A 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

ISN/Protocol 2215-CL-0301

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

1 Astellas Way

Northbrook, IL 60062

A 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-0301

Version 9.1 [JP]

Incorporating Country-specific Non-Substantial Amendment 3

[See Attachment 1]

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

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Version 9.0 [KR] Incorporating Country-specific Substantial Amendment 8 [20Sep2017]
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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 14, Sponsor's Signatures; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

A 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

ISN/Protocol 2215-CL-0301

Version 9.1 [JP] / Incorporating Country-specific Non-Substantial Amendment 3

16 May 2018

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

Principal Investigator:

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

Date (DD Mmm YYYY)

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

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

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24 h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	[redacted] **Astellas Pharma Global Development** **1 Astellas Way, Northbrook, IL 60062** [redacted]
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CRO's personnel: [redacted]

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[redacted]

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 corrected relative to baseline
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
APGD	Astellas Pharma Global Development, Inc.
AST	Aspartate aminotransferase
AUST	Astellas United States Technologies
AXL	AXL tyrosine kinase
BCRP	Breast cancer resistance protein
BFI	Brief Fatigue Inventory
Ca^{2+}	Calcium
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
CR	Complete remission
CR/CRh	Complete remission and complete remission with partial hematological recovery
CRc	Composite complete remission
CRF	Case report form
CRh	Complete remission with partial hematologic recovery
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
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
EQ-5D-5L	EuroQol Group-5 Dimension-5 Level Instrument

Abbreviations	Description of Abbreviations
FACIT-Dys-SF	Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Forms
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FAS	Full Analysis Set
FLAG-IDA	Fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin
FLT3	FMS-like tyrosine kinase
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
GPSP	Good Post-marketing Study 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 Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
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
LA-CRF	Liver Abnormality-Case Report Form
LFS	Leukemia-free survival
LFT	Liver function tests
LLN	Lower limit of normal
LoDAC	Low-dose cytarabine
logMAR	Logarithm of the Minimum Angle of Resolution
LVEF	Left ventricular ejection fraction
MATE1	Multidrug and toxin extrusion protein 1
MDS	Myelodysplastic syndrome
MEC	Mitoxantrone, etoposide and intermediate-dose cytarabine
mRAS	Modified Response Analysis Set
MTD	Maximum tolerated dose
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application

Abbreviations	Description of Abbreviations
NE	Not evaluable
NOAEL	No observed adverse effect level
NR	No response
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
OS	Overall survival
PD	Protocol deviation
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PH	Proportional hazards
PIA	Plasma inhibitory assay
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	Partial remission
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcome
PT	Preferred term
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RAS	Response analysis set
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TK	Tyrosine kinase
TKD	Tyrosine kinase domain
TLFs	Tables, listings and figures
ULN	Upper limit of normal
VAS	Visual analogue scale
VOD	Veno-occlusive disease
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.
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.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who signed consent but did not meet 1 or more criteria required for participation in a trial and did not randomize to the trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	16 May 2018 / Version 9.1 [JP]
Sponsor: Astellas Pharma Global Development, Inc. (APGD)	**Protocol Number:** 2215-CL-0301
Name of Study Drug: ASP2215	
Phase of Development: Phase 3 In case that ASP2215 is approved for marketing with the indication of relapsed or refractory acute myeloid leukemia with FLT3 mutation, the study will continue as "Phase 4 post-marketing study" in accordance with Good Post-marketing Study Practice (GPSP) after the next day of marketing authorization. In this case, "Study" in the protocol is read as "Post-marketing study."	
Title of Study: A 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 August 2015 to March 2020 (including long-term follow-up period)	
Study Objective(s): The primary objectives are 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. • Determine the efficacy of ASP2215 therapy as assessed by the rate of complete remission and complete remission with partial hematological recovery (CR/CRh) in subjects with FLT3 mutated AML who are refractory to or have relapsed after first-line AML therapy. 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 • complete remission with partial hematologic recovery (CRh) rate • composite complete remission (CRc) rate • transfusion conversion rate; transfusion maintenance rate • transplantation rate • patient reported fatigue (Brief Fatigue Inventory [BFI]) • adverse events (AEs), safety labs, vital signs, ophthalmologic exams, electrocardiograms (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance scores	

- Evaluation of ASP2215 (and metabolites as appropriate) plasma concentration and population pharmacokinetics

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
  - mechanisms of acquired resistance
- 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 140 centers
North America, Europe, Asia and rest of the world

Study Population:

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

Number of Subjects to be Enrolled/Randomized:

369 subjects will be randomized

Study Design Overview:

This is a 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 sixty nine subjects will be randomized in a 2:1 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 low-dose cytarabine (LoDAC), azacitidine, mitoxantrone, etoposide and intermediate-dose cytarabine (MEC) or fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin (FLAG-IDA). 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 of the protocol.

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

Subjects receiving MEC or FLAG-IDA 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 marrow cellularity is between 5% and 20%, the investigator should make the decision whether a subject should receive another treatment cycle or be observed for recovery. If bone 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. Subject 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 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 ≥ 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 the OS endpoint.

After treatment discontinuation, subjects will have a pre-HSCT/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 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.

Two interim analyses by an Independent Data Monitoring Committee (IDMC) will be conducted. The first interim analysis is planned when approximately 141 subjects are randomized into the ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug). The first interim analysis will be performed to evaluate the efficacy endpoint of CR/CRh rate and the study conduct will not be impacted by the result of the CR/CRh rate.

The second interim analysis will be performed when approximately 50% of the planned total number of deaths (death events = 129 of planned 258 death events) by any cause have occurred. The second interim 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 second interim analysis demonstrates a more favorable outcome for ASP2215 based on OS, enrollment to the study may be stopped. 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 or upon marketing authorization and commercial availability of ASP2215 in the country of residence.

Inclusion/Exclusion Criteria:

Inclusion:

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

1. Institutional Review Board-/Independent Ethics Committee-approved written Informed Consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization for United States sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation 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:
     - 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:
     - Subject must have achieved a CR/CRi/CRp (criteria as defined by [Cheson et al, 2003], see Section 5.3) 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.
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 180 days after the final study drug administration
  - And have a negative 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 180 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 180 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.

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 that is ≥ 45%.
12. Subjects with mean of triplicate Fridericia-corrected QT interval (QTcF) > 450 ms at Screening based on central reading.
13. Subjects with Long QT Syndrome at Screening.
14. Subjects 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.

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 salvage chemotherapy 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.

Azacitidine [Itzykson et al, 2015]

- 75 mg/m^2 azacitidine will be administered daily by SC or IV injection for 7 days. Follow Institution's guidelines if dose reduction is needed after cycle 1.

MEC Induction Chemotherapy [Levis et al, 2011]

- Mitoxantrone 8 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-IDA Induction Chemotherapy [Parker et al, 1997; Paul et al, 2014]

- 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).
- Idarubicin 10 mg/m^2 per day will be administered by IV for 3 days (days 2 through 4).

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.

Duration of Treatment:

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

Subjects receiving MEC or FLAG-IDA 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 marrow cellularity is between 5% and 20%, the investigator should make the decision whether a subject should receive another treatment cycle or be observed for recovery. If bone 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 and commercial availability of ASP2215 in the country of residence.

Discontinuation 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-IDA and has NR or progressive disease following cycle 1.
- Subject is receiving LoDAC, azacitidine 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.

The subject will be discontinued from the posttreatment 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.
- Death.

Endpoints for Evaluation:

Co-Primary Efficacy Endpoints:

- OS
- CR/CRh rate

Key Secondary Efficacy Endpoints:

- EFS
- CR rate

Secondary Efficacy Endpoints:

- LFS
- Duration of remission
- CRh rate
- CRc (CR + CRi + CRp) rate
- Transfusion conversion rate; transfusion maintenance rate
- Transplantation rate
- BFI

Exploratory Endpoints:

- PGx
- FLT3 gene mutation status
  - mutation types and frequency
  - relationship to efficacy and safety
  - mechanisms of acquired resistance
- 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
- Ophthalmologic assessments
- ECGs
- ECOG performance scores

Pharmacokinetics

- ASP2215 (and metabolites as appropriate) concentration in blood

Statistical Methods:

Sample Size Justification:

This is a group sequential design based co-primary endpoint of OS using the O'Brien-Fleming boundaries (non-binding) as implemented by Lan-DeMets alpha/beta spending method (East®).

The overall 0.025 one-sided type I error rate is allocated by 0.0005 and 0.0245 (0.001 and 0.049 for two-sided type I error rate) for the two co-primary efficacy endpoints of CR/CRh and OS, respectively. The type I error (alpha) in the first interim analysis will not be recycled in the second interim analysis and final analysis.

The first interim analysis is planned when approximately 141 subjects are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug). The second interim analysis is planned when approximately 129 death events have occurred and the final analysis is planned when approximately 258 death events have occurred.

OS:

Approximately 369 subjects (the planned sample size with 10% dropout rate) will be randomized in a 2:1 ratio to receive ASP2215 or salvage chemotherapy (246 subjects in the ASP2215 treatment arm and 123 subjects in the salvage chemotherapy arm). The planned 258 death events will provide about 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 1-sided 0.0245 significance level.

