to induce remission for this subject as per investigator's assessment.
   - Untreated first hematologic relapse is defined as:
     a. Subject must have achieved a CR/CRi/CRp (criteria as defined by [Cheson et al, 2003], see [Section 5.3 Efficacy Assessment]) with first-line treatment and has hematologic relapse.
5. Subject is positive for FLT3 mutation in bone marrow or whole blood as determined by the central lab. In the investigator's opinion, a subject with rapidly proliferative

disease and unable to wait for the central lab results can be enrolled based on a local test performed after completion of the last interventional treatment. Subjects can be enrolled from a local test result if they have any of the following FLT3 mutations: FLT3 internal tandem duplication (ITD), FLT3 tyrosine kinase domain (TKD)/D835 or FLT3-TKD/I836.

6. Subject has an ECOG performance status ≤ 2.
7. Subject is eligible for preselected salvage chemotherapy according to investigator assessment.
8. Subject must meet the following criteria as indicated on the clinical laboratory tests:
   - Serum aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x upper limit of normal (ULN)
   - Serum total bilirubin ≤ 1.5 x ULN
   - Serum creatinine ≤ 1.5 x ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation [Levey et al, 1999].
9. Subject is suitable for oral administration of study drug.
10. Female subject must either:
    - Be of non-childbearing potential:
      - Postmenopausal (defined as at least 1 year without any menses) prior to screening, or
      - Documented as surgically sterile (at least 1 month prior to screening)
    - Or, if of childbearing potential,
      - Agree not to try to become pregnant during the study and for 60 days after the final study drug administration
      - And have a negative serum or urine pregnancy test at screening
      - And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to barrier method starting at screening and throughout the study period and for 60 days after the final study drug administration.
11. Female subject must agree not to breastfeed at screening and throughout the study period and for 60 days after the final study drug administration.
12. Female subject must not donate ova starting at screening and throughout the study period and for 60 days after the final study drug administration.
13. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 120 days after the final study drug administration.
14. Male subject must not donate sperm starting at screening and throughout the study period and
    for 120 days after the final study drug administration.
15. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will NOT be allowed.

Inclusion for COE portion:

Subject is eligible for the COE if they meet the following criteria when the subject is evaluated for eligibility to participate in the COE portion of the study:

1. Institutional Review Board (IRB) -/Independent Ethics Committee (IEC) -approved written Informed Consent and privacy language as per national regulations 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 has received study treatment of either LoDAC, MEC or FLAG and has no response or progressive disease.
3. Subject has not received other antileukemic therapy after EoT (hydroxyurea is allowed for the control of peripheral leukemic blasts in patients with leukocytosis).
4. Subject must meet the following criteria as indicated on the clinical laboratory tests:
   - Serum AST and ALT ≤ 2.5 x upper limit of normal (ULN)
   - Serum total bilirubin ≤ 1.5 x ULN
   - Serum creatinine ≤ 1.5 x ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation [Levey et al, 1999].
   - Serum potassium ≥ lower limit of normal (LLN) (Repletion of potassium levels prior to C1D1 of COE is allowed).
   - Serum magnesium ≥ LLN (Repletion of magnesium levels prior to C1D1 of COE is allowed).
5. Subject has an ECOG performance status ≤ 2.
6. Female subject must either:
   - Be of non-childbearing potential:
     - Postmenopausal (defined as at least 1 year without any menses) prior to screening, or
     - Documented as surgically sterile (at least 1 month prior to screening)
   - Or, if of childbearing potential,
     - Agree not to try to become pregnant during the study and for 60 days after the final study drug administration
     - And have a negative serum or urine pregnancy test at screening
     - And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to barrier method starting at screening and throughout the study period and for 60 days after the final study drug administration.
7. Female subject must agree not to breastfeed at screening and throughout the study period and for 60 days after the final study drug administration.
8. Female subject must not donate ova starting at screening and throughout the study period and for 60 days after the final study drug administration.
9. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 120 days after the final study drug administration.

10. Male subject must not donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
11. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the COE inclusion criteria will NOT be allowed.

Exclusion:

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

1. Subject was diagnosed as acute promyelocytic leukemia.
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has AML secondary to prior chemotherapy for other neoplasms (except for MDS).
4. Subject is in second or later hematologic relapse or has received salvage therapy for refractory disease.
5. Subject has clinically active central nervous system leukemia.
6. Subject has been diagnosed with another malignancy, unless disease-free for at least 5 years. Subjects with treated nonmelanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed. Subjects with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
7. Subject has received prior treatment with ASP2215 or other FLT3 inhibitors (with the exception of sorafenib and midostaurin used in first-line therapy regimen as part of induction, consolidation and/or maintenance).
8. Subject has clinically significant abnormality of coagulation profile, such as disseminated intravascular coagulation.
9. Subject has had major surgery within 4 weeks prior to the first study dose.
10. Subject has radiation therapy within 4 weeks prior to the first study dose.
11. Subject has congestive heart failure New York Heart Association (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 1 month prior to study entry results in a left ventricular ejection fraction (LVEF) that is ≥ 45%.
12. Subject with mean of triplicate Fridericia-corrected QT interval (QTcF) > 450 ms at Screening based on central reading.
13. Subject with Long QT Syndrome at Screening.
14. Subject with hypokalemia and hypomagnesemia at Screening (defined as values below lower limit of normal [LLN]).
15. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.
16. Subject requires treatment with concomitant drugs that are strong inhibitors or

inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.

17. Subject requires treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 ($5HT_1R$) or 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
18. Subject has an active uncontrolled infection.
19. Subject is known to have human immunodeficiency virus infection.
20. Subject has active hepatitis B or C or other active hepatic disorder.
21. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
22. Subject has active clinically significant GVHD or is on treatment with systemic corticosteroids for GVHD.
23. Subject has an FLT3 mutation other than the following: FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836

Waivers to the exclusion criteria will NOT be allowed.

Exclusion for COE portion:

Subject will be excluded from participation in the COE if any of the following apply when the subject is evaluated for eligibility to participate in the COE portion of the study:

1. Subject has been diagnosed with another malignancy, unless disease-free for at least 5 years. Subjects with treated nonmelanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed. Subjects with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
2. Subject has congestive heart failure New York Heart Association (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 1 month prior to study entry results in a left ventricular ejection fraction (LVEF) that is ≥ 45%.
3. Subjects with mean of triplicate Fridericia-corrected QT interval (QTcF) > 450 ms at COE Screening based on central reading.
4. Subject has clinically active central nervous system leukemia.
5. Subject has clinically significant abnormality of coagulation profile, such as disseminated intravascular coagulation.
6. Subject has had major surgery within 4 weeks prior to the first study dose.
7. Subject has radiation therapy within 4 weeks prior to the first study dose.
8. Subject with Long QT Syndrome at Screening.
9. Subject with hypokalemia and hypomagnesemia at Screening (defined as values below lower limit of normal [LLN]).
10. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.

11. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.
12. Subject requires treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 (5HT1R) or 5-hydroxytryptamine receptor 2B (5HT2BR) or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
13. Subject has an active uncontrolled infection.
14. Subject is known to have human immunodeficiency virus infection.
15. Subject has active hepatitis B or C or other active hepatic disorder.
16. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the COE exclusion criteria will NOT be allowed.

Investigational Product:
ASP2215 tablets containing 40 mg of active ingredient.

Dose:

ASP2215 120 mg will be administered once daily.

Mode of Administration:
ASP2215 will be administered orally.

Comparative Drugs:

The specific regimen will be preselected by the investigator prior to randomization of each subject. All regimens will be administered as 28-day cycles and per institutional guidelines for chemotherapy product preparation and administration.

Options for comparative salvage chemotherapies are limited to the following (all dose levels as defined below must be followed):

LoDAC [Burnett & Knapper, 2007]

- 20 mg cytarabine will be administered twice daily by SC or IV injection for 10 days.

MEC Induction Chemotherapy [Amadori et al, 1991]

- Mitoxantrone 6 mg/m^2 per day will be administered by IV for 5 days (days 1 through 5).
- Etoposide 100 mg/m^2 per day will be administered by IV for 5 days (days 1 through 5).
- Cytarabine 1000 mg/m^2 per day will be administered by IV for 5 days (days 1 through 5).

FLAG Induction Chemotherapy [Montillo et al, 1998]

- Granulocyte colony-stimulating factor (G-CSF) 300 µg/m^2 per day will be administered by SC/IV for 5 days (days 1 through 5). Additional G-CSF by SC/IV is recommended 7 days after completing chemotherapy until ANC > 0.5 x 10^9/L.
- Fludarabine 30 mg/m^2 per day will be administered by IV for 5 days (days 2 through 6).
- Cytarabine 2000 mg/m^2 per day will be administered by IV for 5 days (days 2 through 6).

Concomitant Medication Restrictions or Requirements:

ASP2215 group only:

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 inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be monitored for AEs.

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

ASP2215 group and chemotherapy group:

Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with the exception of hydroxyurea daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L and prophylactic intrathecal chemotherapy, cranial radiation, and donor lymphocyte infusion as part of the HSCT treatment plan. Participating in another

interventional study while on treatment is prohibited.

COE receiving ASP2215 group:

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 inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be monitored for AEs.

Precaution should be used in treatment of ASP2215 with concomitant drugs that are known to prolong QT or QTc intervals.
In addition, any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with the exception of hydroxyurea daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L and prophylactic intrathecal chemotherapy, cranial radiation, and donor lymphocyte infusion as part of the HSCT treatment plan. Prior to starting protocol treatment, hydroxyurea is allowed for the control of peripheral leukemic blasts in patients with leukocytosis (e.g., white blood cell [WBC] counts > 30 x 10^9/L). Participating in another interventional study while on treatment is prohibited.

Duration of Treatment:

For subjects taking ASP2215, LoDAC, treatment should continue until the subject meets a treatment discontinuation criterion.

- Subjects receiving MEC or FLAG will receive 1 cycle of therapy and will be assessed for response on or after day 15, per institutional guidelines. If the bone marrow cellularity is 20% or greater with at least a 50% reduction in blasts, the subject may receive a second cycle of the same chemotherapy. If bone cellularity is between 5% and 20%, the investigator should make the decision whether the subject should receive another treatment cycle or be observed for recovery. If marrow cellularity is 5% or less, the subject will be observed for recovery. Subjects achieving CR, CRi or CRp may receive a second cycle of chemotherapy at the investigator's discretion. Subjects with NR or progressive disease following cycle 1 will discontinue study treatment.

Discontinuation Criteria

Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined below or upon marketing authorization, commercial availability and applicable reimbursement of ASP2215 in the country of residence. Once a subject(s) transitions to commercial supply, the subject(s) will be discontinued from the study.

Discontinuation Criteria from Treatment for Individual Subjects:

- Subject declines further study participation (i.e. withdrawal of consent).
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit may be kept in the study after discussion with the medical monitor).
- Subject develops an intolerable or unacceptable toxicity.
- Subject receives any antileukemic therapy other than the assigned treatment, with the exceptions of hydroxyurea up to 2 weeks, prophylactic intrathecal chemotherapy or cranial irradiation, and donor lymphocyte infusion as part of the HSCT treatment plan.
- 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.
- Subject is receiving MEC or FLAG and has NR or progressive disease following cycle 1.
- Subject is receiving LoDAC or ASP2215 and has progressive disease or NR and the subject, in the opinion of the investigator, is no longer deriving clinical benefit.
- Subject is in comparator group (chemotherapy) and goes on for HSCT.
- Female subject becomes pregnant.
- Death.

Discontinuation Criteria for COE group

Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined below or upon marketing authorization, commercial availability and applicable reimbursement of ASP2215 in the country of residence. Once a subject(s) transitions to commercial supply, the subject(s) will be discontinued from the study.

Discontinuation Criteria from Treatment for Individual Subjects:

- Subject declines further study participation (i.e. withdrawal of consent).
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit may be kept in the study after discussion with the medical monitor).
- Subject develops an intolerable or unacceptable toxicity.
- Subject receives any antileukemic therapy other than the assigned treatment, with the

exceptions of hydroxyurea up to 2 weeks, prophylactic intrathecal chemotherapy or cranial irradiation, and donor lymphocyte infusion as part of the HSCT treatment plan.
- 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.
- Subject is receiving ASP2215 and has progressive disease or NR and the subject, in the opinion of the investigator, is no longer deriving clinical benefit.
- Female subject becomes pregnant.
- Death.
- ASP2215 reimbursement becomes available in the country of residence.

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 subject's end of treatment visit.
- The implementation and reconsent of protocol version 7.0.
- Death.

Endpoints for Evaluation:

Primary Efficacy Endpoint:

- OS

Key Secondary Efficacy Endpoints:

- EFS
- CR

Secondary Efficacy Endpoints:

- LFS
- Duration of remission
- CRc (CR + CRi + CRp)
- Transplantation
- BFI

Exploratory Endpoints:

- Pharmacogenomics (PGx)
- FLT3 gene mutation status
    - mutation types and frequency
    - relationship to efficacy and safety

- Exploratory (predictive) biomarkers of ASP2215 activity
- Resource utilization including hospitalization, blood transfusion, antibiotic iv infusions, medication for AEs and opioid usage
- FACIT-Dys-SF
- FACT-Leu and dizziness and mouth sore items
- EQ-5D-5L

Safety endpoints

- AEs
- Serum chemistry, hematology, coagulation and urinalysis
- Vital signs
- ECGs
- ECOG performance scores

Pharmacokinetics

- ASP2215 concentration in blood
- Pharmacokinetic parameters of ASP2215 in Chinese population

Statistical Methods:

Sample Size Justification:

This is a group sequential design using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method (East®). One interim analysis and 1 final analysis are planned. The interim and final analyses will be performed after the prespecified number of death events. All statistical tests of treatment effects will be conducted at the 2-sided 0.05 level of significance.

Approximately 318 subjects (the planned sample size with 10% dropout rate) will be randomized in a 1:1 ratio to receive ASP2215 or salvage chemotherapy (159 subjects in the ASP2215 treatment arm and 159 subjects in the salvage chemotherapy arm). The planned 230 events during the study will provide 90% power to detect a difference in OS between the ASP2215 arm with 7.7 months median survival time and salvage chemotherapy arm with 5 months median survival time (hazard ratio = 0.65) at the overall 2-sided 0.05 significance level.

The planned sample size with 250 EFS events will provide 90% power to detect the difference in EFS (6 months median EFS for ASP2215 arm and 3.9 months for salvage chemotherapy arm with hazard ratio = 0.65) and > 90% power to detect a difference in CR rate between ASP2215 with 25% CR rate and the salvage chemotherapy with 10% CR rate.

Randomization will be stratified by response to first-line AML therapy and preselected salvage chemotherapy:

Response to first-line therapy:

- Relapse within 6 months after allogeneic HSCT
- Relapse after 6 months after allogeneic HSCT
- Primary refractory without HSCT
- Relapse within 6 months after CRc and no HSCT
- Relapse after 6 months after CRc and no HSCT

Preselected chemotherapy:

- High intensity chemotherapy (FLAG or MEC)
- Low intensity chemotherapy (LoDAC)

Primary Efficacy Analysis:

The primary efficacy endpoint of OS will be analyzed using the stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on the Intention to Treatment Set (ITT). The ITT is defined as all randomized subjects.

The hypothesis testing on the primary analysis will be performed at overall 2-sided 0.05 significance level to test the null hypothesis that OS is equal between the 2 treatment arms versus the alternative hypothesis that OS is different between the ASP2215 arm versus the salvage chemotherapy arm.

The sensitivity analysis for the primary efficacy endpoint will be performed on the Full Analysis Set (FAS), which includes all randomized subjects who are FLT3-mutated subjects based on the central test. The sensitivity analysis for OS with censoring at the time of HSCT for subjects who undergo HSCT will be conducted on the ITT. If the FLT3-mutated subjects constitute less than 90% of the total number of randomized subjects, the difference in the primary efficacy endpoint will be evaluated between FLT3-mutated subjects and FLT wild type subjects per central lab test.

Key Secondary Efficacy Analysis:

The key secondary efficacy endpoint of EFS will be analyzed using the stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on the ITT. To maintain the overall Type I error rate at the 0.05 significance level, the hypothesis testing on EFS will be performed only if the null hypothesis on the primary analysis is rejected at the overall 2-sided 0.05 significance level.

The key secondary efficacy endpoint of CR rate will be analyzed using the Cochran-Mantel-Haenszel (CMH) test to control for response to first-line AML therapy and preselected salvage chemotherapy on the ITT. To maintain the overall Type I error rate at the 0.05 significance level, the hypothesis testing on CR rate will be performed only if the null hypothesis on EFS is rejected at the overall 2-sided 0.05 significance level.

The sensitivity analysis for the key secondary efficacy endpoints will be performed on the FAS, which included all randomized subjects who are FLT3-mutated subjects based on the central test. Additional sensitivity analysis will be performed to evaluate the impact on the

analysis of EFS due to any missing data/assessments and any loss to follow-up or discontinuation of assessments of EFS not due to an event.

Secondary Efficacy Analyses:

The statistical analyses on secondary efficacy endpoints include:

- Stratified Cox proportional hazard model on duration of remission and LFS
- CMH method on the CRc rate and transplantation rate
- Analysis of variance (ANOVA) model to analyze the change in the BFI global fatigue score (average of all 9 items) from baseline to post-baseline visits

Safety Analyses:

The Safety Analysis Set (SAS) is defined as all subjects who received at least 1 dose of study treatment (ASP2215 or salvage chemotherapy).

The safety evaluation will be based mainly on AEs, clinical laboratory, vital signs, ECG and ECOG. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment.

All summaries of AEs will include only treatment-emergent events unless otherwise stated. AEs will be categorized by SOC and preferred term using MedDRA and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Since the cross-over choice of chemotherapy patients were introduced as a result of the interim analysis of the efficacy, the main statistical analysis of efficacy and safety should be conducted on the data up to the implementation of this choice to maintain the integrity of the study conclusion.

All eligible salvage chemotherapy arm subjects who cross to COE ASP2215 treatment will be summarized separately to support the safety conclusion for the ASP2215. More details will be included in the SAP.

Pharmacokinetics Analyses:

Population pharmacokinetic modeling will be conducted for ASP2215 using nonlinear mixed effects methodology. Data from this study may be pooled with other studies for analysis. A covariate analysis will be performed to relate the effect of intrinsic and extrinsic subject factors to exposure. After the subject reconsents under this protocol version 7.0, no PK assessments will be performed.

Plasma concentrations and PK parameters will be summarized using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, and coefficient of variation (CV) of the 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 (non-compartmental analysis).

Pharmacodynamics Analyses:

Not applicable

Exploratory Analyses:

An exploratory analysis of FLT3 mutation status and clinical efficacy will be conducted. FLT3 mutation status, including subgroups of FLT3 internal tandem duplication mutation, D835/I836 tyrosine kinase domain mutations and allelic ratio, will be analyzed.

CMH method will be used for resource utilization status (hospitalization, blood transfusion, antibiotic iv infusions, medication for AEs and opioid medication); and ANOVA model will be used for resource utilization counts (hospital stays, duration of medications, blood transfusions, antibiotic iv infusions, medication for AEs and opioid medication).

ANOVA model will be used to analyze the change in the FACIT-Dys-SF domain scores from baseline to post-baseline visits.

ANOVA model will be used to evaluate change from baseline to post-baseline visits for the global and domain scores, individual items and item clusters of the FACT-Leu. The same analytic approach will be used for the dizziness and mouth sore items.

ANOVA model will be used for the change from baseline of EQ-5D-5L visual analogue scale (VAS) and shift table for the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) baseline to post-baseline visits.

Interim Analysis:

To evaluate whether ASP2215 is particularly beneficial or harmful compared to the salvage chemotherapy group while the study is ongoing, a formal interim analysis is planned when approximately 50% of the planned death events have occurred in the study. A group sequential design using the O'Brien-Fleming type alpha-spending function [Lan & DeMets, 1983] will be used to control the overall 2-sided 0.05 significance level (East®).

The IDMC may recommend terminating the trial for favorable or unfavorable results at the interim analysis. In the case of favorable results, the 2-sided significance levels for superiority are 0.0031 for the interim analysis and 0.0490 for the final analysis. If the estimated hazard ratio (HR) is less than 1 and the 2-sided P of the interim analysis is less than 0.0031, the IDMC may recommend terminating the trial for success. In the case of unfavorable results in the interim analysis, the 2-sided significance level for futility (nonbinding) is 0.8458. If the estimated HR is less than 1 and the 2-sided P of the interim analysis is greater than 0.8458 or the estimated HR is greater than 1, the IDMC may recommend terminating the trial for futility.

