A Phase 3 Multicenter, Open-label, Randomized Study of ASP2215 (Gilteritinib), Combination of ASP2215 Plus Azacitidine and Azacitidine Alone in the Treatment of Newly Diagnosed Acute Myeloid Leukemia with FLT3 Mutation in Patients Not Eligible for Intensive Induction Chemotherapy

Protocol for Phase 3 Study of ASP2215

ISN/Protocol 2215-CL-0201

Version 13.0

Incorporating Substantial Amendment 12

14 June 2022

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way
Northbrook, IL 60062

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Version 3.0 Incorporating Substantial Amendment 2 [09Feb2016]
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Version 9.0 Incorporating Substantial Amendment 8 [18Oct2019]
Version 10.0 [US] Incorporating Country-specific Substantial Amendment 9 [20May2020]
Version 11.0 [DE] Incorporating Country-specific Substantial Amendment 10 [13Oct2020]
Version 12.0 Incorporating Substantial Amendment 11 [28Feb2022]

Investigator:
Investigator information is on file at Astellas

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

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

2. INVESTIGATOR'S SIGNATURE

A Phase 3 Multicenter, Open-label, Randomized Study of ASP2215 (Gilteritinib), Combination of ASP2215 Plus Azacitidine and Azacitidine Alone in the Treatment of Newly Diagnosed Acute Myeloid Leukemia with FLT3 Mutation in Patients Not Eligible for Intensive Induction Chemotherapy

ISN/Protocol 2215-CL-0201

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14 June 2022

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 subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See [Section 5.5.5]**	PPD **Astellas Pharma Global Development, Inc.** PPD **Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Pharmacovigilance** **North America Fax Number: 888-396-3750** **(North America Alternate Fax: 847-317-1241)** **International Fax Number: +44-800-471-5263** **Email: safety-us@astellas.com** **For investigational sites in Japan:** **PAREXEL International** **Global Monitoring Operations** **Fax: 03-6888-1486**
Medical Monitor/Medical Expert:	PPD Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 PPD
Clinical Research Contacts Global:	PPD Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 PPD
Clinical Research Contacts Japan:	Corporate Name: Astellas Pharma Inc. Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo Phone No.: 03-3244-1097 Fax: 03-3243-5737 Sponsor's personnel: PPD. Contact numbers during nonbusiness hours and for emergency: Phone No.: PPD

Contact Information for the Clinical Research Organization (CRO) Japan:	Corporate Name: PAREXEL International Location: Kayaba-cho First Building, 1-17-21, Shinkawa, Chuo-ku, Tokyo 104-0033, Japan Phone No.: 03-3537-5878 Fax: 03-6888-1486 CRO's personnel: PPD Contact numbers during nonbusiness hours and for emergency: Phone No.: PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
$5HT_{2B}R$	5-hydroxytryptamine receptor 2B
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
APEB	Astellas Pharma Europe BV
APEL	Astellas Pharma Europe Ltd.
APGD	Astellas Pharma Global Development, Inc.
APL	Acute promyelocytic leukemia
AST	Aspartate aminotransferase
AUST	Astellas United States Technologies
AXL	AXL tyrosine kinase
BCRP	Breast cancer resistance protein
BFI	Brief Fatigue Inventory
BUN	Blood urea nitrogen
CMH	Cochran-Mantel-Haenszel
CR	Complete remission
CR/CRh	Complete remission and complete remission with partial hematological recovery
CRc	Composite complete remission
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
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DLCO	Diffusion capacity of lung for carbon monoxide
DEC	Dose Escalation Committee
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
E_F	Ejection fraction

Abbreviations	Description of abbreviations
EFS	Event-free survival
EML4-ALK	Echinoderm microtubule-associated protein-like 4-ALK variant 1
EQ-5D-5L	EuroQol Group 5-dimension 5-level
EU	European Union
FACIT-Dys-SF	Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Form
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FAS	Full analysis set
FEV1	Forced expiratory volume in the first second
FLT3	FMS-like tyrosine kinase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GVHD	Graft-versus-host disease
HBsAG	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HSCT	Hematopoietic stem cell transplant
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITD	Internal tandem duplication
KM	Kaplan-Meier
LA-CRF	Liver abnormality-case report form
LAR	Legally authorized representative
LFS	Leukemia-free survival
LFT	Liver function test
LLN	Lower limit of normal
LTK	Leukocyte receptor TK
MATE	Multidrug and toxin extrusion
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application

Abbreviations	Description of abbreviations
NSCLC	Non-small cell lung cancer
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OS	Overall survival
PD	Protocol deviation
P-gp	P-glycoprotein
PGx	Pharmacogenomic
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic analysis set
PND	Postnatal day
PPS	Per protocol set
PR	Partial remission
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcome
PT	Preferred term
QTcF	Fridericia-corrected QT interval
Rac	Accumulation index
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAFSC	Safety cohort analysis set
SAP	Statistical analysis plan
SOP	Standard operating procedure
STAT5	Signal transducer and activator of transcription 5
TEAE	Treatment-emergent adverse event
TK	Tyrosine kinase
TKD	Tyrosine kinase domain
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VOD	Veno-occlusive disease
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded as the observed starting point(s) for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
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. PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 13.0 Incorporating Substantial Amendment 12	14 Jun 2022
Version 12.0 Incorporating Substantial Amendment 11	28 Feb 2022
Version 11.0 [DE] Incorporating Country-specific Substantial Amendment 10	13 Oct 2020
Version 10.0 [US] Incorporating Country-specific Substantial Amendment 9	20 May 2020
Version 9.0 Incorporating Substantial Amendment 8	18 Oct 2019
Version 8.0 [US] Incorporating Country-specific Substantial Amendment 7	02 Jan 2019
Version 7.0 Incorporating Substantial Amendment 6	05 Sep 2018
Version 6.0 Incorporating Substantial Amendment 5	08 May 2017
Version 5.0 Incorporating Substantial Amendment 4	20 Dec 2016
Version 4.0 [KR] Incorporating Country-Specific Substantial Amendment 3	09 Mar 2016
Version 3.3 [FR] Incorporating Country-Specific Nonsubstantial Amendment 3	13 Jul 2016
Version 3.2 [DE] Incorporating Country-Specific Nonsubstantial Amendment 2	11 Jul 2016
Version 3.1 [UK] Incorporating Country- Specific Nonsubstantial Amendment 1	24 May 2016
Version 3.0 Incorporating Substantial Amendment 2 [09Feb2016]	09 Feb 2016
Version 2.0 Incorporating Substantial Amendment 1	01 Dec 2015
Original Protocol	11 Jun 2015

Version 13.0 Incorporating Substantial Amendment 12 14 JUN 2022

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

Overall Rationale for the Amendment:

The primary reason for the amendment is as a result of regulatory feedback, the protocol has been amended to add collection of nonserious adverse events for participants who continue to receive study treatment.

Summary of Changes

Substantial Changes

Section Number	Description of Change	Brief Rationale
V, 2.2.1.2, 5.4.2, 5.5.5, 6.1, 12.7, (Table 13 footnote a)	Text amended to add collection of adverse events for participants who continue to receive study treatment. In addition, text added to clarify AE and SAE collection details.	Based on regulatory feedback the Sponsor will also collect nonserious adverse events for safety monitoring.
5.1.2.1 (Table 8)	Guidelines for ASP2215 Dose Interruption or Reduction has been added in the event of posterior reversible encephalopathy syndrome (PRES) and Differentiation syndrome.	To ensure participant safety and to be consistent with the gilteritinib product insert.
V, 6.1	Clarification is added to specify that discontinuation of study due to hematopoietic stem cell transplant (HSCT) only applies to Arm C subjects. Clarification is also included that prophylactic cranial irradiation and leukapheresis is an exception.	This is a clarification. The study protocol allows Arm AC subjects to proceed to HSCT and return back to the study if they meet the protocol defined criteria. However, subjects in Arm C requiring HSCT will be discontinued from the study. Clarification of prophylactic cranial irradiation and leukapheresis is included to align with the Previous and Concomitant Treatment section.
1.2.2.2, 5.1.3, 12.2	Amended text to add substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, rosuvastatin) and OCT1 (e.g., metformin)	To align with the current version of the ASP2215 IB
1.3.2, 1.3.1	Reference to the current version of the Investigator's Brochure (IB) made regarding contraindications, warnings and precautions and safety observations from clinical studies. Reference to IB also made to provide further details on expected serious adverse reactions.	To align with the current version of the ASP2215 IB

Section Number	Description of Change	Brief Rationale
5.1.3	Text added to clarify that all patients who resume ASP2215 after HSCT should receive standard post-HSCT therapy, e.g., GVHD prophylaxis, infection prophylaxis. Localized radiation for palliation removed from exceptions to prohibited treatments and clarification is also included that prophylactic cranial irradiation is an exception.	To align with the current version of the ASP2215 IB

Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
V	Planned study period updated from 2Q 2022 to 4Q 2022.	Updated based upon current study timeline projections
V, IV (Table 2 footnote c), 2.2.1.2, 5.3.3.1, 6.1, 12.7	Wording added to clarify that subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until the implementation of the current version of the protocol at which time they will discontinue from the study.	Further survival data is no longer needed
8.2.4 (Specific to Germany)	Technical and organizational aspects of data protection relevant to the General Data Protection Regulation (GDPR) are included. In addition, a statement on risk assessment and/or assessment of the consequences of data protection as per Article 35, paragraph 1 GDPR is added.	The statements are included based on the requirements from the Central Ethics Committee of Germany.
12.1	The requirement for using contraception by male study participant after study completion is corrected.	This is a correction.
Throughout	Minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol.	To provide clarifications to the protocol and to ensure complete understanding of study procedures.

V. SYNOPSIS

Date and Version # of Protocol Synopsis:	14 June 2022, Version 13.0
Sponsor: Astellas Pharma Global Development, Inc. (APGD)	**Protocol Number:** 2215-CL-0201
Name of Study Drug: ASP2215/Gilteritinib	**Phase of Development:** 3
Title of Study: A Phase 3 Multicenter, Open-label, Randomized Study of ASP2215 (Gilteritinib), Combination of ASP2215 Plus Azacitidine and Azacitidine Alone in the Treatment of Newly Diagnosed Acute Myeloid Leukemia with FLT3 Mutation in Patients Not Eligible for Intensive Induction Chemotherapy	
Planned Study Period: From 2Q 2016 to 4Q 2022 (including long-term follow-up period). The study will continue until the last subject discontinues study treatment.	

Study Objective(s):

The primary objective is to:

- Determine the efficacy superiority of ASP2215 plus azacitidine versus azacitidine as measured by overall survival (OS).

The key secondary objective is to:

- Determine the efficacy superiority of ASP2215 plus azacitidine versus azacitidine as measured by event-free survival (EFS).

The additional secondary objectives are to:

Evaluate the safety and efficacy of ASP2215 plus azacitidine versus azacitidine in terms of:

- Best response
- Complete remission (CR) rate
- Composite complete remission (CRc) rate
- Complete remission with partial hematologic recovery (CRh) rate
- CR/CRh rate
- Transfusion conversion rate; transfusion maintenance rate
- Leukemia-free survival (LFS)
- Duration of remission
- Patient-reported fatigue (Brief Fatigue Inventory [BFI])
- Adverse events (AEs), clinical laboratory results, physical examinations, vital signs, electrocardiograms (ECGs), and Eastern Cooperative Oncology Group (ECOG) performance scores

The exploratory objectives are to:

Evaluate the efficacy of ASP2215 plus azacitidine versus azacitidine in terms of:

- Transplantation rate
- Minimal residual disease (MRD)
- FMS-like tyrosine kinase (FLT3) gene mutation status
    - Mutation types and frequency
    - Relationship to efficacy and safety
    - Mechanisms of acquired resistance
- Exploratory (predictive) biomarkers of ASP2215 activity

- Patient reported dyspnea (Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Form [FACIT-Dys-SF])
- Patient reported signs, symptoms and impacts of acute myeloid leukemia (AML) (Functional Assessment of Cancer Therapy-Leukemia [FACT-Leu] and dizziness and mouth sores items)
- Health-related quality of life assessed by the EuroQol Group 5-dimension 5-level (EQ-5D-5L) instrument
- Resource utilization including hospitalization, blood transfusion, antibiotic intravenous infusions, medication for AEs and opioid usage
- Characterize the pharmacokinetics (PK) of ASP2215 and azacitidine given as a single agent and/or as combination treatment
- Evaluate and compare the PK of ASP2215 and azacitidine in a subset of Non-Japanese and Japanese subjects

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

Approximately 185 centers in North America, South America, Europe and Asia/Pacific.

Study Population:

Newly diagnosed, FLT3 mutated AML subjects not eligible for intensive induction.

Number of Subjects to be Enrolled/Randomized:

Approximately 250 subjects in the randomized trial and up to 12 subjects in the safety cohort. (Note: enrollment has stopped with a total of 183 subjects).

Study Design Overview:

This is a phase 3 multicenter, open-label, randomized study to compare the efficacy and safety of ASP2215 plus azacitidine versus azacitidine in newly diagnosed FLT3 mutated AML subjects not eligible for intensive induction chemotherapy.

Safety Cohort:

Prior to initiation of the randomized trial, 8 to 12 subjects will be enrolled to evaluate the safety and tolerability of ASP2215 given with azacitidine therapy in the study population. Groups of 3 to 6 subjects in a cohort may be enrolled at the same time. The subjects will initially be treated with ASP2215 80 mg daily (days 1 to 28) (with dose reductions or increases permitted after cycle 1) and azacitidine 75 mg/m^2 daily (days 1 to 7) (with dose reductions or increases permitted after cycle 1).

The Sponsor, principal investigators and, if appropriate, expert consultants, will review safety data through the dose-limiting toxicity (DLT) observation period in the safety cohort. The DLT observation period will be from day 1 through day 28 of cycle 1. Evaluable subjects are defined as subjects who experience a DLT or in the absence of DLT, receive at least 23/28 doses of ASP2215 and at least 5/7 doses of azacitidine. Subjects who are not evaluable for reasons other than DLT will be replaced. Based on review of the safety cohort data, the decision to initiate the randomized trial at the targeted dose (120 mg) or the initial dose (80 mg) will be made by the Sponsor in consultation with the investigators.

Dose escalation rules are as follows:

- At ASP2215 80 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7):
  - If 0 of 3 subjects experiences a DLT, 6 subjects will be enrolled at ASP2215 120 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7).

- If 1 of 3 subjects experiences a DLT, up to an additional 3 subjects will be enrolled at ASP2215 80 mg plus azacitidine 75 mg/m^2.
  - If 1 of 6 subjects experiences a DLT, 6 subjects will be enrolled in ASP2215 120 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7).
  - If ≥ 2 of 4 to 6 subjects experience DLT, the trial will be stopped.
- If 2 or more of 3 subjects experience a DLT, the trial will be stopped.

- At ASP2215 120 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7):
  - If 0 out of 5 or 6 subjects or 1 out of 6 subjects experiences a DLT, the randomization will be initiated with ASP2215 120 mg dose for the combination arm.
  - If ≥ 2 of 2 to 6 subjects experience a DLT,
    - If less than 6 subjects were previously treated at ASP2215 80 mg dose, then up to 3 more subjects will be enrolled at ASP2215 80 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7).
      - If 0 out of 5 or 6 subjects or 1 of 6 subjects experiences a DLT, randomization will be initiated with ASP2215 80 mg dose for the combination arm.
      - If ≥ 2 of 3 to 6 subjects experience a DLT, the trial will be stopped.
    - If a total of 6 subjects were previously treated at ASP2215 80 mg dose, randomization will be initiated with ASP2215 80 mg dose for the combination arm.