Statistical Methods continued:

CR/CRh rate:

The first interim analysis will be conducted only to evaluate the co-primary endpoint of CR/CRh in ASP2215 arm only. One hundred and forty-one subjects randomized to ASP2215 arm (211 subjects in total: 141 in the ASP2215 arm and 70 in the salvage chemotherapy arm) with a minimum follow-up of 4 treatment cycles are considered to achieve a maximum width of 15.78% for the two-sided 95% exact confidence interval (CI) when the CR/CRh is expected to be in the 5% to 30% range as summarized in below Table 1. A sample size of 141 subjects provides 80% power to exclude a CR/CRh rate of 12% using the two-sided 95% exact CI when the CR/CRh rate of ASP2215 is assumed to be 21%.

Table 1: Observed CR/CRh with Exact 95% CI (N=141 in ASP2215 arm)

Observed CR/CRh (n and %)	Exact 95% CI
43 (30.50%)	(23.03%, 38.80%)
36 (25.53%)	(18.57%, 33.55%)
29 (20.57%)	(14.23%, 28.18%)
28 (19.86%)	(13.62%, 27.41%)
27 (19.15%)	(13.01%, 26.62%)
26 (18.44%)	(12.41%, 25.84%)
25 (17.73%)	(11.82%, 25.05%)
24 (17.02%)	(11.22%, 24.26%)
23 (16.31%)	(10.63%, 23.46%)
22 (15.60%)	(10.04%, 22.66%)
15 (10.64%)	(6.08%, 16.94%)
8 (5.67%)	(2.48%, 10.87%)

EFS and CR rate:

The planned sample size with 258 EFS events will provide about 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 at the overall 1-sided 0.0245 significance level.

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-IDA or MEC)
- Low intensity chemotherapy (LoDAC or azacitidine)

Primary Efficacy Analysis:

OS:

The co-primary efficacy endpoint of OS will be analyzed using the stratified log-rank test with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on the Intention to Treatment (ITT) Analysis Set. The ITT is defined as all randomized subjects and the analysis is based on the randomized treatment.

The hypothesis testing on the primary analysis of OS will be performed to test the null hypothesis that OS in the ASP2215 arm is worse than or equal to OS in the salvage chemotherapy arm versus the alternative hypothesis that OS in the ASP2215 arm is better than OS in the salvage chemotherapy arm.

The sensitivity analysis for the primary efficacy endpoint of OS will be performed as follows:

- Same analysis as primary analysis, but on Full Analysis Set (FAS), which included all randomized subjects who are FLT3 mutated subjects based on central test;
- Same analysis as primary analysis, but on PPS, which include all subjects in ITT and do not have any major PDs;
- Stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on ITT;
- Same analysis as primary analysis on ITT, but censoring the subjects who undergo HSCT at the time of HSCT;
- To account for the possible confounding effect due to subsequent anti-leukemia therapies, a sensitivity analysis of OS that censors subjects at the time of initiation of new therapy will be performed and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate will also be conducted.
- Additional sensitivity analysis may be performed to compare the survival curves when the proportional hazards (PH) assumption is plausible.

CR/CRh rate:

The two-sided 95% exact confidence interval of CR/CRh rate will be calculated for approximately 141 subjects who are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug), i.e., 2215 subjects in response analysis set (RAS). The lower limit will be used to compare with the benchmark of CR/CRh rate of 12%.

Sensitivity analyses will be performed to assess the robustness of the CR/CRh rate based on:

- Same population as for the primary analysis, but only include subjects in modified response analysis set (mRAS);
- Same population as for the primary analysis, but only include subjects who took at least one dose of ASP2215;
- Same population as for the primary analysis, but only include subjects who had at least one post-baseline bone marrow assessment;
- Same population as for the primary analysis, but evaluate the CR/CRh by cycle 4, which is defined as the number of subjects who achieve CR/CRh by cycle 4 divided by the number of subjects in the analysis population.
- Same population as for the primary analysis, but evaluate the CR/CRh prior to HSCT, which is defined as the number of subjects who achieve CR/CRh prior to HSCT divided by the number of subjects in the analysis population.

Key Secondary Efficacy Analysis:

EFS:

The key secondary efficacy endpoint of EFS will be analyzed using the stratified log-rank test 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 0.0245 significance level, the hypothesis testing on EFS will be performed only if the null hypothesis on the primary analysis of OS is rejected at its corresponding significance level at the second interim analysis and final analysis.

The sensitivity analysis for the key secondary efficacy endpoint of EFS will be performed as follows:

- Same analysis as primary analysis, but on FAS, which includes all randomized subjects who are FLT3 mutated subjects based on central test;
- Same analysis as primary analysis, but on PPS, which includes all subjects in ITT and do not have any major PDs;
- Stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on ITT;
- EFS will be defined similarly as in Section 5.3.2.2 however the date of the first new anti-leukemia therapy after end of study treatment or the last treatment evaluation (when new anti-leukemia therapy date is not available) will be used as the event date of treatment failure;
- EFS will be defined similarly as in Section 5.3.2.2 however subjects who discontinued the treatment due to "Lost to follow up" will also be considered as an EFS event and the subjects will be censored at the date of "Lost to follow up".

CR rate:

The key secondary efficacy endpoint of CR rate will be tested 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 0.0245 significance level, the hypothesis testing on CR rate will be performed only if the null hypothesis on EFS is rejected at its corresponding significance level at the second interim analysis and final analysis.

Sensitivity analyses for CR rate will be performed as follows:

- CMH test on subjects in ITT and received at least one dose of study treatment
- CMH test on subjects in ITT with at least one post-baseline bone marrow assessment
- Un-stratified Fisher's exact test on subjects in ITT

Secondary Efficacy Analyses:

The statistical analyses on secondary efficacy endpoints include:

- Stratified log-rank test on duration of remission and LFS
- CMH method on the CRc rate and transplantation rate
- Transfusion conversion rate and transfusion maintenance rate will be summarized by descriptive statistics
- Analysis of covariance (ANCOVA) 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 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, ophthalmologic assessments 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.

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.

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 ANCOVA model will be used for resource utilization counts (hospital stays, duration of medications, blood transfusions, antibiotic iv infusions, medication for AEs and opioid medication).

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

ANCOVA 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.

ANCOVA model will be used for the change from baseline of EQ-5D-5L visual analogue scale 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 benchmark data or the salvage chemotherapy group while the study is ongoing, two interim analyses are planned.

<u>First Interim Analysis</u>

The first interim analysis is planned when approximately 141 subjects are randomized into the ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug). At the first interim analysis, only the co-primary endpoint of CR/CRh rate will be evaluated in the ASP2215 arm only. The descriptive statistics including two-sided 95% exact CI of CR/CRh rate will be provided to IDMC. The historical control of the CR/CRh rate is considered to be 12%. The IDMC will evaluate the CR/CRh rate and inform the Sponsor if the lower limit is higher than the historical control or not. The study conduct will not be impacted by the first interim analysis result.

A nominal 1-sided p-value 0.0005 (i.e., 2-sided p-value 0.001), which is arbitrarily selected, will be spent to acknowledge the single-arm CR/CRh rate evaluation at the first interim analysis and will not be recycled in the second interim analysis and final analysis. No formal hypothesis testing will be conducted for CR/CRh rate for the study, only the descriptive statistics including 2-sided 95% exact CI of CR/CRh rate will be provided to IDMC at the first interim. The hypothesis testing for the primary and secondary endpoints of OS, EFS and CR rate at the secondary interim analysis and final analysis are well controlled at an overall 1-sided type I error rate 0.0245 based on a sequential testing procedure.