The decision rules based on the P and estimated HR at the formal interim analysis are further described in the table below.

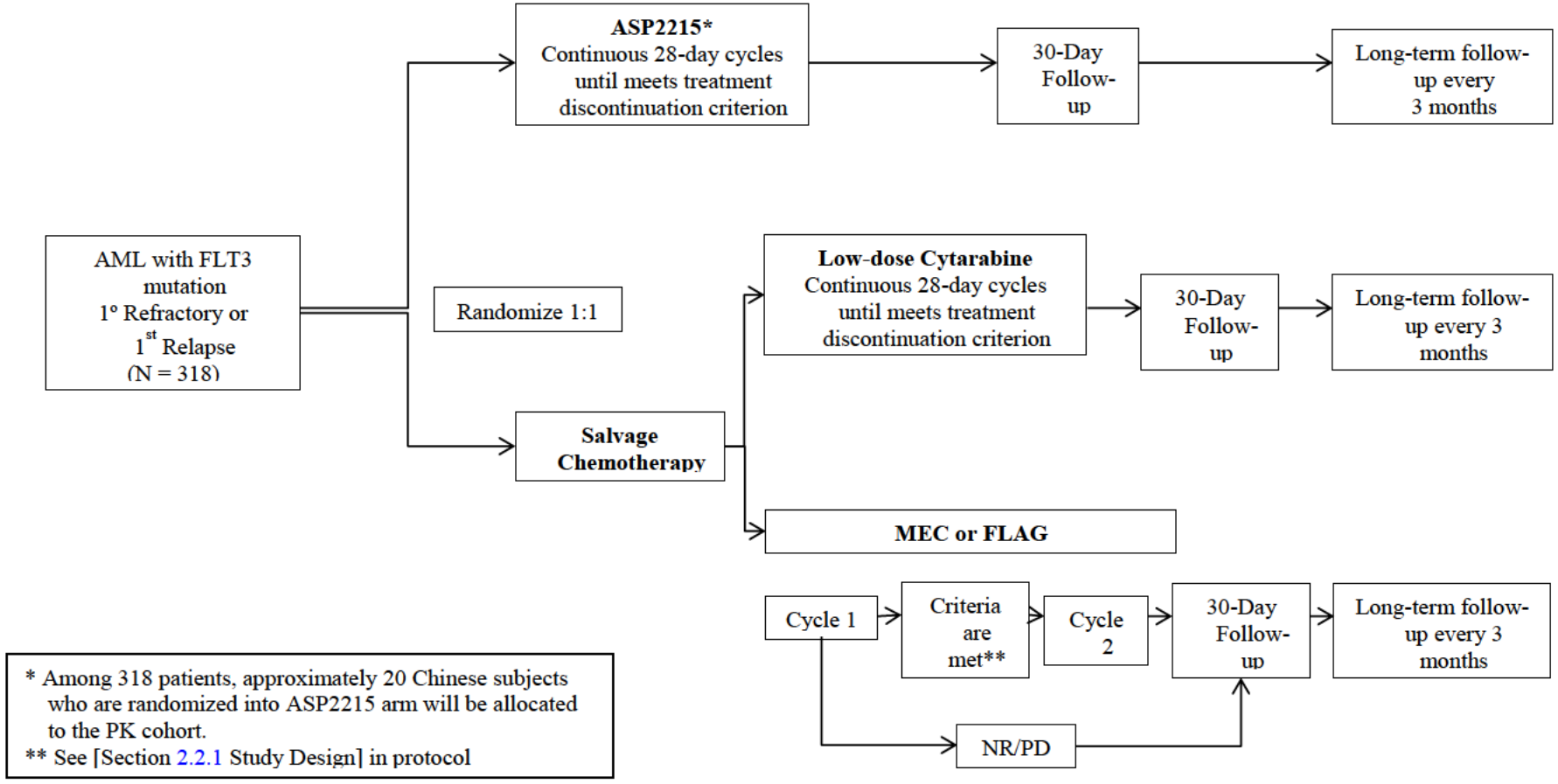
Decision Rules based on P Value and HR obtained at Interim Analysis

- HR < 1
    - P value < 0.0031 : Termination due to success
    - 0.0031 ≤ P value ≤ 0.8458 : Continuation of study
    - P value > 0.8458 : Termination due to futility
- HR ≥ 1
    - Termination due to futility

Details for the interim analysis, monitoring subject safety, enrollment rates and event (death) rates will be contained in the Interim Analysis Plan (IAP) and IDMC Charter. Recommendations regarding study conduct will be made by the IDMC based on their assessment of these rates. If the study is not stopped after the interim analysis, a final analysis will occur after 100% of events have been observed.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

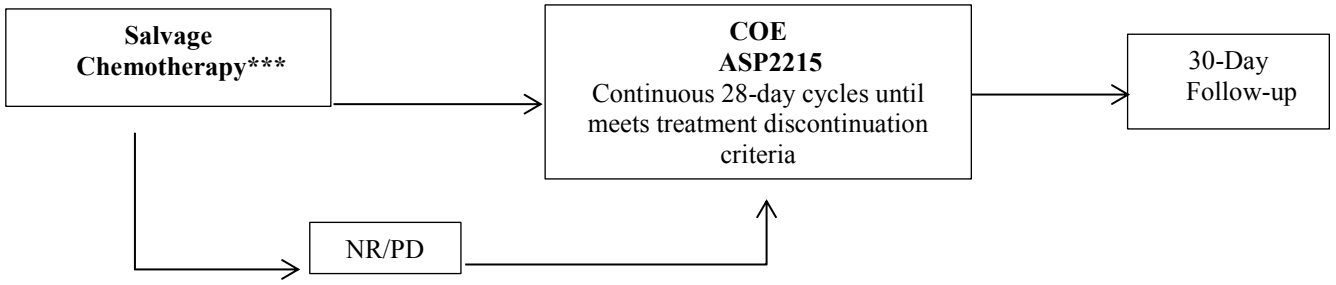
Flow Chart



1°: primary; AML: acute myeloid leukemia; FLT3: FMS-like tyrosine kinase; FLAG: fludarabine, cytarabine and granulocyte colony-stimulating factor; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; NR: no response; PD: progressive disease

Once protocol version 7.0 has been implemented, no follow-up visits are required after the end of treatment. Subjects in long-term follow-up will discontinue from the study, as further survival data are no longer needed.

Flow Chart for Crossover Extension



*** Active salvage chemotherapy arm subjects who are participating in COE, will have an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up for salvage chemotherapy arm. 30-day follow-up assessment on salvage chemotherapy arm shold be completed even if the subjects are in COE.

Table 1 Schedule of Assessments for ASP2215 Arm

Activity	Screening (Day -14 to -1)	Cycle 1					Cycle 2		Subsequent Cycles
		Day 1	Day 4 ± 1	Day 8 ± 1	Day 9	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
Signed ICF	X								
Medical and Disease History	X								
Randomization		X[o]							
Physical Examination[b]	X	X[a]	X	X		X	X	X	X
Vital Signs	X	X[a]	X	X		X	X	X	X
ECOG Performance	X	X[a]				X	X	X	X
Prior and Concomitant Medications	X[c]	X	X	X		X	X	X	X
Pregnancy Test for Woman of Childbearing Potential	X[d]	X					X		X
Chest X-ray (or CT of chest)[n]	X								
12-lead ECG[e]	X[g]	X		X[r]	X[r]	X	X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[f]	X[g]	X[a]	X[a]	X[a]		X[a]	X[a]	X[a]	X[a]
Thyroid Function Test[s]	X								X[s]
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	X								
MUGA or ECHO[h]	X								
FLT3 Mutation Status[i] (bone marrow aspirate or whole blood)	X								
Bone Marrow Aspiration and/or Biopsy	X[j]						X[j]		X[j]
AE/SAE Assessment	X	X	X	X		X	X	X	X
PK (whole blood samples for plasma PK)		X[k]		X[k]		X[k]	X[k]		X[k]
PGx[l]		X							
Patient Reported Outcome Tools[p, q]		X[a]		X[p]		X[p]	X	X[p]	X
EQ-5D-5L[q]		X[a]					X		X
Resource Utilization		X[a]					X		X
IRT Transaction Required[o]	X	X					X		X
ASP2215 Dosing at the Clinic[m]		X	X	X		X	X	X	X

AE: adverse event; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EDTA: ethylenediaminetetraacetic acid; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; FLAG: fludarabine, cytarabine and granulocyte colony-stimulating factor; FLT3: FMS-like tyrosine kinase; ICF: Informed Consent Form; INR: international normalization ratio; IRT: interactive response technology; LoDAC: low-dose cytarabine; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; MUGA: multigated acquisition scan; PGx: pharmacogenomics; PK: pharmacokinetic; PT: prothrombin time; SAE: serious adverse event

Footnotes continued on next page

a. Obtained predose.

b. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

c. Includes medications taken within 28 days prior to cycle 1 day 1.

d. Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.

e. Screening ECG is required. ECG assessment will be evaluated at predose of cycle 1 day 1, cycle 1 day 8, cycle 1 day 15 and day 1 of each subsequent cycle. Predose assessments should be taken within 1 hour before drug administration. 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. The mean QTcF of the triplicate ECG tracings based on central reading will be used for final treatment decisions and AE reporting. If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less) by central reading within 14 days, the subject may resume dosing at the reduced dose.

f. Urinalysis only required at screening. Uric acid will be tested on days 1, 4, 8, and 15 in cycle 1. Additional laboratory tests should be performed according to institutional standard of care.

g. Subjects may be screened and randomized from local labs only. However, samples must also be submitted for central lab. Labs and/or ECG can be repeated during screening period.

h. MUGA scans or ECHO (per standard of care) are to be performed at screening for subjects with history of congestive heart failure New York Heart Association Class 3 or 4 (unless MUGA scans or ECHO performed either within 1 month prior revealed left ventricular ejection fraction ≥ 45%).

i. FLT3 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. Subjects must be screened by the central laboratory. All subjects including those with rapidly proliferative disease must have screening sample sent to the central lab. If central result is negative, central FLT3 testing can be repeated during screening period. Bone marrow sample before the informed consent date may be used for screening if the patient has already performed bone marrow assessment within 14 days prior to the planned Cycle 1 Day 1, and the sample should be stored at 2˚C to 8˚C and can be started testing within 7 days after sample collection.

j. Bone marrow samples are required during screening, cycle 2 day 1 and cycle 3 day 1. For subjects who do not achieve a CRc (CR, CRp or CRi), the bone marrow assessments will be repeated at day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow sampling will be repeated on 1 month after the date of remission and every 3 subsequent cycles, or if there is suspicion of relapse in the whole blood. Bone marrow samples are also required at the pre-HSCT visit /end of treatment visit and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required. Bone marrow assessment for blasts counts and cell counts and flow cytometry will be conducted at local lab. Bone marrow assessment data before the IC date may be used for screening if the patient has already performed bone marrow assessment 14 days prior to the planned Cycle 1 Day 1.

k. PK samples for ASP2215 will be collected on cycle 1 day 1 predose, cycle 1 day 8 predose, and at cycle 1 day 15 and day 1 predose of each subsequent cycle (within 1 hour before drug administration). See Section 7.6.

l. Whole blood and buccal swab collected at day 1 for optional pharmacogenomics study. Optional pharmacogenomics study is not conducted in China.

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

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

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

p. Includes Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items. The Brief Fatigue Inventory will be administered at cycle 1 day 1 predose, cycle 1 day 8 (± 1 day), day 15 (± 1 day), cycle 2 day 1 (± 2 days), day 15 (± 1 day) and all subsequent cycles day 1 (± 2 days). Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days).

q. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

r. 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 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 Interruption, Reduction or Escalation in Dose of the Study Drug].

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

Table 2 Schedule of Assessments for ASP2215 Arm in PK cohort

Activity	Screening (Day -14 to -1)	Cycle 1					Cycle 2		Subsequent Cycles
		Day 1	Day 4 ± 1	Day 8 ± 1	Day 9	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
Signed ICF[a]	X								
Hospitalization[b]		X				X			
Medical and Disease History	X								
Randomization		X[r]							
Physical Examination[d]	X	X[c]	X	X		X	X	X	X
Vital Signs	X	X[c]	X	X		X	X	X	X
ECOG Performance	X	X[c]				X	X	X	X
Prior and Concomitant Medications	X[e]	X	X	X		X	X	X	X
Pregnancy Test for Woman of Childbearing Potential	X[f]	X					X		X
Chest X-ray (or CT of chest)[q]	X								
12-lead ECG[g]	X[i]	X		X[u]	X[u]	X[v]	X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[h]	X[i]	X[c]	X[c]	X[c]		X[c]	X[c]	X[c]	X[c]
Thyroid Function Test	X								X[w]
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	X								
MUGA or ECHO[j]	X								
FLT3 Mutation Status[k] (bone marrow aspirate or whole blood)	X								
Bone Marrow Aspiration and/or Biopsy	X[l]						X[l]		X[l]
AE/SAE Assessment	X	X	X	X		X	X	X	X
PK (whole blood samples for plasma PK)		X[m, n]		X[m]		X[m, n]	X[m]		X[m]
PGx[o]		X							
Patient Reported Outcome Tools[s, t]		X[c]		X[s]		X[s]	X	X[s]	X
EQ-5D-5L[t]		X[c]					X		X
Resource Utilization		X[c]					X		X
IRT Transaction Required[r]	X	X					X		X
ASP2215 Dosing at the Clinic[p]		X	X	X		X	X	X	X

AE: adverse event; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EDTA: ethylenediaminetetraacetic acid; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; FLAG: fludarabine, cytarabine and granulocyte colony-stimulating factor; FLT3: FMS-like tyrosine kinase; FMS-like tyrosine kinase; ICF: Informed Consent Form; INR: international normalization ratio; IRT: interactive response technology; LoDAC: low-dose cytarabine; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; MUGA: multigated acquisition scan; PGx: pharmacogenomics; PK: pharmacokinetic; PT: prothrombin time; SAE: serious adverse event

Footnotes continued on next page

a. For the subjects who will be enrolled at a PK cohort site, specific informed consent form (to explain additional blood sampling for PK measurement in the ASP2215 arm)

b. The subjects who are randomized to ASP2215 will be requested to be hospitalized from the date of C1D1 and C1D15 to at least the completion of PK sample collection at 24 hours post dose planned on C1D2 and C1D16, respectively.

c. Obtained predose.

d. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

e. Includes medications taken within 28 days prior to cycle 1 day 1.

f. Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.

g. Screening ECG is required. ECG assessment will be evaluated at predose of cycle 1 day 1, cycle 1 day 8, cycle 1 day 15 and day 1 of each subsequent cycle. Predose assessments should be taken within 1 hour before drug administration. 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. The mean QTcF of the triplicate ECG tracings based on central reading will be used for final treatment decisions and AE reporting. If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less) by central reading within 14 days, the subject may resume dosing at the reduced dose.

h. Urinalysis only required at screening. Uric acid will be tested on days 1, 4, 8, and 15 in cycle 1. Additional laboratory tests should be performed according to institutional standard of care.

i. Subjects may be screened and randomized from local labs only. However, samples must also be submitted for central lab. Labs and/or ECG can be repeated during screening period.

j. MUGA scans or ECHO (per standard of care) are to be performed at screening for subjects with history of congestive heart failure New York Heart Association Class 3 or 4 (unless MUGA scans or ECHO performed either within 1 month prior revealed left ventricular ejection fraction ≥ 45%).

k. FLT3 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. Subjects must be screened by the central laboratory. All subjects including those with rapidly proliferative disease must have screening sample sent to the central lab. If central result is negative, central FLT3 testing can be repeated during screening period. Bone marrow sample before the informed consent date may be used for screening if the patient has already performed bone marrow assessment within 14 days prior to the planned Cycle 1 Day 1, and the sample should be stored at 2˚C to 8˚C and can be started testing within 7 days after sample collection.

l. Bone marrow samples are required during screening, cycle 2 day 1 and cycle 3 day 1. For subjects who do not achieve a CRc (CR, CRp or CRi), the bone marrow assessments will be repeated at day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow sampling will be repeated on 1 month after the date of remission and every 3 subsequent cycles or if there is suspicion of relapse in the whole blood. Bone marrow samples are also required at the pre-HSCT visit /end of treatment visit and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required. Bone marrow assessment for blasts counts and cell counts and flow cytometry will be conducted at local lab. Bone marrow assessment data before the IC date may be used for screening if the patient has already performed bone marrow assessment 14 days prior to the planned Cycle 1 Day 1.

m. PK samples for ASP2215 will be collected on cycle 1 day 1 predose, cycle 1 day 8 predose, and at cycle 1 day 15 and day 1 predose of each subsequent cycle (within 1 hour before drug administration). See [Section 7.6 Analysis of Pharmacokinetics].

n. For the subjects who are randomized to ASP2215 arm at a PK cohort site, PK samples will be collected additionally at 0.5, 1, 2, 3, 4, 6, 10, 24 hours post dose on C1D1 and C1D15. PK sample collection at 24 hours post dose should be done prior to ASP2215 administration on C1D2 and C1D16.

o. Whole blood and buccal swab collected at day 1 for optional pharmacogenomics study. Optional pharmacogenomics study is not conducted in China.

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

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

s. Includes Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items. The Brief Fatigue Inventory will be administered at cycle 1 day 1 predose, cycle 1 day 8 (± 1 day), day 15 (± 1 day), cycle 2 day 1 (± 2 days), day 15 (± 1 day) and all subsequent cycles day 1 (± 2 days). Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days).

t. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

u. 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 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 Interruption, Reduction or Escalation in Dose of the Study Drug].

v. A cycle 1 day 15 ECG will be taken predose and 4 hours post dose on C1D15.

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

Table 3 Schedule of Assessments for Chemotherapy Arm

Activity	Screening (Day -14 to -1)	Cycle 1				Cycle 2		Subsequent Cycles
		Day 1	Day 4 ± 1	Day 8 ± 1	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
Signed ICF	X							
Medical and Disease History	X							
Randomization		X[o]						
Physical Examination[b]	X	X[a]	X	X	X	X	X	X
Vital Signs	X	X[a]	X	X	X	X	X	X
ECOG Performance	X	X[a]			X	X	X	X
Prior and Concomitant Medications	X[c]	X	X	X	X	X	X	X
Pregnancy Test for Woman of Childbearing Potential	X[d]	X				X		X
Chest X-ray (or CT of chest)[n]	X							
12-lead ECG[e]	X[g]	X			X	X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[f]	X[g]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Thyroid Function Test[r]	X							X[r]
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	X							
MUGA or ECHO[h]	X							
FLT3 Mutation Status[i] (bone marrow aspirate or whole blood)	X							
Bone Marrow Aspiration and/or Biopsy	X[j]				X[j]	X[j]		X[j]
AE/SAE Assessment	X	X	X	X	X	X	X	X
PGx[k]		X						
Patient Reported Outcome Tools[p,q]		X[a]		X[p]	X[p]	X	X[p]	X
EQ-5D-5L[q]		X[a]				X		X
Resource Utilization		X[a]				X		X
IRT Transaction Required[o]	X	X				X		X
LoDAC Dosing		See Footnote[l]						
MEC or FLAG Dosing		See Footnote[m]						

AE: adverse event; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EDTA: ethylenediaminetetraacetic acid; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; FLAG: fludarabine, cytarabine and granulocyte colony-stimulating factor; FLT3: FMS-like tyrosine kinase; ICF: Informed Consent Form; INR: international normalization ratio; IRT: interactive response technology; LoDAC: low-dose cytarabine; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; MUGA: multigated acquisition scan; PGx: pharmacogenomics; PT: prothrombin time; SAE: serious adverse event

Footnotes continued on next page

a. Obtained predose.

b. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

c. Includes medications taken within 28 days prior to cycle 1 day 1.

d. Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.

e. Screening ECG is required. ECG assessment will be evaluated at predose of cycle 1 day 1, cycle 1 day 15 and day 1 each subsequent cycle. Predose assessments should be taken within 1 hour before drug administration. 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 7.5.5 Electrocardiograms].

f. Urinalysis only required at screening. Uric acid will be tested on days 1, 4, 8, and 15 in cycle 1. Additional laboratory tests should be performed according to institutional standard of care.

g. Subjects may be screened and randomized from local labs only. However, samples must also be submitted for central lab. Labs and/or ECG can be repeated during Screening period.

h. MUGA scans or ECHO (as per standard of care) are to be performed at screening for subjects with history of congestive heart failure New York Heart Association Class 3 or 4 (unless MUGA scans or ECHO performed either within 1 month prior revealed left ventricular ejection fraction ≥ 45%).

i. FLT3 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. Subjects must be screened by the central laboratory. All subjects including those with rapidly proliferative disease must have screening sample sent to the central lab. If central result is negative, central FLT3 testing can be repeated during screening period. Bone marrow sample before the informed consent date may be used for screening if the patient has already performed bone marrow assessment within 14 days prior to the planned Cycle 1 Day 1, and the sample should be stored at 2˚C to 8˚C and can be started testing within 7 days after sample collection.

j. For MEC and FLAG, bone marrow samples are required during screening and at cycle 2 day1. Also, an additional bone marrow sample is required at cycle 1 day 15 or later, per institutional guidelines, to assess the need for a second cycle. For LoDAC, bone marrow samples are required during screening and at cycle 2 day 1 and at cycle 3 day1. For subjects who do not achieve a CRc (CR, CRp or CRi), the bone marrow assessments will be repeated at day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow sampling will be repeated at 1 month after the date of remission and at every 3 subsequent cycles or if there is suspicion of relapse in the whole blood. Bone marrow samples are also required at the end of treatment visit and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required. Bone marrow assessment for blasts counts and cell counts and flow cytometry will be conducted at local lab. Bone marrow assessment data before the IC date may be used for screening if the patient has already performed bone marrow assessment 14 days prior to the planned Cycle 1 Day 1.

k. Whole blood and buccal swab collected at day 1 for optional pharmacogenomics study. Optional pharmacogenomics study is not conducted in China.

l. LoDAC dosing may continue past cycle 2.

m. Additional clinic visits are allowed per institutional guidelines for subjects receiving MEC (days 1 through 5) or FLAG (days 1 through 6). MEC and FLAG are administered for up to 2 cycles depending on response and safety assessments as described in [Section 5.1 Dosing and Administration of Study Drugs and Other Medications].