If the safety cohort is stopped, the randomized trial will not open. However, an alternative dosing schedule might be explored via an amendment.

Randomized Trial:

Approximately 250 subjects (note: enrollment has stopped with a total of 183 subjects) will be randomized in a 2:1* ratio to receive ASP2215 plus azacitidine (Arm AC) or azacitidine only (Arm C). The randomization will be stratified based on age group described below:

- Age ≥ 75 years
- Age < 75 years

Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment over 28-day cycles.

ASP2215 starting dose will be 120 mg for Arm A* (ASP2215 alone), and either 120 mg or 80 mg for Arm AC depending on safety cohort outcome. Based on the safety cohort outcome, the starting dose of ASP2215 was determined to be 120 mg for Arm AC subjects. Dose increases and reductions are permitted for ASP2215 and azacitidine.

Note: Japan only – for the first 6 subjects enrolled or randomized to arm AC in Japan (either in the safety cohort or randomization portion of the study), only 1 subject may begin study drug administration in a day (i.e., no 2 subjects will receive their initial dose of study medication on the same day).

For all subjects taking ASP2215, ASP2215 plus azacitidine or azacitidine only, treatment should continue until the subject no longer receives clinical benefit from therapy in the opinion of the investigator, unacceptable toxicity occurs or the subject meets another treatment discontinuation criterion.

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 at any time. Subjects in safety cohort, Arm A* and Arm AC proceeding for HSCT can remain on the study and resume treatment with ASP2215 only after HSCT if certain conditions are met [Refer Section 5.1.5 Resumption of Treatment After Hematopoietic Stem Cell Transplantation]. If the subject discontinues the study during or post HSCT, then they should follow the Post-treatment Schedule of Assessments (Table 2) for long term follow-up.

Subject in Arm C proceeding for HSCT will discontinue treatment by performing an EOT visit and should follow the Post-treatment Schedule of Assessments for long term follow-up.

Subjects will have an end-of-treatment visit within 7 days after last dose of study treatment (ASP2215 and/or azacitidine), followed by a 30-day follow-up for safety, after which the subjects will enter the long-term follow-up period of up to 3 years for collection of subsequent AML treatment, EQ-5D-5L, remission status and survival (cause of death and date of death). Subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until the implementation of the current protocol version 13.0, at which time they will discontinue from the study as further survival data is no longer needed.

A formal interim analysis by an independent Data Monitoring Committee (IDMC) will be performed when approximately 50% (i.e., death events = 70) of the planned total number of deaths (i.e., death events = 140) by any cause have occurred. The interim analysis will be utilized to determine whether Arm AC has more favorable or unfavorable outcome compared to Arm C. If the interim analysis demonstrates a more favorable or unfavorable outcome for Arm AC based on OS, enrollment to the study may be stopped. Based on the planned interim analysis in Dec 2020, an IDMC recommended terminating the study based on protocol specified boundaries for futility, concluding results are unlikely to show a statistically significant increase in overall survival, Astellas made decision to stop enrollment for the study.

Subjects can continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine until they meet a discontinuation criterion as outlined in [Section 6 Discontinuation]. Subjects will be managed per the local institution's standard of care for safety and efficacy assessments while on study drug treatment. No data will be collected in the eCRFs after subjects reconsent under this protocol Version 13.0, as the clinical database will be locked. Only AEs and serious adverse events (SAEs) (as defined in [Section 5.5.2 Definition of Serious Adverse Events]) will be collected and reported to Astellas Pharma Global Development Product Safety & Pharmacovigilance (Japan will continue reporting to PAREXEL International). AE and SAE data will be reported in the safety database. Once subjects receiving treatment meet the study discontinuation criteria, subjects will be discontinued from the study. AE and SAE collection will continue until 30 days after last dose of study treatment (ASP2215 and/or azacitidine).

Subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until implementation of the current protocol version 13.0, at which time they will discontinue from the study as further survival data is no longer needed.

The EFS will be evaluated at the time of OS interim analysis, only if the OS result is positive. By the time of OS interim analysis with 70 events, 88 EFS events are expected (the actual number of events may vary).

[*] Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

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

1. Institutional Review Board-/Independent Ethics Committee (IRB/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 obtaining informed consent.
3. Subject has a diagnosis of previously-untreated AML according to World Health Organization classification [Swerdlow et al, 2008] as determined by pathology review at the treating institution.
4. Subject is positive for FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD] [D835/I836] mutation) (or for ***Korea only***: ITD alone or ITD with concurrent TKD activating mutation) in bone marrow or whole blood as determined by central laboratory. Note: Requirement of FLT3 mutation assessment by central laboratory is only applicable to the randomization portion of the study.
5. Subject is ineligible for intensive induction chemotherapy by meeting at least 1 of the following criteria:
   a) Subject is ≥ 65 years of age and ineligible for intensive induction chemotherapy per investigator's discretion.
   b) Subject is ≥ 18 to 64 years of age and has any of the following comorbidities:
      i Congestive heart failure (New York Heart Association (NYHA) class ≤ 3) or ejection fraction (E_F) ≤ 50%;
      ii Creatinine > 2 mg/dL (177 µmol/L), dialysis or prior renal transplant
      iii ECOG performance status ≥ 2;
      iv Prior or current malignancy that does not require concurrent treatment;
      v Subject has received a cumulative anthracycline dose above 400 mg/m2 of doxorubicin (or cumulative maximum dose of another anthracycline);
      vi Known pulmonary disease with decreased diffusion capacity of lung for carbon monoxide (DLCO > 50%) and/or requiring oxygen ≤ 2 liters per minute
      vii Any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy must be reviewed and approved by the Medical Monitor during screening and before randomization.
6. Subject must meet the following criteria as indicated on the clinical laboratory tests:
   - Serum aspartate aminotransferase and alanine aminotransferase ≤ 3.0 × institutional upper limit normal (ULN)
   - Serum total bilirubin ≤ 1.5 × institutional ULN
   - Serum potassium ≥ institutional lower limit of normal (LLN)
   - Serum magnesium ≥ institutional LLN

   Repletion of potassium and magnesium levels during the screening period is allowed

7. Subject is suitable for oral administration of study drug.
8. A female subject is eligible to participate if she is not pregnant [see Appendix 12.1 Contraception Requirements] and at least one of the following conditions apply:
   a) Not a woman of childbearing potential (WOCBP) as defined in [Appendix 12.1 Contraception Requirements];

      OR

   b) WOCBP agrees to follow the contraceptive guidance as defined in [Appendix 12.1 Contraception Requirements] starting at screening and continue through the study period, and for at least 180 days after the final study drug administration.
9. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 60 days after the final study drug administration.
10. Female subject must not donate ova starting at screening and throughout the study period, and for 180 days after the final study drug administration.
11. A male subject with female partner(s) of childbearing potential must agree to use contraception as detailed in [Appendix 12.1 Contraception Requirements] starting at screening and continue through the study period, and for at least 120 days after the final study drug administration.
12. Male subject must not donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
13. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will NOT be allowed.

Exclusion Criteria:

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

1. Subject was diagnosed with acute promyelocytic leukemia (APL).
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has received previous therapy for AML, with the exception of the following:
   - Emergency leukapheresis
   - Hydroxyurea
   - Preemptive treatment with retinoic acid prior to exclusion of APL ≤ 7 days
   - Growth factor or cytokine support
   - Steroids
4. Subject has clinically active central nervous system leukemia.
5. Subject has been diagnosed with another malignancy that requires concurrent treatment (with the exception of hormone therapy limited to those therapies that prevent recurrence and/or spread of cancer) or hepatic malignancy regardless of the need for treatment.
6. Subject has clinically significant coagulation abnormality unless secondary to AML in the opinion of the investigator.
7. Subject has had major surgery within 4 weeks prior to the first study dose.
8. Subject has had radiation therapy within 4 weeks prior to the first study dose.
9. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP)3A/ P-glycoprotein (P-gp).
10. This criterion has been removed.

11. This criterion has been removed.
12. Subject has congestive heart failure classified as New York Heart Association Class IV.
13. Subject with mean Fridericia-corrected QT interval (QTcF) > 480 ms at screening based on central reading.
14. Subject with a history of Long QT Syndrome at screening.
15. Subject has known pulmonary function tests with DLCO ≤ 50%, forced expiratory volume in the first second (FEV1) ≤ 60%, dyspnea at rest or any pleural neoplasm. (Transient use of supplemental oxygen is allowed.)
16. Subject has an active uncontrolled infection. If an infection is present, the patient must be receiving definitive therapy and have no signs of progressing infection. Progressing infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
17. Subject is known to have human immunodeficiency virus infection.
18. Subject has active hepatitis B or C or other active hepatic disorder.
    - Subjects with positive hepatitis B surface antigen (HBsAg) or detectable hepatitis B DNA are not eligible.
    - Subjects with negative HBsAg, positive hepatitis B core antibody and negative hepatitis B surface antibody will be eligible if hepatitis B DNA is undetectable.
    - Subjects with antibodies to hepatitis C virus will be eligible if hepatitis C RNA is undetectable.
19. Subject has any condition, which in the investigator's opinion, makes the subject unsuitable for study participation, including any contraindications of azacitidine listed in the country package insert.
20. Subject has a known or suspected hypersensitivity to ASP2215, azacitidine or any components of the formulations used.

Waivers to the exclusion criteria will NOT be allowed.

CYTOREDUCTION GUIDELINES

Subjects who present with leukocytosis are required to achieve a myeloblast count < 50 x 10^9/L prior to initiating study treatment to reduce the risk of differentiation syndrome. The following cytoreduction guidelines can be used to achieve this myeloblast count.

Cytoreduction options [a, b]	Dose	Frequency	Maximum days allowed before study treatment	Myeloblast count prior to study treatment
Hydroxyurea [c]	Up to 6 g oral	Daily in divided doses	NA	50 x 10^9/L
Leukapheresis	NA [d]	NA [d]	NA [d]	50 x 10^9/L

NA: Not Applicable.

[a] May be used concurrently with leukapheresis

[b] Cytoreduction may start prior to screening

[c] Hydroxyurea is also allowed after enrollment for an additional ≤ 14 days

[d] Institutional standard should be followed

Investigational Product(s):

ASP2215 tablets containing 40 mg of active ingredient.

Dose(s):

ASP2215 40 mg, 80 mg, 120 mg, or 200 mg will be administered once daily in 28-day cycles.

For US Only: ASP2215 40 mg, 80 mg or 120 mg will be administered once daily in 28-day cycles. The 200 mg dose will not be used.

Mode of Administration:

ASP2215 will be administered orally.

Comparative Drug(s):

Azacitidine

Dose(s):

75 mg/m^2 azacitidine will be administered daily for 7 days (days 1 through 7) of each 28-day cycle.

Mode of Administration:

Azacitidine will be administered by subcutaneous injection or intravenous infusion. Refer to the pharmacy manual for administration instructions. Refer to Section 5.1.1.2 for specific instructions for subjects participating in the dense PK subset. The route of administration of azacitidine outside of label instructions is not recommended and is a clinical decision of the investigator.

Concomitant Medication Restrictions or Requirements:

Treatment with concomitant drugs that are strong inducers of CYP3A/ P-gp **are prohibited** in combination with ASP2215.

Treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) or sigma nonspecific receptor are to be avoided with ASP2215 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 ASP2215 with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If strong CYP3A/Pgp inhibitors are used concomitantly, subjects should be closely monitored for AEs.

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

Duration of Treatment

For all subjects taking ASP2215, ASP2215 plus azacitidine or azacitidine only, treatment should continue until the subject no longer receives clinical benefit from therapy in the opinion of the investigator, unacceptable toxicity occurs or the subject meets another treatment discontinuation criterion.

Discontinuation Criteria:

Based on the planned interim analysis in Dec 2020, an IDMC recommended terminating the study based on protocol specified boundaries for futility, concluding results are unlikely to show a statistically significant increase in overall survival, Astellas made decision to stop enrollment for the study.

Subjects can continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine until they meet a discontinuation criteria. Subjects will be managed per the local institution's standard of care for safety and efficacy assessments while on study drug treatment. No data will be collected in the eCRFs after subjects reconsent under this protocol Version 13.0, as clinical database will be locked. Only adverse events (AEs) and serious adverse events (SAEs), as defined in [Section 5.5.2 Definition of Serious Adverse Events], will be collected and reported to Astellas Pharma Global Development Product Safety & Pharmacovigilance (Japan will continue reporting to PAREXEL International). AE and SAE data will be reported in the safety database. Once subjects receiving treatment meet the study discontinuation criteria, subjects will be discontinued from the study. AE and SAE collection will continue until 30 days after last dose of study treatment (ASP2215 and/or azacitidine).

Subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until the implementation of the current protocol version 13.0, at which time they will discontinue from the study as further survival data is no longer needed.

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 (including HSCT for Arm C) other than the assigned treatment, with the exception of hydroxyurea up to 6 g daily for up to 2 weeks, intrathecal chemotherapy, or prophylactic cranial irradiation and leukapheresis.
- Investigator/subinvestigator 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.
- Female subject becomes pregnant.
- Death.
- Subject is receiving ASP2215, azacitidine, or the combination of ASP2215 plus azacitidine and has progressive disease, recurrence under treatment, or no response, and in the opinion of the investigator, the subject is no longer deriving clinical benefit.

Discontinuation Criteria from Posttreatment Follow-up for Individual Subjects:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death.
- More than 3 years has passed from the subject's 30-day follow up visit.

Endpoints for Evaluation:

Primary Endpoint

Primary Efficacy Endpoint:

- OS

Secondary Endpoints

Key Secondary Efficacy Endpoint:

- EFS

Secondary Efficacy Endpoints:

- Best response
- CR
- CRc
- CRh
- CR/CRh
- Transfusion conversion rate; transfusion maintenance rate
- LFS
- Duration of remission
- Patient-reported fatigue from BFI

Safety Endpoints:

- AEs
- Clinical laboratory (serum chemistry, hematology, coagulation and urinalysis) results
- Physical examinations
- Vital sign measurements
- ECGs
- ECOG performance scores

Exploratory Endpoints

- Transplantation rate
- MRD measured by change in FLT3 mutation to total FLT3 ratio compared to baseline.
- 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 intravenous infusions, medication for AEs and opioid usage
- FACIT-Dys-SF assessments
- FACT-Leu and dizziness and mouth sores items
- EQ-5D-5L assessments

Pharmacokinetic Endpoints

- ASP2215 concentration in plasma
- ASP2215 and azacitidine concentrations in plasma (subset of non-Japanese and Japanese subjects)

Safety Cohort and First 6 Japanese Subjects on Arm AC (either in safety cohort or randomization portion) - Definition of DLT:

A DLT is defined as any of the following events that occur during the observation period and that is considered to be possibly or probably related to study regimen. The observation period for DLT for dose escalation decisions will be from the start of the treatment until day 28 of the first treatment cycle.