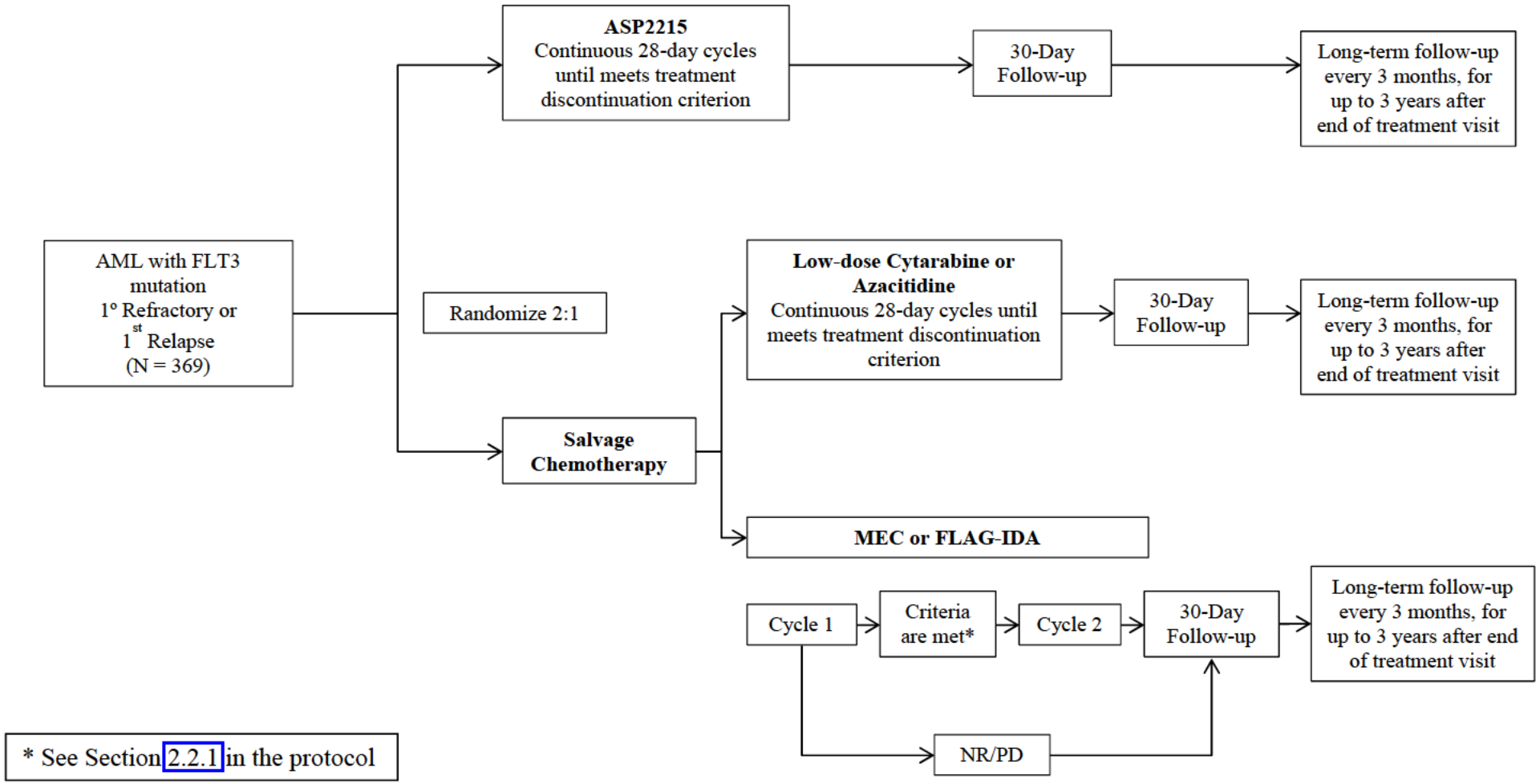
Second Interim Analysis

The second interim analysis will be performed when approximately 50% of the total planned death events (death events = 129) have occurred in the study. OS will be tested at 1-sided 0.00147/0.38674 significant level for efficacy/futility according to the O'Brien-Fleming type alpha/beta spending function.

The IDMC may recommend terminating the trial for favorable or unfavorable results at the second interim analysis based on OS endpoint. In the case of favorable results (i.e., the 1-sided P-value is less than 0.00147), the IDMC may recommend terminating the trial for success. In the case of unfavorable results (i.e., the 1-sided P-value is greater than 0.38674), the IDMC may recommend terminating the trial for futility.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



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

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[p]							
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)[o]	X								
12-lead ECG[e]	X[g]	X		X[s]	X[s]	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[t]	X								X[t]
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	X								
MUGA or ECHO[h]	X								
Ophthalmologic Assessment[i]	X						X		X
FLT3 Mutation Status[j] (bone marrow aspirate or whole blood)	X								
Bone Marrow Aspiration and/or Biopsy	X[k]						X[k]		X[k]
AE/SAE Assessment	X	X	X	X		X	X	X	X
PK (whole blood samples for plasma PK)		X[l]		X[l]		X[l]	X[l]		X[l]
PGx[m]		X							
Patient Reported Outcome Tools[q, r]		X[a]		X[q]		X[q]	X	X[q]	X
EQ-5D-5L[r]		X[a]					X		X
Resource Utilization		X[a]					X		X
IRT Transaction Required[p]	X	X					X		X
ASP2215 Dosing at the Clinic[n]		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;

Footnotes continued on next page

FLAG-IDA: fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin; 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.

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 read. 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. Ophthalmologic assessment to be performed by visual acuity measurement and ophthalmoscopy during the screening period, day 1 (± 7 days) of cycle 2, day 1 (± 7 days) of every 2 cycles thereafter, and when clinically indicated. In symptomatic subjects, the ophthalmologic assessment should also include slit lamp biomicroscopy, visual fields performed by Humphrey method and optical coherence tomography.

j. 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.

k. 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.

l. 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 (within1 hour before drug administration). See Section 7.6

m. Whole blood and buccal swab collected at day 1 for optional pharmacogenomic study.

Footnotes continued on next page

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

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

p. 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.

q. 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).

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

s. A cycle 1 day 8 ECG will be taken and the central read results will be provided to the site 24 hours after receipt of the tracing. A confirmatory ECG should be performed on cycle 1 day 9 if the mean QTcF from 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.

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

Table 2 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[p]						
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)[o]	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[s]	X							X[s]
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	X							
MUGA or ECHO[h]	X							
Ophthalmologic Assessment	X[t]					X[t]		X[t]
FLT3 Mutation Status[j] (bone marrow aspirate or whole blood)	X							
Bone Marrow Aspiration and/or Biopsy	X[k]				X[k]	X[k]		X[k]
AE/SAE Assessment	X	X	X	X	X	X	X	X
PGx[l]		X						
Patient Reported Outcome Tools[q, r]		X[a]		X[q]	X[q]	X	X[q]	X
EQ-5D-5L[r]		X[a]				X		X
Resource Utilization		X[a]				X		X
IRT Transaction Required[p]	X	X				X		X
LoDAC or Azacitidine Dosing		See Footnote[m]						
MEC or FLAG-IDA Dosing		See Footnote[n]						

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-IDA: fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin; 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
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 read. 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. Ophthalmologic assessment to be performed by visual acuity measurement and ophthalmoscopy during the screening period, day 1 (± 7 days) of cycle 2, day 1 (± 7 days) of every 2 cycles thereafter, and when clinically indicated. In symptomatic subjects, the ophthalmologic assessment should also include slit lamp biomicroscopy, visual fields performed by Humphrey method and optical coherence tomography.
j. 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 lab. 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.
k. For MEC and FLAG-IDA, 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 a second cycle. For LoDAC or azacitidine, bone marrow samples are required during screening, and at cycle 2 day 1 and at 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 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.
l. Whole blood and buccal swab collected at day 1 for optional pharmacogenomic study.
m. LoDAC or azacitidine dosing may continue past cycle 2.
n. Additional clinic visits are allowed per institutional guidelines for subjects receiving MEC (days 1 through 5) or FLAG-IDA (days 1 through 6). MEC and FLAG-IDA are administered for up to 2 cycles depending on response and safety assessments as described in Section 5.1
o. Chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of screening.
p. 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.
q. 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).
r. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.
s. For subjects receiving LoDAC or azacitidine, thyroid function tests will be repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1, etc.).

Table 3 Posttreatment Schedule of Assessments

Activity	Pre-HSCT Visit / End of Treatment Visit[a]	30-Day Follow-up (+ 7 days Post Pre-HSCT Visit/Post End of Treatment Visit)	Long-term Follow-up (+/- 7 days)[h]
Physical Examination	X[b]		
Vital Signs	X[b]		
ECOG Performance	X[b]		
Concomitant Medications	X[l]		
Pregnancy Test for Woman of Childbearing Potential	X		
12-lead ECG	X		
Ophthalmologic Assessment[j]	X		
Clinical Laboratory Tests (chemistry, hematology, coagulation)	X[b]		
Thyroid Function Tests	X		
Bone Marrow Aspiration and/or Biopsy	X[c]		
FLT3 Mutations[d] (bone marrow or whole blood)	X		
Patient Reported Outcome Tools[i, k]	X		
EQ-5D-5L[k]	X	X	X
Resource Utilization	X		
AE/SAE Assessment	X	X[e,f]	X[g]
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.

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.

d. FLT3 mutation analysis will be performed on the bone marrow samples collected post study treatment.

Footnotes continued on next page

e. For subjects who plan to proceed to HSCT and resume ASP2215 treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen and AE collection will resume upon the resumption of ASP2215 treatment until 30 days after the last dose of study drug. For subjects who do not plan to resume ASP2215 treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen or 30 days after the last dose of study drug, whichever comes first. However, the following AE/SAEs will continue to be collected until 30 days after the last dose of study drug, regardless of the time of the HSCT conditioning regimen:
   - Any study drug related AE that is ongoing will be followed until resolved
   - Any SAE that is deemed to be related to study drug by the investigator
   - Any event of veno-occlusive disease (VOD) of the liver, cardiac failure, Grade 3 or higher QT prolongation, rhabdomyolysis, drug-induced liver injury, or posterior reversible encephalopathy syndrome (PRES)
   - Adverse events leading to death

f. Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.

g. Only SAE data that is related to ASP2215 will be collected.

h. Telephone contact every 3 months. Ad hoc contact will be required during interim analysis.

i. 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.

j. Ophthalmologic assessment to be performed by visual acuity measurement and ophthalmoscopy, at the preHSCT/end of treatment (± 7 days). In symptomatic subjects, the ophthalmologic assessment should also include slit lamp biomicroscopy, visual fields and optical coherence tomography.

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

l. Concomitant medications should be collected for reported AE/SAEs through 30 days post dose for subjects who have discontinued. For subjects who undergo HSCT, concomitant medications should be collected for reported AE/SAEs through start of conditioning treatment or 30 days post dose, whichever comes first.