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

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

p. Includes Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items. The Brief Fatigue Inventory will be administered at cycle 1 day 1 predose, cycle 1 day 8 (± 1 day), day 15 (± 1 day), cycle 2 day 1 (± 2 days), day 15 (± 1 day) and all subsequent cycles day 1 (± 2 days). Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days).

q. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

r. For subjects receiving LoDAC, thyroid function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1, etc.).

Table 4 Treatment Schedule of Assessments for Crossover Extension

Activity	Screening[l]	Cycle 1					Cycle 2		Subsequent Cycles
		Day 1	Day 4 ± 1	Day 8 ± 1	Day 9	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
Signed ICF for COE portion of the study	X								
Physical Examination[b]	X	X[a]	X	X		X	X	X	X
Vital Signs	X	X[a]	X	X		X	X	X	X
ECOG Performance	X	X[a]				X	X	X	X
Prior and Concomitant Medications	X[c]	X	X	X		X	X	X	X
Pregnancy Test for Woman of Childbearing Potential	X	X[d]					X		X
12-lead ECG[e]	X	X[g]		X[j]	X[j]	X	X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[f]	X	X[a,g]	X[a]	X[a]		X[a]	X[a]	X[a]	X[a]
Thyroid Function Test[k]	X								X
AE/SAE Assessment	X	X	X	X		X	X	X	X
Enrollment and IRT Transaction Required[h]		X					X		X
ASP2215 Dosing at the Clinic[i]		X	X	X		X	X	X	X

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ICF: Informed Consent Form; IRT: interactive response technology; SAE: serious adverse event

a. Obtained predose.

b. Weight measurement should be performed at day 1 of each cycle.

c. Includes medications taken within 28 days prior to C1D1. If EoT was performed within 28 days prior to C1D1, only includes medication after EoT of salvage chemotherapy arm and prior to C1D1.

d. Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.

e. ECG assessment will be evaluated at predose of cycle 1 day 1, cycle 1 day 8, cycle 1 day 15 and day 1 of each subsequent cycle. Predose assessments should be taken within 1 hour before drug administration. 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. The mean QTcF of the triplicate ECG tracings based on central reading will be used for final treatment decisions and AE reporting. If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less) by central reading within 14 days, the subject may resume dosing at the reduced dose.

f. Uric acid will be tested on days 1, 4, 8, and 15 in cycle 1. Additional laboratory tests should be performed according to institutional standard of care.

g. Subjects may be enrolled from local labs only. However, samples must also be submitted for central lab.

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

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

j. 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 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 Interruption, Reduction or Escalation in Dose of the Study Drug].

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

l. Screening assessment can be performed from the results of the assessments of the EOT of salvage chemotherapy arm if the EOT was performed within 14 days of the planned start of COE C1D1. Eligibility assessments (clinical labs and ECG) can be repeated to ensure the subject meets eligibility for COE. The start of COE can be extended to repeat safety assessments with the approval of the Medical Monitor.

Table 5 Post-treatment Schedule of Assessments for ASP2215 Arm and Chemotherapy Arm

Activity	pre-HSCT Visit / End of Treatment Visita	30-Day Follow-up (+ 7 days)	Long-term Follow-up (+/- 7 days) g
Physical Examination	X[b]		
Vital Signs	X[b]		
ECOG Performance	X[b]		
Concomitant Medications	X		
Pregnancy Test for Woman of Childbearing Potential	X		
12-lead ECG	X		
Clinical Laboratory Tests (chemistry, hematology, coagulation)	X[b]		
Thyroid Function Tests	X		
Bone Marrow Aspiration and/or Biopsy	X[c]		
Patient Reported Outcome Tools[h, i]	X		
EQ-5D-5L[i]	X	X	X
Resource Utilization	X		
AE/SAE Assessment[j]	X	X[d, e]	X[f]
IRT Transaction Required	X		
Survival and Subsequent Antileukemic Treatments and Their Outcomes		X[f]	X

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EDTA: ethylenediaminetetraacetic acid; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; FLT3: FMS-like tyrosine kinase; HSCT: hematopoietic stem cell transplant; IRT: interactive response technology; SAE: serious adverse event

a. End of treatment visit is to be performed within 7 days after treatment discontinuation, and before initiation of any other systemic antileukemic treatment or conditioning regimen for HSCT. Once protocol version 7.0 has been implemented, no follow-up visits are required after the end of treatment. Subjects in long-term follow-up will discontinue from the study, as further survival data are no longer needed.
b. Does not need to be repeated if collected at a regularly scheduled visit within 3 days of the end of treatment visit.
c. Bone marrow aspiration and/or biopsy for morphology are preferred, but biopsy may be omitted if the aspirate is considered to be adequate. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of peripheral blood should be collected instead. Bone marrow assessment for blasts counts and cell counts and flow cytometry will be conducted at local lab.
d. AE collection will continue during HSCT for subjects who plan to resume ASP2215 treatment after HSCT.
e. Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.
f. Only SAE data that are related to ASP2215 will be collected.
g. Telephone contact every 3 months. Ad hoc contact will be required during interim analysis. Long-term Follow-up is not applicable for the subjects enters COE.
h. Includes Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items. The Brief Fatigue Inventory will be administered at preHSCT/end of treatment visit. Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items will be administered at preHSCT/end of treatment visit.
i. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

Table 6 Post-treatment Schedule of Assessments for Crossover Extension

Activity	pre-HSCT Visit / End of Treatment Visita	30-Day Follow-up (+ 7 days)
Physical Examination	X[b]	
Vital Signs	X[b]	
ECOG Performance	X[b]	
Concomitant Medications	X	
Pregnancy Test for Woman of Childbearing Potential	X	
12-lead ECG	X	
Clinical Laboratory Tests (chemistry, hematology, coagulation)	X[b]	
Thyroid Function Tests	X	
AE/SAE Assessment	X	X[c,d]
IRT Transaction Required	X	

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HSCT: hematopoietic stem cell transplant; IRT: interactive response technology; SAE: serious adverse event

a. End of treatment visit is to be performed within 7 days after treatment discontinuation, and before initiation of any other systemic antileukemic treatment or conditioning regimen for HSCT.

b. Does not need to be repeated if collected at a regularly scheduled visit within 3 days of the end of treatment visit.

c. AE collection will continue during HSCT for subjects who plan to resume ASP2215 treatment after HSCT.

d. Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs. SAE data that is related to ASP2215 will be collected after 30-Day Follow-up as well.

1 INTRODUCTION

1.1 Background

Over 90% of leukemia cases are diagnosed in adults 20 years of age and older, among whom the most common types are chronic lymphocytic leukemia (35%) and acute myeloid leukemia (AML) (32%) [American Cancer Society, 2014]. The median age at diagnosis is 67 years of age, with 54% of patients diagnosed at 65 years or older [O'Donnell et al, 2012]. It was estimated that 18860 people (11530 men and 7330 women) were to be diagnosed with AML, and 10460 were to die from the disease in 2014 in the United States [American Cancer Society, 2014]. While 60% to 80% of younger patients achieve a complete remission (CR) with standard therapy, only about 30% to 40% of the overall patient population has long-term disease-free survival [Tallman, 2005]. Outcomes are worse for patients aged 60 years or over, with CR rates in the range of 40% to 55% and poor long-term survival rates.

Along with age, remission rates and overall survival (OS) depend on a number of other factors, including cytogenetics, previous bone marrow disorders (such as myelodysplastic syndrome [MDS]) and comorbidities. Currently, there is no effective cure for the disease.

FMS-like tyrosine kinase (FLT3) is a member of the class III receptor tyrosine kinase (TK) 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 overexpressed in the majority of AML cases. In addition, activated FLT3 with internal tandem duplication (ITD) in and around the juxtamembrane domain and tyrosine kinase domain (TKD) mutations at around D835 in the activation loop are present in 28% to 34% and 11% to 14% of AML cases, respectively [Schlenk & Döhner, 2009]. These activated mutations in FLT3 are oncogenic and show transforming activity in cells [Yamamoto et al, 2001]. Patients with FLT3-ITD mutation show poor prognosis in clinical studies, with a higher relapse rate, a shorter duration of remission from initial therapy (6 months versus 11.5 months for those without FLT3-ITD mutations) as well as reduced disease-free survival (16% to 27% versus 41% at 5 years) and OS (15% to 31% versus 42% at 5 years) [Patel et al, 2012; Gale et al, 2008; Yanada et al, 2005; Tiesmeier et al, 2004; Moreno et al, 2003]. The incidence of relapse after hematopoietic stem cell transplant (HSCT) is also higher for patients with FLT3-ITD (30% versus 16% at 2 years for those without FLT3-ITD mutations) [Brunet et al, 2012]. Similar to their prognosis for first line therapy, patients with relapsed/refractory FLT3-mutation positive AML have lower remission rates with salvage chemotherapy, shorter durations of remission to second relapse and decreased OS relative to FLT3-mutation negative patients [Konig & Levis, 2015; Chevallier et al, 2011; Levis et al, 2011].

AXL tyrosine kinase (AXL) is a member of TAM family (Tyro-3, AXL and Mer) receptor TKs 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 AML [Linger et al, 2008]. AXL overexpression in AML confers drug resistance [Hong et al, 2008] and is associated with adverse prognosis [Ben-Batalla et al, 2013; Rochlitz et al, 1999]. AXL inhibition suppresses the growth of human FLT3-positive AML in vivo

[Park et al, 2013]. In addition, AXL inhibition is also effective against FLT3-negative AML expressing AXL in vivo [Ben-Batalla et al, 2013].

ASP2215 is a new chemical entity discovered by Astellas Pharma Inc. in collaboration with Kotobuki Pharmaceutical Co., Ltd. ASP2215 has an inhibitory effect on TKs, mainly FLT3, AXL and anaplastic lymphoma kinase (ALK). ASP2215 demonstrated favorable efficacy in a non-clinical AML model, with 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 FLT3-ITD, FLT3-D835Y or FLT3-ITD-D835Y.

There is no universally accepted standard chemotherapy regimen for patients with relapsed or refractory AML and the National Comprehensive Cancer Network (NCCN) guideline for AML strongly recommends clinical trial as the first option for any patient. The guidelines also provide a list of commonly used regimens for relapsed/refractory AML. The choice of specific regimen is based on factors such as prior treatment, eligibility for allogeneic HSCT and institutional preference. Additionally, there are no definitive studies that demonstrated superiority of any single regimen. In this study, a limited list of regimens listed in NCCN guidelines are provided as comparator chemotherapy regimens for the investigators to choose from. Similar to the guidelines, both aggressive (mitoxantrone, etoposide and intermediate-dose cytarabine [MEC] and fludarabine, cytarabine and granulocyte colony-stimulating factor [FLAG]) and less-aggressive (low-dose cytarabine [LoDAC]) regimens are included in the study.

1.2 Non-clinical and Clinical Data

1.2.1 Non-clinical Data

ASP2215 inhibited activities of FLT3, nucleophosmin-1 gene-ALK, leukocyte receptor TK, ALK and AXL kinases at 1 and 5 nmol/L and tropomyosin receptor kinase A, ROS, RET and MER kinases at 5 nmol/L by over 50%. ASP2215 inhibited FLT3, echinoderm microtubule-associated protein-like 4-ALK variant 1 and KIT kinase activities with the half maximal inhibitory concentration (IC_{50}) values of 0.291, 1.2 and 229 nmol/L, respectively.

ASP2215 inhibited each radioligand binding to adenosine A1 receptor (rat), serotonin 5-hydroxytryptamine receptor 1 ($5HT_1R$) (nonselective, rat), serotonin 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) (human) and sigma receptor (nonselective, guinea pig) with IC_{50} values of 4.57, 4.90, 0.190 and 0.615 μmol/L, respectively.

ASP2215 inhibited human $5HT_{2B}R$ function in a cell function assay with an IC_{50} value of 5.82 μmol/L without showing agonistic activity.

ASP2215 inhibited the cell growth of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y and FLT3-ITD-D835Y with IC_{50} values of 1.8, 1.6 and 2.1 nmol/L, respectively. ASP2215 inhibited the growth of MV4-11 cells with IC_{50} value of 0.92 nmol/L. In MV4-11 cells, treatment of ASP2215 at 0, 0.1, 1 and 10 nmol/L resulted in FLT3 phosphorylation of 100%, 86%, 19% and 7%, respectively.

ASP2215 induced significant growth inhibition of MV4-11 tumors and tumor regression in vivo. Further, ASP2215 at 6 and 10 mg/kg per day induced complete tumor regression for 4 and 6 out of 6 mice, respectively. Body weight of the mice treated with ASP2215 was not affected at any tested doses.

These results indicate ASP2215 should show the antitumor efficacy against AML subjects with FLT3-ITD and FLT3 mutation at D835.

The IC_{50} value of ASP2215 against FLT3 kinase was about 800-fold lower than that against KIT kinase, and neutropenia was not observed in the toxicity studies in rats and dogs.

In Caco-2 cells, the permeability of ASP2215 was between that of known low and high permeability markers. ASP2215 was a substrate for P-glycoprotein (P-gp), but not a substrate for breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3 or organic cation transporter 1. ASP2215 demonstrated a potential to inhibit BCRP and multidrug and toxin extrusion protein 1 (MATE1) at clinically relevant concentrations of ASP2215. However, preliminary results from the drug-drug interaction assessment of coadministration of ASP2215 and cephalexin, a MATE1 substrate, in Relapse/Refractory AML subjects indicate lack of a clinically-significant interaction between ASP2215 and MATE1 substrate [see Section 1.2.2.1 Clinical Pharmacokinetics and Pharmacodynamics].

No major human-specific ASP2215 metabolites were formed by liver microsomes or hepatocytes. The main enzyme involved in the metabolism of ASP2215 was estimated to be cytochrome P450 (CYP)3A4. ASP2215 has a potential to induce CYP enzyme activities (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5) and messenger RNA levels (CYP2B6, CYP2C8, CYP2C9 and CYP3A4). However, these results should be interpreted with caution because these effects were not uniformly observed in all donor samples and the concentration-dependency of these effects could not be evaluated. For CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2D6 inhibition, IC_{50} values were > 100 µmol/L. Very weak direct inhibition of CYP2C19 and CYP3A was observed. Overall, ASP2215 showed minimal direct inhibition of CYP enzymes at clinically relevant concentrations.

1.2.2 Clinical Data

1.2.2.1 Clinical Pharmacokinetics and Pharmacodynamics

The pharmacokinetic parameters of unchanged drug after single and multiple dosing of ASP2215 to AML subjects were investigated in the dose escalation cohort of Study 2215-CL-0101. Assessment of observed trough concentration (C_{trough}) over time for individual subjects (both dose escalation and dose expansion cohorts) showed that in most subjects, the trough concentration of ASP2215 appeared to reach steady state by day 15 of multiple administrations of ASP2215 from 20 to 120 mg once daily.

Plasma inhibitory assay (PIA) from the samples collected predose and postdose on days 1, 8, 15 and 29 demonstrated sustained inhibition of phospho-FLT3 at doses 80 mg and higher.

The effect of strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers on ASP2215 exposure was assessed in Relapse/Refractory AML subjects (Study 2215-CL-0101) and healthy subjects (Study 2215-CL-0108). In Relapse/Refractory AML subjects, there was a less than 2-fold increase in ASP2215 exposure when ASP2215 was coadministered with moderate or strong CYP3A4 inhibitors. In healthy subjects, ASP2215 exposure increased approximately 2-fold when ASP2215 was coadministered with itraconazole, a strong CYP3A4 and P-gp inhibitor. Coadministration of ASP2215 with rifampicin, a strong CYP3A4 inducer, resulted in an approximate 70% decrease in ASP2215 exposure. Collectively, these data support monitoring subjects who require concomitant medications that are strong CYP3A4 inhibitors and restricting use of concomitant medications that are strong CYP3A4 inducers.

Preliminary results from a drug-drug interaction assessment in a subset of Relapse/Refractory AML subjects (2215-CL-0101) indicate cephalexin (MATE 1 substrate) exposure was comparable after single dose administration of cephalexin alone and in combination with ASP2215 (administered once daily). These results suggest coadministration of MATE1 substrates and ASP2215 is not expected to result in a clinically-relevant drug-drug interaction.

1.2.2.2 Clinical Efficacy

As of the cutoff date of 01 April 2016, a clinical study in AML patients and 3 studies in healthy volunteers are complete. In addition, 1 study in patients with solid tumors, 4 studies in AML patients and 1 study in combination with erlotinib in patients with Non-small cell lung cancer (NSCLC) whose tumors harbor an Epidermal Growth Factor Receptor (EGFR) activating mutation (EGFR mutation positive (EGFRm+) NSCLC) are ongoing. Overall, 147 healthy volunteers and 319 patients have received at least 1 dose of gilteritinib.

Data from Study 2215-CL-0101 as of the cutoff date of 24 November 2015, a phase 1/2 study in patients with relapsed/refractory AML are provided. Patients were assessed for FLT3 mutational status by local lab at the screening visit.

Primary analysis results from Study 2215-CL-0101 indicate that of the 252 patients who received at least 1 dose of gilteritinib, the majority of composite complete remission (CRc) and partial remission (PR) events were observed in FLT3-mutation positive patients in dose groups of 80 mg and greater. The derived response rate (CRc + PR) at the end of treatment in the 191 FLT3-mutation positive patients was 48.7% overall and 66.7%, 55.4%, 47.2%, 60.0% and 50.0% in the 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups, respectively.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 ASP2215

The non-clinical and clinical studies which are referred to in this section are described in more detail in the ASP2215 Investigator's Brochure [2016].

1.3.1.1 ASP2215 Non-clinical Data

Major findings in the safety pharmacology studies were vomiting, positive fecal occult blood and increased/decreased blood Ca2+ in dogs, and decreased urination and defecation in rats. In the oral 13-week repeated dose toxicity study in rats, and the 4- and 13-week repeated dose toxicity studies in dogs, mortality occurred at 20 mg/kg per day, and at 10 and 5 mg/kg per day, respectively. With respect to other major target organ toxicities, effects on the urinary bladder, epithelial tissue, gastrointestinal tract, lymphohematopoietic system, eye, liver, kidney and/or lung were observed in rats and dogs at 2.5 mg/kg per day or more. All major findings were reversible and monitorable.

Gilteritinib has a potential to induce genotoxicity in vivo.

Gilteritinib showed suppressed fetal growth, embryo-fetal deaths and teratogenicity in the embryo-fetal development study in rats.

Gilteritinib showed no potential to induce phototoxicity in cultured mammalian cells.

When gilteritinib was dosed to juvenile rats from PND 4 to 42, the minimum lethal dose level was 2.5 mg/kg per day and this dose level was lower than that (20 mg/kg per day) in adult rats in the 13-week dose study. In the preliminary (non-GLP) dose range finding study (dosing from PND 4 to 21), gastrointestinal bleeding indicated as abnormal stool color (dark red) were noted at 10 mg/kg per day and higher, which was not noted in adult rats in the 13-week dose study.