- Any grade ≥ 3 nonhematologic or extramedullary toxicity with the following exceptions:
  - Anorexia or fatigue
  - Grade 3 nausea and/or vomiting if not requiring tube feeding or total parenteral nutrition, or diarrhea if not requiring or prolonging hospitalization that can be managed to grade ≤ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 7 days of onset
  - Grade 3 mucositis that resolves to grade ≤ 2 within 7 days of onset
  - Grade 3 fever with neutropenia, with or without infection
  - Grade 3 infection
- Prolonged myelosuppression defined as absolute neutrophil count ≤ 0.5×10^9/L for more than 21 days from the onset of severe neutropenia in the absence of evidence of active leukemia in the marrow or blood.
- Any toxicity that requires a dose reduction

Statistical Methods:

Sample size justification

This is an open-label, randomized study. One interim analysis and one final analysis are planned. This is a group sequential design based on OS using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha/beta spending method (East®). The interim analysis will occur when approximately 50% (i.e., death events = 70) of the planned total number of deaths (i.e., death events = 140) by any cause have occurred. The IDMC will evaluate the test of OS and inform the sponsor the result if Arm AC has favorable outcome (i.e., P value < 0.003) or unfavorable outcome (i.e., P value ≥ 0.724, non-binding for the futility boundary) compared to Arm C with respect to OS, the study may be stopped due to efficacy or futility, respectively. Otherwise, the study will continue without impact. The final analysis will be performed after the planned 140 death events have been observed. Additionally, OS will be tested at 2-sided 0.049 significant level for efficacy.

The planned sample size of approximately 250 subjects (note: enrollment has stopped with a total of 183 subjects) will be randomized in a 2:1 ratio to receive ASP2215 plus azacitidine (AC) or azacitidine (C). The study will provide at least 80% power to detect a difference in OS between AC and C, assuming 16.7 months median survival time from AC and 10 months median survival time from C (hazard ratio = 0.6) at the overall 2-sided 0.05 significance level.

Based on the planned sample size and final OS analysis timing, 176 EFS events are expected, which will provide above 80% power to detect a hazard ratio of 0.6 in EFS (11.2 months median EFS for Arm AC and 6.7 months for Arm C). The EFS will be evaluated at the time of OS interim analysis, only if the OS result is positive at the interim analysis. By the time of OS interim analysis with 70 events, 88 EFS events are expected (the actual number of events may vary). An O'Brien-Fleming stopping boundary based on Lan-DeMets alpha spending method will be used for EFS. Based on a projected number of events of 88 at the interim, the efficacy stopping boundary is 2-sided nominal alpha of 0.003 for interim analysis and 0.049 for the final analysis. The actual

rejection boundary for EFS may vary according to the actual number of EFS events that occur at the interim analysis.

The sample size for the safety cohort is not based on a statistical power calculation. The planned number of subjects up to 12 would provide adequate information for the objectives of the safety cohort.

Efficacy:

Primary Efficacy Analysis:

The primary efficacy endpoint of OS will be analyzed on the Full Analysis Set (FAS) using the stratified log-rank test with strata of age and risk groups and FLT3 mutation status described below:

- Age Group
  - Age ≥ 75 years
  - Age < 75 years
- Risk Group
  - Favorable or intermediate cytogenetic risk
  - Unfavorable cytogenetic risk or secondary AML (regardless of cytogenetic risk)
- FLT3 Mutation Status
  - FLT3-TKD
  - FLT3-ITD low allelic ratio (<0.5, LAR)
  - FLT3-ITD high allelic ratio (≥ 0.5, HAR)

The FAS is defined as the intention-to-treat population, which includes all subjects who were randomized and is based on the randomized treatment.

The hypothesis testing on the primary endpoint will be performed at the overall 2-sided 0.05 significance level to test the null hypothesis that OS of Arm AC is equal to that of Arm C versus the alternative hypothesis that OS of Arm AC is different from that of Arm C.

The sensitivity analyses for the primary efficacy endpoint will be performed as described below:

- Stratified Cox proportional hazard model on the FAS
- Stratified log-rank test/Cox proportional hazard model on the FAS with subjects who are censored at the time of HSCT
- Stratified log-rank test/Cox proportional hazard model with strata of age group on the FAS
- Unstratified log-rank test/Cox proportional hazard model on the FAS
- Stratified log-rank test/Cox proportional hazard model with strata of age and risk group and FLT3 mutation status on the per protocol set (PPS), which includes all subjects in the FAS who do not have any major protocol deviations

Statistical Methods (continued)

Key Secondary Efficacy Analysis:

The key secondary efficacy endpoint of EFS for Arm AC and Arm C will be analyzed on the FAS using the stratified log-rank test with strata of age and risk group and FLT3 mutation status. The null hypothesis for the key secondary endpoint is EFS of Arm AC is not different from that of Arm C. To control for overall type I error at the 2-sided 0.05 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 interim analysis or final analyses. The rejection boundary of EFS will be based on the actual number of events at the interim and final analyses.

The sensitivity analyses of the key secondary efficacy endpoints will be performed as described below:

- With strata of age and risk groups and FLT3 mutation status
  - Stratified Cox proportional hazard model on the FAS
  - Stratified log-rank test/Cox proportional hazard model on the FAS with subjects who are censored at the time of HSCT
  - Stratified log-rank test/Cox proportional hazard model on the PPS
  - Stratified interval-censored survival analysis [Wellner and Zhan, 1997] on the FAS to evaluate the impact of different assessment schedules for response and non-response subjects
- Other sensitivity analysis
  - Stratified log-rank test/Cox proportional hazard model with strata of age group on the FAS
  - Unstratified log-rank test/Cox proportional hazard model on the FAS
- Sensitivity analysis on different timing and censoring for EFS by
  - defining EFS as the time from randomization to relapse from CR (for subjects who achieved CR), or death from any cause, whichever comes first;
  - setting time to treatment failure as the date of permanent discontinuation of all study treatment or the end of 6 cycles of therapy, whichever is earlier.

Secondary Efficacy Analyses:

The statistical analyses on secondary efficacy endpoints for Arm AC and Arm C include:

- Stratified log-rank test/Cox proportional hazard model on duration of remission and LFS
- Cochran-Mantel-Haenszel (CMH) test on the CR rate, CRc rate, CR/CRh rate, CRh rate, transfusion conversation rate and transfusion maintenance rate
- Analysis of variance (ANOVA) model to analyze the change in the BFI global fatigue score (average of all 9 items) from baseline to post-baseline visits

Safety Analyses:

The safety analysis set (SAF) is defined as all randomized subjects who received at least 1 dose of study treatment (ASP2215 or azacitidine).

The safety evaluation will be based mainly on AEs, clinical laboratory results, vital sign measurements, ECGs, physical examination findings and ECOG performance scores. 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 the MedDRA dictionary and will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [National Cancer Institute, 2010].

Pharmacokinetic Analyses:

Based on PK data obtained within this study, a separate population PK analysis will be performed.

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.

In a subset of non-Japanese and Japanese subjects with dense PK sampling, plasma concentrations and PK parameters will be summarized for ASP2215 and azacitidine by treatment arm using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) of the mean and geometric mean. Time-course of mean drug plasma concentrations will be plotted as appropriate.

Subjects with sufficient PK samples will have PK parameter estimates for ASP2215 to include calculation of AUC_t, C_{max}, C_{trough} and t_{max} and for azacitidine AUC_t, C_{max}, C_{trough} and t_{max} using standard noncompartmental analysis.

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 and D835/I836 tyrosine kinase domain mutations, will be analyzed.

ANOVA model will be used to analyze the change from baseline of MRD for post-baseline visits. Cochran-Mantel-Haenszel (CMH) method will be used for the cumulative proportion of subjects with undetectable MRD by visit.

CMH method will be used for transplantation rate and resource utilization status (hospitalization, blood transfusion, antibiotic intravenous infusions, medication for AEs and opioid medication).

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

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

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

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

Other Analyses:

Due to limited number of subjects randomized to Arm A,[*] there will be no hypothesis testing for Arm A.[*] There will be descriptive summary of efficacy and safety assessments for the subjects in Arm A.[*]

Interim Analysis:

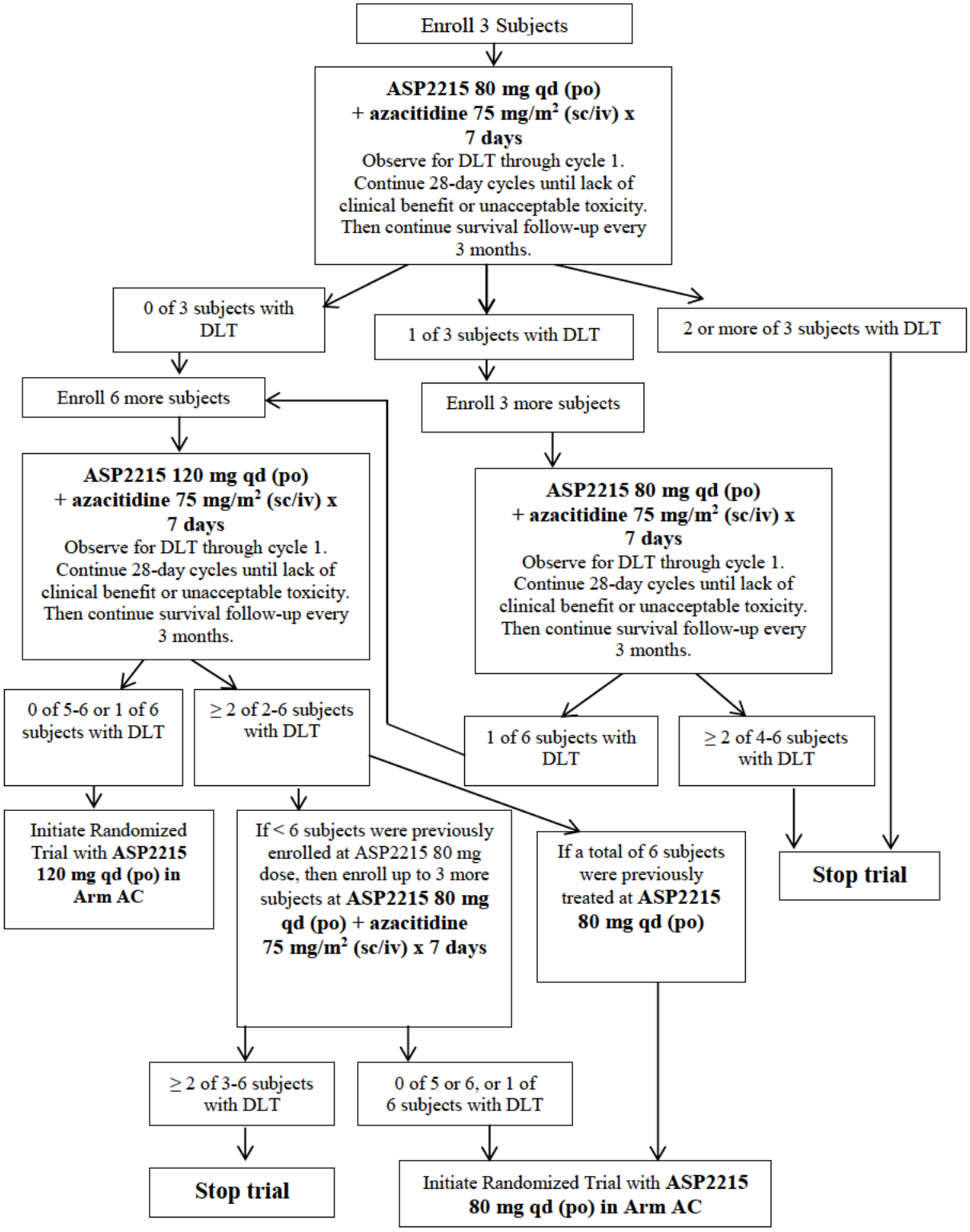
The interim analysis will occur when approximately 50% (i.e., death events = 70) of the planned total number of deaths (i.e., death events = 140) by any cause have occurred. The IDMC will evaluate the test of OS and inform the sponsor the result if Arm AC has favorable outcome (i.e., P value < 0.003) or unfavorable outcome (i.e., P value ≥ 0.724) compared to Arm C with respect to OS, the study may be stopped due to efficacy or futility, respectively. Otherwise, the study will continue without impact.

The EFS will be evaluated at the time of OS interim analysis, only if the OS result is positive at the interim analysis. By the time of OS interim analysis with 70 events, 88 EFS events are expected (the actual number of events may vary). An O'Brien-Fleming stopping boundary based on Lan-DeMets alpha spending method will be used for EFS. Based on a projected number of events of 88 at the interim, the efficacy stopping boundary is 2-sided nominal alpha of 0.003 for interim analysis and 0.049 for the final analysis. The actual rejection boundary for EFS may vary according to the actual number of EFS events that occur at the interim analysis.

[*] Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

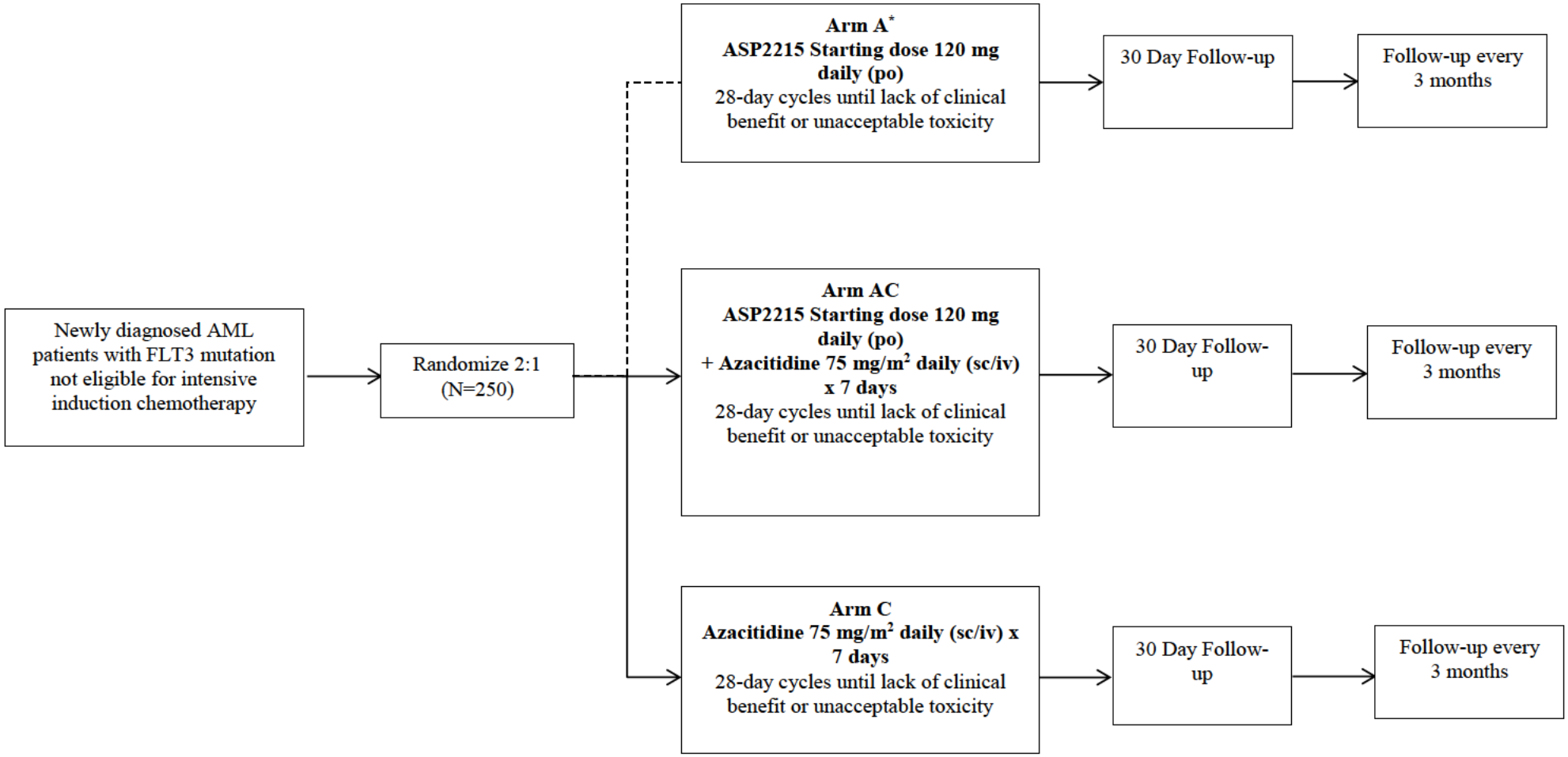
VI. FLOW CHARTS AND SCHEDULE OF ASSESSMENTS

Flow Chart 1 Safety Cohort



DLT: dose limiting toxicity.