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]. In a recent international randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia, the CR rate in the control arm was only 12% [Roboz et al, 2014]. In this study, the treatment options available in the control arm (physician's choice) reflect contemporary clinical practice, rather than a strict selection of only patients that are eligible for intensive salvage regimens. As a result, this control arm should more appropriately represent what can be expected in standard clinical practice.

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 [redacted] ASP2215 has an inhibitory effect on TKs, mainly FLT3, AXL and anaplastic lymphoma kinase (ALK). ASP2215 demonstrated favorable efficacy in a nonclinical 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 with idarubicin [FLAG-IDA]) and less-aggressive (low-dose cytarabine [LoDAC] and azacitidine) regimens are included in the study.

1.2 Nonclinical and Clinical Data

1.2.1 Nonclinical 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 substrates (see Section 1.2.2.1).

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

In Study 2215-CL-0101, as of 02 Feb 2015, 154 subjects were evaluable for response. The response assessments were done based on central laboratory evaluation of samples supplemented with local results when the central results were not available (derived response).

Based on the derived response at end of treatment in the 154 subjects (both FLT3-mutation positive and negative) who received at least 1 dose of ASP2215, 41 (26.6%) subjects achieved composite complete remission (CRc), and the best overall response rate (CRc + partial remission [PR]) was 35.7%.

Nearly all subjects that achieved a derived response of PR or CRc at the end of treatment were FLT3-mutation positive. Based on the derived response in the 98 FLT3-mutation positive subjects at the end of treatment, 36 (36.7%) subjects achieved CRc, and the best overall response rate was 49.0%. Five (5.1%) subjects achieved CR, 3 (3.1%) subjects achieved complete remission with incomplete platelet recovery (CRp), 28 (28.6%) subjects achieved complete remission with incomplete hematologic recovery (CRi) and 12 (12.2%) subjects achieved PR.

CRc rates for 80, 120 and 200 mg dose groups were 41.7%, 48.6% and 45.8% respectively. Among the 77 FLT3-mutation positive subjects in the 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups, 34 (44.2%) had achieved CRc as the derived response at the end of treatment and the overall response rate was 55.8%. Four (5.2%) subjects achieved CR,

3 (3.9%) subjects achieved CRp, 27 (35.1%) subjects achieved CRi and 9 (11.7%) subjects achieved PR.

Based on the derived response in the 47 FLT3-mutation negative subjects at the end of treatment, 2 (4.3%) subjects achieved CRc, and the best overall response rate (CRc + PR) was 8.5%. Two (4.3%) subjects each achieved CRi and PR.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 ASP2215

The nonclinical and clinical studies which are referred to in this section are described in more detail in the ASP2215 Investigator's Brochure [2015].

1.3.1.1 ASP2215 Nonclinical Data

ASP2215 showed a concentration-dependent suppression effect on the human ether-a-go-go related gene current in HEK293 cells at concentrations of 3×10^{-6}, 1×10^{-5} and 3×10^{-5} mol/L with compensated suppression rates of 18.1%, 32.8% and 70.7%, respectively; no suppression was observed at 1×10^{-6} mol/L. The IC_{50} was 1.6×10^{-5} mol/L.

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

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

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

In the 1-week oral repeated dose toxicity study in rats, interstitial pneumonia in the lung and vacuolar change in the rod-cone layer of the retina were observed in a male at 30 mg/kg per day. In the 13-week oral repeated dose toxicity study in rats, deaths occurred at 20 mg/kg per day in both sexes. Target organ toxicity was identified in the gastrointestinal tract, immune system, hematopoietic system, eye, lung, kidney and liver. The no observed adverse effect level (NOAEL) was lower than 2.5 mg/kg per day for males and females. The changes noted during the dosing period recovered or tended to recover during the 4-week recovery period. In the 4-week oral repeated dose study in dogs, mortality occurred at 10 mg/kg per day or

more. Target organ toxicity was identified in the gastrointestinal tract, immune system, hematopoietic system, eye, kidney and liver. The NOAEL was 1 mg/kg per day for males and females. Reversibility of most of the test article related changes was indicated by the end of the 4-week recovery period. In the 13-week oral repeated dose study in dogs, mortality occurred at 5 mg/kg per day. Target organ toxicity was identified in the lung, lacrimal gland, urinary bladder, epithelial tissue, gastrointestinal tract, immune system, hematopoietic system, eye, kidney and liver. The NOAEL was 1 mg/kg per day for males and females. Reversibility of most of the test article-related changes was indicated by the end of the 4-week recovery period.

ASP2215 did not induce gene mutation in the definitive in vitro reversion test in bacteria. Similarly, ASP2215 did not induce chromosomal aberrations in the definitive in vitro chromosomal aberration test in mammalian cells. The definitive in vivo micronucleus test showed that ASP2215 has a potential to induce micronuclei in mice. Based on the results of the battery of genotoxicity studies above, it was concluded that ASP2215 has a potential to induce genotoxicity in vivo.

ASP2215 showed teratogenic potential and embryo-fetal deaths in the embryo-fetal development study in rats. The NOAEL of ASP2215 for dams and embryo-fetal development was 10 mg/kg per day.

ASP2215 showed no potential to induce phototoxicity to cultured mammalian cells.

1.3.1.2 ASP2215 Clinical Data

As of February 2016, 447 subjects (300 AML patients; 131 healthy subjects and 16 subjects with mild or moderate hepatic impairment) have been enrolled in phase 1 studies. Study 2215-CL-0101 is a first-in-human phase 1/2 open-label, dose-escalation study initiated in October, 2013, and as of 31 Oct 2015, 262 subjects had been enrolled. Of the subjects in that study who received ASP2215, 245 (97.2%) developed at least 1 treatment -emergent adverse event (TEAE) during the study. Overall, the most frequently reported TEAEs (occurring in at least 10% of subjects) included febrile neutropenia (38.5%), diarrhea (33.7%), anemia (29.0%), fatigue (28.2%), aspartate aminotransferase (AST) increased (23.0%), edema peripheral (22.6%), pyrexia and dyspnea (21.8% each), constipation and cough (18.7% each), epistaxis (17.9%), nausea (17.5%), dizziness (17.1%), hypotension and alanine aminotransferase (ALT) increased (16.7% each), vomiting (15.9%), hypokalemia (15.1%), hypocalcemia (14.7%), platelet count decreased (13.5%), blood creatinine increased (13.1%), hyponatremia and AML (12.7% each), pneumonia (12.3%), sepsis (11.9%), fall (11.5%), thrombocytopenia, hypomagnesemia, and arthralgia (11.1% each), headache and blood alkaline phosphatase (ALP) increased (10.7% each), and hypoxia (10.3%). A total of 183 (72.6%) subjects experienced at least 1 TEAE considered by the investigator to be possibly or probably related to study drug. Common drug-related TEAEs (occurring in at least 5% of subjects) included diarrhea (16.3%), fatigue (13.1%), increased AST (11.9%), anemia (9.1%), constipation, increased ALT and peripheral edema (8.3% each), decreased platelet count and nausea (7.5% each), thrombocytopenia and vomiting (6.7% each),

increased creatine phosphokinase, dizziness and dysgeusia (6.3% each) and increased transaminases (6.0%).

A total of 198 (78.6%) of the subjects developed at least 1 serious TEAE. The most commonly reported serious TEAEs (occurring in at least 5% of subjects) included febrile neutropenia (30.6%), AML (12.7%), sepsis (11.9%), pneumonia (9.5%), renal failure acute (8.3%), pyrexia (6.7%) and bacteremia (5.2%). Of the serious TEAEs, 69 (27.4%) subjects had serious TEAEs that were considered by the investigators to be related to ASP2215. Drug-related serious TEAEs that occurred in 2 or more subjects included febrile neutropenia (2.4%); renal failure acute, gastrointestinal hemorrhage and increased AST (1.6% each); blood bilirubin increased, blood creatine phosphokinase increased, hypotension (1.2% each); nausea, liver function test abnormal, pyrexia, sepsis, increased ALT, muscular weakness, transaminases increased, small intestinal obstruction, hypoxia, posterior reversible encephalopathy syndrome (PRES) and vomiting (0.8% each).

Eighty-seven (34.5%) subjects experienced a TEAE that resulted in death: AML in 32 (12.7%) subjects; multi-organ failure in 7 (2.8%) subjects; respiratory failure in 6 (2.4%) subjects; sepsis and septic shock in 4 (1.6%) subjects each, pneumonia, cardiac arrest and intracranial hemorrhage in 3 (1.2%) subjects each; disease progression and renal failure in 2 (0.8%) subjects each; anemia, neutropenia, peripheral edema, bronchopulmonary aspergillosis, enterococcal infection, lung infection, pyoderma, staphylococcal bacteremia, staphylococcal sepsis, malignant neoplasm progression, cerebral ischemia, loss of consciousness, acute respiratory failure, hypoxia, pulmonary embolism, colitis, ventricular fibrillation, ventricular tachycardia, neutropenic colitis, bacteremia, cellulitis, diabetic ketoacidosis, sudden death and hemoptysis each in 1 (0.4%) subject.