1.3.1.2 ASP2215 Clinical Data

As of the cutoff date of 01 April 2016, a clinical study in AML patients and 3 studies in healthy volunteers are complete. In addition, 1 study in patients with solid tumors, 4 studies in AML patients and 1 study in combination with erlotinib in patients with NSCLC whose tumors harbor an EGFR activating mutation (EGFRm+ NSCLC) are ongoing. Overall, 147 healthy volunteers and 319 patients have received at least 1 dose of gilteritinib.

The majority of the 249 patients (98.8%) in Study 2215-CL-0101 who received at least 1 dose of gilteritinib experienced at least 1 treatment-emergent adverse event (TEAE), and 74.6% of patients experienced at least 1 TEAE considered by the Investigator to be possibly or probably related to study drug. Common TEAEs (occurring in at least 10% of patients) included febrile neutropenia, thrombocytopenia, constipation, diarrhea, nausea, stomatitis, vomiting, asthenia, fatigue, peripheral edema, pyrexia, pneumonia, sepsis, fall, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood alkaline phosphatase, increased blood creatinine, decreased neutrophil count, decreased platelet count, decreased appetite, hypoalbuminemia, hypocalcaemia, hypokalemia, hypomagnesaemia, hyponatraemia, arthralgia, acute myeloid leukaemia, dizziness, dysgeusia, headache, cough, dyspnea, epistaxis, hypoxia and hypotension. No clear dose-dependent patterns were observed for overall TEAEs, TEAEs of grade 3 or higher, drug-related TEAEs, serious TEAEs or drug-related serious TEAEs. Ninety-five patients experienced TEAEs leading to death. The incidence of deaths in the 20 mg, 40 mg, 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups was 31.3%, 37.5%, 45.8%, 30.0%, 41.7%, 40.0% and

33.3%, respectively. Twenty-eight patients experienced dose-limiting toxicities (DLTs). None of the doses below 450 mg met the criteria for pausing enrollment. Thus, the maximum tolerated dose (MTD) in Study 2215-CL-0101 is considered to be 300 mg.

Additionally, primary analysis of the relationship between gilteritinib plasma concentration and Fridericia-corrected QT interval (QTcF) change from baseline (ΔQTcF) was performed on data from the 2215-CL-0101 study. This assessment included 1801 observations from 249 patients. A concentration related increase in ΔQTcF was observed; however, the mean ΔQTcF at the mean steady-state C_{max} was predicted to be less than 10 msec and the upper 1-sided 95% confidence interval were predicted to be less than 10 msec and not considered as clinically significant. Additionally, less than 5% of relapse/refractory subjects had a maximum post baseline QTcF interval > 500 msec and approximately 8% of subjects had a > 60 msec change in their maximum Corrected QT interval (QTc) relative to baseline. Although these data indicate clinically relevant QTc prolongation is not anticipated, the sponsor has implemented additional eligibility criteria for enrollment in gilteritinib clinical trials (exclusion of subjects with QTcF > 450 ms, long QT syndrome, hypokalemia, or hypomagnesemia) and electrocardiogram (ECG) assessments at multiple timepoints. Astellas will continue to monitor for arrhythmias and clinically significant QT prolongation during the conduct of gilteritinib clinical trials.

An exposure-related increase was observed between gilteritinib plasma concentration and Creatine kinase (CK) change from baseline (ΔCK) in patients with relapsed/refractory AML based on pharmacokinetic/ pharmacodynamic modeling that included 1519 time-matched data points (n = 243 patients). Additionally, the incidence of higher Common Terminology Criteria for Adverse Events (CTCAE) grades related to elevated CK appears to have increased with increasing gilteritinib dose. However, almost all of the observed elevations in CK laboratory values were grade 1 and grade 2, and the incidence of grade ≥ 3 related adverse events reported in the study population was low (4.4%). The preferred term of blood creatine phosphokinase increased has been identified as an expected Adverse Drug Reaction (ADR) of gilteritinib.

There was a trend towards an increasing incidence of AEs and shifts in laboratory values related to hepatotoxicity with increasing gilteritinib doses as well. Similar to ΔCK, an exposure-related increase was observed between gilteritinib plasma concentration and AST change from baseline (ΔAST) based on pharmacokinetic/pharmacodynamic modeling that included 1517 time-matched data points (n = 243) with low incidence of Grade ≥ 3 related adverse events observed (6.0%). The preferred terms of alanine aminotransferase increased and aspartate aminotransferase increased have been identified as expected ADRs.

Twenty-eight patients experienced DLTs as of the data cutoff; most (26/28) patients were in the dose expansion cohort. One patient in the 20 mg dose group experienced grade 5 intracranial hemorrhage. One patient in the 40 mg dose group experienced grade 3 toxic shock syndrome. Two patients in the 80 mg dose group experienced DLTs including grade 3 conjunctival edema and grade 5 septic shock. Seven patients in the 120 mg dose group experienced the following DLTs: grade 3 hypoxia and pleural effusion; grade 3 hematochezia

and lower gastrointestinal hemorrhage; grade 5 ventricular fibrillation; grade 4 renal tubular necrosis; grade 3 hyperbilirubinemia; grade 3 blood lactate dehydrogenase increased; and grade 3 liver function test abnormal. Twelve patients in the 200 mg dose group experienced DLTs including: grade 3 transaminases increased (2 patients); grade 3 abdominal pain; grade 3 hematochezia; grade 3 intestinal perforation; grade 3 blood creatine phosphokinase increased; grade 3 electrocardiogram QT prolonged, grade 4 hypoxia and grade 3 acute promyelocytic leukemia differentiation syndrome; grade 3 gamma-glutamyltransferase increased; grade 3 hypotension; grade 3 dizziness and myalgia; and grade 3 hypotension and acidosis and grade 4 hypoxia. Three patients in the 300 mg dose group experienced the following DLTs: grade 3 disseminated intravascular coagulation, grade 3 gastrointestinal hemorrhage, grade 3 hypertension and grade 3 aspartate aminotransferase increased; grade 5 pulmonary embolism; and grade 4 blood creatine phosphokinase increased and grade 3 rhabdomyolysis. Two patients in the 450 mg dose group experienced DLTs including grade 3 diarrhea and grade 3 aspartate aminotransferase increased. The MTD in Study 2215-CL-0101 is considered to be 300 mg.

Expected adverse drug reactions for ASP2215 include (by preferred term) diarrhea, peripheral edema, increased blood creatine phosphokinase, electrocardiogram QT prolonged, increased ALT, increased AST, myopathy, and posterior reversible encephalopathy syndrome.

There were 2 patients who experienced retinoic acid syndrome (differentiation syndrome) that was considered by the investigator to be related to ASP2215. FLT3 inhibitors may differentiate leukemic blasts to mature neutrophils. Patients who develop differentiation syndrome may present with increases in neutrophil counts, unexplained fever, acute respiratory distress with interstitial pulmonary infiltrates, and/or vascular capillary leak syndrome.

1.3.2 Comparative Chemotherapy Regimens

Detailed information on the toxicities and common AEs associated with the comparative chemotherapy regimens can be found within the Package Insert, Summary of Product Characteristics or local product information.

1.4 Risk-Benefit Assessment

Approximately 30% of adult AML subjects are refractory to induction therapy. Furthermore, of those who achieve CR, approximately 75% will relapse. Subjects with AML with FLT3 mutations comprise an especially poor prognosis group. Generally, there is no established standard for relapsed subjects with FLT3 mutations and less than 20% will achieve CR with subsequent treatment. Duration of remission for the small minority who achieve remission is also limited with most of the subjects relapsing.

In phase 1/2 Study (2215-CL-0101), ASP2215 has resulted in CRc in over 40% of subjects receiving 80 mg or higher dose. The median survival was over 7 months in 120 mg dose level. The majority of subjects in the trial have received multiple treatments prior to receiving ASP2215. Furthermore, ASP2215 was well tolerated at the proposed doses in this study.

Subjects with AML who relapse or do not respond to initial treatment have a very poor prognosis. Although there are various chemotherapy options available, they are by no means curative. The response to salvage chemotherapy is poor, and especially for subjects with FLT3 mutation. Although it is not known whether response to ASP2215 treatment would lead to longer survival, in light of the very poor prognosis of relapsed or refractory AML subjects with FLT3 mutations, the potential for ASP2215 to improve outcome outweighs the risk of potential toxicities.

2 STUDY OBJECTIVES, DESIGN AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to determine the clinical benefit of ASP2215 therapy in subjects with FLT3-mutated AML who are refractory to or have relapsed after first-line AML therapy as shown with OS compared to salvage chemotherapy.

2.1.2 Secondary Objectives

The key secondary objectives are to:

- Determine the overall efficacy in event-free survival (EFS) of ASP2215 compared to salvage chemotherapy.
- Determine the overall efficacy in CR rate of ASP2215 compared to salvage chemotherapy.

The secondary objectives are to evaluate the safety and efficacy of ASP2215 therapy versus salvage chemotherapy in terms of:

- leukemia-free survival (LFS)
- duration of remission
- CRc rate
- transplantation rate
- patient reported fatigue (Brief Fatigue Inventory [BFI])
- adverse events (AEs), safety labs, vital signs, electrocardiograms (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance scores
- evaluate the PK of ASP2215 therapy in the Chinese population

2.1.3 Exploratory Objectives

Evaluate the safety and efficacy of ASP2215 therapy versus salvage chemotherapy in terms of:

- Pharmacogenomics (PGx)
- FLT3 gene mutation status
    - mutation types and frequency
    - relationship to efficacy and safety
- exploratory (predictive) biomarkers of ASP2215 activity

- resource utilization in this study population including hospitalization, blood transfusion, antibiotic iv infusions, medication for AEs and opioid usage
- patient reported dyspnea (Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Forms [FACIT-Dys-SF])
- patient reported signs, symptoms and impacts of AML (Functional Assessment of Cancer Therapy-Leukemia [FACT-Leu], dizziness and mouth sore items)
- EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L)

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is phase 3, open-label, multicenter, randomized study to compare the efficacy and safety of ASP2215 therapy to salvage chemotherapy in FLT3-mutated AML subjects who are refractory to or have relapsed after first-line AML therapy. Approximately 50 centers in China, Russia, Singapore, Thailand, and Malaysia will participate in this study.

Three hundred eighteen subjects will be randomized. The randomization of the 318 subjects will be in a 1:1 ratio to receive ASP2215 or salvage chemotherapy. Subjects will enter the screening period up to 14 days prior to the start of treatment. Prior to randomization, the investigator will preselect a salvage chemotherapy regimen for each subject; options will include LoDAC, MEC or FLAG. The randomization will be stratified by response to first-line therapy and preselected salvage chemotherapy. Subjects will be administered treatment over continuous 28-day cycles and per institutional guidelines for chemotherapy product preparation and administration. The dose and duration of study treatments are outlined in [Section 5.1.1 Dose/Dose Regimen and Administration Period] of the protocol.

Two (or more) study sites in China will be designated as a “pharmacokinetic analysis site” (PK analysis site). Approximately 20 Chinese subjects (10 male and 10 female subjects) (they will be included in 318 subjects) at PK analysis sites, who are randomized to the ASP2215 arm will be allocated to the “PK cohort”. Subjects in the PK cohort will be requested to be hospitalized on Day 1 and Day15 until the completion of all the assessments. Subjects in the PK cohort will be administered ASP2215 in the same manner and undergo the same efficacy and safety assessments as other subjects except for blood sampling for additional PK analysis. For subjects in the PK cohort, written informed consent must be obtained by the specific informed consent form (ICF) explaining that more frequent blood sampling will be done.

The first 20 subjects (10 male and 10 female) randomized into ASP2215 arm at PK cohort sites will participate in PK cohort.

For subjects taking ASP2215 or LoDAC, treatment should continue until the subject meets a treatment discontinuation criterion.

Subjects receiving MEC or FLAG will receive 1 cycle of therapy and will be assessed for response on or after day 15, per institutional guidelines. If the bone marrow cellularity is 20% or greater with at least a 50% reduction in blasts, the subject may receive a second cycle of the same chemotherapy. If bone cellularity is between 5% and 20%, the investigator should

make the decision whether the subject should receive another treatment cycle or be observed for recovery. If marrow cellularity is 5% or less, the subject will be observed for recovery. Subjects achieving CR, CRi or CRp may receive a second cycle of chemotherapy at the investigator's discretion. Subjects with no response (NR) or progressive disease following cycle 1 will discontinue study treatment.

Dose adjustments for ASP2215 are described in [Section 5.1.2 Interruption, Reduction or Escalation in Dose of the Study Drug] of the protocol.

Subjects who have a donor identified and achieve a response allowing them to undergo HSCT per each institution's assessment can undergo HSCT without leaving the study. However, ASP2215 should be stopped and a pre-HSCT 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 - 90 days post HSCT
- Subject has had successful engraftment as demonstrated by absolute neutrophil count (ANC) $\geq 500/mm^3$ and platelets $\geq 20000/mm^3$ without transfusions
- Subject does not have $\geq$ grade 2 acute graft-versus-host disease (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. Subjects who do not resume ASP2215 will be followed for primary endpoint.

After treatment discontinuation, subjects will have an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up, in which a telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs. After which the subjects will enter the long-term follow-up period for collection of patient reported outcome (PRO) using EQ-5D-5L, subsequent AML treatment, remission status and survival (cause of death and date of death). The long-term follow-up will be every 3 months, for up to 3 years from the subject's end of treatment visit until the implementation and reconsent of the current protocol version 7.0, at which time they will discontinue from the study.

A formal interim analysis by an Independent Data Monitoring Committee (IDMC) will be done when approximately 50% of deaths by any cause have occurred. This analysis will be utilized to determine whether the study should be terminated earlier than planned if ASP2215 has more favorable or harmful outcome than the salvage chemotherapy group. If the interim analysis demonstrates a more favorable outcome for ASP2215, enrollment to the study may be stopped in advance. If it demonstrates a harmful outcome, the enrollment will be stopped. However, any subject continuing to derive clinical benefit from ASP2215 as assessed by the investigator will be allowed to continue treatment until they meet a discontinuation criterion as outlined in [Section 6 Discontinuation] or upon marketing authorization, commercial availability and applicable reimbursement of ASP2215 in the country of residence.

Subjects will be managed per the local institution's standard of care for safety and efficacy assessments while on study treatment after subjects reconsents under this protocol version 7.0. No data (including PK assessments) will be collected in the eCRFs after subjects' reconsent under this protocol version 7.0. Only SAEs, as defined in [Section 5.5.2 Definition of Serious Adverse Events], will be collected and reported to Astellas Pharma Inc. Product Safety & Pharmacovigilance. SAE data will be reported in the safety database. SAE collection will continue until 30 days after the last dose of study treatment. Once subjects receiving study treatment meet the study discontinuation criteria or upon marketing authorization, commercial availability and applicable reimbursement of ASP2215 in the country of residence, subjects will be discontinued from the study.

Subjects in long-term follow-up who are no longer receiving study treatment will be followed every 3 months for up to 3 years until implementation and reconsent of the current protocol version 7.0, at which time they will discontinue from the study.

The detailed assessments and procedures are presented in [Appendix 12.8]

The interim analysis of the study demonstrated a positive outcome and hence the Crossover Extension (COE) as outlined in [Section 12.7 Crossover Extension] was implemented.

2.2.2 Dose Rationale

2.2.2.1 ASP2215

In the first-in-human phase 1/2 clinical Study [2215-CL-0101], relapsed/refractory AML subjects were treated with ASP2215 at doses ranging from 20 to 450 mg administered once daily. The primary objectives for this study were to determine the safety and pharmacokinetics of ASP2215 following single and repeat dosing. In addition, preliminary efficacy as assessed by response rates was evaluated.

Clinical safety data indicated an MTD of 300 mg. Clinical efficacy data supports doses of 120 mg and greater to ensure efficacy in FLT3-mutation positive subjects. PIA has shown substantial reduction of phospho-FLT3, with > 90% inhibition at doses of 80 mg or greater. Although, none of the dose levels within the expansion cohort have reached the threshold to stop enrollment (> 20% DLT with posterior probability of 80%), 120 mg and 200 mg doses especially had low DLT rates. However, CK and AST elevations correlating with increasing dose and increasing exposure were observed. Overall, 120 mg provides a good balance of ensuring effective drug levels for virtually all subjects with a low incidence of safety concerns, while still preserving the 200 mg dose available for dose escalation.

2.2.2.2 Comparator Chemotherapy Regimens

Doses of chemotherapy regimens were taken from representative publications as listed in [Section 5.1.1.2 Comparative Drugs]. Doses used in randomized trials were chosen where available.

2.3 Endpoints

2.3.1 Primary Endpoint

- OS

2.3.2 Secondary Endpoints

Key Secondary Efficacy Endpoints

- EFS
- CR

Secondary Efficacy Endpoints

- LFS
- Duration of remission
- CRc (CR + CRi + CRp)
- Transplantation
- BFI

2.3.3 Exploratory Endpoints

- Pharmacogenomics (PGx)
- FLT3 gene mutation status
    - mutation types and frequency
    - relationship to efficacy and safety
- Exploratory (predictive) biomarkers of ASP2215 activity
- Resource utilization, including hospitalization, blood transfusion, antibiotic iv infusions, medication for AEs and opioid usage
- FACIT-Dys-SF
- FACT-Leu and dizziness and mouth sore items
- EQ-5D-5L

2.3.4 Safety Endpoints

- AEs
- Serum chemistry, hematology, coagulation and urinalysis
- Vital signs
- ECGs
- ECOG performance scores

2.3.5 Pharmacokinetics

- ASP2215 concentration in blood
- Pharmacokinetic parameters of ASP2215 in Chinese population

3 STUDY POPULATION

3.1 Selection of Study Population

FLT3-mutated subjects with relapsed or refractory AML after first-line therapy will be selected for this study. Rescreening is allowed, with a limit of 2 rescreenings for any potential subject. Screening assessments (central FLT3) completed within 28 days prior to first dose do not need to be repeated.

3.2 Inclusion Criteria

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 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 considered an adult according to local regulation (e.g., age ≥ 18 years old in China) at the time of signing informed consent.
3. Subject has a diagnosis of primary AML or AML secondary to MDS according to World Health Organization (WHO) classification [Swerdlow et al, 2008] as determined by pathology review at the treating institution.
4. Subject is refractory to or relapsed after first-line AML therapy (with or without HSCT) (see definition of line of therapy in Appendix 12.6).
   - Refractory to first-line AML therapy is defined as:
     a. Subject did not achieve CR/CRi/CRp under initial therapy. A subject eligible for standard therapy must receive at least 1 cycle of an anthracycline containing induction block in standard dose for the selected induction regimen. A subject not eligible for standard therapy must have received at least 1 complete block of induction therapy seen as the optimum choice of therapy to induce remission for this subject as per investigator's assessment.
   - Untreated first hematologic relapse is defined as:
     a. Subject must have achieved a CR/CRi/CRp (criteria as defined by [Cheson et al, 2003], see [Section 5.3 Efficacy Assessment]) with first-line treatment and has hematologic relapse.
5. Subject is positive for FLT3 mutation in bone marrow or whole blood as determined by the central lab. In the investigator's opinion, a subject with rapidly proliferative disease and unable to wait for the central lab results can be enrolled based on a local test performed after completion of the last interventional treatment. Subjects can be enrolled from a local test result if they have any of the following FLT3 mutations: FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836.
6. Subject has an ECOG performance status ≤ 2.