Flow Chart 2 Subject Flow in Randomized Trial



AML: acute myeloid leukemia; FLT3: FMS-like tyrosine kinase; TBD: to be determined.

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

Table 1 Schedule of Assessments

Assessments	Screening (Days -14 to -1)[w]	Cycle 1 [z]					Cycle 2 [z]		Subsequent Cycles [z]
		D 1	D 4 ±1	D 8 ±1	D 9	D 15	D 1 ±1	D 15 ±1	D 1 ±2
Signed ICF	X								
Medical and disease history	X								
Randomization [v]		X[w]							
Physical examination [a, b]	X	X	X	X		X	X	X	X
Vital signs [b]	X	X	X	X		X	X	X	X
ECOG performance [b]	X	X [b]				X	X	X	X
Prior and concomitant medications	X [c]	X	X	X		X	X	X	X
Pregnancy test for WOCBP [d]	X	X					X		X
Chest X-ray (or CT of chest)	X[x]								
12-lead ECG - All Subjects [b, e]	X	X		X [f]	X [f]	X	X		X
12-lead ECG - Dense PK Sampling subset – additional time points			X [g]			X [g]			
Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) [b, h]	X [i]	X	X	X		X	X	X	X
Thyroid Function Test	X								X [b, u]
Coagulation profile (PT/INR, d-dimer, fibrinogen)	X								
MUGA or ECHO [j]	X								
FLT3 mutation status (bone marrow or whole blood)	X[k]								
Bone marrow aspiration and/or biopsy for disease assessment and MRD analysis (or whole blood)	X[k]						X [l]		X[l]
AE/SAE assessment [m]	X	X	X	X		X	X	X	X
Pharmacokinetic sampling – Arms A* and AC (whole blood samples for plasma pharmacokinetics) [n]		X		X		X	X		X
Pharmacokinetic sampling – Dense PK Sampling subset – all arms (whole blood samples for plasma pharmacokinetics) – additional time points [o]			X			X			
PGx (whole blood and buccal swab) [p]		X							
Patient reported outcome tools - Brief Fatigue Inventory [q]		X		X		X	X	X	X
Patient reported outcome tools – all others [q, r]		X					X		X
Resource utilization		X					X		X
IRT Transaction [y]	X	X					X		X
ASP2215 dosing at the clinic [s]		X		X		X	X	X	X
Azacitidine dosing at the clinic [t]		X	X [o]				X		X

Footnotes appear on next page

AE: adverse event; C: cycle; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; CT: computed tomography; D: day; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; FLT3: FMS-like tyrosine kinase; ICF: informed consent form; INR: international normalized ratio; IRT: interactive response technology; MRD: minimal residual disease; MUGA: multigated acquisition scan; PK: pharmacokinetic; PGx: pharmacogenomics; PT: prothrombin time; QTcF: Fridericia-corrected QT interval; SAE: serious adverse event; WOCBP: women of childbearing potential.

a. Height measurement performed only at screening. Weight measurement should be performed at screening and on day 1 of each cycle.
b. Obtained predose of study drug (ASP2215 and/or azacitidine).
c. Includes medications taken within 28 days prior to C1D1.
d. WOCBP 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. If screening pregnancy test was performed within 72 hours prior to start of study treatment, then it does not need to be repeated at day 1.
e. Screening ECG is required. ECG assessment will be evaluated before dosing on C1D1, C1D8, C1D15 and day 1 of each subsequent cycle. Predose assessments should be taken within 1 hour before study treatment (ASP2215 and/or azacitidine) administration. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs with 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 all treatment decisions. If the mean triplicate QTcF is > 500 ms at any time point, the ECG will be repeated (within 2 hours if identified on machine read or as soon as possible if identified by central read). See [Section 5.4.5]. ECGs can be repeated during screening period.
f. If the mean QTcF from C1D1 to C1D8 has increased > 30 ms with no other known etiology, a confirmatory ECG should be performed on C1D9. If the C1D8 and C1D9 ECGs confirm the > 30 ms increase from C1D1 in QTcF, then the investigator should assess if ASP2215 dose modification should occur as per the dose interruption or reduction guideline in [Section 5.1.2]. On C1D1, 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 C1D9 visit is scheduled later in the day in order to allow for receipt and assessment of the C1D8 central read ECG. This also allows for a subject to be contacted if the C1D9 ECG is no longer required.
g. For subjects participating in the dense PK sampling subset only, additional ECGs will be performed on C1D4 and C1D15. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs with 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. Triplicate ECGs are to be performed prior to obtaining the time-matched PK sample, therefore must be started at least 10 to 15 minutes before the PK draw.:
   See Table 3.
h. Uric acid will be tested on days 1, 4, 8 and 15 in cycle 1. Urinalysis is only required at screening. Additional laboratory tests may be performed according to institutional standard of care.
i. Subjects may be screened and randomized from local labs. However, samples must also be submitted for central read. Labs can be repeated during screening period.
j. MUGA scans or ECHO (per standard of care) are to be performed at screening for subjects with history of New York Heart Association Class 3 heart failure. NOTE: MUGA scans are not applicable to Germany.
k. FLT3 mutation status must be determined from central read results. At screening, 2 bone marrow aspirate samples are required: one will be sent to Invivoscribe (central FLT3 mutation testing laboratory) and the other to Hematogenix (central disease assessment laboratory). A bone marrow aspirate is preferred for FLT3 assessment. However, if a bone marrow aspirate sample is unavailable at screening -
   - a whole blood sample can be sent to Invivoscribe for FLT3 testing, provided there are measurable leukemic cells present and
   - the bone marrow biopsy from initial diagnosis and a whole blood sample should be sent to Hematogenix for disease assessment.

   Aspirate from initial diagnosis can be sent to Invivoscribe if it was collected in a sodium heparin tube, stored at 2 to 8°C and can be sent within 5 days of collection and testing can occur within 7 days of sample collection. Subjects in the safety cohort only should still send a FLT3 sample to the central laboratory; however, the results are not required to enroll.

Footnotes continued on next page

l. Subsequent bone marrow samples are required during, C2D1 and C3D1. For subjects who do not achieve a CR, CRp or CRi, the bone marrow assessments will be repeated on day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow will be repeated 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 end-of-treatment visit and as clinically indicated. If bone marrow aspirate is unavailable then an EDTA tube of whole blood along with bone marrow core biopsy (block or slides) should be collected instead. Post screening bone marrow samples only need to be sent to Hematogenix and remaining bone marrow aspirate and/or whole blood samples will be used for MRD analysis and other biomarker analyses.

m. For Safety Cohort and First 6 Japanese Subjects on Arm AC (either in safety cohort or randomization portion of the study): DLT observation period will occur from day 1 through day 28 of cycle 1 only.

n. For subjects in randomized portion of the trial only: PK samples for ASP2215 will be collected for all subjects in Arm A* and Arm AC at predose (within 1 hour before ASP2215 administration) on C1D1, C1D8, C1D15 and on day 1 of each subsequent cycle. See Table 3.

o. Dense PK is applicable to randomization portion of the trial only, and will include the first 12 non-Japanese and 12 Japanese subjects randomized at the sites participating in the dense PK sampling subset. For subjects participating in dense PK sampling subset only, additional PK samples will be collected on C1D4 for ASP2215 (Arms A* and Arm AC) and/or azacitidine (Arm AC and Arm C) at predose (within 1 hour before ASP2215 for Arm A and AC and within 1 hour before azacitidine administration for Arm C), and at 0.25 (± 5 min), 0.5 (± 5 min), 1 (± 10 min), 2 (± 10 min), 4 (± 20 min), and 6 (± 20 min) hours post dose. Subjects on Arms AC and C should receive azacitidine via subcutaneous injection only for cycle 1. Intravenous infusion will be allowed after cycle 1. For subjects on Arm AC who will have 2 tubes collected per time point, the ASP2215 PK sample will be drawn before the azacitidine sample. On day 4, azacitidine will be administered immediately following ASP2215 administration. Dense PK samples will also be collected for ASP2215 for subjects on arms A* and AC on C1D15 at 4 hours (± 20 min) post dose. See Table 3.

p. Whole blood and buccal swab collected at cycle 1 day 1 predose for optional PGx study.

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

r. Includes EuroQol Group 5-dimension 5-level instrument, Functional Assessment of Chronic Illness Therapy–Dyspnea-Short Form, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items.

s. ASP2215 is taken daily at home except for visits marked where it will be taken at the clinic.

t. Azacitidine regimen (75 mg/m^2) to be administered daily by subcutaneous injection or intravenous infusion on days 1 to 7 of each 28-day cycle. Refer to the pharmacy manual for administration instructions. The route of administration of azacitidine outside of label instructions is not recommended and is a clinical decision of the investigator. On all visits indicated for azacitidine administration, the dosing should occur in clinic. For subjects in Arm AC, whenever possible, azacitidine will be administered immediately following ASP2215 administration. Subjects in the dense PK sampling subset on Arms AC and C should receive azacitidine daily by subcutaneous injection only for cycle 1.

u. Thyroid Function Tests is performed during screening visit, C3D1 and will be repeated after every 2 cycles of therapy thereafter (C5D1, C7D1, C9D1 etc.).

v. Japan only – for the first 6 subjects enrolled or randomized to the combination arm in Japan (either in safety cohort or randomization portion of the study), only 1 subject may begin study drug administration per day (i.e., no 2 subjects will receive their initial dose of study medication on the same day).

w. Safety eligibility assessments (clinical labs and ECG) can be repeated to ensure the patient meets eligibility during screening period. The screening period can be extended to repeat safety assessments with the approval of the Medical Monitor.

Footnotes continued on next page

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

x. A chest X-ray (or CT of chest) does not need to be repeated if a chest x-ray result performed within 2 weeks prior to start of screening is available to assess subject eligibility.

y. Randomization in the IRT can occur a day prior to C1D1. For the purposes of drug preparation and dispensing activities during subsequent visits, IRT transaction may be done prior to the visit and do not need to fall within the protocol visit window.

z. Unscheduled visits may be performed at any time during the study whenever necessary to assess for AEs or follow-up on AEs, or if deemed necessary by the investigator. Unscheduled visits can include AE assessment, additional assessments (e.g., laboratory testing, ECG etc) as deemed appropriate by the investigator. If dose interruption of study treatment exceeds more than 28 days (exception HSCT), then safety assessments (clinical labs and ECG) will be repeated every 28 days as an unscheduled visit from the time of interruption of the study treatment to the resumption of the study treatment by the subject.

Table 2 Posttreatment Schedule of Assessments

Assessments	Pre-HSCT Visit/ EOT [a]	30-day Follow-up (+ 7 days) [b]	Long-term Follow-up [c] (+/- 7 days)
Physical examination	X [d]		
Vital signs	X [d]		
ECOG performance	X [d]		
Pregnancy test for WOCBP	X		
12-lead ECG	X		
Clinical laboratory tests (serum chemistry, hematology, coagulation)	X [d]		
Thyroid Function Test	X		
Bone marrow aspiration and/or biopsy for disease assessment and MRD analysis(or whole blood) [e]	X		
Concomitant medications [f]	X	X [f]	
AE/SAE assessment[g]	X	X [h]	X [i]
Patient reported outcome tools – EQ-5D-5L [j]	X	X	X
Patient reported outcome tools – all others [j, k]	X		
Resource utilization	X	X	
Survival and subsequent antileukemic treatments and their outcomes		X	X
IRT Transaction	X		

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EDTA: ethylenediaminetetraacetic acid; EOT: end-of-treatment; EQ-5D-5L: EuroQol Group 5-dimension 5-level instrument; FLT3: FMS-like tyrosine kinase; HSCT: Hematopoietic stem cell transplant; IRT: interactive response technology; MRD: minimal residual disease; SAE: serious adverse event; WOCBP: women of childbearing potential.

a. End-of-treatment visit is to be performed within 7 days after last dose of study treatment (ASP2215 and/or azacitidine). For subjects who will undergo HSCT and plan to resume ASP2215 treatment after HSCT, a pre-HSCT visit will be performed. For subjects in Arm C who will undergo HSCT, an EOT visit will be performed followed by the Posttreatment Schedule of Assessments for long term follow-up.

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

c. Telephone contact every 3 months for up to 3 years. Additional contacts will be made during interim analysis/final analysis or as needed. Subjects in long-term follow-up will be followed every 3 months until they are reconsented to the current protocol version 13.0, at which time they will discontinue from the study.

d. Assessment does not need to be repeated if collected at a regularly scheduled visit within 3 days before the end-of-treatment visit.

e. Bone marrow aspiration and biopsy are not required if a sample was obtained within 14 days before end-of-treatment visit. If bone marrow aspirate is unavailable then an EDTA tube of whole blood along with bone marrow core biopsy (block or slides) should be collected instead. Post screening bone marrow samples only need to be sent to Hematogenix and remaining bone marrow aspirate and/or whole blood samples will be used for MRD analysis and other biomarker analyses.

Footnotes continued on next page

f. Concomitant medications should be collected for reported or ongoing AE/SAEs through 30 days after the last dose of study treatment (ASP2215 and/or azacitidine) for subjects who have discontinued treatment. For subjects who undergo HSCT, concomitant medications should be collected for reported or ongoing AE/SAEs through start of conditioning treatment or 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), whichever comes first. For subjects who resume ASP2215 treatment after HSCT, concomitant medications collection will resume upon the resumption of ASP2215 treatment and continue until 30 days after the last dose of study drug.

g. For subjects who continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine under local standard of care (see [Section 12.7 Continuation of Study Drug Treatment with ASP2215 and/or ASP2215 Plus Azacitidine]), only AEs and SAEs, as defined in [Section 5.5.2], will be collected and reported to Astellas Pharma Global Development Product Safety & Pharmacovigilance (Japan will continue reporting to PAREXEL International).

h. For subjects who plan to proceed to HSCT, AE (included SAE) collection will continue until the start of the HSCT conditioning regimen or until 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), whichever comes first. However, the following AE/SAEs will continue to be collected until 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), 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

   For subjects who resume ASP2215 treatment after HSCT, AE (including all SAE) collection will resume upon the resumption of ASP2215 treatment and continue until 30 days after the last dose of study drug.

i. Only SAEs related to ASP2215 alone, azacitidine alone or ASP2215 + azacitidine will be collected.

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

k. Includes Brief Fatigue Inventory, Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Form, Functional Assessment of Cancer Therapy-Leukemia and dizziness and mouth sores items.