A preliminary analysis of the relationship between ASP2215 plasma concentration and Fridericia-corrected QT interval (QTcF) change from baseline (ΔQTcF) was performed on data from the 2215-CL-0101 study (data cutoff 31 Oct 2015). This assessment included 1359 observations from 199 subjects. A model-averaging approach was used to develop a robust model to describe and predict the ASP2215 concentration-ΔQTcF relationship. A concentration-related increase in ΔQTcF was observed and the mean ΔQTcF at the mean steady-state C_{max} was predicted to be less than the 10 msec threshold considered clinically significant. Additionally, less than 5% of Relapsed/Refractory AML subjects had a maximum post-baseline QTcF interval > 500 msec. These data indicate clinically-relevant QTc prolongation is not anticipated.

An exposure-related increase in circulating creatine kinase (CK) concentration relative to baseline was also observed in Relapse/Refractory AML subjects enrolled in Study 2215-CL-0101. Almost all CK elevations were grade 1 and grade 2, however, Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and 4 adverse events (AEs) related to elevated CK occurred in higher ASP2215 dose groups. Similarly, a significant correlation between ASP2215 concentration and aspartate aminotransferase change from baseline (ΔAST) was also observed. However, the incidence of ≥ Grade 3 events related to elevated AST was < 3% (data cutoff 31 Oct 2015).

As of 31 Oct 2015, 23 subjects experienced a dose limiting toxicity (DLT). All DLTs occurred in the dose expansion cohort, with the exception of 2 subjects in the 450 mg dose escalation cohort that experienced grade 3 increased AST and grade 3 diarrhea. No further subjects will be enrolled in the 450 mg dose group. None of the doses below 450 mg met the criteria for pausing enrollment. The maximum tolerated dose (MTD) in Study 2215-CL-0101 is considered 300 mg.

Expected adverse drug reactions for ASP2215 include (by preferred term) diarrhea, peripheral edema, increased blood creatine phosphokinase, increased ALT, increased AST and myopathy.

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 Objectives

The primary objectives are 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.
- Determine the efficacy of ASP2215 therapy as assessed by the rate of complete remission and complete remission with partial hematological recovery (CR/CRh) in subjects with FLT3-mutated AML who are refractory to or have relapsed after first-line AML therapy.

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
- CRh rate
- CRc rate
- Transfusion conversion rate; transfusion maintenance rate
- Transplantation rate
- Patient reported fatigue (Brief Fatigue Inventory [BFI])
- AEs, safety labs, vital signs, ophthalmologic exams, electrocardiograms (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance scores
- Evaluation of ASP2215 (and metabolites as appropriate) plasma concentration and population pharmacokinetics

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
    - mechanisms of acquired resistance

- 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 a 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 140 centers in North America, Europe, Asia and rest of the world will participate in this study.

Three hundred sixty nine subjects will be randomized. The randomization of the 369 subjects will be in a 2:1 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, azacitidine, MEC or FLAG-IDA. 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 of the protocol.

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

Subjects receiving MEC or FLAG-IDA 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 marrow 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 bone 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] 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) ≥ 500/mm^3 and platelets ≥ 20000/mm^3 without transfusions
- Subject does not have ≥ 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 the OS endpoint.

After treatment discontinuation, subjects will have a pre-HSCT/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.

Two interim analyses by an Independent Data Monitoring Committee (IDMC) will be conducted. The first interim analysis is planned when approximately 141 subjects are randomized into the ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug). The first interim analysis will be performed to evaluate the efficacy endpoint of CR/CRh and the study conduct will not be impacted by the result of the CR/CRh rate.

The second interim analysis will be performed when approximately 50% of the planned total number of deaths (death event = 129 of planned 258 death events) by any cause have occurred. The second interim 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 second interim analysis demonstrates a more favorable outcome for ASP2215 based on OS, enrollment to the study may be stopped. 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 or upon marketing authorization and commercial availability of ASP2215 in the country of residence.

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. Doses used in randomized trials were chosen where available.

2.3 Endpoints

2.3.1 Co-Primary Endpoints

- OS
- CR/CRh rate

2.3.2 Secondary Endpoints

Key Secondary Efficacy Endpoints

- EFS
- CR rate

Secondary Efficacy Endpoints

- LFS
- Duration of remission
- CRh rate
- CRc (CR + CRi + CRp) rate
- Transfusion conversion rate; transfusion maintenance rate
- Transplantation rate
- BFI

2.3.3 Exploratory Endpoints

- PGx
- FLT3 gene mutation status
    - mutation types and frequency
    - relationship to efficacy and safety
    - mechanisms of acquired resistance
- 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
- Ophthalmologic assessments
- ECGs
- ECOG performance scores

2.3.5 Pharmacokinetics

- ASP2215 (and metabolites as appropriate) concentration in blood

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, ophthalmology examination) 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 (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for United States sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation 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 (as defined by [Cheson et al, 2003], see Section 5.3) 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 180 days after the final study drug administration
        - And have a negative 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 180 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 180 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 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 4].

Table 4 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 5]. 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 (e.g., FDA, European Commission or each country regulatory agency).

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)-Astellas United States Technologies (AUST) in accordance with APGD-AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Table 5 Comparator Drug Products Supplied by the Sponsor

Comparator Chemotherapy Drug	Drug Product
LoDAC	
Low-dose cytarabine	Cytarabine 20 mg/mL Injection Solution 100 mg/5mL
Azacitidine	
Azacitidine	Azacitidine 25 mg/mL Powder for Suspension for Injection
MEC Induction Chemotherapy	
Cytarabine intermediate dose	Cytarabine 100 mg/mL Solution for Injection or Infusion
Mitoxantrone	Mitoxantrone 2 mg/mL Concentrate for Solution for Infusion
Etoposide	Etoposide 20 mg/mL Concentrate for Solution for Infusion
FLAG-IDA Induction Chemotherapy	
High-dose cytarabine	Cytarabine 100 mg/mL Solution for Injection or Infusion
G-CSF filgrastim	Filgrastim 30 MU (0.3 mg/mL) Solution for Injection
Idarubicin	Idarubicin 10 mg Powder for Solution for Injection
Fludarabine	Fludarabine Phosphate 25 mg/mL Concentrate for Solution for Injection or Infusion

FLAG-IDA: fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin; 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 qualified staff at APGD-AUST or Sponsor's designee in accordance with APGD-AUST or Sponsor's designee 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.

A qualified person of Astellas Pharma Europe B.V. or Sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

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 APGD-AUST in accordance with APGD-AUST 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.

Specific to Japan

In Japan, the head of the study site or the study drug storage manager should take accountability of the study drugs as follows:

- The study drug storage manager should store and take accountability of the study drugs in conforming to the procedures for handling the study drugs written by the Sponsor.
- The study drug storage manager should prepare and retain records of the study drug's receipt, the inventory at the study site, the use by each subject and the return to the Sponsor or alternative disposal of unused study drugs. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the study drugs and subjects.
- The study drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all the study drugs supplied from the Sponsor.

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. 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.

Azacitidine [Itzykson et al, 2015]

- 75 mg/m^2 azacitidine will be administered daily by SC or IV injection for 7 days. Follow Institution's guidelines if dose reduction is needed after cycle 1.

MEC Induction Chemotherapy [Levis et al, 2011]

- Mitoxantrone 8 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-IDA Induction Chemotherapy [Parker et al, 1997; Paul et al, 2014]

- 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).
- Idarubicin 10 mg/m^2 per day will be administered by IV for 3 days (days 2 through 4).

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

Subjects receiving MEC or FLAG-IDA 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 marrow 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 bone 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 6].

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 6]. 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 6]. 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.

Any subjects that have been off treatment for more than 14 days other than for HSCT can only resume treatment after discussion with the medical monitor.

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

Table 6 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 1day 1 to cycle 1 day 8 has increased > 30 ms based on central read ECG without any other etiology, a confirmatory ECG will be performed on day 9. If the cycle 1 day 9 central read ECG is confirmatory, a dose reduction should be considered. QTcF values based on central reading from triplicate ECGs should be used for this determination (i.e., day 8 mean QTcF from triplicate ECGs at predose minus the day 1 mean QTcF from triplicate ECGs at predose).
Retinopathy	
Grade 2	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ grade 1 within 14 days, the subject may resume dosing at the reduced dose.
Grade 3/4	Treatment will be discontinued.
Nonhematological Events	
Grade 3 toxicity at least possibly 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 related to ASP2215	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 7].

Table 7 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 Nonmedication Therapy)

All medications and concomitant treatments administered from 28 days prior to cycle 1 day 1 must be recorded in the Case Report Form (CRF). Concomitant medications should be collected for reported AE/serious adverse events (SAEs) through 30 days post dose for subjects who have discontinued. For subjects who undergo HSCT, concomitant medications should be collected for reported AE/SAEs through start of conditioning treatment or 30 days post dose, whichever comes first.

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 the above named categories. For concomitant drugs that have the potential to prolong QT or QTc intervals, a cardiology consult should be obtained as medically indicated.

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 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 $\geq$ 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 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. 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. 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 8].

Table 8 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all predisease 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 at a post-baseline visit, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an ANC $\geq 1 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/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 at a post-baseline visit, they must achieve CR except for incomplete platelet recovery ($< 100 \times 10^9$/L).