7. Subject is eligible for preselected salvage chemotherapy according to investigator assessment.
8. Subject must meet the following criteria as indicated on the clinical laboratory tests:
   - Serum AST and ALT ≤ 2.5 x upper limit of normal (ULN)
   - Serum total bilirubin (TBL) ≤ 1.5 x ULN
   - Serum creatinine ≤ 1.5 x ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation.
9. Subject is suitable for oral administration of study drug.
10. Female subject must either:
    - Be of non-childbearing potential:
      - Postmenopausal (defined as at least 1 year without any menses) prior to screening, or
      - Documented as surgically sterile (at least 1 month prior to screening)
    - Or, if of childbearing potential,
      - Agree not to try to become pregnant during the study and for 60 days after the final study drug administration
      - And have a negative serum or urine pregnancy test at screening
      - And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 60 days after the final study drug administration.
11. Female subject must agree not to breastfeed at screening and throughout the study period and for 60 days after the final study drug administration.
12. Female subject must not donate ova starting at screening and throughout the study period and for 60 days after the final study drug administration.
13. Male subject and their female partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 120 days after the final study drug administration.
14. Male subject must not donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration
15. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

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

1. Subject was diagnosed as acute promyelocytic leukemia.
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).

3. Subject has AML secondary to prior chemotherapy for other neoplasms (except for MDS).
4. Subject is in second or later hematologic relapse or has received salvage therapy for refractory disease.
5. Subject has clinically active central nervous system leukemia.
6. Subject has been diagnosed with another malignancy, unless disease-free for at least 5 years. Subjects with treated nonmelanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed. Subjects with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
7. Subject has received prior treatment with ASP2215 or other FLT3 inhibitors (with the exception of sorafenib and midostaurin used in first-line therapy regimen as part of induction, consolidation and/or maintenance).
8. Subject has clinically significant abnormality of coagulation profile, such as disseminated intravascular coagulation.
9. Subject has had major surgery within 4 weeks prior to the first study dose.
10. Subject has radiation therapy within 4 weeks prior to the first study dose.
11. Subject has congestive heart failure New York Heart Association (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 (ECHO) performed within 1 month prior to study entry results in a left ventricular ejection fraction (LVEF) that is ≥ 45%.
12. Subject with mean of triplicate QTcF > 450 ms at Screening based on central reading.
13. Subject with Long QT Syndrome at Screening.
14. Subject with hypokalemia and hypomagnesemia at Screening (defined as values below lower limit of normal [LLN]).
15. Subject requires treatment with concomitant drugs that are strong inducers of CYP3A.
16. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-gp with the exception of drugs that are considered absolutely essential for the care of the subject.
17. Subject requires treatment with concomitant drugs that target serotonin $5HT_1R$ or $5HT_{2B}R$ receptors or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
18. Subject has an active uncontrolled infection.
19. Subject is known to have human immunodeficiency virus infection.
20. Subject has active hepatitis B or C or other active hepatic disorder.

21. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
22. Subject has active clinically significant GVHD or is on treatment with systemic corticosteroids for GVHD.
23. Subject has an FLT3 mutation other than the following: FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Products

4.1.1 ASP2215

ASP2215 tablets containing 40 mg of active ingredient. The tablets are contained within the high-density polyethylene bottle.

The study centers will be provided bottles of ASP2215 each containing 30 tablets. The study site personnel will fill out the label to indicate the dispensing date, subject's ASP2215 dose and the corresponding number of tablets that need to be taken each day. The ASP2215 40 mg tablet product information is listed in [Table 7].

Table 7 Test Drug (ASP2215 Tablets 40 mg)

Test Drug	**ASP2215 Tablets 40 mg**
Code name	ASP2215
Active ingredient	Chemical name: $C_{29}H_{44}N_8O_3$•1/2 $C_4H_4O_4$
Composition and dosage form	One tablet contains 40 mg of ASP2215 in free form. ASP2215 Tablets are round light-yellow film-coated tablets.
Lot No.	Described in separately prepared "Study Drug Handling Procedures"
Storage	ASP2215 should be stored according to labeled storage conditions and should not be stored above the temperature specified on the ASP2215 label. Store in original container.

4.1.2 Comparative Drug(s)

The specific regimen will be preselected by the investigator prior to randomization of each subject [Table 8]. All regimens will be administered per institutional guidelines for chemotherapy product preparation and administration. All cycles will be 28 days.

The comparative chemotherapy regimen will be supplied by the responsible site pharmacy of each investigational site or by the Sponsor if applicable. Sites are permitted to use generic chemotherapy drug that is approved by the respective regulatory authority.

Refer to the approved package insert, summary of product characteristics or local product information for comparative chemotherapy drug product information and storage condition supplied by the manufacturers.

In the situation when comparator chemotherapy products are supplied by the Sponsor, comparator chemotherapy products used in this study will be packaged by the manufacturer, but labeled under the responsibility of Astellas Pharma Global Development, Inc. (APGD) and Astellas Pharma Inc. (API) in accordance with the packaging vendor qualified by API QA Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Table 8 Comparator Drug Products Supplied by the Sponsor

Comparator Chemotherapy Drug	Drug Product (Example)
LoDAC	
Low-dose cytarabine	Cytarabine 20 mg/mL (100 mg/5 mL) Solution for Injection/ concentrate for Solution for Infusion Cytarabine 100 mg/mL (100 mg/1 mL) Solution for Injection/ concentrate for Solution for Infusion (For China) Cytarabine 0.1 g powder for Solution for Injection or Infusion + 1 ampoule diluent (5 mL) Cytarabine 0.1 g powder for Solution for Injection or Infusion
MEC Induction Chemotherapy	
Cytarabine intermediate dose	Cytarabine 100 mg/mL (5 g/50 mL) Concentrate for Solution for Infusion (For China) Cytarabine 0.5g powder for Solution for Injection or Infusion + 1 ampoule diluent (10 mL) Cytarabine Hydrochloride 0.1g powder for Solution for Injection or Infusion
Mitoxantrone	Mitoxantrone 20 mg/10 mL (2 mg/mL) Concentrate for Solution for Infusion (For China) Mitoxantrone 5 mg/5 mL Concentrate for Solution for Injection
Etoposide	Etoposide 20 mg/mL (100 mg/5 mL) Concentrate for Solution for Infusion (For China) Etoposide 20 mg/mL (0.1 g/5 mL) Concentrate for Solution for Infusion
FLAG Induction Chemotherapy	
High-dose cytarabine	Cytarabine 100 mg/mL (5 g/50 mL) Concentrate for Solution for Infusion (For China) Cytarabine 0.5g powder for solution for Injection or Infusion + 1 ampoule diluent (10 mL) Cytarabine Hydrochloride 0.1g powder for Solution for Injection or Infusion
G-CSF	Filgrastim 30 million U/0.5 mL Solution for Injection or Solution for Infusion (For China) Lenograstim 34 million IU/mL, powder and solvent for Solution for Injection/Infusion
Fludarabine	Fludarabine Phosphate 25 mg/mL (50 mg/2 mL) Concentrate for Solution for Injection or Infusion (For China) Fludarabine Phosphate 50 mg/vial Powder for Injection after dilution

FLAG: fludarabine, cytarabine and granulocyte colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; LoDAC: low-dose cytarabine; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine

4.2 Packaging and Labeling

ASP2215 used in this study will be prepared, packaged and labeled under the responsibility of an authorized person at API Quality Assurance (QA)-API Technology in accordance with SOPs, GMP guidelines, ICH GCP guidelines and applicable local laws/regulations.

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

In the situation when comparative drug(s) are supplied by the Sponsor, comparative drugs used in this study will be labeled under the responsibility of API Technology in accordance with the packaging vendor qualified by API QA SOPs, GMP guidelines, ICH GCP guidelines and applicable local laws/regulations.

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 standard procedures for the alternative disposition of unused study drug are followed.

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 unused study drug including ASP2215 and comparative chemo-therapy drugs supplied by Sponsor back to the Sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

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

4.5 Assignment and Allocation

Randomization and study drug assignment will be performed via Interactive Response Technology (IRT). Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment. Specific procedures for randomization through the IRT are contained in the study procedures manual.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 ASP2215

ASP2215 is an oral tablet that subjects will take once daily without food in continuous 28-day cycles. Subjects will be instructed to take the daily 120 mg dose with water as close to the same time each morning as possible. ASP2215 can be taken at least 2 hours after or 1 hour before food. ASP2215 will be self-administered at home when subjects are not scheduled for clinic visits. For the subjects in the PK cohort, study drug should be taken in the clinic on Day 1 and Day 15. If a subject forgets to take a dose in the morning and within 6 hours of the planned dosing time, they should be instructed to take their dose. If the subject forgets to take their daily dose and more than 6 hours has passed the planned dosing time, 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.

ASP2215 will be given daily in continuous 28-day cycles. For subjects taking ASP2215 treatment should continue until the subject meets a treatment discontinuation criterion.

5.1.1.2 Comparative Drugs

All regimens will be administered as 28-day cycles and per institutional guidelines for chemotherapy product preparation / administration. Options for comparative salvage chemotherapies are limited to the following (all dose levels as defined below must be followed):

LoDAC [Burnett & Knapper, 2007]

- 20 mg cytarabine will be administered twice daily by SC or IV injection for 10 days.

MEC Induction Chemotherapy [Amadori et al, 1991]

- Mitoxantrone 6 mg/m^2 per day will be administered by IV for 5 days (days 1 through 5).
- Etoposide 100 mg/m^2 per day will be administered by IV for 5 days (days 1 through 5).
- Cytarabine 1000 mg/m^2 per day will be administered by IV for 5 days (days 1 through 5).

FLAG Induction Chemotherapy [Montillo et al, 1998]

- Granulocyte colony-stimulating factor (G-CSF) 300 µg/m^2 per day will be administered by SC/IV for 5 days (days 1 through 5). Additional G-CSF by SC/IV is recommended 7 days after completing chemotherapy until ANC > 0.5 x 10^9/L.
- Fludarabine 30 mg/m^2 per day will be administered by IV for 5 days (days 2 through 6).
- Cytarabine 2000 mg/m^2 per day will be administered by IV for 5 days (days 2 through 6).

Subjects receiving LoDAC treatment should continue until the subject meets a treatment discontinuation criterion.

Subjects receiving MEC or FLAG will receive 1 cycle of therapy and will be assessed for response on or after day 15, per institutional guidelines. If the bone marrow cellularity is 20% or greater with at least a 50% reduction in blasts, the subject may receive a second cycle of the same chemotherapy. If bone cellularity is between 5% and 20%, the investigator should make the decision whether the subject should receive another treatment cycle or be observed for recovery. If marrow cellularity is 5% or less, the subject will be observed for recovery. Subjects achieving CR, CRi or CRp may receive a second cycle of chemotherapy at the investigator's discretion. Subjects with NR or progressive disease following cycle 1 will discontinue study treatment.

5.1.2 Interruption, Reduction or Escalation in Dose of the Study Drug

Guidelines for ASP2215 dose interruption and reduction are provided in [Table 9].

The ASP2215 dose may be initially reduced to 80 mg per day. The ASP2215 dose can be further reduced to 40 mg per day if the subject has already experienced clinical benefit. Note that dose reductions should occur in a step-wise manner. Dose reduction can occur during the treatment cycle based on the dose reduction guideline in [Table 9]. No further dose reductions are allowed. (i.e., if a subject is receiving ASP2215 40 mg and further dose reduction is required, study treatment will be discontinued).

Additionally, if the investigator deems it necessary to ensure subject safety, dosing may be interrupted or reduced for reasons other than those provided in [Table 9]. In the unusual circumstance that dosing is interrupted or reduced for reasons not specified in the tables, the investigator should promptly inform the study medical monitor or his/her designee.

Under the protocol version 7.0, any subjects that have been off treatment for more than 14 days for any reasons other than for HSCT cannot resume the treatment.

If the ASP2215 dose has been reduced, the ASP2215 dose will not be re-escalated.

Table 9 Guidelines for ASP2215 Dose Interruption or Reduction Event

ASP2215 Dosing Instructions	
Event	**Action**
QTc prolongation	
QTcF > 500 ms	If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less) by central reading within 14 days, the subject may resume dosing at the reduced dose.
QTcF cycle 1 day 8 increase > 30 ms	If the mean of the triplicate 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).
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 dose reduction is permitted if dosing 1 full cycle at the reduced dose has not resulted in the desired hematologic recovery.

AE: adverse event; ANC: absolute neutrophil count; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; ECG: electrocardiogram; QTcF: Fridericia-corrected QT interval

Subjects who do not achieve a CRc may dose escalate to 200 mg per day. Dose escalation can occur during the treatment cycle based on bone marrow and hematology results. No further dose escalation is allowed. Guidelines for ASP2215 dose escalation are provided in [Table 10].

Table 10 Guidelines for ASP2215 Dose Escalation Event

ASP2215 Dosing Instructions	
Event	**Action**
No CRc (CR, CRp or CRi) after cycle 1	Subjects on 120 mg dose level can escalate to 200 mg dose level.

CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery

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

All medications and concomitant treatments (except for the medications for the purpose other than treatment for disease or event such as contrast agent, laboratory examination, etc.) administered from 28 days prior to cycle 1 day 1 must be recorded in the electronic Case Report Form (eCRF).

5.1.3.1 ASP2215 Group Only

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 inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be monitored for AEs.

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

Precaution should be used in treatment of ASP2215 with concomitant drugs that are substrates of BCRP, since the transporter has been shown to be inhibited by ASP2215 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 in [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 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.

5.1.3.2 ASP2215 Group and Chemotherapy Group

Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with the exception of hydroxyurea daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L and prophylactic intrathecal chemotherapy, cranial radiation, and donor lymphocyte infusion as part of the HSCT treatment plan. Participating in another interventional study while on treatment is prohibited.

5.1.4 Resumption of Treatment After Hematopoietic Stem Cell Transplantation

Subjects in ASP2215 group and COE group who have donor identified and achieve a response allowing them to undergo HSCT per each institution's assessment can undergo HSCT without leaving the study. However, ASP2215 should be stopped and a preHSCT 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 - 90 days post HSCT
- Subject has had successful engraftment as demonstrated by ANC $\geq 500/mm^3$ and platelets $\geq 20000/mm^3$ 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

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug at each monthly visit after baseline. When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of ASP2215 will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

The dose and schedule of ASP2215 and comparative chemotherapy administered to each subject will be recorded. Reasons for dose delay, reduction or omission will also be recorded when applicable.

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.).

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected for all subjects and will include age, 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 as baseline condition on the Medical History Electronic Case Report Form (eCRF).

Details that will be collected include the onset date and recovery date and CTCAE 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 (red blood cell [RBC], white blood cell [WBC] and differential, cytospin results) and related genetic syndromes. Dates for diagnostic procedures will be collected.

Prior HSCT and AML therapy including induction, consolidation and maintenance chemotherapy will be collected. Response to HSCT and AML therapy as well as the duration of the response will also be collected.

5.2.4 FLT3 Mutation Status

FLT3 mutation status will be analyzed by a Sponsor designated central laboratory or contracted 3 clinical sites in China using bone marrow aspirate samples. If bone marrow sample is unavailable (e.g., dry tap), the whole blood sample taken at the screening visit will be used.

Subjects will be screened from the central lab. If the central result is negative, FLT3 testing can be repeated during the screening period. Bone marrow sample before the informed consent date may be used for screening if the patient has already performed bone marrow assessment within 14 days prior to the planned Cycle 1 Day 1, and the sample should be stored at 2˚C to 8˚C and can be started testing within 7 days after sample collection. All subjects including those with rapidly proliferative disease must have screening sample sent to central lab. If institutional FLT3 assay is available, then the institutional results will be recorded and can be used for randomization only if, in the investigator's opinion, subject has rapidly proliferative disease and cannot wait for the central lab results. The institutional FLT3 test must have been performed after completion of subject's last interventional treatment. For randomization only, institutional FLT3 result prior to informed consent can be used if it has been performed after completion of subject's last interventional treatment. However, central testing will still be performed. Subjects can remain on assigned treatment if the randomization is based on the local test, but central lab result is discordant.

Bone marrow/blood sampling, processing, storage and shipment instructions will be provided in the Lab Manual. Refer to the Lab Manual for more detailed information.

5.2.5 Performance Status

The ECOG Scale [Oken et al, 1982] will be used to assess performance status [Table 11].

Table 11 ECOG Performance Status

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.

ECOG: Eastern Cooperative Oncology Group

5.3 Efficacy Assessment

5.3.1 Response Definitions

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

5.3.1.1 Complete Remission

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 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 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.

5.3.1.2 Complete Remission with Incomplete Platelet Recovery

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

5.3.1.3 Complete Remission with Incomplete Hematologic Recovery

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 x 10^9/L with or without complete platelet recovery. RBC and platelet transfusion independence is not required.

5.3.1.4 Composite Complete Remission Rate

Defined as the remission rate of all CR, CRp and CRi (i.e., CR + CRp + CRi).

5.3.1.5 Partial Remission

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 to treatment for all visits (in the order of CR, CRp, CRi, PR, NR and NE) post-treatment. Subjects with best responses of CR, CRp, CRi or PR will be considered responders. Subjects who do not achieve at least a best response of PR will be considered nonresponders.

5.3.2 Survival Time, Duration and Other Efficacy Endpoints

5.3.2.1 Overall Survival

OS is defined as the time from the date of randomization until the date of death from any cause. For a subject who is not known to have died by the end of study follow-up, OS is censored at the date of last contact.

Date of last contact is defined as the death date or the latest of the following dates: treatment discontinuation date, last dosing administration date, last disease assessment date or the last follow-up date on which the subject was known to be alive.

5.3.2.2 Event-free Survival

EFS is defined as the time from the date of randomization until the date of documented relapse (including relapse after CR, CRp and CRi), treatment failure, death, reported off-treatment relapse or new AML therapy start (excluding subsequent HSCT) whichever occurs first, including the long-term follow-up data. Treatment failure is defined as subject who ends treatment without having a previous response. For a subject who is not known to have EFS events, EFS is censored at the date of last relapse-free disease assessment or subsequent HSCT date (whichever is later). Subject is not censored at on-study HSCT.

5.3.2.3 Leukemia-free Survival

LFS is defined as the time from the date of first CRc until the date of documented relapse or death for subjects who achieve CRc. For a subject who is not known to have relapsed or died, LFS is censored on the date of last relapse-free disease assessment date.

5.3.2.4 Duration of Remission

Duration of Remission

This includes duration of CRc, duration of CR, duration of CRi, duration of CRp and duration of response (CRc + PR).

Duration of CRc

Duration of CRc is defined as the time from the date of first CRc until the date of documented relapse for subjects who achieve CRc. Subjects who die without report of relapse are considered nonevents and censored at their last relapse-free disease assessment date. Subjects who undergo an allogeneic HSCT will be considered nonevents and censored at the time of HSCT. Other subjects who do not relapse on study are considered nonevents and censored at the last relapse-free disease assessment date.

Duration of CR, CRp, CRi

Duration of CR, CRp, CRi is defined similarly as duration of CRc.

Duration of Response

Duration of response is defined as the time from the date of either first CRc or PR until the date of documented relapse of any type for subjects who achieve CRc or PR. Subjects who die without report of relapse are considered nonevents and censored at their last relapse-free disease assessment date. Subjects who undergo an allogeneic HSCT will be considered nonevents and censored at the time of HSCT. Other subjects who do not relapse on study are considered nonevents and censored at the last relapse-free assessment date.

5.3.2.5 Transplantation Rate

Transplantation rate is defined as the percentage of subjects undergoing HSCT during the study period.

5.3.3 Bone Marrow Aspiration and/or Biopsy

For ASP2215 group, bone marrow samples are required during screening, cycle 2 day 1 and cycle 3 day 1. For subjects who do not achieve a CRc (CR, CRp or CRi), the bone marrow assessments will be repeated at day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow sampling will be repeated on 1 month after the date of remission and every 3 subsequent cycles or if there is suspicion of relapse in the whole blood.

For the MEC and FLAG groups, bone marrow samples are required during screening and at cycle 2 day 1. Also, an additional bone marrow sample is required at cycle 1 day 15 or later, per institutional guidelines, to assess the need for second cycle. For the LoDAC group, bone marrow samples are required during screening and at cycle 2 day 1 and cycle 3 day 1. Subjects who do not achieve a CRc (CR, CRp or CRi), the bone marrow assessments will be repeated at day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow sampling will be repeated on 1 month after the date of remission and every 3 subsequent cycles or if there is suspicion of relapse in the whole blood.

Bone marrow samples are also required at the pre-HSCT visit /end of treatment visit and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone

marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.

Bone marrow assessment for blasts counts and cell counts and flow cytometry will be conducted at local lab.

5.3.4 Survival Status and Subsequent Antileukemic Treatments and Their Outcomes

Information on survival status, subsequent antileukemic treatments and outcomes will be collected for all subjects.

The first survival status will occur at the 30-day follow-up where telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs. After the 30-day follow-up, the subject or caregiver will continue to be contacted via telephone by site personnel for follow-up every 3 months up to 3 years after end of treatment visit or subject's reconsent under this protocol version 7.0, whichever comes first. Data may be supplemented by site records when available at the time of the contact (e.g., treatment records, outcomes). Additional contacts may be made to support key analyses (e.g., interim analysis or analyses by the Independent Data Monitoring Committee).

Reasonable effort should be made to contact any subjects lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Following unsuccessful telephone contact, an effort to contact the subject by mail using a method that provides proof of receipt should be attempted. Contact via an alternate, preapproved contact is permissible if the subject is not reachable. Such efforts should be documented in the source documents.