Table 3 Sampling Time points for ECG, PK and Dense PK for each Treatment Arm in Randomization Cohort

ASSESSMENT	CYCLE 1					CYCLE 2		SUBSEQUENT CYCLES
	D 1	D 4	D 8	D 9	D 15	D 1	D 15	D 1
ECG [a] [All Subjects]	Predose		Predose	Predose [only if C1D8 is ≥ 30 ms from baseline]	Predose	Predose	Predose	Predose
ECG [a, b] [Dense PK Subjects- Arm A & AC]		Predose Postdose: 4 hrs (-30 min)			Postdose: 4 hrs (-30 min)			
ECG [a, b] [Dense PK Subjects- Arm C]		Predose Postdose: 4 hrs (-30 min)						
PK Samples - ASP2215 [c] [Subjects in Arms A and AC]	Predose		Predose		Predose	Predose		Predose
Dense PK Samples - ASP2215 [c] [Subjects in Arms A and AC]		Predose *Postdose:* ▪ 0.25 hrs (± 5 min), ▪ 0.5 hrs (± 5 min), ▪ 1 hrs (± 10 min), ▪ 2 hrs (± 10 min), ▪ 4 hrs (± 20 min), ▪ 6 hrs (± 20 min)			*Postdose:* ▪ 4 hrs (± 20 min)			
Dense PK Samples – Azacitidine [c] [Subjects in Arms C and AC]		Predose *Postdose:* ▪ 0.25 hrs (± 5 min), ▪ 0.5 hrs (± 5 min), ▪ 1 hrs (± 10 min), ▪ 2 hrs (± 10 min), ▪ 4 hrs (± 20 min), ▪ 6 hrs (± 20 min)						

C: cycle; D: day; ECG: electrocardiogram; PK: pharmacokinetic.

a. Triplicate ECG predose assessments should be taken within 1 hour before study treatment (ASP2215 and/or azacitidine) administration and at least 10 to 15 minutes before the predose PK draw (includes dense PK).

b. Triplicate ECG post dose are to be performed prior to obtaining the time-matched PK sample, therefore must be started at least 10 to 15 minutes before the PK draw.

c. Predose PK samples will be collected after triplicate ECG and prior to administration of ASP2215 and/or azacitidine. Both predose triplicate ECG and predose PK sample should be collected within 1 hour prior study treatment (ASP2215 and/or azacitidine) administration

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 (37%) and acute myeloid leukemia (AML) (32%) [American Cancer Society, 2018]. 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 19520 people (10380 men and 9140 women) were to be diagnosed with AML, and 10670 were to die from the disease in 2018 in the United States [American Cancer Society, 2018]. While 60% to 80% of younger patients achieve a complete remission (CR) with standard therapy, only about 30% to 40% of such patients are alive and disease-free at 5 years because relapsing AML subsequent to CR is common [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 syndromes [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]. Furthermore, patients with activated FLT3 show poor prognosis, with a higher relapse rate, more rapid relapse, reduced disease-free survival and OS [Patel et al, 2012; Gale et al, 2008; Yanada et al, 2005; Tiesmeier et al, 2004; Moreno et al, 2003].

AXL tyrosine kinase (AXL) has been detected in AML and has been shown to play a role in mediating migration and invasiveness of cancer cells. Inhibition of AXL has been shown to increase apoptosis and inhibit proliferation of FLT3-ITD and FLT3 wild-type AML cell lines and primary AML cells in vitro, and reduced tumor burden and prolonged survival in mouse models [Janning et al, 2015].

ASP2215 hemifumarate, also referred to as ASP2215, is a new chemical entity discovered by Astellas Pharma Inc. in collaboration with Kotobuki Pharmaceutical Co., Ltd. ASP2215 also has inhibitory effect on tyrosine kinases, mainly FLT3, AXL, leukocyte receptor tyrosine kinase (LTK) and anaplastic lymphoma kinase (ALK).

XOSPATA (ASP2215/Gilteritinib) tablets have been approved by U.S. FDA and MHLW for the treatment of adult patients who have relapsed or refractory AML with FLT3 mutations.

The National Comprehensive Cancer Network (NCCN) Guidelines for AML strongly recommend clinical trials as the first option for any patient [National Comprehensive Cancer

Network, 2015]. There are also standard intense chemotherapy regimens with strong evidence of efficacy for newly diagnosed patients. However, there is no universally accepted standard chemotherapy regimen for newly diagnosed AML patients, with or without unfavorable risk based on cytogenetics or molecular markers, who cannot tolerate or are unfit for intensive induction chemotherapy due to performance status, age, or comorbidities. The NCCN Guidelines for AML provide a list of commonly used regimens including clinical trials and the hypomethylating agent azacitidine (Vidaza) for patients who cannot tolerate intensive induction chemotherapy. In a phase 3 trial in older patients with AML, azacitidine resulted in a median OS of 10.4 months compared to 6.5 months for conventional care regimens (including low dose cytarabine with a median OS of 6.4 months) [Dombret et al, 2015]. Azacitidine was approved in 2015 by EMA for use in AML. Combining FLT3 inhibition plus hypomethylation with azacitidine has resulted in inhibition of growth and induction of apoptosis and differentiation of FLT3/ITD acute leukemia cell lines and primary patient blasts [Chang et al, 2016].

The combination of ASP2215 with azacitidine in xenograft models has been studied. ASP2215 in combination with azacitidine showed superior antitumor efficacy in mice xenografted with MV4-11 cells endogenously expressing FLT3-ITD compared to the ASP2215 or the azacitidine-treated groups [2215-PH-0025]. Similarly, combination of ASP2215 with standard chemotherapy was also synergistic [Mori et al, 2014].

1.2 Nonclinical and Clinical Data

The nonclinical and clinical studies which are referred to in this section are described in more detail in the ASP2215 Investigator's Brochure [2018]. Please refer to the current version of the ASP2215 Investigator's Brochure.

1.2.1 Nonclinical Data

1.2.1.1 Summary of In Vitro Pharmacology Studies

ASP2215 in vitro studies showed the inhibition of activities of a series of tyrosine kinases: FLT3, nucleophosmin 1-ALK, LTK, 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, LTK, AXL, echinoderm microtubule-associated protein-like 4-ALK (EML4-ALK) variant 1 and KIT kinase activities with half-maximal inhibitory concentration (IC_{50}) values of 0.291, 0.350, 0.726, 1.2 and 229 nmol/L, respectively.

ASP2215 inhibited each radioligand binding to adenosine A1 receptor (rat), serotonin $(5HT)_1$ receptor (nonselective, rat), serotonin $5HT_{2B}$ receptor (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 $5HT_{2B}$ receptor 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 (IC_{50} values ranged from 1.6 to 2.1 nmol/L) and the growth of MV4-11 cells, a human AML cell line expressing FLT3-ITD, with an IC_{50} value of 0.92 nmol/L.

In MV4-11 cells, treatment with ASP2215 at 0.1, 1 and 10 nmol/L resulted in signal transducer and activator of transcription 5 (STAT5) phosphorylation of 114%, 23% and 0%, respectively; AKT phosphorylation of 65%, 48% and 9%, respectively; and extracellular signal-regulated kinase phosphorylation of 54%, 22% and 1%, respectively, compared to the vehicle-treated control (2215-PH-0014).

In a study to investigate the effect of ASP2215 on cell cycle distribution, the percentages of MV4-11 cells in G1 phase treated with vehicle or ASP2215 at 1, 3 and 10 nmol/L were 60%, 65%, 69% and 71%, respectively (2215-PH-9004). ASP2215 at 3 and 10 nmol/L significantly increased the population of MV4-11 cells in G1 phase.

ASP2215 at 10 and 30 nmol/L significantly increased the annexin V-positive population in MV4-11 cells, indicating that ASP2215 induces apoptosis in this cell line (2215-PH-9005).

ASP2215 also inhibited cell growth and ALK phosphorylation in National Cancer Institute (NCI) H2228 cells, human non-small cell lung cancer (NSCLC) cells endogenously expressing EML4-ALK.

ASP2215 inhibited AXL phosphorylation in AXL-overexpressed PC9 (PC9 AXL) cells. The combination treatment of ASP2215 and erlotinib showed more effective growth inhibition in PC9 AXL cells compared to erlotinib alone, suggesting that overexpression of AXL confers resistance to erlotinib in NSCLC cells.

The affinity of ASP2215 to 46 receptors, 5 ion channels, 3 transporters and the inhibitory effect of ASP2215 on 3 enzyme reactions were evaluated. ASP2215 inhibited radioligand binding to adenosine A1 (rat) receptor, serotonin 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) receptor (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 $5HT_{2B}R$ receptor function in a cell function assay with an IC_{50} value of 5.82 μmol/L without showing agonistic activity.

1.2.1.2 Summary of In Vivo Pharmacology Studies

ASP2215 induced significant growth inhibition of MV4-11 tumors and tumor regression in vivo. At 6 and 10 mg/kg per day, ASP2215 induced complete tumor regression for 4 out of 6 and 6 out of 6 mice, respectively. Body weight of the mice treated with ASP2215 was not affected at any tested doses. After single oral administration of ASP2215 in the xenograft mice, the phosphorylation of FLT3 and STAT5 in MV4-11 tumors was inhibited at doses of 1, 3, 6 and 10 mg/kg.

1.2.1.3 Summary of Nonclinical Pharmacokinetics

After a single oral administration, C_{max} and AUC_{inf} increased more than dose-proportionally from 1 to 10 mg/kg in rats and slightly more than dose proportionally from 0.3 to 3 mg/kg in dogs. The absolute oral bioavailability was 26.8% at 1 mg/kg in rats and 88.2% at 0.3 mg/kg in dogs.

[^{14}C]-ASP2215-derived radioactivity in nonpigmented rats was distributed to be the highest in the liver and detectable at 72 hours in many tissues. In pigmented rats, the concentration

of radioactivity in all tissues except the eyeball decreased to less than 3% of their respective maxima or below the level of detection at 30 days postdose. Radioactivity in the eyeball decreased over time and was 36.4% of the maxima at 270 days postdose. The radioactivity in the eyeball was found in the ciliary body, retina and choroid, and was derived from unchanged ASP2215. After repeated oral administration to nonpigmented rats, tissue concentrations of radioactivity reached steady state up to day 21. On day 28, tissue concentrations of radioactivity reached their maxima at 4 or 8 hours postdose and decreased to less than 28% of their respective maxima or below the detection limit at 336 hours postdose. In pregnant rats, ASP2215 and/or its metabolite(s) passed the placental barrier and were transferred to the fetus. In lactating rats, ASP2215 and/or its metabolite(s) were distributed in the tissues of infants via the milk.

The plasma protein binding ratios of ASP2215 in mice, rats, rabbits, dogs and monkeys ranged between approximately 75% and 90%, and ranged from 90.2% to 90.5% in humans. The major binding protein in human plasma was human serum albumin.

After a single oral administration of [^{14}C]-ASP2215 at 1 mg/kg to rats and dogs, the major the major radioactive component of plasma was ASP2215. ASP2215 was suggested to be metabolized by oxidation, N-dealkylation and glutathione conjugation. Except for 2 minor metabolites, all metabolites detected in humans were detected in rats and/or dogs.

After oral administration to nonpigmented rats, the urinary and fecal excretion of radioactivity within 168 hours was 1.4% and 89.9% of the dose, respectively. The urinary and biliary excretion of radioactivity within 48 hours was 8.6% and 29.3% of the dose, respectively, suggesting that the oral absorption was at least 37.9%. After a single oral administration to dogs, the urinary and fecal excretion of radioactivity was 9.5% and 88.1% of the dose, respectively. A part of the biliary excretion is assumed to undergo enterohepatic circulation.

Refer to [Section 1.2.2.2] for assessments using human biomaterials.

1.2.1.4 Summary of Nonclinical Safety

Major findings in the safety pharmacology studies were vomiting, positive fecal occult blood and increased/decreased blood Ca^{2+} in dogs, and decreased urination and defecation in rats. In the oral 13-week repeated dose toxicity study in rats, and the 4- and 13-week repeated dose toxicity studies in dogs, mortality occurred at 20, 10 and 5 mg/kg per day, respectively. With respect to other major target organ toxicities, effects on the urinary bladder, epithelial tissue, gastrointestinal tract, lymphohematopoietic system, eye, liver, kidney and/or lung were observed in rats and dogs at 2.5 mg/kg per day or more. All major findings were reversible and monitorable.

ASP2215 has a potential to induce genotoxicity in vivo.

ASP2215 showed suppressed fetal growth, embryo-fetal deaths and teratogenicity in the embryo-fetal development studies in rats.

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

In juvenile rats (dosing from postnatal day [PND] 4 to 42), no mortality was noted at 5 mg/kg per day, but 1 animal was moribund sacrificed at 2.5 mg/kg per day. The cause of moribundity was considered to be deteriorated general conditions due to the unexpectedly high exposure. In the preliminary non-GLP dose range finding study (dosing from PND 4 to 21), gastrointestinal bleeding detected as abnormal stool color (dark red) was noted at 10 mg/kg per day and higher. Gastrointestinal bleeding was suggested to be a target organ at 10 mg/kg per day or higher as in adult rats in the 13-week dose study (2215-TX-0002). The minimum lethal dose level of 2.5 mg/kg per day in juvenile rats was lower than that in adult rats in the 13-week dose study (20 mg/kg per day).

1.2.2 Clinical Data

1.2.2.1 Clinical Pharmacokinetics and Pharmacodynamics

In Study 2215-CL-0101, a phase 1/2 study in patients with relapsed/refractory AML, ASP2215 generally exhibited linear, approximately dose-proportional pharmacokinetics (PK) after once daily administration over the dose range evaluated (20 to 450 mg). Median t_{max} was observed between 2 and 6 hours following single and repeat dosing of ASP2215. After multiple dose administration, ASP2215 exhibited a long half-life, ranging from 45 to 159 hours and up to 10-fold accumulation based on the accumulation index (R_{ac}).

In Study 2215-CL-0102, a phase 1 study in Japanese patients with relapsed/refractory AML, ASP2215 administration resulted in a median t_{max} between 3 and 7 hours following single and multiple dosing, with a median C_{max} of 680.23 ng/mL and a median AUC_{tau} of 13464.35 ng·h/mL. After multiple dose administration, ASP2215 exhibited a mean half-life ranging from 84 to 126 hours, and up to approximately 8-fold accumulation based on R_{ac}.

Study 2215-CL-0105 was a phase 1 open-label mass-balance study in patients with solid tumors investigating the absorption, metabolism and excretion of ^{14}C-gilteritinib (^{14}C-labeled ASP2215) and the metabolic profile of ASP2215 in plasma, urine and feces after a single oral dose of ^{14}C-gilteritinib. Mean total recovery of the administered dose of [^{14}C]-radioactivity was 80.9% with 64.5% recovered in feces and 16.4% recovered in urine. The majority (77%) of [^{14}C]-radioactivity was recovered in feces and urine within 288 hours postdose. The primary route of [^{14}C]-radioactivity elimination is into feces, with renal excretion being a minor route.

The effect of food on ASP2215 PK was examined in phase 1 Study 2215-CL-0113 in healthy adult subjects. ASP2215 $t_{½}$, CL/F and V_Z/F were comparable in the fasted and fed treatment groups. Although C_{max} decreased approximately 26% under fed conditions, overall exposure of ASP2215 was comparable under fasted and fed conditions as evidenced by the less than 10% difference in AUC.

The effect of strong and moderate cytochrome P450 (CYP)3A4 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-glycoprotein (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.

An assessment of the effect of ASP2215 on the PK of cephalexin, a multidrug and toxin extrusion (MATE)1 substrate, was also performed in patients with relapsed/refractory AML (Study 2215-CL-0101). Cephalexin exposure decreased less than 10% and urinary excretion decreased less than 20% when cephalexin was administered in combination with ASP2215 compared to administration of cephalexin alone. These results indicate that a clinically-relevant interaction is not expected when ASP2215 is coadministered with a MATE1 substrate.