5.3.1.3 Complete Remission with Incomplete Hematologic Recovery

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

5.3.1.4 Composite Complete Remission

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

5.3.1.5 Complete Remission with Partial Hematologic Recovery

At a post baseline visit, subjects will be classified as CRh if they have marrow blasts < 5%, partial hematologic recovery ANC ≥ 0.5 x 10^9/L and platelets ≥ 50 x 10^9/L, no evidence of extramedullary leukemia and cannot be classified as CR.

5.3.1.6 Partial Remission

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

5.3.1.7 Not Evaluable/No Response

In the situation where no bone marrow assessments are performed or myeloblast value is missing, blast value from peripheral blood is missing or ≤ 2%, and extramedullary leukemia is missing or not done, the response will be classified as not evaluable (NE). In any case response cannot be categorized as CR, CRp, CRi, PR or NE, it will be categorized as NR.

5.3.1.8 Relapse

Relapse after CR, CRh, 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.

5.3.1.9 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-baseline. 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.

5.3.1.10 Complete Remission Rate

CR rate is defined as the number of subjects who achieve the best response of CR divided by the number of subjects in the analysis population.

5.3.1.11 Composite Complete Remission Rate

CRc rate is defined as the number of subjects who achieve the best response of CRc (CR, CRp or CRi) divided by the number of subjects in the analysis population.

5.3.1.12 Complete Remission with Partial Hematologic Recovery Rate

CRh is defined as the number of subjects who achieve CRh at any of the post-baseline visits and do not have best response of CR divided by the number of subjects in the analysis population.

5.3.1.13 Complete Remission and Complete Remission with Partial Hematologic Recovery Rate

CR/CRh is defined as the number of subjects who achieve either CR or CRh at any of the post-baseline visits divided by the number of subjects in the analysis population.

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 the latest date the subject is known to be alive by the cutoff date.

5.3.2.2 Event-free Survival

EFS is defined as the time from the date of randomization until the date of documented relapse (excluding relapse after PR), treatment failure or death, whichever occurs first. If a subject experiences relapse or death, the subject is defined as having EFS event related to either “relapse” or “death”, and the event date is the date of relapse or death. If a subject fails to achieve any of the response of CR, CRp, CRi or PR during the treatment period, the subject is defined as having EFS event related to treatment failure, and the event date is the randomization date. For a subject who is not known to have had a relapse or treatment failure or death event, EFS is censored at the date of last relapse-free disease assessment. Subject is not censored at 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

Duration of remission includes duration of CRc, duration of CR/CRh, duration of CRh, 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. Other subjects who do not relapse on study are considered nonevents and censored at the last relapse-free disease assessment date.

Duration of CR/CRh, CRh, CR, CRp, CRi

Duration of CR/CRh, CRh, 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. 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-IDA 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 or azacitidine groups, bone marrow samples are required during screening and at cycle 2 day 1 and at 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.

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 post pre-HSCT/end of treatment visit 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 for up to 3 years after end of treatment visit. Data may be supplemented by site records when available at the time of the contact (e.g., treatment records, outcomes). Follow-up will continue until the final database lock, which is estimated to be up to 3 years of follow-up. 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 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.

5.4 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.

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

For subjects who plan to proceed to HSCT and resume ASP2215 treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen and AE collection will resume upon the resumption of ASP2215 treatment until 30 days after the last dose of study drug. For subjects who do not plan to resume ASP2215 treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen or 30 days after the last dose of study drug, whichever comes first. However, the following AE/SAEs will continue to be collected until 30 days after the last dose of study drug, regardless of the time of the HSCT conditioning regimen:

- Any study drug related AE that is ongoing will be followed until resolved
- Any SAE that is deemed to be related to study drug by the investigator
- Any event of veno-occlusive disease (VOD) of the liver, cardiac failure, Grade 3 or higher QT prolongation, rhabdomyolysis, drug-induced liver injury or PRES
- AEs leading to death

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].

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].

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.

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 $\geq$ 45%).

5.4.8 Ophthalmologic Exam

Ophthalmologic examinations will be conducted during the screening period, day 1 (± 7 days) of cycle 2, day 1 (± 7 days) of every 2 cycles thereafter, at the preHSCT/end of treatment (± 7 days) and when clinically indicated. The following tests and exams are required at every visit:

- Visual Acuity: best-corrected visual acuity as per ETDRS or Snellen charts or other visual acuity chart testing reported as Logarithm of the Minimum Angle of Resolution (logMAR) scores (For the visual acuity testing using a near card at bedside, the results must indicate the vision was tested with a near card.)
- Ophthalmoscopy (A dilated ophthalmoscopy can be performed at bedside.)

In symptomatic subjects, the ophthalmologic assessment should also include slit lamp biomicroscopy, visual fields performed by Humphrey method and optical coherence tomography.

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)

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 "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

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).

5.5.4 Criteria for Defining the Severity of an Adverse Event

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

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

5.5.5 Reporting of Serious Adverse Events

SAE collection will begin from time of informed consent through 30 days after last dose of study medication. During the long-term follow-up period, only SAE data for the event that is related to ASP2215 will be collected. Progressive Disease should not be reported as an AE/SAE unless the disease progression is the cause of death.

In the case of a SAE, the investigator must contact the Sponsor by telephone, email or fax immediately (within 24 hours of awareness).

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

Specific to Japan: In Japan, in the case of a SAE, the investigator or sub-investigator must report to the head of the study site and must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the Regulatory Authorities to the Sponsor by fax immediately (within 24 hours of awareness) and to the head of the hospital. If the faxing of JUTOKUNA YUUGAIJISHOU HOUKOKUSHO is not possible or is not possible within 24 hours, the Sponsor should be informed by phone.

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

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

Specific to Japan:

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE Worksheet to:

[redacted]

or

Astellas Pharma Inc.-Japan
Japan/Asia Clinical Development I
Fax: 03-3243-5737

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., IND Safety Reports, CIOMS-I) to the regulatory agencies (e.g., FDA, EMA) per current local regulations, 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 (e.g., EU, (e)CTD, FDA) 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.

5.5.6 Follow-up of Adverse Events

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

If during AE follow-up, the 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.

5.5.7 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 5.5.5 Reporting of Serious Adverse Events].

5.5.8 Procedure in Case of Pregnancy

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

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

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

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator

- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

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

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected ASP2215 overdose, the subject should receive supportive care and monitoring. The medical monitor/expert should be contacted as applicable.

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.

5.5.10 Supply of New Information Affecting the Conduct of the Study

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

Specific to Japan:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, the Sponsor should inform all the investigators involved in the clinical study, the head of the study site and the regulatory authorities of such information. The head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of Written Information].
2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator's Brochure, protocol or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly or documents to be examined by the IRB should be sent to the IRB.

5.5.11 Deviations from the Protocol and Other Actions Taken to Avoid Life-threatening Risks to Subjects (Japan Only)

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

- Describe the contents of the deviation or amendment and the reasons for it in a written notice and immediately send the document stating the deviation or amendment and the reasons to the Sponsor and the head of the study site. Keep a copy of the notice.
- Consult with the Sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the Sponsor.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

Plasma concentrations of ASP2215 will be evaluated as outlined in Schedule of Assessments. For each sample, 2 mL of blood will be collected and processed.

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.

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 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 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.

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-0301),
- 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 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 90 mL.

The maximum amount of blood collected for study specific assessments in cycle 2 is approximately 35 mL.

The maximum amount of blood collected for study specific assessments in cycle 3 and beyond is approximately 20 mL per cycle.

Discontinuation

Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined in [Section 6] or upon marketing authorization and commercial availability of ASP2215 in the country of residence.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued 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 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-IDA and has NR or progressive disease following cycle 1.
- Subject is receiving LoDAC, azacitidine 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.
- Death.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor (in Japan: and the head of the study site).

6.3 Discontinuation of the Study

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

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD-United States. 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 based on co-primary endpoint of OS using the O'Brien-Fleming boundaries (non-binding) as implemented by Lan-DeMets alpha/beta spending method (East®) [Lan & DeMets, 1983].

The overall 0.025 one-sided type I error rate is allocated by 0.0005 and 0.0245 (0.001 and 0.049 for two-sided type I error rate) for the two co-primary efficacy endpoints of CR/CRh and OS, respectively. The type I error (alpha) in the first interim analysis will not be recycled in the second interim analysis and final analysis.

The first interim analysis is planned when approximately 141 subjects are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug). The second interim analysis is planned when approximately 129 death events have occurred and the final analysis is planned when approximately 258 death events have occurred.

OS:

Approximately 369 subjects (the planned sample size with 10% dropout rate) will be randomized in a 2:1 ratio to receive ASP2215 or salvage chemotherapy (246 subjects in the ASP2215 treatment arm and 123 subjects in the salvage chemotherapy arm). The planned 258 death events will provide about 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 1-sided 0.0245 significance level.

CR/CRh rate:

The first interim analysis will be conducted only to evaluate the co-primary endpoint of CR/CRh. One hundred and forty-one subjects randomized to ASP2215 arm (211 subjects in total: 141 in the ASP2215 arm and 70 in the salvage chemotherapy arm) with a minimum follow-up of 4 treatment cycles are considered to achieve a maximum width of 15.78% for the two-sided 95% exact confidence interval (CI) when the CR/CRh is expected to be in the 5% to 30% range as summarized in below table. A sample size of 141 subjects provides 80% power to exclude a CR/CRh rate of 12% using the two-sided 95% exact CI when the CR/CRh rate of ASP2215 is assumed to be 21%.