If a subject death occurs during the serious adverse event (SAE) reporting period or if the death occurs after the SAE reporting period, but is determined by the investigator to be possibly related to study drug, then the associated AE with outcome of death will also be reported on the CRF and SAE form. If a subject death does not meet the criteria of an SAE, then death and antileukemic treatment and outcome up through the date of death should be collected and entered in CRF.

5.3.5 Pharmacokinetics Assessment

Blood sampling for pharmacokinetic analysis in approximately 20 Chinese subjects (10 male and 10 female subjects) enrolled in the PK cohort will be done at the following time points;

Cycle 1 Day 1: predose, 0.5, 1, 2, 3, 4, 6, 10, 24 hour after dosing of study drug

Cycle 1 Day 8: predose

Cycle 1 Day 15: predose, 0.5, 1, 2, 3, 4, 6, 10, 24 hours after dosing of study drug

Day 1 of each subsequent Cycle: predose

Blood sampling for pharmacokinetic analysis in subjects other than PK Cohort will be done at the following time points;

Cycle 1 Day 1: predose, Cycle 1 Day 8: predose, Cycle 1 Day 15: predose, Day 1 predose of each subsequent Cycle

Acceptable time ranges for blood sampling for measurement of plasma concentrations are as follows (The time of administration on Day 1 is defined as "0" minutes):

Predose	Scheduled date, Within 1 hour before dosing
Day1/Day 15: 0.5 hour post-dose	Scheduled date, scheduled time ± 5 minutes
Day 1/Day 15: 1, 2, 3, 4, 6, 10 hours post-dose	Scheduled date, scheduled time ± 10 minutes
Day 2/Day 16: 24 hours post-dose	Scheduled date, scheduled time ± 20 minutes

After the subject reconsents under this protocol version 7.0, no PK assessments will be performed.

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mm Hg), 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 AE 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

AE collection will begin from time of informed consent and continue through the 30-day follow-up visit. AEs will be documented at each clinic visit, but can be collected at any time. Any AE that meets the definition of a 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 AE collection and data handling. See [Appendix 12.8 Continuation of Study Treatment with ASP2215] for information regarding SAE collection while subjects are receiving study drug treatment with ASP2215 until they meet discontinuation criteria or applicable reimbursement becomes available in the country of residence.

5.4.2.1 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 tests (LFTs) (e.g., AST, ALT, TBL, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.2.2 Adverse Events during Hematopoietic Stem Cell Transplant

AE collection will continue during HSCT for subjects who plan to resume ASP2215 treatment after HSCT.

5.4.3 Laboratory Assessments

[Appendix 12.3] contains 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. Subjects may be screened and randomized from local labs only. However, samples must also be submitted for central read. Labs can be repeated during the screening period. Additional laboratory tests should be performed according to institutional standard of care. Local testing of hematology and bone marrow aspirate and/or biopsy at screening and day 1 of each cycle will be reported in the eCRF. 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.

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 exams 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 day 1 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 AE 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

ECGs will be conducted at visits as outlined in the Schedule of Assessments. Screening ECG is required. ECG can be repeated during the screening period. ECG assessment will be evaluated at screening, predose of cycle 1 day 1, cycle 1 day 8, cycle 1 day 15, day 1 of each subsequent cycle and pre-HSCT/end of treatment visit. Predose assessments should be taken within 1 hour before drug administration. 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. The mean QTcF of the triplicate ECG tracings based on central reading will be used for final treatment decisions and AE reporting.

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 Interruption, Reduction or Escalation in Dose of the Study Drug].

If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If QTcF > 500 ms is confirmed, then the investigator will interrupt and reduce ASP2215 per the interruption or reduction guidelines in [Section 5.1.2 Interruption, Reduction or Escalation in Dose of the Study Drug].

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 pharmacokinetic time points and is not mandatory.

<PK cohort>

In addition to above, a cycle 1 day 15 ECG will be taken predose and 4 hours post dose.

5.4.6 Chest X-ray or Computed Tomography Scan

Chest X-ray or computed tomography (CT) scan is to be performed at screening. A chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of screening.

5.4.7 Multigated Acquisition Scan or Echocardiogram

Multigated acquisition scans or ECHO (as per standard of care) are to be performed at screening for subjects with history of congestive heart failure NYHA Class 3 or 4 (unless multigated acquisition scans or ECHO performed either within 1 month prior revealed LVEF ≥ 45%).

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

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.

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 eCRF accordingly.

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 1 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.

5.5.2 Definition of Serious Adverse Events

An AE 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 AE 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 AE 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 in-subject 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 1 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 and 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 exposure to the Sponsor medicinal product, e.g., name confusion)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. For example, admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition such as transfusion for preexisting anemia, leukopenia, or thrombocytopenia.

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

The Sponsor has a list of events that they classify as "important medical" or "always serious" events. If an AE is reported that is considered to be an event per this classification as "important medical" or "always serious", additional information on the event may be requested and they may be reported as SAE in the CSR.

5.5.3 Special Situations

Special Situations observed in association with the study drug(s) (e.g., test drug, comparator, or background therapy) administered to the subject as part of the study are collected as described in the table below. These Special Situations are not considered adverse events but can be associated with or result in an AE. An AE that may be associated with or result from a Special Situation is to be assessed separately from the Special Situation and captured in the eCRF or electronic data source. If the AE meets the definition of serious, these SAEs are to be collected via the SAE/Special Situation worksheet together with the details of the associated Special Situation and reported as described in [Section 5.5.6 Reporting of Serious Adverse Events].

Special Situation	**Collected**		
	SAE/Special Situation worksheet	**eCRF**	**Protocol Deviation [see Section 8.1.6]**
Lack of Efficacy		X	
Uses outside what is stated in the protocol ("off label use")			X
Medication error			X

Special Situation	**Collected**		
	SAE/Special Situation worksheet	**eCRF**	**Protocol Deviation [see Section 8.1.6]**
Overdose of the medicinal product(s) [see Section 5.5.10 Emergency Procedures and Management of Overdose]			X
Suspected misuse/abuse of the investigational medicinal product(s)	X		X
Occupational exposure (e.g. of site staff) to the investigational medicinal product(s)	X		
Suspected Drug-Drug interaction		X	
Suspected Transmission of Infectious Agents	X		

5.5.4 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AE 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 readministration (rechallenge) or withdrawal (dechallenge).

5.5.5 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-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

Grade	Assessment Standard
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 adverse event

5.5.6 Reporting of Serious Adverse Events

SAE collection will begin from the time of informed consent through the 30 days follow-up visit until the implementation and reconsent of protocol version 7.0. After subjects reconsent under the protocol version 7.0, SAE collection will continue through 30 days after the last dose of study treatment. During the long-term follow-up period, only SAE data for the event that is related to ASP2215 will be collected. In the case of a 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/Special Situation Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor/delegated Contract Research Organization (CRO) by email immediately (within 24 hours of awareness). If the email of an SAE/Special Situation 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 email the SAE/Special Situation Worksheet to:

IQVIA Lifecycle Safety Department
IQVIA RDS East Asia Pte. Ltd.
Email address: QLS_ASP2215@iqvia.com

For more information, please refer to the SAE/Special Situation worksheet completion guideline.

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 (see 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 eCRF.

The following minimum information is required:

- International study number/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 (e.g., Investigational New Drug (IND) Safety Reports, CIOMS-I) to the regulatory agencies as required and will

inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/local IEC within timelines set by regional regulations where required. Documentation of the submission to and receipt by the IRB/local 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 IRB/IEC/head of the study site.

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

The investigators should provide written documentation of IRB/IEC 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.

5.5.7 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 AE 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.

5.5.8 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in [Appendix 12.4 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 12.4 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 5.5.6 Reporting of Serious Adverse Events].

5.5.9 Procedure in Case of Pregnancy

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.

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 is 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.

5.5.10 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.

In the event of suspected overdose of salvage chemotherapy, please refer to the approved Package Insert, Summary of Product Characteristics or local product information supplied by the manufacturer for each agent.

5.5.11 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.

5.5.12 Urgent Safety Measures

An urgent safety measure (USM) is an intervention that is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant competent authorities (CA), IRB/IEC, where applicable, in order to protect participants from any immediate hazard to their health and/or safety. Either the investigator

or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

5.5.13 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the study physician within 24 hours of awareness. Full details of the potential USM are to be recorded in the participant's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the participants. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

Plasma concentrations of ASP2215 will be evaluated as outlined in Schedule of Assessments, and Schedule of Assessments for PK cohort. For each sample, 2 mL of blood will be collected and processed. Plasma concentration of ASP2215 metabolite may be also evaluated for each sample.

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 (CSR).

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.

After the subject reconsents under this protocol version 7.0, no PK assessments will be performed.

5.7 Other Measurements, Assessments or Methods

5.7.1 Patient Reported Outcome Measures

BFI, EQ-5D-5L, FACIT-Dys-SF, FACT-Leu and dizziness and mouth sore items will be assessed during the study period to report subjects experience of symptoms/treatment and quality of life.

5.7.1.1 Brief Fatigue Inventory

The BFI [Mendoza et al, 1999] was developed to assess the severity of fatigue and the impact of fatigue on daily functioning in patients with fatigue due to cancer and cancer treatment. The BFI short form has 9 items and a 24-hour recall. A global fatigue score is computed by

averaging the 9 items. The BFI will be administered at site visits directly to the subjects via an electronic PRO device. The BFI will be administered at cycle 1 day 1 predose, cycle 1 day 8 (± 1 day), day 15 (± 1 day), cycle 2 day 1 (± 2 days), day 15 (± 1 day) and all subsequent cycles day 1 (± 2 days) as well as preHSCT/end of treatment visit. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

5.7.1.2 EuroQol Group-5 Dimension-5 Level Instrument

The EQ-5D-5L is a self-reported questionnaire. The EQ-5D-5L is being used as a measure of respondents' health related quality of life. The EQ-5D-5L consists of the EuroQol Group-5 Dimension descriptive system and the EuroQol Group visual analogue scale (VAS). The EuroQol Group-5 Dimension descriptive system comprises of 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The VAS records the respondent's self-rated health status on a graduated (0 - 100) scale, where the endpoints are labeled ‘best imaginable health state’ and ‘worst imaginable health state’ with higher scores for higher health related quality of life. It will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days) as well as preHSCT/end of treatment visit and the 30-day follow-up, if a visit is required. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day. During 30-day follow-up and long-term follow up, subjects will be contacted by site personnel via telephone to provide responses to the questionnaire.

5.7.1.3 Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms

The FACIT-Dys-SF [Choi et al, 2011] was developed to assess dyspnea severity and related functional limitations. It has a 7-day recall period and 20 items. The FACIT-Dys-SF is scored with 2 domains: dyspnea and function limitations. This instrument will be administered at site visits directly to the subjects via an electronic PRO device. It will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days) as well as preHSCT/end of treatment visit. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

5.7.1.4 Functional Assessment of Cancer Therapy-Leukemia

The FACT-Leu [Cella et al, 2012] is designed to measure leukemia-specific signs, symptoms and the impact of AML on patients. The 44-item scale has global and domain scores including physical well-being, social/ family well-being, emotional well-being, functional well-being and additional leukemia-specific concerns. The FACT-Leu contains most of the common patient reported impacts of AML. The FACT-Leu has a 7-day recall period. The FACT-Leu will be administered at site visits directly to the subjects via an electronic PRO device. It will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days) as well as preHSCT/end of treatment visit. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

5.7.1.5 Dizziness and Mouth Sores Items

Two additional questionnaires evaluating commonly reported impacts on AML on patients, dizziness and mouth sores, will be administered to subjects. These 2 questionnaires will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days) as well as preHSCT/end of treatment visit. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

5.7.2 Resource Utilization

Resource utilization in this study population will include hospitalization, blood transfusion, antibiotic iv infusions, medication for AEs and opioid usage.

5.7.3 Exploratory Biomarker Analysis

FLT3 mutation status will be assessed from bone marrow samples taken at the screening visit and may be assessed from pre-HSCT visit/EOT visit. Additional genetic biomarkers related to AML and ASP2215 activity may be analyzed. All biomarker samples collected will be stored for a period of up to 15 years following study database hard lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. If bone marrow sample is unavailable (e.g., dry tap), the whole blood samples taken at the screening visit and end of study will be used.

The FLT3 mutation assay is an investigational use only companion diagnostic that is being used to determine a subject's FLT3 mutation status. The manufacturer of the assay or the contracted clinical sites with the manufacturer in China will analyze the samples collected from this study and utilize it to seek regulatory approval of the FLT3 mutation assay companion diagnostic that will be used with ASP2215.

Bone marrow/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.

Specific to China:

All biomarker samples collected will be stored until all clinical study database hard lock.

5.7.4 Whole Blood and Buccal Sample for Future Pharmacogenomics Analysis (Retrospective Pharmacogenomics Analysis) (Optional)

PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues. After randomization (see Schedule of Assessments), a whole blood and buccal swab sample for possible retrospective PGx analysis will be collected for subjects who provide separate consent.

Samples will be shipped to a Sponsor designated banking CRO. Labels should uniquely identify each sample and contain at least:

- Protocol number [2215-CL-0303],
- Subject number and

- Purpose and biological matrix (i.e., “biobanking”, “whole blood”).

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

See [Appendix 12.5 Retrospective PGx Sub-study (Optional)] 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, or if laboratory results are needed before central laboratory results are available, additional blood may be drawn for local laboratory testing.

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 during the screening and cycle 1 period is approximately 60 mL. For subjects in PK cohort, the maximum amount of blood collected for study specific assessment during the screening and cycle 1 period is approximately 90 mL.

The maximum amount of blood collected for study specific assessments in cycle 2 is approximately 20 mL.

The maximum amount of blood collected for study specific assessments in cycle 3 and beyond is approximately 15 mL per cycle.

Specific to China:

PGx Sub-study (Optional) is not conducted in China.

6 DISCONTINUATION

Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion or upon marketing authorization, commercial availability and applicable reimbursement of ASP2215 in the country of residence.

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 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 AE 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.

Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined below or upon marketing authorization and commercial availability and applicable reimbursement of ASP2215 in the country of residence.

6.1.1 Discontinuation Criteria from Treatment for Individual Subjects

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit may be kept in the study after discussion with the medical monitor).
- Subject develops an intolerable or unacceptable toxicity.
- Subject receives any antileukemic therapy other than the assigned treatment, with the exceptions of hydroxyurea for up to 2 weeks, prophylactic intrathecal chemotherapy or cranial irradiation, and donor lymphocyte infusion as part of the HSCT treatment plan.
- 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.
- Subject is receiving MEC or FLAG and has NR or progressive disease following cycle 1.
- Subject is receiving LoDAC or ASP2215 and has progressive disease or no response and the subject, in the opinion of the investigator, is no longer deriving clinical benefit.
- Subject is in comparator group (chemotherapy) and goes on for HSCT.
- Female subject becomes pregnant.
- Death.

6.1.2 Discontinuation Criteria from the Posttreatment Period for Individual Subjects

- 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 subject's end of treatment visit.
- The implementation and reconsent of protocol version 7.0.
- 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. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures (TLFs) 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 justified in the 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

This is a group sequential design using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method (East®). One interim analysis and 1 final analysis are planned. The interim and final analyses will be performed after the prespecified number of death events. All statistical tests of treatment effects will be conducted at the 2-sided 0.05 level of significance.

Approximately 318 subjects (the planned sample size with 10% dropout rate) will be randomized in a 1:1 ratio to receive ASP2215 or salvage chemotherapy (159 subjects in the ASP2215 treatment arm and 159 subjects in the salvage chemotherapy arm). The planned 230 events during the study will provide 90% power to detect a difference in OS between the ASP2215 arm with 7.7 months median survival time and salvage chemotherapy arm with 5 months median survival time (hazard ratio = 0.65) at the overall 2-sided 0.05 significance level.

The planned sample size with 250 EFS events will provide 90% power to detect the difference in EFS (6 months median EFS for ASP2215 arm and 3.9 months for salvage chemotherapy arm with hazard ratio = 0.65) and > 90% power to detect a difference in CR rate between ASP2215 with 25% CR rate and the salvage chemotherapy with 10% CR rate.

Randomization will be stratified by response to first-line AML therapy and preselected salvage chemotherapy:

Response to first-line therapy:

- Relapse within 6 months after allogeneic HSCT
- Relapse after 6 months after allogeneic HSCT
- Primary refractory without HSCT
- Relapse within 6 months after CRc and no HSCT
- Relapse after 6 months after CRc and no HSCT

Preselected chemotherapy:

- High intensity chemotherapy (FLAG, MEC)
- Low intensity chemotherapy (LoDAC)

Approximately 20 Chinese subjects (10 male and 10 female subjects) will be allocated to the PK cohort. This sample size is calculated based on the following considerations:

- "The Technical Guidelines for Clinical Pharmacokinetics Research of Chemical Drugs" in China (March 2005) require 8 to 12 subjects of each gender in each dose group.
- To account for several subjects dropping out from the study and to ensure at least 16 evaluable subjects in the ASP2215 arm, approximately 20 subjects will be enrolled.

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 Intention to Treatment Set

The Intention to Treatment Set (ITT) will consist of all subjects who are randomized. The subjects will be analyzed based on the randomized treatments.

7.2.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects who are randomized with FLT3 mutation based on the central test and will be used for efficacy analysis. The subjects will be analyzed based on the randomized treatments.

7.2.3 Safety Analysis Set

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 1 dose of study treatment (ASP2215 or salvage chemotherapy) and will be used for safety analyses. The subjects will be analyzed based on the actual treatment received.

7.2.4 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) consists of the administered population for which sufficient plasma concentration data is available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling is

known. Additional subjects may be excluded from the PKAS at the discretion of the Pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the Classification Specifications and determined the Classification Meeting.

7.3 Demographics and Other Baseline Characteristics

7.3.1 Demographics

Demographics and other baseline characteristics will be summarized by treatment group. 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 treatment group.

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 mutation status.

7.3.4 Previous and Concomitant Medications

The frequency of concomitant medications (prescription, over-the-counter and nutritional supplements) will be summarized by treatment group and preferred term (PT) 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 per treatment group, study drug administration, subject completion, premature discontinuation and major protocol violations.

7.3.6 Drug Exposure

Drug exposure including duration of exposure, cumulative dose, average daily dose, dose intensity and relative dose intensity will be summarized by treatment group. The number and proportion of subjects with dose reduction, dose escalation and dose interruption will be tabulated. Details of the calculation will be provided in SAP.

7.4 Analysis of Efficacy

OS, EFS, CR rate, CRc rate, duration of remission, LFS and transplantation rate 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% CI.

7.4.1 Analysis of Primary Endpoint

The primary efficacy endpoint of OS will be analyzed using the stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on the ITT. The ITT is defined as all randomized subjects.

The hypothesis testing on the primary analysis will be performed at overall 2-sided 0.05 significance level to test the null hypothesis that OS is equal between the 2 treatment arms versus the alternative hypothesis that OS is different between the ASP2215 arm versus the salvage chemotherapy arm.

The sensitivity analysis for the primary efficacy endpoint will be performed on the FAS, which includes all randomized subjects who are FLT3-mutated subjects based on the central test. The sensitivity analysis for OS with censoring at the time of HSCT for subjects who undergo HSCT will be conducted on the ITT. If the FLT3-mutated subjects constitute less than 90% of the total number of randomized subjects, the difference in the primary efficacy endpoint will be evaluated between FLT3-mutated subjects and FLT wild type subjects per central lab test.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Key Secondary Efficacy Analysis

The key secondary efficacy endpoint of EFS will be analyzed using the stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on the ITT. To maintain the overall Type I error rate at the 0.05 significance level, the hypothesis testing on EFS will be performed only if the null hypothesis on the primary analysis is rejected at the overall 2-sided 0.05 significance level.

The key secondary efficacy endpoint of CR rate will be analyzed using the Cochran-Mantel-Haenszel (CMH) test to control for response to first-line AML therapy and preselected salvage chemotherapy on the ITT. To maintain the overall Type I error rate at the 0.05 significance level, the hypothesis testing on CR rate will be performed only if the null hypothesis on EFS is rejected at the overall 2-sided 0.05 significance level.

The sensitivity analysis for the key secondary efficacy endpoints will be performed on the FAS, which included all randomized subjects who are FLT3-mutated subjects based on the central test. Additional sensitivity analysis will be performed to evaluate the impact on the analysis of EFS due to any missing data/assessments and any loss to follow-up or discontinuation of assessments of EFS not due to an event.