1.2.2.2 Studies Using Human Biomaterials

In Caco-2 cells, the permeability of ASP2215 was between that of known low and high permeability markers. ASP2215 was a substrate for P-gp and breast cancer resistance protein (BCRP) but not a substrate for organic anion transporting polypeptide (OATP)1B1, OATP1B3 or organic cation transporter (OCT)1. ASP2215 was suggested to be metabolized by oxidation, N-dealkylation, glutathione conjugation and glucuronidation. The main enzyme involved in the metabolism of ASP2215 was estimated to be CYP3A4.

ASP2215 has a potential to induce CYP enzyme activities (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5) and mRNA 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.

Overall, ASP2215 demonstrated a potential to inhibit CYP3A, BCRP and P-gp in the small intestine, OCT1 in the liver, and MATE1 in the kidney at clinically relevant concentrations of ASP2215 based on FDA Draft Guidance for Industry (2012), EMA Guideline on the Investigation of Drug Interactions (2012), and PMDA Draft Guideline on Drug Interactions (2013). Clinical assessments were performed to evaluate the effect of ASP2215 on the PK of cephalexin, a MATE1 substrate and midazolam, a CYP3A substrate.

1.2.2.3 Clinical Safety

Of the 252 patients in Study 2215-CL-0101 who received at least 1 dose of ASP2215, the majority (249 [98.8%]) experienced at least 1 treatment-emergent adverse event (TEAE), and most (189 [75.0%]) patients experienced at least 1 TEAE considered by the investigator to be possibly or probably related to study drug. No clear dose-dependent patterns were observed for overall TEAEs, TEAEs of grade 3 or higher, drug-related TEAEs, serious TEAEs or drug

related serious TEAEs. Overall, 105 patients experienced TEAEs leading to death. The majority of the deaths were attributed to disease progression. Thirty-one patients experienced dose-limiting toxicities (DLTs). None of the doses below 450 mg met the criteria for pausing enrollment. Thus, the maximum tolerated dose (MTD) in Study 2215-CL-0101 is considered to be 300 mg.

Study 2215-CL-0101 demonstrated efficacy in FLT3 mutation-positive patients with relapsed/refractory AML, with a tolerable safety profile.

In Study 2215-CL-0102, all patients receiving the study drug experienced at least 1 adverse event (AE), and 91.7% (22/24) of patients experienced a drug-related AE.

In Study 2215-CL-0103, of the 49 patients who received at least 1 dose of ASP2215, 98.0% (48/49) of patients reported at least 1 TEAE and 91.8% (45/49) of patients reported at least 1 drug-related TEAE. None of the patients experienced TEAEs leading to death.

In Study 2215-CL-0201, a phase 2/3 study of ASP2215 and/or ASP2215 plus azacitidine versus azacitidine in newly-diagnosed AML patients, the DLT observation period (days 1 to 28 of cycle 1) for the Safety Cohort has been completed. Overall, 15 patients were enrolled in the Safety Cohort of Study 2215-CL-0201, of whom 11 were evaluable for DLT observation per the protocol. A DLT (tumor lysis syndrome) was experienced by 1/6 evaluable patients in the 80 mg/day ASP2215 in combination with azacitidine dosing cohort and by 0/5 evaluable patients in the 120 mg/day ASP2215 in combination with azacitidine dosing cohort.

Study 2215-CL-0301 is a phase 3, open-label, multicenter, randomized study of ASP2215 120 mg versus salvage chemotherapy in patients with relapsed or refractory AML with FLT3 mutation, Of the 219 patients who received at least 1 dose of ASP2215 120 mg, 213 (97.3%) patients experienced at least 1 TEAE and 173 (79.0%) patients experienced at least 1 drug-related TEAE. TEAEs leading to death were experienced by 25.6% (56/219) of patients. AML disease progression was the most common TEAE leading to death (9.1% [20/219]), followed by septic shock (2.7% [6/219]), cardiac arrest (1.8% [4/219]) and pneumonia (1.4% [3/219]); all other TEAEs leading to death were reported in < 1% of patients.

1.2.2.4 Clinical Efficacy

In Study 2215-CL-0101, as of 06 Jun 2018, 252 patients 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).

Results from Study 2215-CL-0101 indicate that of the 252 patients who received at least 1 dose of ASP2215, the majority of composite complete remission (CRc) and partial remission (PR) events were observed in FLT3 mutation-positive AML patients in dose groups of 80 mg and greater. The derived response rate (CRc + PR) at the end of treatment in the 191 FLT3 mutation-positive patients was 48.7% overall and 66.7%, 53.6%, 48.3%, 60.0% and 50.0% in the 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups, respectively. The median duration of response in FLT3 mutation positive patients in ≥ 80 mg dose levels was 147.0 days (95% CI: 97.0, 307.0). In FLT3 mutation positive patients with a response of

complete remission (CR)/complete remission with partial hematological recovery (CRh), the median duration of response was 383.0 days (95% CI: 136.0, NE). The median OS from Kaplan-Meier (KM) estimates in FLT3 mutation positive patients in ≥ 80 mg dose levels was 218.0 days, with survival probabilities of 56.2% at 26 weeks and 24.9% at 1 year.

In Study 2215-CL-0102, a phase 1 study in Japanese patients with relapsed/refractory AML, after ASP2215 treatment at doses ranging from 20 mg to 300 mg per day, a CRc rate of 36.8% and a response rate of 47.4% was attained. Patients in the 200 mg dose group had the highest CRc and response rate, of 57.1% (for both measures) at end of treatment. At end of treatment, 3 of the FLT3 mutation-positive patients achieved CRc (60.0%) and the response rate in this group was 80.0%. Across all dose groups, the median duration of CRc was 86.5 days and the median duration of remission was 113.5 days.

In Study 2215-CL-0103, a phase 1 study of ASP2215 in combination with induction and consolidation chemotherapy in patients with newly diagnosed AML, there were 22 evaluable patients with a positive FLT3 mutation status. By end of treatment, 19/22 patients had a best overall response of CR (82.6%; 95% CI: 61.2, 95.0). The CRc rate was 91.3% (95% CI: 72.0, 98.9).

In the ADMIRAL trial (2215-CL-0301), in total, 371 patients (39.4% refractory AML; 60.6% relapsed AML) were included, with 247 on ASP2215 and 124 on salvage chemotherapy [Samson, 2019]. Results of the study show the median OS for patients who received ASP2215 was 9.3 months compared to 5.6 months for patients who received salvage chemotherapy (hazard ratio = 0.637 (95% CI 0.490, 0.830), P=0.0007); one-year survival rates were 37% for patients who received ASP2215 compared to 17% for patients who received salvage chemotherapy.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 ASP2215 Data

Clinical data presented in Section 1.2.2.4 demonstrate efficacy of ASP2215 in FLT3 mutation-positive patients with relapsed/refractory AML, with a tolerable safety profile.

Expected serious adverse reactions for ASP2215 are provided in the Reference Safety Information which can be found in the current version of Investigator's Brochure [Section 5.2.3 Expected Serious Adverse Drug Reactions].

Refer to the current version of Investigator's Brochure [Section 6.2 Guidance to the Investigator] for an overview of contraindications, warnings and precautions (including the potential to influence the ability to drive and use machines) and safety observations from clinical studies.

1.3.2 Comparative Chemotherapy Regimen

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

1.4 Risk-Benefit Assessment

There is no universally accepted standard approach to treating AML in older patients. Commonly used therapeutic options include best supportive care alone, standard induction chemotherapy, and low-dose ara-c.

The NCCN guidelines recommend induction chemotherapy for patients with AML age ≥ 60 years with more favorable prognostic features and the treatment recommendations for older patients with newly diagnosed AML include the hypomethylating agents azacitidine and decitabine.

Azacitidine was shown to prolong OS compared with conventional care regimens in the subset of older patients and has been associated with a median OS of approximately 9 to 10 months in patients with AML.

The results from a phase 3 AZA-AML-001 study evaluating the efficacy and safety of azacitidine compared with conventional care regimens (i.e., doctor's choice of best supportive care only, low-dose ara-c, or standard induction chemotherapy) in patients age ≥ 65 years with newly diagnosed AML and > 30% bone marrow blasts showed that compared to current, commonly used AML treatments, azacitidine increased median OS by 3.8 months (6.5 versus 10.4 months; P = 0.1009) [Dombret et al, 2015].

Combination treatment regimens may further improve outcomes for older patients with AML. Results of early trial of azacitidine in combination with first generation FLT3 inhibitor are promising [Dombret et al, 2015; Ravandi et al, 2013; Larrosa-Garcia et al, 2017].

ASP2215/Gilteritinib is a second-generation oral FLT3 inhibitor that has been approved by FDA and PMDA for the treatment of adult patients who have relapsed or refractory AML with an FLT3 mutation [Short et al, 2019].

In 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 the 120 mg dose level. The majority of subjects in the trial received multiple treatments prior to receiving ASP2215. Furthermore, ASP2215 was well tolerated at the proposed doses in this study.

In the ADMIRAL trial (2215-CL-0301), the median OS for relapsed/refractory AML patients who received ASP2215 was 9.3 months compared to 5.6 months for relapsed/refractory AML patients who received salvage chemotherapy [Samson, 2019].

Patients with newly diagnosed AML who are unfit for standard intensive induction therapy have a very poor prognosis. Although there are various chemotherapy options available, they are by no means curative. The response to chemotherapy is poor, especially for patients 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 newly diagnosed AML patients with FLT3 mutations, the potential for ASP2215 to improve outcome outweighs the risk of potential toxicities at the proposed doses in this study.

Addition of ASP2215 to azacitidine is not expected to have significant overlapping toxicity due to differing mechanisms of action.

Based on the risks and benefits associated, the combination of ASP2215 and azacitidine as an additional treatment option for older patients with newly diagnosed AML is worth exploring.

2 STUDY OBJECTIVE(S), DESIGN AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to determine the efficacy superiority of ASP2215 plus azacitidine versus azacitidine as measured by OS.

2.1.2 Secondary Objectives

2.1.2.1 Key Secondary Objective

The key secondary objective is to determine the efficacy superiority of ASP2215 plus azacitidine versus azacitidine as measured by event-free survival (EFS).

2.1.2.2 Additional Secondary Objectives

The additional secondary objectives are to evaluate the safety and efficacy of ASP2215 plus azacitidine versus azacitidine in terms of:

- Best response
- Complete remission (CR) rate
- CRc rate
- CRh rate
- CR/CRh rate
- Transfusion conversion rate; transfusion maintenance rate
- Leukemia-free survival (LFS)
- Duration of remission
- Patient-reported fatigue (Brief Fatigue Inventory [BFI])
- Adverse events (AEs), clinical laboratory results, physical examinations, vital signs, ECGs) and Eastern Cooperative Oncology Group (ECOG) performance scores

2.1.3 Exploratory Objectives

The exploratory objectives are to:

- Evaluate the efficacy of ASP2215 plus azacitidine versus azacitidine in terms of:
    - Transplantation rate
    - Minimal residual disease (MRD)
    - FLT3 gene mutation status
        - Mutation types and frequency
        - Relationship to efficacy and safety
        - Mechanisms of acquired resistance
    - Exploratory (predictive) biomarkers of ASP2215 activity
    - Patient reported dyspnea (Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Form [FACIT-Dys-SF])

  - Patient reported signs, symptoms and impacts of AML (Functional Assessment of Cancer Therapy-Leukemia [FACT-Leu] and dizziness and mouth sores items)
  - Health-related quality of life assessed by the EuroQol Group 5-dimension 5-level (EQ-5D-5L) instrument
  - Resource utilization including hospitalization, blood transfusion, antibiotic intravenous infusions, medication for AEs and opioid usage
- Characterize the PK of ASP2215 and azacitidine given as single agent and/or as combination treatment
- Evaluate and compare the PK of ASP2215 and azacitidine in a subset of Non-Japanese and Japanese subjects

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a phase 3 multicenter, open-label, randomized study to compare the efficacy and safety of ASP2215 plus azacitidine versus azacitidine in newly diagnosed FLT3 mutated AML subjects not eligible for intensive induction chemotherapy.

2.2.1.1 Safety Cohort

Prior to initiation of the randomized trial, 8 to 12 subjects will be enrolled to a safety cohort to evaluate the safety and tolerability of ASP2215 given with azacitidine therapy in the study population. Groups of 3 to 6 subjects in a cohort may be enrolled at the same time. The subjects will initially be treated with ASP2215 80 mg daily (days 1 to 28) (with dose reductions or increases permitted after cycle 1) and azacitidine 75 mg/m^2 daily (days 1 to 7).

The Sponsor, principal investigators and, if appropriate, expert consultants, will review safety data through the DLT observation period in the safety cohort. The DLT observation period will be from day 1 through day 28 of cycle 1. Evaluable subjects are defined as subjects who experience a DLT or in the absence of DLT, receive at least 23/28 doses of ASP2215 and at least 5/7 doses of azacitidine. Subjects who are not evaluable for reasons other than DLT will be replaced. Based on review of the safety cohort data, the decision to initiate the randomized trial at the targeted dose (120 mg) or the initial dose (80 mg) will be made by the Sponsor in consultation with the investigators.

Dose escalation rules are as follows:

- At ASP2215 80 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7):
  - If 0 of 3 subjects experiences a DLT, 6 subjects will be enrolled at ASP2215 120 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7).
  - If 1 of 3 subjects experiences a DLT, up to an additional 3 subjects will be enrolled at ASP2215 80 mg plus azacitidine 75 mg/m^2.
    - If 1 of 6 subjects experiences a DLT, 6 subjects will be enrolled in ASP2215 120 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7).
    - If $\geq$ 2 of 4 to 6 subjects experience DLT, the trial will be stopped.
  - If 2 or more of 3 subjects experience a DLT, the trial will be stopped.

- At ASP2215 120 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7):
  - If 0 out of 5 or 6 subjects or 1 out of 6 subjects experiences a DLT, the randomization will be initiated with ASP2215 120 mg dose for the combination arm.
  - If ≥ 2 of 2 to 6 subjects experience a DLT,
    - If less than 6 subjects were previously treated at ASP2215 80 mg dose, then up to 3 more subjects will be enrolled at ASP2215 80 mg daily plus azacitidine 75 mg/m^2 daily (days 1 to 7).
      - If 0 out of 5 or 6 subjects or 1 of 6 subjects experiences a DLT, randomization will be initiated with ASP2215 80 mg dose for the combination arm.
      - If ≥ 2 of 3 to 6 subjects experience a DLT, the trial will be stopped.
    - If a total of 6 subjects were previously treated at ASP2215 80 mg dose, randomization will be initiated with ASP2215 80 mg dose for the combination arm.

If the safety cohort is stopped, the randomized trial will not open. However, an alternative dosing schedule might be explored via an amendment.

2.2.1.2 Randomized Trial

Approximately 250 subjects (note: enrollment has stopped with a total of 183 subjects) will be randomized in a 2:1* ratio to receive ASP2215 plus azacitidine (Arm AC) or azacitidine only (Arm C). The randomization will be stratified based on age group described below.

- Age ≥ 75 years
- Age < 75 years

Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment over 28-day cycles. The dose and duration of study treatments are outlined in [Section 5.1.1] of the protocol.