Observed CR/CRh with Exact 95% CI (N = 141 in ASP2215 arm)	
Observed CR/CRh (n and %)	Exact 95% CI
43 (30.50%)	(23.03%, 38.80%)
36 (25.53%)	(18.57%, 33.55%)
29 (20.57%)	(14.23%, 28.18%)
28 (19.86%)	(13.62%, 27.41%)
27 (19.15%)	(13.01%, 26.62%)
26 (18.44%)	(12.41%, 25.84%)
25 (17.73%)	(11.82%, 25.05%)
24 (17.02%)	(11.22%, 24.26%)
23 (16.31%)	(10.63%, 23.46%)
22 (15.60%)	(10.04%, 22.66%)
15 (10.64%)	(6.08%, 16.94%)
8 (5.67%)	(2.48%, 10.87%)

EFS and CR rate:

The planned sample size with 258 EFS events will provide about 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 at the overall 1-sided 0.0245 significance level.

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-IDA, MEC)
- Low intensity chemotherapy (LoDAC or azacitidine)

7.2 Analysis Sets

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 and will be used for primary efficacy analysis. The subjects will be analyzed based on the randomized treatments.

7.2.2 Response Analysis Set

The Response Analysis Set (RAS) consists of subjects who are at least 112 days post first dose or randomization (for subjects who received no study drug). The subjects will be analyzed based on the randomized treatments.

The RAS will be used only at the interim analyses and will be used for primary analyses of response related efficacy data.

7.2.3 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 sensitivity analysis. The subjects will be analyzed based on the randomized treatments.

7.2.4 Per Protocol Set

The Per Protocol Set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant nonadherence to the protocol and will be defined in the SAP. The sensitivity analysis for the primary and key secondary efficacy endpoints will be performed on PPS. Select demographic and baseline characteristics may also be summarized for the PPS.

7.2.5 Modified Response Analysis Set

The modified Response Analysis Set (mRAS) will consist of the subset of the RAS who do not meet the criteria for mRAS exclusion. These criteria are to capture relevant nonadherence to the protocol and other factors may impact the response assessment and will be defined in the SAP. The sensitivity analysis for the primary endpoint of CR/CRh rate will be performed on mRAS.

7.2.6 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.

7.2.7 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF for which at least 1 plasma concentration data is available 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, CR/CRh rate, EFS, CR rate, CRc rate, CRh rate, duration of remission, transfusion conversion rate, transfusion maintenance rate, 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 Co-Primary Endpoints

OS:

The co-primary efficacy endpoint of OS will be analyzed using the stratified log-rank test with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on the Intention to Treatment (ITT) Analysis Set. The ITT is defined as all subjects who are randomized and the analysis is based on the randomized treatment.

The hypothesis testing on the primary analysis of OS will be performed to test the null hypothesis that OS in the ASP2215 arm is worse than or equal to OS in the salvage chemotherapy arm.

The sensitivity analysis for the primary efficacy endpoint of OS will be performed as follows:

- Same analysis as primary analysis, but on FAS, which included all randomized subjects who are FLT3 mutated subjects based on central test;
- Same analysis as primary analysis, but on PPS, which include all subjects in ITT and do not have any major PDs;
- Stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on ITT;
- Same analysis as primary analysis on ITT, but censoring the subjects who undergo HSCT at the time of HSCT;
- To account for the possible confounding effect due to subsequent anti-leukemia therapies, a sensitivity analysis of OS that censors subjects at the time of initiation of new therapy will be performed and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate will also be conducted.
- Additional sensitivity analysis may be performed to compare the survival curves when the proportional hazards (PH) assumption is plausible.

CR/CRh:

The two-sided 95% exact confidence interval of CR/CRh rate will be calculated for approximately 141 subjects who are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug), i.e., 2215 subjects in RAS. The lower limit will be used to compare with the benchmark of CR/CRh rate of 12%.

Sensitivity analyses will be performed to assess the robustness of the CR/CRh rate based on:

- Same population as for the primary analysis, but only include subjects in mRAS;
- Same population as for the primary analysis, but only include subjects who took at least one dose of ASP2215;
- Same population as for the primary analysis, but only include subjects who had at least one post-baseline bone marrow assessment;
- Same population as for the primary analysis, but evaluate the CR/CRh by cycle 4, which is defined as the number of subjects who achieve CR/CRh by cycle 4 divided by the number of subjects in the analysis population.
- Same population as for the primary analysis, but evaluate the CR/CRh prior to HSCT, which is defined as the number of subjects who achieve CR/CRh prior to HSCT divided by the number of subjects in the analysis population.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Key Secondary Efficacy Analysis

EFS:

The key secondary efficacy endpoint of EFS will be analyzed using the stratified log-rank test 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 0.0245 significance level, the hypothesis testing on EFS will be performed only if the null hypothesis on the primary analysis of OS is rejected at its corresponding significance level for the second interim analysis and final analysis.

The sensitivity analysis for the key secondary efficacy endpoint of EFS will be performed as follows:

- Same analysis as primary analysis, but on FAS, which includes all randomized subjects who are FLT3 mutated subjects based on central test;
- Same analysis as primary analysis, but on PPS, which includes all subjects in ITT and do not have any major PDs;
- Stratified Cox proportional hazard model with strata to control for response to first-line AML therapy and preselected salvage chemotherapy on ITT;
- EFS will be defined similarly as in Section 5.3.2.2, however the date of the first new anti-leukemia therapy after end of study treatment or the last treatment evaluation (when new anti-leukemia therapy date is not available) will be used as the event date of treatment failure;
- EFS will be defined similarly as in Section 5.3.2.2, however subjects who discontinued the treatment due to “Lost to follow up” will also be considered as an EFS event and the subjects will be censored at the date of “Lost to follow up”.

CR rate:

The key secondary efficacy endpoint of CR rate will be tested 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 0.0245 significance level, the hypothesis testing on CR rate will be performed only if the null hypothesis on EFS is rejected at its corresponding significance level for second interim analysis and final analysis.

Sensitivity analysis for CR rate will be performed as follows:

- CMH test on subjects in ITT and received at least one dose of study treatment
- CMH test on subjects in ITT with at least one post-baseline bone marrow assessment
- Un-stratified Fisher's exact test on subjects in ITT

7.4.2.2 Secondary Efficacy Analyses

The statistical analyses on secondary efficacy endpoints include:

- Stratified log-rank test on duration of remission and LFS
- CMH method on the CRc rate and transplantation rate
- Transfusion conversion rate and transfusion maintenance rate will be summarized by descriptive statistics
- Analysis of covariance (ANCOVA) model to analyze the change in the BFI global fatigue score (average of all 9 items) 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 ANCOVA model will be used for resource utilization counts (hospital stays, duration of medications, blood transfusions, antibiotic iv infusions, medication for AEs and opioid medication).

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

ANCOVA 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.

ANCOVA 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, race, region, 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, ophthalmologic assessments 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 to 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.

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 Ophthalmologic Assessment

Ophthalmologic variables will be summarized by treatment group at each visit for each eye.

7.5.7 Eastern Cooperative Oncology Group Performance Scores

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

7.6 Analysis of Pharmacokinetics

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 benchmark data or the salvage chemotherapy group while the study is ongoing, two interim analyses are planned.

First Interim Analysis

The first interim analysis is planned when approximately 141 subjects are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug). At the first interim analysis, only the co-primary endpoint of CR/CRh rate will be evaluated in the ASP2215 arm only. The descriptive statistics including two-sided 95% exact CI of CR/CRh rate will be provided to IDMC. The historical control of the CR/CRh rate is considered to be 12%. The IDMC will evaluate the CR/CRh rate and inform the Sponsor if the lower limit is higher than the historical control or not. The study conduct will not be impacted by the first interim analysis result.

A nominal 1-sided p-value 0.0005 (i.e., 2-sided p-value 0.001), which is arbitrarily selected, will be spent to acknowledge the single-arm CR/CRh rate evaluation at the first interim analysis, and will not be recycled in the second interim analysis and final analysis. No formal hypothesis testing will be conducted for CR/CRh rate for the study, only the descriptive statistics including 2-sided 95% exact CI of CR/CRh rate will be provided to IDMC at the first interim. The hypothesis testing for the primary and secondary endpoints of OS, EFS and CR rate at the secondary interim analysis and final analysis are well controlled at an overall 1-sided type I error rate 0.0245 based on a sequential testing procedure.

Second Interim Analysis

The second interim analysis will be performed when approximately 50% of the total planned death events (death events = 129) have occurred in the study. OS will be tested at 1-sided 0.00147/0.38674 significant level for efficacy/futility according to the O'Brien-Fleming type alpha/beta spending function.

The IDMC may recommend terminating the trial for favorable or unfavorable results at the second interim analysis based on OS endpoint. In the case of favorable results (i.e., the 1-sided P-value is less than 0.00147), the IDMC may recommend terminating the trial for success. In the case of unfavorable results (i.e., the 1-sided P-value is greater than 0.38674), the IDMC may recommend terminating the trial for futility.