7.4.2.2 Secondary Efficacy Analyses

The statistical analyses on secondary efficacy endpoints include:

- Stratified Cox proportional hazard model on duration of remission and LFS
- CMH method on the CRc rate and transplantation rate

- ANOVA model to analyze the change in the BFI global fatigue score (average of all 9 items) from baseline to post-baseline visits.

7.4.3 Analysis of Exploratory Endpoints

An exploratory analysis of FLT3 mutation status and clinical efficacy will be conducted. FLT3 mutation status, including subgroups of FLT3 ITD mutation, D835/I836 TKD mutations and allelic ratio, will be analyzed. Additional biomarkers related to AML and ASP2215 activity may be analyzed.

CMH method will be used for resource utilization status (hospitalization, blood transfusion, antibiotic iv infusions, medication for AEs and opioid medication); and ANOVA model will be used for resource utilization counts (hospital stays, duration of medications, blood transfusions, antibiotic iv infusions, medication for AEs and opioid medication).

ANOVA model will be used to analyze the change in the FACIT-Dys-SF domain scores from baseline to post-baseline visits.

ANOVA model will be used to evaluate change from baseline to post-baseline visits for the global and domain scores, individual items and item clusters of the FACT-Leu. The same analytic approach will be used for the dizziness and mouth sore items.

ANOVA model will be used for the change from baseline of EQ-5D-5L VAS and shift table for the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/ depression) baseline to post-baseline visits.

7.4.4 Subgroup Analysis

Subgroup analysis will be performed on primary and key secondary efficacy endpoints for age (< 65 vs ≥ 65 years), gender, ECOG performance scores, region (China vs ex-China), response to first-line therapy, and preselected salvage chemotherapy.

7.5 Analysis of Safety

The safety evaluation will be based mainly on AEs, clinical laboratory, vital signs, ECG and ECOG. Descriptive statistics will be used to summarize safety data. All safety data will be performed on the SAF.

7.5.1 Adverse Events

All AEs recorded on treatment including within 30 days from the last study treatment will be summarized. AEs will be categorized by SOC and PT using MedDRA and will be graded according to the NCI-CTCAE version 4.03.

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

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

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 AEs 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.

SAE information may be added to update patient narratives for subjects who continue to receive study treatment with ASP2215 upon reconsent until they meet discontinuation criteria or applicable reimbursement becomes available in the country of residence.

7.5.2 Laboratory Assessments

Clinical laboratory evaluations (including hematology, 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.

7.5.3 Vital Signs

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

7.5.4 Physical Examination

Physical examination will be listed by treatment group. All clinically significant abnormal findings will be recorded as medical history or AEs and graded using NCI-CTCAE guidelines.

7.5.5 Electrocardiograms

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) will be provided. ECG parameters and their change from baseline will be summarized by treatment group using descriptive statistics.

7.5.6 ECOG Performance Scores

ECOG performance scores will be summarized by treatment group and visit.

7.6 Analysis of Pharmacokinetics

7.6.1 Estimation of Pharmacokinetic Parameters

PK Analysis in Chinese subjects (PK cohort)

Plasma concentrations and PK parameters will be summarized using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, and

coefficient of variation (CV) of the 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 non-compartmental analysis (NCA).

PK Analysis in subjects other than PK cohort

Based on pharmacokinetic data obtained within this study, a separate population pharmacokinetic analysis will be performed. Data from this study may be pooled with other studies for analysis. The prospective details of this analysis will be specified in a separate population pharmacokinetic analysis plan.

7.7 Protocol Deviations

PDs 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 PD 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.

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

To evaluate whether ASP2215 is particularly beneficial or harmful compared to the salvage chemotherapy group while the study is ongoing, a formal interim analysis is planned when approximately 50% of the planned death events have occurred in the study. A group sequential design using the O'Brien-Fleming type alpha-spending function [Lan & DeMets, 1983] will be used to control the overall 2-sided 0.05 significance level (East®). The IDMC may recommend terminating the trial for favorable or unfavorable results at the interim analysis. In the case of favorable results, the 2-sided significance levels for superiority are 0.0031 for the interim analysis and 0.0490 for the final analysis. If the estimated hazard ratio (HR) is less than 1 and the 2-sided P value of the interim analysis is less than 0.0031, the IDMC may recommend terminating the trial for success. In the case of unfavorable results in the interim analysis, the 2-sided significance level for futility (nonbinding) is 0.8458. If the estimated HR is greater than 1 and the 2-sided P value of the interim analysis is greater than 0.8458 or the estimated HR is greater than 1, the IDMC may recommend terminating the trial for futility. The decision rules based on P value and estimated HR at the formal interim analysis are as follows.

Decision Rules based on P Value and HR obtained at Interim Analysis

- HR < 1
    - P value < 0.0031 : Termination due to success
    - 0.0031 ≤ P value ≤ 0.8458 : Continuation of study
    - P value > 0.8458 : Termination due to futility
- HR ≥ 1
    - Termination due to futility

Details for the interim analysis, monitoring subject safety, enrollment rates and event (death) rates will be contained in the Interim Analysis Plan (IAP) and IDMC Charter. Recommendations regarding study conduct will be made by the IDMC based on their assessment of these rates. If the study is not stopped after the interim analysis, a final analysis will occur after 100% of events have been observed.

7.9 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.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The relevant study data will be collected in English, and will be translated from English to Chinese by sponsor/CRO if required.

The investigator or site designee will enter data collected using an Electronic Data Capture 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 laboratory. 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 laboratory. 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 AEs will be collected in the eCRF.

Subject questionnaires will be completed by the subject on an electronic device. The information completed by the subject on the electronic device will be automatically uploaded into a central website. The investigator or site designee should review the diaries and questionnaire data on the website for correct completion while the subject is at the site. The questionnaire data will be transferred electronically to Sponsor or designee at predefined intervals during the study. The vendor will provide Sponsor or designee with a complete and clean copy of the data.

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 (ICFs)
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- AEs 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

(refer to [Section 8.1.2 Specification of Source Documents]) 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 Japan-Asia Data Science department of the Sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary respectively.

8.1.6 Protocol Deviations

A PD 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.

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/Independent Ethics Committee/Competent Authorities

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 SAE 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 1 year.

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 ICF 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.

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 reconsent 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 ICF. A copy of the signed ICF 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 reconsent 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 obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., Health Insurance Portability and Accountability Act [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 Sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)
- Investigator's Brochure (and amendments, where applicable)
- eCRFs
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study site is required to provide the following documentation to the Sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54
- Signed Investigator's Statement in this protocol and eCRF
- Current Curricula Vitae of all investigators
- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

At the end of the study, the Sponsor is responsible for the collection of:

- Study related documentation,
- Unused study drug, if applicable

The investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. The Sponsor will notify the site/investigator if the New Drug Application (NDA)/Marketing Authorization Application/IMPD.
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 eCRFs supplied for each subject.

The following are the major documents to be retained at the study site, wherever applicable.

1. Source documents (clinical data, documents, and records for preparing the eCRF), hospital records, medical records, test records, memoranda, subject diary or check lists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, x-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the Sponsor, records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals.
2. Contracts, written ICFs, written information, and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), Curricula Vitae of investigators, list of sub-investigators, list of signatures and print of seals (copy), and case report forms (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study, documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds 1 year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained. An agreed-upon protocol (including revisions), Investigator's Brochure (including revisions), operational procedures for the investigator, materials and information supplied by the Sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), the list of names of the IRB members, materials for IRB review, IRB review records, and the review result report of the IRB, etc.
4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs, and the prescriptions for concomitant medications.

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 Insurance of Subjects and Others

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and European Union 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, CRFs and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC)

The IDMC will be responsible for the review of subject safety, enrollment rates and event (death) rates during interim analysis when approximately 50% of the planned death events

have occurred in the study. The IDMC may recommend terminating the trial for favorable or unfavorable results at the interim analysis.

Members of the IDMC will be independent from the Sponsor and also will not participate as investigators in the trial. Additional details regarding responsibilities and membership requirements will be included in the IDMC Charter.

10.2 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 List of Excluded and Cautionary Concomitant Medications

The following list describes medications and foods that are common strong 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. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the co-chairs and protocol officer is strongly encouraged.

Strong CYP3A Inhibitors	
Drug Type	**Generic Drug Name**
Human Immunodeficiency Virus Protease Inhibitors	Indinavir Nelfinavir Lopinavir Ritonavir Saquinavir
Food/Juice	Grapefruit juice
Others	Boceprevir Telaprevir Clarithromycin Telithromycin Conivaptan Itraconazole Ketoconazole Posaconazole Voriconazole Nefazodone

CYP: cytochrome P450

Source: Table 4 in FDA Draft Guidance for Industry - Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Recommendations (February 2012)
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited. 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.

Strong CYP3A Inducers	
Drug Type	**Generic Drug Name**
Antiepileptic, Anticonvulsant	carbamazepine phenytoin
Antibiotic	rifampicin
Food/Juice Supplement	St. John's wort

CYP: cytochrome P450

Source: Table 4 in FDA Draft Guidance for Industry - Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Recommendations (February 2012)
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

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 $5HT_{2B}R$	eletriptan hydrobromide
Affinity or Function to $5HT_1R$	almotriptan malate aripiprazole avitriptan buspirone hydrochloride dihydroergotamine mesylate droperidol eletriptan hydrobromide ergoloid mesylates ergonovine maleate ergotamine tartrate frovatriptan succinate haloperidol haloperidol decanoate lesopitron methylergonovine maleate methylergotamine methysergide maleate naratriptan hydrochloride pizotifen quetiapine fumarate rizatriptan benzoate sumatriptan succinate tegaserod maleate thioridazine thioridazine hydrochloride ziprasidone hydrochloride ziprasidone mesylate zolmitriptan zotepine

$5HT_1R$: 5-hydroxytryptamine receptor 1; $5HT_{2B}R$: 5-hydroxytryptamine receptor 2B

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

P-gp: P-glycoprotein

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

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

Precaution is advised in the use of ASP2215 with concomitant drugs that are substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, rosuvastatin), and OCT1 (e.g., metformin) since these transporters have been shown to be inhibited by ASP2215 in in vitro studies.

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 to > 3 × ULN (to > 5 × ULN in subjects with liver metastases) or TBL > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase [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		**TBL**
Moderate	> 3 x ULN (in subjects without liver metastases), > 5 x ULN (in subjects 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 International normalization ratio (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) 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 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 'AEs' on the AE page of eCRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
    - Obtain a history of concomitant drug use (including nonprescription 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 eCRF. 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 LFTs, such as viral hepatitis, preexisting 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 subjects 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 2 "requirements" for Hy's Law are the following:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 × ULN (2 × ULN elevations are too common in treated and untreated subjects to be discriminating)
2. Cases of increased TBL (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome

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

Reference

FDA. Guidance for industry-drug-induced liver injury: premarketing clinical evaluation. 2009.

12.3 Laboratory Tests

Panel/ Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Hematology	2 mL into EDTA tube	White Blood Cell Count[a] White Blood Cell Differential[a] Red Blood Cell Count Hemoglobin[a] Hematocrit[a] Mean Corpuscular Volume Platelet Count[a] Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Hemoglobin Blast count[a]
Chemistry[a]	7.5 mL into serum tube	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Uric acid[b] Glucose Calcium Phosphate Magnesium Albumin Total Protein Alkaline Phosphatase Lactate Dehydrogenase Creatine Phosphokinase Aldolase Triglycerides Total Cholesterol Phospholipid Globulin Liver Function Tests including: Total Bilirubin Alanine Aminotransferase Aspartate Aminotransferase Thyroid Function Tests including TSH Free T4
Pregnancy Test	1 mL serum and/or urine[c]	Human Chorionic Gonadotropin
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	1.8 mL into sodium citrate tube	INR PT 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 around 3 mL, 2 - 3 bedside smear slides and/or biopsy (or peripheral blood in the event of a dry tap) (Local Test)	Blast Count and Cell Counts Flow Cytometry for Blasts
Bone Marrow Aspirate and/or Blood	Aspirate 0.25 mL – 0.75 mL in sodium heparin Blood 1 mL – 3 mL in sodium heparin	FLT3 Mutation Status
PK	2 mL into dipotassium EDTA	ASP2215
PGx	3 mL into dipotassium EDTA tube and a buccal swab sample	Pharmacogenomics analysis

aPTT: activated partial thromboplastin time; eCRF: Electronic Case Report Form;
EDTA: ethylenediaminetetraacetic acid; FLT3: FMS-like tyrosine kinase; INR: international normalization ratio;
PK: pharmacokinetics; PT: prothrombin time; T4: thyroxin; TSH: thyroid stimulating hormone.

a. In addition to the central read of these values, available local results will also be entered into the eCRF.

b. On days 1, 4, 8 and 15 in cycle 1.

c. Refer to Schedule of Assessments.

12.4 Common Serious Adverse Events

The following is a list of SAEs 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 AE meeting the definition of an SAE as detailed in [Section 5.5.2 Definition of Serious Adverse Events]**. 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 5.5.6 Reporting of Serious Adverse Events].

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 indicates 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
Petechiae	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

AE: adverse event; AML: acute myeloid leukemia; GVHD: graft-versus-host disease; INR: International normalization ratio

12.5 Retrospective PGx Sub-Study (Optional)

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, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 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 blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to AML subjects' clinical response, pharmacokinetics and toxicity/safety concerns in relation to ASP2215 treatment.

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 written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

For subjects study, 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 blood 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 3 mL whole blood sample and a buccal swab per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

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.

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

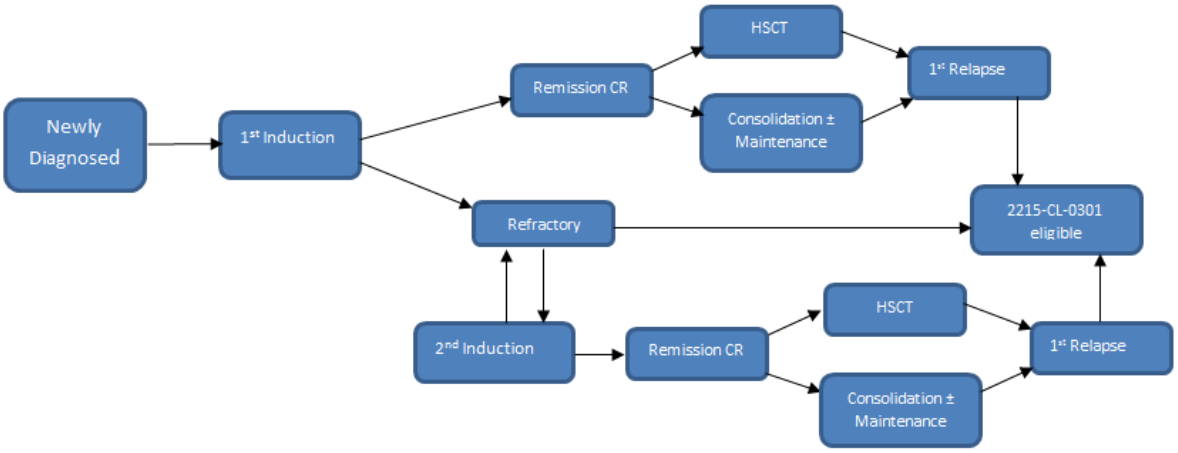
destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

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.

12.6 Definitions of Line of Therapy and Tools to Determine Study Eligibility

Schematic representation of AML treatment and eligible path for study participation after treatment with 1 line of therapy.



Below are examples of the treatment paths that would qualify the patient to participate in the study:

- First induction → Refractory
- First induction → Refractory → Second Induction*→ Refractory
- First induction → Refractory → Second Induction*→ Remission→ Relapse (*can include different treatment from first induction)
- First induction → Remission → Consolidation/Maintenance with HSCT→ Relapse
- First induction → Consolidation/Maintenance without HSCT → Relapse

Please note: Induction with consolidation/maintenance followed by HSCT is considered as one line of therapy. HSCT by itself and hydroxyurea are not considered to be lines of therapy.

12.7 Crossover Extension

The Crossover Extension (COE) was implemented. With the exception of those procedures and processes indicated below, this extension study will be performed using the same general approach of ASP2215 arm as described in the protocol. Refer to the main protocol for any study details not contained in the supplemental COE appendix.

12.7.1 Rationale and design for COE portion of the study

The study planned interim analysis demonstrated superior OS outcome for the ASP2215 arm compared to the Salvage chemotherapy arm. The IDMC concluded that the primary endpoint of OS crossed the predefined efficacy stopping boundary and recommended that the study should stop for efficacy. According to IDMC's recommendation, the sponsor determined that no further screening/enrollment is required. In addition, COE is implemented to allow active

salvage chemotherapy arm subjects and salvage chemotherapy arm subjects in follow to receive ASP2215 treatment on the study based on the investigators' discretion.

All eligible subjects must be evaluated and meet the eligibility criteria for COE.

Subjects on active salvage chemotherapy arm who are participating in COE, will have an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up, in which a telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.

Day 1 of the COE will occur after COE informed consent form is signed and eligibility is confirmed.

In COE portion of the study, subjects will receive treatment with ASP2215 over continuous 28-day cycles. Subjects taking ASP2215 should continue until the subject meets a treatment discontinuation criterion. The subjects will have an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up, in which a telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs. Dose interruption and reduction due to adverse events related to ASP2215 must be followed [Table 9].

Study procedures during the COE will be limited to safety data collection including AE/SAE collection/assessment, clinical laboratory, ECGs, physical exams, vital signs and concomitant treatment as detailed in the schedule of assessment [Table 4 and Table 6].

12.7.2 Inclusion Criteria

Subject is eligible for the COE if they meet the following criteria when the subject is evaluated for eligibility to participate in the COE portion of the study:

1. Institutional Review Board (IRB) -/Independent Ethics Committee (IEC) -approved written Informed Consent and privacy language as per national regulations 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 has received study treatment of either LoDAC, MEC or FLAG and has no response or progressive disease.
3. Subject has not received other antileukemic therapy after EoT (hydroxyurea is allowed for the control of peripheral leukemic blasts in patients with leukocytosis).
4. Subject must meet the following criteria as indicated on the clinical laboratory tests:
   - Serum AST and ALT ≤ 2.5 x upper limit of normal (ULN)
   - Serum total bilirubin ≤ 1.5 x ULN
   - Serum creatinine ≤ 1.5 x ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation [Levey et al, 1999].
   - Serum potassium ≥ lower limit of normal (LLN) (Repletion of potassium levels prior to C1D1 of COE is allowed).
   - Serum magnesium ≥ LLN (Repletion of magnesium levels prior to C1D1 of COE is allowed).

5. Subject has an ECOG performance status ≤ 2.
6. Female subject must either:
   - Be of non-childbearing potential:
     - Postmenopausal (defined as at least 1 year without any menses) prior to screening, or
     - Documented as surgically sterile (at least 1 month prior to screening)
   - Or, if of childbearing potential,
     - Agree not to try to become pregnant during the study and for 60 days after the final study drug administration
     - And have a negative serum or urine pregnancy test at screening
     - And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to barrier method starting at screening and throughout the study period and for 60 days after the final study drug administration.
7. Female subject must agree not to breastfeed at screening and throughout the study period and for 60 days after the final study drug administration.
8. Female subject must not donate ova starting at screening and throughout the study period and for 60 days after the final study drug administration.
9. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 120 days after the final study drug administration.
10. Male subject must not donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
11. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the COE inclusion criteria will NOT be allowed.

12.7.3 Exclusion Criteria

Subject will be excluded from participation in the COE if any of the following apply when the subject is evaluated for eligibility to participate in the COE portion of the study:

1. Subject has been diagnosed with another malignancy, unless disease-free for at least 5 years. Subjects with treated nonmelanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed. Subjects with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
2. Subject has congestive heart failure New York Heart Association (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 1 month prior to study entry results in a left ventricular ejection fraction (LVEF) that is ≥ 45%.

3. Subjects with mean of triplicate Fridericia-corrected QT interval (QTcF) > 450 ms at COE Screening based on central reading.
4. Subject has clinically active central nervous system leukemia.
5. Subject has clinically significant abnormality of coagulation profile, such as disseminated intravascular coagulation.
6. Subject has had major surgery within 4 weeks prior to the first study dose.
7. Subject has radiation therapy within 4 weeks prior to the first study dose.
8. Subject with Long QT Syndrome at Screening.
9. Subject with hypokalemia and hypomagnesemia at Screening (defined as values below lower limit of normal [LLN]).
10. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.
11. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.
12. Subject requires treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 (5HT1R) or 5-hydroxytryptamine receptor 2B (5HT2BR) or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
13. Subject has an active uncontrolled infection.
14. Subject is known to have human immunodeficiency virus infection.
15. Subject has active hepatitis B or C or other active hepatic disorder.
16. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the COE exclusion criteria will NOT be allowed.