ASP2215 starting dose will be 120 mg for Arm A (ASP2215 alone),* and either 120 mg or 80 mg for Arm AC depending on safety cohort outcome. Based on the safety cohort outcome, the starting dose of ASP2215 was determined to be 120 mg for Arm AC subjects. Dose increases and reductions are permitted for ASP2215 and azacitidine. Note: Japan only - for the first 6 subjects enrolled or randomized in Japan to the combination arm (Arm AC) (either in safety cohort or randomization portion of the study), only 1 subject may begin study drug administration in a day (i.e., no 2 subjects will receive their initial dose of study medication on the same day). A subset of sites are participating in the dense PK substudy. The first 12 non-Japanese and 12 Japanese subjects randomized at those sites will participate in the

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

dense PK subset. Dense PK subjects on Arms AC and C should receive azacitidine via subcutaneous injection only for cycle 1. Intravenous infusion will be allowed after cycle 1.

For all subjects taking ASP2215, ASP2215 plus azacitidine or azacitidine, treatment should continue until the subject no longer receives clinical benefit from therapy in the opinion of the investigator, unacceptable toxicity occurs or the subject meets another treatment discontinuation criterion.

Dose adjustments for ASP2215 and azacitidine are described in [Section 5.1.2] of the protocol.

Subjects in safety cohort, Arm A* and Arm AC proceeding for HSCT can remain on the study and resume treatment with ASP2215 only after HSCT if certain conditions are met [Refer to Section 5.1.5 Resumption of Treatment After Hematopoietic Stem Cell Transplantation]. If the subject discontinues the study during or post HSCT, then they should follow the Post-treatment Schedule of Assessments (Table 2) for long term follow-up.

Subjects in Arm C proceeding for HSCT will discontinue treatment by performing an EOT visit and should follow the Post-treatment Schedule of Assessments (Table 2) for long term follow-up.

Subjects will have an end-of-treatment visit within 7 days after last dose of study treatment (ASP2215 and/or azacitidine), followed by a 30-day follow-up for safety, after which the subjects will enter the long-term follow-up period of up to 3 years for collection of subsequent AML treatment, EQ-5D-5L, remission status and survival (cause of death and date of death). Subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until the implementation of protocol version 13.0, at which time they will discontinue from the study as further survival data is no longer needed. See Posttreatment Schedule of Assessments (Table 2).

A formal interim analysis by an Independent Data Monitoring Committee (IDMC) will be performed when approximately 50% (i.e., death events = 70) of the planned total number of deaths (i.e., death events = 140) by any cause have occurred. The interim analysis will be utilized to determine if Arm AC has a more favorable or unfavorable outcome compared to Arm C. If the interim analysis demonstrates a more favorable or unfavorable outcome for Arm AC based on OS, enrollment to the study may be stopped.

Based on the planned interim analysis in Dec 2020, an IDMC recommended terminating the study based on protocol specified boundaries for futility, concluding results are unlikely to show a statistically significant increase in overall survival, Astellas made decision to stop enrollment for the study.

Subjects can continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine until they meet a discontinuation criterion as outlined in [Section 6

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

Discontinuation]. Subjects will be managed per the local institution's standard of care for safety and efficacy assessments while on study drug treatment. No data will be collected in the eCRFs after subjects reconsent under this protocol Version 13.0, as the clinical database will be locked. Only AEs and SAEs, (as defined in [Section 5.5.2 Definition of Serious Adverse Events]) will be collected and reported to Astellas Pharma Global Development Product Safety & Pharmacovigilance (Japan will continue reporting to PAREXEL International). AE and SAE data will be reported in the safety database. Once subjects receiving treatment meet the study discontinuation criteria, subjects will be discontinued from the study.

Subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until the implementation of the current protocol version 13.0, at which time they will discontinue from the study as further survival data is no longer needed.

The EFS will be evaluated at the time of OS interim analysis, only if the OS result is positive. By the time of OS interim analysis with 70 events, 88 EFS events are expected (the actual number of events may vary).

2.2.2 Dose Rationale

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 PK 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. Plasma inhibitory assays have 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, creatine kinase 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, except for sites in US.

A dose of 80 mg ASP2215 given in combination with azacitidine is chosen as a starting dose for the safety run-in cohort to maintain a more efficacious ASP2215 dose while confirming the safety of the combination in a population that is not able to tolerate intense therapy.

The study of azacitidine 75 mg/m^2 daily given on days 1 through 7 of each 28-day treatment cycle via subcutaneous injection or intravenous infusion has been previously reported [Dombret et al, 2015].

2.3 Endpoints

2.3.1 Primary Endpoints

Primary Efficacy Endpoint:

- OS

2.3.2 Secondary Endpoints

Key Secondary Efficacy Endpoint:

- EFS

Secondary Efficacy Endpoints:

- Best Response
- CR
- CRc
- CRh
- CR/CRh
- Transfusion conversion rate; transfusion maintenance rate
- LFS
- Duration of remission
- Patient-reported fatigue from BFI

Safety Endpoints:

- AEs
- Clinical laboratory (serum chemistry, hematology, coagulation and urinalysis) results
- Physical examinations
- Vital sign measurements
- ECGs
- ECOG performance scores

2.3.3 Exploratory Endpoints

- Transplantation
- MRD measured by change in FLT3 mutation to total FLT3 ratio compared to baseline
- 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 intravenous infusions, medication for AEs and opioid usage
- FACIT-Dys-SF assessments
- FACT-Leu and dizziness and mouth sores items
- EQ-5D-5L assessments

2.3.4 Pharmacokinetic Endpoints

- ASP2215 concentration in plasma
- ASP2215 and azacitidine concentrations in plasma (subset of non-Japanese and Japanese subjects)

2.3.5 Safety Cohort and First 6 Japanese Subjects on Arm AC (either in the Safety Cohort or Randomization Portion of the Study) - Definition of DLT

A DLT is defined as any of the following events that occur during the observation period and that is considered to be possibly or probably related to study regimen. The observation period for DLT for dose escalation decisions will be from the start of the treatment until day 28 of the first treatment cycle.

- Any grade ≥ 3 nonhematologic or extramedullary toxicity with the following exceptions:
  - Anorexia or fatigue
  - Grade 3 nausea and/or vomiting if not requiring tube feeding or total parenteral nutrition, or diarrhea if not requiring or prolonging hospitalization that can be managed to grade ≤ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 7 days of onset
  - Grade 3 mucositis that resolves to grade ≤ 2 within 7 days of onset
  - Grade 3 fever with neutropenia, with or without infection
  - Grade 3 infection
- Prolonged myelosuppression defined as absolute neutrophil count ≤ 0.5×10^9/L for more than 21 days from the onset of severe neutropenia in the absence of evidence of active leukemia in the marrow or blood.
- Any toxicity that requires a dose reduction (see [Section 5.1.2])

2.3.6 Safety Evaluation for the First 6 Subjects Enrolled or Randomized to the Combination Arm (either in the Safety Cohort or the Randomization Portion) in Japan (Specific to Japan)

For the first 6 subjects enrolled or randomized to the combination arm (either in the safety cohort or randomization portion of the study) in Japan, DLTs will be evaluated. The observation period for DLTs will be from the start of the treatment until day 28 of the first treatment cycle. If concerns about the tolerability in Japanese subjects in the combination arm arise, enrollment will be suspended in Japan.

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects with newly diagnosed, FLT3 mutated AML subjects not eligible for intensive induction are eligible.

3.2 Inclusion Criteria

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

1. Institutional Review Board-/Independent Ethics Committee (IRB/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 [US] 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 obtaining informed consent.
3. Subject has a diagnosis of previously-untreated AML according to World Health Organization (WHO) classification [Swerdlow et al, 2008] as determined by pathology review at the treating institution.
4. Subject is positive for FLT3 mutation (ITD or TKD [D835/I836] mutation) (or for ***Korea only***: ITD alone or ITD with concurrent TKD activating mutation) in bone marrow or whole blood as determined by central laboratory. NOTE: Requirement of FLT3 mutation assessment by central laboratory is only applicable to the randomization portion of the study.
5. Subject is ineligible for intensive induction chemotherapy by meeting at least 1 of the following criteria:
    a. Subject is ≥ 65 years of age and ineligible for intensive induction chemotherapy per investigator's discretion.
    b. Subject is ≥ 18 to 64 years of age and has any of the following comorbidities:
        i. Congestive heart failure (New York Heart Association (NYHA) class ≤ 3) or ejection fraction (E_F) ≤ 50%;
        ii. Creatinine > 2 mg/dL (177 µmol/L), dialysis or prior renal transplant;
        iii. ECOG performance status ≥ 2;
        iv. Prior or current malignancy that does not require concurrent treatment;
        v. Subject has received a cumulative anthracycline dose above 400 mg/m^2 of doxorubicin (or cumulative maximum dose of other another anthracycline
        vi. Known pulmonary disease with decreased diffusion capacity of lung for carbon monoxide (DLCO > 50%) and/or requiring oxygen ≤ 2 liters per minute
        vii. Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the Medical Monitor during screening and before randomization.
6. Subject must meet the following criteria as indicated on the clinical laboratory tests:
    - Serum AST and ALT ≤ 3.0 × institutional upper limit of normal (ULN)
    - Serum total bilirubin ≤ 1.5 × institutional ULN
    - Serum potassium ≥ institutional lower limit of normal (LLN)

- Serum magnesium ≥ institutional LLN

Repletion of potassium and magnesium levels during the screening period is allowed.

7. Subject is suitable for oral administration of study drug.
8. A female subject is eligible to participate if she is not pregnant [see Appendix 12.1 Contraception Requirements] and at least one of the following conditions applies:
   a) Not a woman of childbearing potential (WOCBP) as defined in [Appendix 12.1 Contraception Requirements]

   OR

   b) WOCBP agrees to follow the contraceptive guidance as defined in [Appendix 12.1 Contraception Requirements] starting at screening and continue throughout the study period, and for at least 180 days after the final study drug administration.
9. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 60 days after the final study drug administration.
10. Female subject must not donate ova starting at screening and throughout the study period, and for 180 days after the final study drug administration.
11. A male subject with female partner(s) of childbearing potential must agree to use contraception as detailed in [Appendix 12.1 Contraception Requirements] starting at screening and continue throughout the study period, for at least 120 days after the final study drug administration.
12. Male subject must not donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
13. Subject agrees not to participate in another interventional study while on treatment.

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 with acute promyelocytic leukemia (APL).
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has received previous therapy for AML, with the exception of the following:
   - Emergency leukapheresis
   - Hydroxyurea
   - Preemptive treatment with retinoic acid prior to exclusion of APL ≤ 7 days
   - Growth factor or cytokine support
   - Steroids
4. Subject has clinically active central nervous system leukemia.
5. Subject has been diagnosed with another malignancy that requires concurrent treatment (with the exception of hormone therapy limited to those therapies that prevent recurrence and/or spread of cancer) or hepatic malignancy regardless of need for treatment.

6. Subject has clinically significant coagulation abnormality unless secondary to AML in the opinion of the investigator.
7. Subject has had major surgery within 4 weeks prior to the first study dose.
8. Subject has had radiation therapy within 4 weeks prior to the first study dose.
9. Subject requires treatment with concomitant drugs that are strong inducers of CYP3A/P-gp.
10. This criterion has been removed.
11. This criterion has been removed.
12. Subject has congestive heart failure classified as New York Heart Association Class IV.
13. Subject with mean Fridericia-corrected QT interval (QTcF) > 480 ms at screening based on central reading.
14. Subject with a history of Long QT Syndrome at screening.
15. Subject has known pulmonary function tests with DLCO ≤ 50%, forced expiratory volume in the first second (FEV1) ≤ 60%, dyspnea at rest or any pleural neoplasm. (Transient use of supplemental oxygen is allowed.)
16. Subject has an active uncontrolled infection. If an infection is present, the patient must be receiving definitive therapy and have no signs of progressing infection. Progressing infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
17. Subject is known to have human immunodeficiency virus infection.
18. Subject has active hepatitis B or C or other active hepatic disorder.
    - Subjects with positive hepatitis B surface antigen (HBsAg) or detectable hepatitis B DNA are not eligible.
    - Subjects with negative HBsAg, positive hepatitis B core antibody and negative hepatitis B surface antibody will be eligible if hepatitis B DNA is undetectable.
    - Subjects with antibodies to hepatitis C virus will be eligible if hepatitis C RNA is undetectable.
19. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation, including any contraindications of azacitidine listed in the country package insert.
20. Subject has a known or suspected hypersensitivity to ASP2215, azacitidine or any components of the formulations used.

Waivers to the exclusion criteria will NOT be allowed.

3.4 Cytoreduction Guidelines

Subjects who present with leukocytosis are required to achieve a myeloblast count of $< 50 \times 10^9$/L prior to initiating study treatment to reduce the risk of differentiation syndrome. The following cytoreduction guidelines can be used to achieve this myeloblast count.

Table 4 Cytoreduction Guidelines

Cytoreduction options[a,b]	Dose	Frequency	Maximum days allowed before study treatment	Myeloblast count prior to study treatment
Hydroxyurea[c]	Up to 6 g oral	Daily in divided doses	NA	50 x10^9/L
Leukapheresis	NA[d]	NA[d]	NA[d]	50 x10^9/L

NA: Not Applicable.

[a] May be used concurrently with leukapheresis

[b] Cytoreduction may start prior to screening

[c] Hydroxyurea is also allowed after enrollment for an additional ≤ 14 days

[d] Institutional standard should be followed

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

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 5].

Table 5 Test Drug (ASP2215 Tablets 40 mg)

Test Drug	ASP2215 Tablets 40 mg
Code name	ASP2215
Active ingredient	Chemical name: $(C_{29}H_{44}N_8O_3)_2 \cdot C_4H_4O_4$
Composition and dosage form	One tablet contains 40 mg of ASP2215 in free form. ASP2215 Tablets are round light-yellow film-coated tablets.
Batch No.	Refer to drug product label
Storage	Bottled ASP2215 should be stored according to labeled storage instructions. Store in original container.

4.1.2 Comparative Drug(s)

The comparative drug is azacitidine [Table 6]. Refer to the approved package insert or summary of product characteristics for product information and storage condition supplied by the manufacturers.

Table 6 Comparative Drug (Azacitidine)

Comparative Drug	Azacitidine
Code name (specific to Japan)	AS3156378
Active ingredient	4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one
Composition and dosage form	Azacitidine for injection lyophilized powder in 100 mg single-use vials
Batch No.	Refer to drug product label.
Storage	Refer to approved package insert or summary of product characteristics supplied by manufacturer.

4.2 Packaging and Labeling

ASP2215 used in this study will be prepared, packaged and labeled under the responsibility of qualified staff at Astellas Pharma Global Development, Inc. (APGD)-Astellas United States Technologies (AUST) or Sponsor's designee in accordance with APGD-AUST or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (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.

ASP2215 bottle labels indicate food reference statement that "no food is allowed for at least 2 hours before and 1 hour after each dose". IB and study protocol clarify that food does not have an impact on ASP2215 dosing. ASP2215 bottle labels are being revised to remove food restriction instructions; however, some batches of ASP2215 bottle labels will still detail food restriction requirements.

In the situation when azacitidine is supplied by the sponsor, azacitidine used in this study will be packaged and labeled under the responsibility of APGD-AUST in accordance with APGD-AUST SOPs, GMP guidelines, ICH GCP guidelines and applicable local laws/regulations.

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.

Azacitidine supplied to Japan sites for this study will be packaged and labeled under the responsibility of API in accordance with API's designee SOP, GMP guidelines, ICH GCP guidelines.