EFS will be tested when the null hypothesis of OS is rejected at the second interim. CR rate will be tested when the null hypotheses of both OS and EFS are rejected at the second interim. Their significance levels at the second interim and final interim will be based on Pocock/ O'Brien-Fleming alpha/beta spending function. See Table 9 below for details about the significance levels at each interim and final analyses for each co-primary and secondary endpoints.

Details for the interim analyses, 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 the available data.

If the study is not stopped after the second interim analysis, a final analysis based on OS will occur after 100% of the total planned death events (death events = 258) have been observed. The 1-sided significance level for the final analysis is 0.02402 for OS.

Table 9 Summary of Timing, Sample Size and Decision Guidance at the Planned Analyses

Analysis	Criteria for Conduct of Analysis (Projected timing)	Endpoint/ Analysis Set	Efficacy Boundary*		Futility Boundary*	
			P-value (1-sided) at the Boundary	Approx. Observed HR at Boundary	P-value (1-sided) at the Boundary	Approx. Observed HR at Boundary
IA1: CR/CRh rate	When 141 subjects are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug)	CR/CRh rate/ASP2215 subjects in RAS	NA (0.0005 nominal)	NA	NA	NA
IA 2: OS; EFS when null hypothesis of OS is rejected; CR rate when null hypotheses of both EFS and OS are rejected	Approx. 129 OS events are observed	OS/ITT	0.00147	0.57	0.38674	0.95
		EFS/ITT	0.01519	0.67	0.30218	0.91
		CR rate/ITT	0.01519	NA	0.30218	NA
Final: OS; EFS when null hypothesis OS is rejected; CR rate when null hypotheses of both EFS and OS are rejected	Approx. 258 OS events are observed	OS/ITT	0.02402	0.77	NA	NA
		EFS/ITT	0.01357	0.75	NA	NA
		CR rate/ITT	0.01357	NA	NA	NA

CR: complete remission; CR/CRh: complete remission and complete remission with partial hematological recovery; EFS: event-free survival; HR: hazard ratio; ITT: intention to treatment set; NA: not applicable; OS: overall survival; RAS: response analysis set.

*: P-value at both efficacy and futility boundaries(except the first interim) are based on 50% information fraction for OS, EFS and CR rate, and need update based on observed information fraction at the second interim

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 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 diaries and 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 diary and 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 Global 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. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies or for Astellas Pharma Europe B.V./Astellas Pharma Europe Ltd.-sponsored studies within 1 year after last subject out or termination of the study.

8.2.2 Ethical Conduct of the Study

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

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed 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

- 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.
- 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., 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.

Specifc to Japan: After agreement between investigator(s) and Sponsor, the manuscript can be submitted for publication.

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
- JUTOKUNA YUUGAIJISHOU HOUKOKUSHO (Specific to Japan)
- 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 and dated FDA form 1572, if conducted under a United States IND
- Signed Investigator's Statement in this protocol and eCRF
- Current Curricula Vitae of all investigators
- List of subinvestigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Instruction and decision of the head of the study site (Specific to Japan)
- 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 (for United States sites, 2 years after approval of the New Drug Application (NDA) or discontinuation of the IND).

The following paragraph does not apply to Japan.

The Sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

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

The following paragraphs are applicable to investigational sites in Japan:

The records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by the head of the study site or the record keeper designated by the head until notice issued by the Sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the Sponsor or regulatory authorities.

The head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date defined in points 1 or 2 below, whichever comes later.

- Approval date of marketing of the test drug (if development of the drug is stopped, until 3 years after the decision to discontinue development is notified)

Until 3 years after discontinuation or termination of the study.

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

- 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.
- 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 subinvestigators, list of signatures and print of seals (copy), and case report forms (copy), etc.
- 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.

- 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). In Japan, it is followed by the approval of the head of the study site.

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.

Specific to Japan:

If a subject suffers any study-related injury, the Sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the Sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

- If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The Sponsor should be notified of the injury.
- When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the Sponsor. Both parties should work together towards compensation settlement.
- The Sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.

- The Sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

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

The IDMC will be responsible for the review of subject safety, enrollment rates and event (death) rates during the second 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. Additionally, during the first interim analysis, the IDMC will inform the Sponsor if the lower boundary of 95% CI of CR/CRh rate in ASP2215 arm is higher than benchmark rate or not.

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

Specific to sites in Japan: The Japan site contact list is kept as a separate attachment to the protocol.

11 REFERENCES

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

Yap GY, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89:1363-72.

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

Source: Yap GY, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89:1363-72.

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, 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:

- 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)
- 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	3 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
Chemistry	10 mL into serum tube	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glomerular filtration rate 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

Table continued on next page

Panel/ Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Coagulation Profile (PT/INR, aPTT, D-dimer, fibrinogen)	2.5 mL into sodium citrate tube	INR PT aPTT Fibrinogen (Screening Only) D-dimer (Screening Only)
Urinalysis	Dipstick	Color Appearance Specific Gravity pH Bilirubin Blood Glucose Ketones Leukocyte Esterase Nitrite Protein Urobilinogen
Bone Marrow	Aspirate 3 mL EDTA, 2 - 3 bedside smear slides and/or biopsy (or peripheral blood in the event of a dry tap)	Blast Count and Cell Counts[a] 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 Event]**. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events." You are required to follow the requirements detailed in [Section 5.5.5 Reporting of Serious Adverse Events].

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

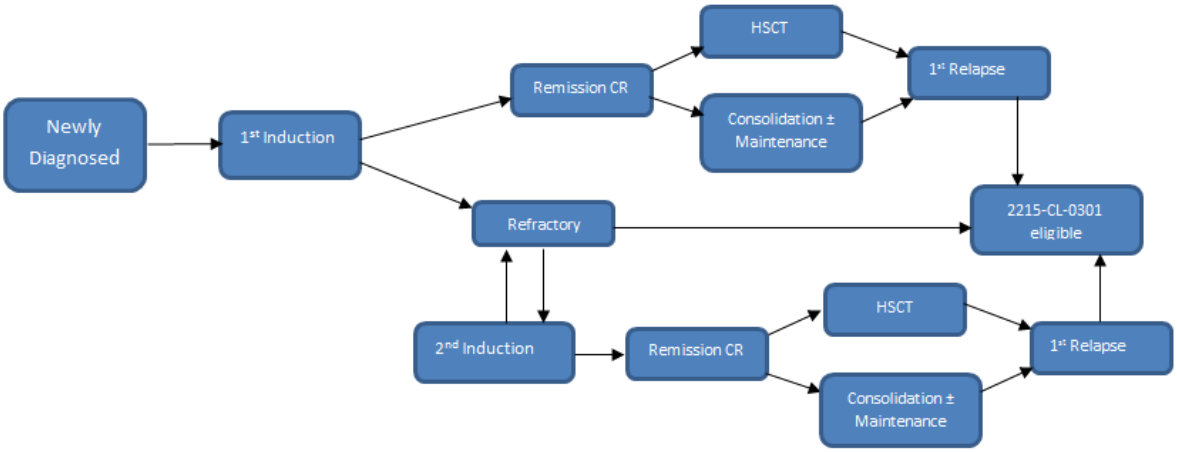
All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw 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 1 line of therapy. HSCT by itself and hydroxyurea are not considered to be lines of therapy.

13 ATTACHMENT 1: COUNTRY-SPECIFIC NON-SUBSTANTIAL AMENDMENT 3 FOR JAPAN

I. The purpose of this amendment is:

Non-Substantial Changes
1. Update Sponsor's Personnel Contact Information
DESCRIPTION OF CHANGE:
Sponsor contact details specific to Japan are updated.
RATIONALE:
Sponsor personnel details specific to Japan are updated based on changes to study team members.
2. Clarify that Study will Continue as "Phase 4 Post-marketing Study" after Marketing Authorization in Japan
DESCRIPTION OF CHANGE:
Language is added to "Phase of Development" in Section IV (SYNOPSIS) to describe the notification that the study will continue as "Phase 4 post-marketing study" after marketing authorization in Japan.
RATIONALE:
Based on Notification No. 1061, dated 01 December 1998 by the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, the study will continue as a post-marketing study after marketing authorization.
3. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering, consistency throughout the protocol and update list of abbreviations).
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

II Contract Details of Key Sponsor's Personnel
WAS:
Specific to Japan: Sponsor's Personnel: [redacted] Contact Numbers during Nonbusiness Hours and for Emergency: Phone No.: [redacted]
IS AMENDED TO:
Specific to Japan: Sponsor's Personnel: [redacted] Contact Numbers during Nonbusiness Hours and for Emergency: Phone No.: [redacted]

IV Synopsis, Phase of Development
ADDED:
In case that ASP2215 is approved for marketing with the indication of relapsed or refractory acute myeloid leukemia with FLT3 mutation, the study will continue as "Phase 4 post-marketing study" in accordance with Good Post-marketing Study Practice (GPSP) after the next day of marketing authorization. In this case, "Study" in the protocol is read as "Post-marketing study".

III. Non-Substantial Amendment Rationale:

Rationale for Non-Substantial Designation
All revisions made to the protocol are administrative in nature and do not impact the safety or scientific value of the clinical study.

14 SPONSOR'S SIGNATURES