12.7.4 Treatment of COE

Subjects participating in COE will receive the following treatment during each 28-day cycle:

ASP2215 orally once daily 120 mg /day from day 1 to 28 of the 28-day cycles.

Dosing guidance for ASP2215 outlined [Section 5.1 Dosing and Administration of Study Drugs and Other Medications] should be followed.

12.7.5 Schedule and Assessments

Salvage chemotherapy arm subjects meeting criteria as indicated in [Section 12.7.2 Inclusion Criteria and 12.7.3 Exclusion Criteria] will sign informed consent prior to initiation of any COE C1D1 procedures. The COE subjects will follow Treatment Schedule of Assessments for Crossover Extension [Table 4] and the Post treatment Schedule of Assessments for Crossover Extension [Table 6].

12.7.6 Previous and Concomitant Treatment (Medication and Non-medication Therapy)

All medications and concomitant treatments (except for the medications for the purpose other than treatment for disease or event such as contrast agent, laboratory examination, etc.) administered from 28 days prior to cycle 1 day 1 must be recorded in the electronic Case Report Form (eCRF). If EoT of salvage chemotherapy arm was performed within 28 days prior to C1D1 of the COE, only the medication after EoT of salvage chemotherapy arm and prior to C1D1 should be recorded.

COE receiving ASP2215 group:

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 inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be monitored for AEs.

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

Precaution should be used in treatment of ASP2215 with concomitant drugs that are substrates of BCRP, since the transporter has been shown to be inhibited by ASP2215 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 in [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 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.

12.7.7 Duration of Treatment and Discontinuation Criteria

Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined below or upon marketing authorization commercial availability and applicable reimbursement of ASP2215 in the country of residence. Once a subject(s) transitions to commercial supply, the subject(s) will be discontinued from the study.

Discontinuation Criteria from Treatment for Individual Subjects:

- Subject declines further study participation (i.e. withdrawal of consent).
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.

- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit may be kept in the study after discussion with the medical monitor).
- Subject develops an intolerable or unacceptable toxicity.
- Subject receives any antileukemic therapy other than the assigned treatment, with the exceptions of hydroxyurea up to 2 weeks, prophylactic intrathecal chemotherapy or cranial irradiation, and donor lymphocyte infusion as part of the HSCT treatment plan.
- 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.
- Subject is receiving ASP2215 and has progressive disease or NR and the subject, in the opinion of the investigator, is no longer deriving clinical benefit.
- Female subject becomes pregnant.
- Death.

12.7.8 Statistical Methods

Since the cross-over choice of chemotherapy patients were introduced as a result of the interim analysis of the efficacy, the main statistical analysis of efficacy and safety should be conducted on the data up to the implementation of this choice to maintain the integrity of the study conclusion.

All eligible salvage chemotherapy arm subjects who cross to COE ASP2215 treatment will be summarized separately to support the safety conclusion for the ASP2215. More details will be included in the SAP.

12.8 Continuation of Study Treatment with ASP2215

Subjects can continue to receive study treatment with ASP2215 upon reconsent under this protocol version 7.0 until subjects meet discontinuation criteria or applicable reimbursement becomes available in the country of residence. ASP2215 will be supplied every 3 months via IRT as applicable to the subjects until subjects' transition to the commercial product or meet discontinuation criteria. IRT notification is required when subjects discontinue from study treatment. Subjects will be managed per the local institution's standard of care for safety and efficacy assessments while on study treatment after subjects reconsent under this protocol version 7.0. Subjects will follow the Schedule of Assessments in [Table 12]. No data (including PK assessment) will be collected in the eCRFs after subjects reconsent under this protocol version 7.0. Only SAEs, as defined in [Section 5.5.2 Definition of Serious Adverse Events], will be collected and reported as outlined in [Section 5.5.6 Reporting of Serious Adverse Events]. Once subjects transition to commercial supply or meet the study discontinuation criteria, subjects will be discontinued from the study, and no further follow-up will be performed.

Table 12 Continuation of Study Treatment with ASP2215 Schedule of Assessments

Activity	Reconsent	Every 3 Months for Subjects Who Reconsent to Receive ASP2215	End of Treatment
Reconsent (Signed ICF)	X		
SAE Assessment		X[a]	X
IRT Transaction Required		X	X[b]
Local Standard of Care		X	X

ICF: Informed Consent Form; IRT: interactive response technology; SAE: serious adverse event

a. All SAEs will be collected and reported as outlined in [Section 5.5.6 Reporting of Serious Adverse Events] until subjects meet discontinuation criteria or applicable reimbursement becomes available in the country of residence. After subjects reconsent under this protocol version 7.0, SAEs collection will continue until 30 days after the last dose of study treatment. Subjects who complete treatment with a SAE for which relationship to ASP2215 is plausibly related should be followed until the event stabilizes or returns to baseline.

b. IRT notification is required when subjects discontinue from study treatment.

Discontinuation Criteria for Subjects who Reconsent Under This Protocol Version 7.0

Subjects will continue to receive study treatment with ASP2215 until 1 of the following occurs:

- Subject develops an intolerable or unacceptable toxicity
- Subject receives any antileukemic therapy other than the assigned treatment
- Pregnancy
- Subject undergoes HSCT
- Investigator/sub-investigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject declines further study participation (i.e., withdrawal of consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death
- Sponsor elects to discontinue the study.
- ASP2215 reimbursement becomes available in the country of residence.

The subject will be considered to have completed the study on their last date of ASP2215 therapy. No follow-up visits are required after the end of treatment. The subjects who complete treatment with an AE or SAE for which the relationship to ASP2215 is plausibly related should be followed until the event stabilizes or returns to baseline.

12.9 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

Alternate methods cannot be implemented for screening and enrolling/randomizing a participant in the study. Screening and randomization procedures have to be performed in

compliance to the study protocol. This section only applies to a participant who has been randomized in the study and entered in COE part of the study.

Since the chemotherapy dosing must be given in the investigative site, all the required assessment can be completed in investigative site in compliance to the study protocol during the dosing period. No alternative methods are applicable for this period.

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6] unless the investigator discusses the need with the Astellas Medical Monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the PI or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible.
- Site facilities have been closed for clinical study conduct.
- Site has been restricted to treating patients with conditions outside of the scope of the study.
- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel.
- Participant(s) have temporarily relocated from the current study site to an alternate study site avoid placing a burden on the participant with respect to travel.

- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel.
- Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety.

Adherence to the original protocol as reflected in the Schedule of Assessment [Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6] is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 13, Table 14 and Table 15] below are only permissible in the event of a crisis, and after discussing the need with the Astellas Medical Monitor to implement the alternate measures. This is to allow for continuity of receiving investigational medicinal product (IMP) and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

All other assessments should be completed as outlined in [Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6].

Table 13 Alternative Schedule of Assessments in Response to a Crisis: Schedule of Assessments for ASP2215 Arm and ASP2215 Arm in PK cohort

Critical Assessments	Alternate Approach(es)	Critical Timepoints							
		Cycle 1					Cycle 2		Subsequent Cycles
Cycle Day		Day 1	Day 4 ± 1	Day 8 ± 1	Day 9	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
TREATMENTS									
ASP2215 Dosing at the Clinic[j]	Courier service directly to patient	X	X	X		X	X	X	X
ASSESSMENTS									
Physical Examination[b]	The exam can be done at a local clinic and the results submitted to PI.	X[a]	X	X		X	X	X	X
Vital Signs	Can be performed at a local clinic per SOC and results submitted to PI for evaluation	X[a]	X	X		X	X	X	X
ECOG Performance	ECOG status can be done by phone contact at each visit.	X[a]				X	X	X	X
12-lead ECG[e]	ECG testing can be completed at local clinic and the results submitted to PI.	X		X[m]	X[m]	X	X		X
AE/SAE Assessment	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X		X	X	X	X
Prior and Concomitant Medications[c]	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X		X	X	X	X
Patient Reported Outcome Tools[k, l]	Since validated scripts for phone contacts are not available, data need to be entered at the hospital.	X[a]		X[k]		X[k]	X	X[k]	X

Table continued on next page

Critical Assessments	Alternate Approach(es)	Critical Timepoints							
		Cycle 1					Cycle 2		Subsequent Cycles
Cycle Day		Day 1	Day 4 ± 1	Day 8 ± 1	Day 9	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
EQ-5D-5L[l]	Phone Script is available for EQ-5D-5L, hence can be collected via phone script.	X[a]					X		X
Resource Utilization	Virtual/Telemedicine Visits allowed for non-dosing visits. In addition, if any resource utilization is done at local facility, that information should be requested to made available to investigative site.	X[a]					X		X
LABORATORY TESTS									
Pregnancy Test for Woman of Childbearing Potential[d]	Visit collection of samples at local facility acceptable if results can be made available to investigative site	X					X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation)[f]	Visit collection of samples at local facility acceptable if results can be made available to investigative site	X[a]	X[a]	X[a]		X[a]	X[a]	X[a]	X[a]
Thyroid Function Test[n]	Visit collection of samples at local facility acceptable if results can be made available to investigative site								X[n]
Bone Marrow Aspiration and/or Biopsy	Perform BM biopsy in a local facility acceptable if results can be made available to investigative site						X[g]		X[g]
SAMPLING									
PK (whole blood samples for plasma PK)	Astellas Medical Monitor to assess. Not allowed at an alternate clinical due to special sample handling	X[h]		X[h]		X[h]	X[h]		X[h]
PGx[i]	Not allowed at an alternate clinical due to special sample handling	X							

AE: adverse event; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EDTA: ethylenediaminetetraacetic acid; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; INR: international normalization ratio; PGx: pharmacogenomics; PK: pharmacokinetic; PT: prothrombin time; SAE: serious adverse event

a. Obtained predose.
b. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.
c. Includes medications taken within 28 days prior to cycle 1 day 1.
d. Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.
e. ECG assessment will be evaluated at predose of cycle 1 day 1, cycle 1 day 8, cycle 1 day 15 and day 1 of each subsequent cycle. Predose assessments should be taken within 1 hour before drug administration. 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. The mean QTcF of the triplicate ECG tracings based on central reading will be used for final treatment decisions and AE reporting. If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less) by central reading within 14 days, the subject may resume dosing at the reduced dose.
f. Uric acid will be tested on days 1, 4, 8, and 15 in cycle 1. Additional laboratory tests should be performed according to institutional standard of care.
g. Bone marrow samples are required at cycle 2 day 1 and cycle 3 day 1. For subjects who do not achieve a CRc (CR, CRp or CRi), the bone marrow assessments will be repeated at day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow sampling will be repeated on 1 month after the date of remission and every 3 subsequent cycles, or if there is suspicion of relapse in the whole blood. Bone marrow samples are also required at the pre-HSCT visit /end of treatment visit and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required. Bone marrow assessment for blasts counts and cell counts and flow cytometry will be conducted at local lab.
h. PK samples for ASP2215 will be collected on cycle 1 day 1 predose, cycle 1 day 8 predose, and at cycle 1 day 15 and day 1 predose of each subsequent cycle (within 1 hour before drug administration). See [Section 7.6 Analysis of Pharmacokinetics].
i. Whole blood and buccal swab collected at day 1 for optional pharmacogenomics study. Optional pharmacogenomics study is not conducted in China.
j. ASP2215 is taken daily at home except for clinic days when it will be taken at the clinic.
k. Includes Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items. The Brief Fatigue Inventory will be administered at cycle 1 day 1 predose, cycle 1 day 8 (± 1 day), day 15 (± 1 day), cycle 2 day 1 (± 2 days), day 15 (± 1 day) and all subsequent cycles day 1 (± 2 days). Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days).
l. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.
m. 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 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 Interruption, Reduction or Escalation in Dose of the Study Drug].
n. Thyroid function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1, etc.)

Table 14 Alternative Schedule of Assessments in Response to a Crisis: Schedule of Assessments for Chemotherapy Arm

Critical Assessments	Alternate Approach(es)	Critical Timepoints						
		Cycle 1				Cycle 2		Subsequent Cycles
Cycle Day		Day 1	Day 4 ± 1	Day 8 ± 1	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
TREATMENTS								
LoDAC Dosing	LoDAC dosing must be given in the investigative site and all the required assessment can be completed in investigative site during the dosing period. No alternative methods are applicable for this period.	See Footnote[i]						
MEC or FLAG Dosing	MEC or FLAG dosing must be given in the investigative site and all the required assessment can be completed in investigative site during the dosing period. No alternative methods are applicable for this period.	See Footnote[j]						
ASSESSMENTS								
Physical Examination[b]	The exam can be done at a local clinic and the results submitted to PI.	X[a]	X	X	X	X	X	X
Vital Signs	Can be performed at a local clinic per SOC and results submitted to PI for evaluation	X[a]	X	X	X	X	X	X
ECOG Performance	ECOG status can be done by phone contact at each visit.	X[a]			X	X	X	X

Table continued on next page

Critical Assessments	**Alternate Approach(es)**	**Critical Timepoints**						
		Cycle 1				**Cycle 2**		**Subsequent Cycles**
Cycle Day		**Day 1**	**Day 4 ± 1**	**Day 8 ± 1**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 15 ± 1**	**Day 1 ± 2**
12-lead ECG[e]	ECG testing can be completed at local clinic and the results submitted to PI.	X			X	X		X
AE/SAE Assessment	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X
Prior and Concomitant Medications[c]	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X
Patient Reported Outcome Tools[k,l]	Since validated scripts for phone contacts are not available, data need to be entered at the hospital.	X[a]		X[k]	X[k]	X	X[k]	X
EQ-5D-5L[l]	Phone Script is available for EQ-5D-5L, hence can be collected via phone script.	X[a]				X		X
Resource Utilization	Virtual/Telemedicine Visits allowed for non-dosing visits. In addition, if any resource utilization is done at local facility, that information should be requested to made available to investigative site.	X[a]				X		X

Table continued on next page

Critical Assessments	Alternate Approach(es)	Critical Timepoints						
		Cycle 1				Cycle 2		Subsequent Cycles
Cycle Day		Day 1	Day 4 ± 1	Day 8 ± 1	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
LABORATORY TESTS								
Pregnancy Test for Woman of Childbearing Potential[d]	Visit collection of samples at local facility acceptable if results can be made available to investigative site	X				X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation)[f]	Visit collection of samples at local facility acceptable if results can be made available to investigative site	X[a]	X[a]	X	X	X[a]	X	X[a]
Thyroid Function Test[m]	Visit collection of samples at local facility acceptable if results can be made available to investigative site							X[m]
Bone Marrow Aspiration and/or Biopsy	Perform BM biopsy in a local facility acceptable if results can be made available to investigative site				X[g]	X[g]		X[g]
SAMPLING								
PGx[h]	Not allowed at an alternate clinical due to special sample handling	X						

AE: adverse event; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EDTA: ethylenediaminetetraacetic acid; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; FLAG: fludarabine, cytarabine and granulocyte colony-stimulating factor; INR: international normalization ratio; LoDAC: low-dose cytarabine; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; PGx: pharmacogenomics; PT: prothrombin time; SAE: serious adverse event

a. Obtained predose.

b. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

c. Includes medications taken within 28 days prior to cycle 1 day 1.

d. Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.

Footnotes continued on next page

e. ECG assessment will be evaluated at predose of cycle 1 day 1, cycle 1 day 15 and day 1 each subsequent cycle. Predose assessments should be taken within 1 hour before drug administration. 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 7.5.5 Electrocardiograms].

f. Uric acid will be tested on days 1, 4, 8, and 15 in cycle 1. Additional laboratory tests should be performed according to institutional standard of care.

g. For MEC and FLAG, bone marrow samples are required at cycle 2 day1. Also, an additional bone marrow sample is required at cycle 1 day 15 or later, per institutional guidelines, to assess the need for a second cycle. For LoDAC, bone marrow samples are required at cycle 2 day 1 and at cycle 3 day1. For subjects who do not achieve a CRc (CR, CRp or CRi), the bone marrow assessments will be repeated at day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow sampling will be repeated at 1 month after the date of remission and at every 3 subsequent cycles or if there is suspicion of relapse in the whole blood. Bone marrow samples are also required at the end of treatment visit and as clinically indicated. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required. Bone marrow assessment for blasts counts and cell counts and flow cytometry will be conducted at local lab.

h. Whole blood and buccal swab collected at day 1 for optional pharmacogenomics study. Optional pharmacogenomics study is not conducted in China.

i. LoDAC dosing may continue past cycle 2.

j. Additional clinic visits are allowed per institutional guidelines for subjects receiving MEC (days 1 through 5) or FLAG (days 1 through 6). MEC and FLAG are administered for up to 2 cycles depending on response and safety assessments as described in [Section 5.1 Dosing and Administration of Study Drugs and Other Medications].

k. Includes Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items. The Brief Fatigue Inventory will be administered at cycle 1 day 1 predose, cycle 1 day 8 (± 1 day), day 15 (± 1 day), cycle 2 day 1 (± 2 days), day 15 (± 1 day) and all subsequent cycles day 1 (± 2 days). Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items will be administered at cycle 1 day 1 predose, cycle 2 day 1 (± 2 days) and all subsequent cycles day 1 (± 2 days).

l. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

m. For subjects receiving LoDAC, thyroid function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1, etc.).

Table 15 Alternative Schedule of Assessments in Response to a Crisis: Schedule of Assessments for Crossover Extension

Critical Assessments	Alternate Approach(es)	Critical Timepoints							
		Cycle 1					Cycle 2		Subsequent Cycles
Cycle Day		Day 1	Day 4 ± 1	Day 8 ± 1	Day 9	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
TREATMENTS									
ASP2215 Dosing at the Clinic[h]	Courier service directly to patient	X	X	X		X	X	X	X
ASSESSMENTS									
Physical Examination[b]	The exam can be done at a local clinic and the results submitted to PI.	X[a]	X	X		X	X	X	X
Vital Signs	Can be performed at a local clinic per SOC and results submitted to PI for evaluation	X[a]	X	X		X	X	X	X
ECOG Performance	ECOG status can be done by phone contact at each visit.	X[a]				X	X	X	X
12-lead ECG[e]	ECG testing can be completed at local clinic and the results submitted to PI.	X[g]		X[i]	X[i]	X	X		X
AE/SAE Assessment	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X		X	X	X	X
Prior and Concomitant Medications[c]	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X		X	X	X	X

Table continued on next page

Critical Assessments	Alternate Approach(es)	Critical Timepoints							
		Cycle 1					Cycle 2		Subsequent Cycles
Cycle Day		Day 1	Day 4 ± 1	Day 8 ± 1	Day 9	Day 15 ± 1	Day 1 ± 2	Day 15 ± 1	Day 1 ± 2
LABORATORY TESTS									
Pregnancy Test for Woman of Childbearing Potential[d]	Visit collection of samples at local facility acceptable if results can be made available to investigative site	X					X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[f]	Visit collection of samples at local facility acceptable if results can be made available to investigative site	X[a,g]	X[a]	X[a]		X[a]	X[a]	X[a]	X[a]
Thyroid Function Test[j]	Visit collection of samples at local facility acceptable if results can be made available to investigative site								X

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; IRT: interactive response technology; SAE: serious adverse event

a. Obtained predose.

b. Weight measurement should be performed at day 1 of each cycle.

c. Includes medications taken within 28 days prior to C1D1. If EoT was performed within 28 days prior to C1D1, only includes medication after EoT of salvage chemotherapy arm and prior to C1D1.

d. Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.

e. ECG assessment will be evaluated at predose of cycle 1 day 1, cycle 1 day 8, cycle 1 day 15 and day 1 of each subsequent cycle. Predose assessments should be taken within 1 hour before drug administration. 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. The mean QTcF of the triplicate ECG tracings based on central reading will be used for final treatment decisions and AE reporting. If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less) by central reading within 14 days, the subject may resume dosing at the reduced dose.

f. Uric acid will be tested on days 1, 4, 8, and 15 in cycle 1. Additional laboratory tests should be performed according to institutional standard of care.

g. Subjects may be enrolled from local labs only. However, samples must also be submitted for central lab.

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

i. 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 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 Interruption, Reduction or Escalation in Dose of the Study Drug].

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

IMP SUPPLY

If any of the conditions outlined above in the Participants Procedures Assessment are met, one or all of the following mitigating strategies will be employed, as needed, to ensure continuity of IMP supply to the participants:

- Increase stock of IMP on site to reduce number of shipments required, if site space will allow.
- Direct-to-Participant (DTP) shipments of IMP (only for ASP2215) from the site to the participant's home.

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis.

13 SPONSOR'S SIGNATURES