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, head of study site (specific to Japan), or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator, or designee agrees not to supply study drug(s) to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator, head of study site (specific to Japan) 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 study 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, head of study site (specific to Japan) 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 chemotherapy drug (azacitidine) 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

Enrollment, 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 of the IRT system.

5 TREATMENTS AND EVALUATION

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

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 ASP2215 Dosing

ASP2215 is an oral tablet that subjects will take once daily for continuous 28-day cycles. Subjects will be instructed to take the daily ASP2215 dose with water as close to the same time each morning as possible. Dose reductions and escalations are permitted (see [Section 5.1.2]).

ASP2215 can be taken without regard to food. ASP2215 tablets cannot be crushed, chewed or compounded.

If a dose of ASP2215 is missed or not taken at the usual time:

- Administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose
- Return to the normal schedule the following day
- Do not administer 2 doses within 12 hours

If vomiting occurs after dosing, the subject should not receive another dose, but just wait until the next morning to dose.

ASP2215 will be self-administered at home when subjects are not scheduled for clinic visits. ASP2215 treatment should continue until the subject no longer receives clinical benefit from therapy in the opinion of the investigator, unacceptable toxicity occurs or the subject meets a treatment discontinuation criterion.

5.1.1.2 Azacitidine Dosing

Azacitidine at a dose of 75 mg/m^2 daily via subcutaneous injection or intravenous infusion will be administered for 7 days (days 1 through 7) of each 28-day treatment cycle [Dombret et al, 2015]. Day 1 of each cycle should be based off on the start of azacitidine treatment (for Arm AC and C). If there is an interruption in azacitidine dosing, day 1 of the appropriate cycle should begin when azacitidine treatment is re-started and the subsequent 28-day cycles

should be scheduled per protocol. On all visits indicated for azacitidine administration, the dosing should occur in clinic.

Azacitidine can be administered by subcutaneous injection or intravenous infusion. Refer to the pharmacy manual for administration instructions. Subjects participating in the dense PK subset on Arms AC and C should receive azacitidine via subcutaneous injection only for cycle 1. The route of administration of azacitidine outside of label instructions is not recommended and is a clinical decision of the investigator. Refer to the pharmacy manual for administration instructions. Azacitidine will be prepared according to the approved package insert or summary of product characteristics supplied by the manufacturers.

Azacitidine treatment should continue until the subject no longer receives clinical benefit from therapy in the opinion of the investigator, unacceptable toxicity occurs or the subject meets a treatment discontinuation criterion.

5.1.1.3 Combination (ASP2215 and azacitidine) Dosing

Dosing of ASP2215 and azacitidine in the combination arm is the same as described for each individual agent.

Azacitidine will be administered immediately following ASP2215 administration for cycle 1 day 4 and whenever possible for all other visits.

If the subject continues on ASP2215 while azacitidine is interrupted, safety labs should be drawn and an ECG performed every 4 weeks until the restart of azacitidine in an unscheduled visit.

If in the opinion of the investigator the subject no longer receives clinical benefit from or experiences unacceptable toxicity that is related to either ASP2215 or azacitidine, then the subject may discontinue either ASP2215 or azacitidine and continue to receive the other agent.

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

5.1.2.1 ASP2215 Dose Interruption or Reduction

Guidelines for ASP2215 dose interruption and reduction are provided in [Table 8]. The dose levels potentially used include the following [Table 7]:

Table 7 ASP2215 Dose Levels

DL	ASP2215 Dose
DL – 2	40 mg
DL – 1	80 mg[b]
DL 1	120 mg[a,b]
DL 2	200 mg[c]

DL: dose level
a. Starting dose for ASP2215 only arm
b. Potential starting doses for safety cohort and ASP2215 + azacitidine arm
c. For US only: DL 2 (200 mg dose of ASP2215) will not apply

The ASP2215 dose may be initially reduced by 1 dose level per day. The ASP2215 dose can be further reduced by a second dose level if the subject has already experienced clinical benefit. Note that dose reductions should occur in a step-wise manner. Only 2 dose level reductions are permitted. Dose reduction can occur during the treatment cycle based on the dose reduction guideline in [Table 8]. 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 8]. 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. If the ASP2215 dose has been reduced, it cannot be re-escalated. Any subjects that have been off treatment for more than 14 days other than for HSCT or a study drug related AE, may only resume treatment after discussion with the Medical Monitor.

Table 8 Guidelines for ASP2215 Dose Interruption or Reduction Event

ASP2215 Dosing Instructions	
Nonhematological Events	
Grade 3 toxicity at least possibly related to ASP2215	Dosing will be interrupted for up to 14 days. If the adverse event resolves to ≤ grade 1 within 14 days, the subject may resume dosing but at a reduced dose as long as they are not currently receiving the dose of 40 mg/day. If the AE does not resolve to ≤ grade 1 within 14 days, the subject will be discontinued from treatment and an EOT visit will be performed. Refer to Section 12.3 Liver Safety Monitoring and Assessment, if the subject is experiencing any AEs related to hepatic toxicity.
Grade 4 toxicity at least possibly related to ASP2215	Treatment will be discontinued.
Mean Triplicate QTcF > 500 ms	If the QTcF is > 500 ms at any time point, the ECG will be repeated (within 2 hours if identified on machine read or as soon as possible if identified from central reading). A cardiology consult will be obtained as medically indicated. 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 machine read, the central reading should be used for final treatment decisions. If QTcF resolves to ≤ 480 ms by central reading within 14 days, the subject may resume dosing but at a reduced dose as long as they are not currently receiving the dose of 40 mg/day. If QTcF does not resolve to ≤ 480 ms within 14 days, the subject will be discontinued from treatment and an EOT visit will be performed. Mean triplicate QTcF value will be used in this case.
Mean Triplicate QTcF cycle 1 day 8 increase > 30 ms	If the QTcF on cycle 1 day 8 has increased > 30 ms compared to the QTcF on cycle 1 day 1 with no other known etiology, then a confirmatory ECG will be performed on cycle 1 day 9. If the cycle 1 day 9 QTcF also shows an increase of > 30 ms compared to that of cycle 1 day 1, then the subject may resume dosing at the same dose or a dose reduction may be considered, as long as they are not currently receiving the dose of 40 mg/day. Mean triplicate QTcF value will be used in this case.
PRES	Discontinue ASP2215 treatment in patients who develop PRES.
Differentiation Syndrome	If differentiation syndrome is suspected, initiate dexamethasone 10 mg iv every 12 hours (or an equivalent dose of an alternative oral or iv corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt ASP2215 until signs and symptoms are no longer severe. Treatment with ASP2215 can be resumed at the same dose when signs and symptoms improve to Grade 2 or lower.
Table continued on next page	

ASP2215 Dosing Instructions	
Myelosuppression	
Myelosuppression in the presence of CR, CRp or CRi	Dose reduction may be considered, as long as the subject is not currently receiving the dose of 40 mg/day, without interruption of treatment if all of the following criteria are met: a) Subject has received a minimum of 2 cycles of ASP2215 b) Platelets $< 25 \times 10^9$/L and/or absolute neutrophil count $\leq 0.5 \times 10^9$/L c) Marrow blasts < 5% d) 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; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; ECG: electrocardiogram; EOT: end-of-treatment; IV: intravenous; PRES: posterior reversible encephalopathy syndrome; QTcF: Fridericia-corrected QT interval

5.1.2.2 ASP2215 Dose Increase

Dose escalation can occur during the treatment cycle based on bone marrow and hematology results. Subjects who do not achieve a CRc may dose escalate to 200 mg per day, except for sites in the US. No further dose escalation is allowed. Guidelines for ASP2215 dose escalation are provided in [Table 9]. Dose escalation is allowed for subjects in the safety cohort after cycle 1.

Dose re-escalation is not allowed following dose reduction unless there is a specific reason not related to ASP2215 for temporarily holding or reducing ASP2215.

Table 9 Guidelines for ASP2215 Dose Increase

ASP2215 Dose Increase Instructions	
Event	**Action**
No CRc (CR, CRp or CRi) after cycle 1	Subjects can increase by 1 dose level.[a]
No CRc (CR, CRp or CRi) after cycle 2 and subsequent cycles	Subjects currently on 120 mg dose can increase by 1 dose level.[a] Subjects on 200 mg dose level cannot increase dose.

[a] For US Only: The last dose level for subjects enrolled in US is Dose Level 1 (120 mg). Dose escalation to 200 mg is not allowed.

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

5.1.2.3 Azacitidine Dose Increase, Interruption, or Reduction

Administrative azacitidine interruptions are permitted for up to 2 days at a time due to local practice (i.e., weekend or other non-working days). A total of 7 doses of azacitidine will still be given, and the cycle length will be maintained at 28 days.

Subjects participating in the dense PK sampling subset cannot interrupt dosing during the first cycle.

Renal impairment:

Azacitidine can be administered to patients with renal impairment without initial dose adjustment [see Section 5.2]. If unexplained reductions in serum bicarbonate levels to < 20 mmol/L occur, the dose should be reduced by 50% on the next cycle. If unexplained

elevations in serum creatinine or blood urea nitrogen (BUN) to ≥ 2-fold above baseline values and above the ULN occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle.

Other toxicities:

Azacitidine dose can be interrupted or reduced as described in prescription information in each region or country.

The azacitidine dose can be increased to 100 mg/m^2, per country label instructions, if no beneficial effect is seen after 2 treatment cycles. Please refer to package insert or label instructions for complete dose increase instructions.

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 through the end-of-treatment visit must be recorded in the electronic case report form (eCRF). Concomitant medications should be collected for reported or ongoing AE/SAEs through 30 days after the last dose of study treatment (ASP2215 and/or azacitidine) for subjects who have discontinued treatment. For subjects who undergo HSCT, concomitant medications should be collected for reported or ongoing AE/SAEs through start of conditioning treatment or 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), whichever comes first. All patients who resume ASP2215 after HSCT should receive standard post-HSCT therapy, e.g., GVHD prophylaxis, infection prophylaxis.

The following are **prohibited** during the course of the study:

- Treatment with strong inducers of CYP3A/P-gp
- Therapies to treat AML including, but not limited to:

  a) Chemotherapy

  b) Surgery

  c) Immunotherapy, cellular therapy or vaccines

  Exceptions: Hydroxyurea (up to 6 g daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L), intrathecal chemotherapy, prophylactic cranial irradiation, and leukapheresis are allowed.
- Any other investigational agent for AML.

Caution is advised when considering the concomitant use of the following medications:

- Treatment with medications known to prolong QT or QTcF intervals. For concomitant drugs that have the potential to prolong QT or QTcF intervals, a cardiology consult should be obtained as medically indicated.
- Strong inhibitors of P-gp and concomitant drugs that target serotonin 5HT$_{2B}$ receptor 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 strong CYP3A inhibitors or strong P-gp inhibitors are used concomitantly, subjects should be closely monitored for AEs.
- Precaution is advised in the use of ASP2215 with concomitant drugs that are substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, rosuvastatin), and OCT1 (e.g., metformin) since these transporters have been shown to be inhibited by ASP2215 in *in vitro* studies.

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 12.2, List of Excluded and Cautionary Concomitant Medications]. Refer to the country-specific azacitidine package insert for additional details on excluded or cautionary use of medications.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. The 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 and/or azacitidine 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/or azacitidine administered to each subject will be recorded. Reasons for dose delay, reduction or omission will also be recorded when applicable. This information, plus tablet accountability for ASP2215 will be used to assess compliance with ASP2215 treatment.

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

5.1.5 Resumption of Treatment After Hematopoietic Stem Cell Transplantation

For Arm C Subjects:

Subjects who have a donor identified and achieve a response allowing them to undergo HSCT per each institution's assessment may discontinue treatment at any time. An EOT visit should be performed prior to starting the conditioning regimen for HSCT. In addition, subjects should follow the Posttreatment Schedule of Assessments (Table 2) for long term follow-up.

For Safety Cohort, Arm A* and Arm AC Subjects:

Pre-HSCT preparation:

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 and azacitidine should be stopped for at least 1 week prior to start of the preparative regimen and a pre-HSCT visit should be performed prior to starting the conditioning regimen for HSCT.

Resumption of Treatment After HSCT:

Azacitidine will not be resumed after HSCT (Safety Cohort and Arm AC Subjects).

ASP2215 should be resumed at the same dose administered prior to HSCT if the following conditions are met:

- Subject is between 30 to 90 days post HSCT
- Subject has had successful engraftment as demonstrated by absolute neutrophil count
- (ANC) $\geq 500/mm^3$ and platelets $\geq 20000/mm^3$ without transfusions
- Subject does not have $\geq$ grade 2 acute graft-versus-host disease (GVHD)
- Subject is in CRc (CR, complete remission with incomplete hematologic recovery [CRi], complete remission with incomplete platelet recovery [CRp])

Subjects resuming ASP2215 treatment will follow the procedures listed under subsequent visits (day 1) in the Schedule of Assessments (Table 1).

Subjects discontinuing the study during or post HSCT should follow the Posttreatment Schedule of Assessments (Table 2) for long term follow-up.

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 conditions on the Medical History eCRF. Details that will be collected include the onset date, recovery date and Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade [National Cancer Institute, 2010], if applicable, for ongoing conditions.

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

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

5.2.3.1 Disease History

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, lumbar puncture results if performed (red blood cells [RBCs], white blood cells [WBCs] with differential, cytospin results) and related genetic syndromes. Dates for diagnostic procedures will be collected.

5.2.3.2 FMS-like Tyrosine Kinase Mutation Status

FLT3 mutations status will be analyzed by a Sponsor-designated central laboratory using bone marrow aspirate/biopsy. Subjects will be screened from the central laboratory result.

At screening, 2 bone marrow aspirate samples are required: one will be sent to Invivoscribe (central FLT3 mutation testing laboratory) and the other to Hematogenix (central disease assessment laboratory). A bone marrow aspirate is preferred for FLT3 assessment.

However, if a bone marrow aspirate sample is unavailable at screening:

- a whole blood sample can be sent to Invivoscribe for FLT3 testing, provided there are measurable leukemic cells present and
- the bone marrow biopsy from initial diagnosis and a whole blood sample should be sent to Hematogenix for disease assessment.

Aspirate from initial diagnosis can be sent to Invivoscribe if it was collected in sodium heparin, stored at 2 to 8°C and can be sent within 5 days of collection and testing can occur within 7 days of sample collection.

Subjects screened in the safety cohort should send a FLT3 sample to the central laboratory; however, the results are not required to enroll the subject.

Subjects in the randomization cohort require positive central FLT3 mutation results in order to be randomized. Bone marrow/blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Refer to the Laboratory Manual for more detailed information.

5.2.4 Performance Status

The ECOG Scale [Oken et al, 1982] will be used to assess performance status [Table 10] and will be obtained and recorded according to the Schedules of Assessments [Table 1 and Table 2].

Table 10 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 Bone Marrow Aspirate and Biopsy

Bone marrow samples will be analyzed by a Sponsor-designated central laboratory and 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 on day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow will be repeated 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 end-of-treatment visit and as clinically indicated. If bone marrow aspirate is unavailable then an EDTA tube of whole blood along with bone marrow core biopsy (block or slides) should be collected instead and sent to the central lab. Additional sampling may be needed for assessment at the local laboratory for diagnosis and disease assessment. Local bone marrow assessment results will also be collected on the eCRF.

5.3.2 Response Definitions and Assessment

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

5.3.2.1 Complete Remission

For subjects to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an absolute neutrophil count $\geq 1 \times 10^9$/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 platelet transfusion). There should be no evidence of extramedullary leukemia.

5.3.2.2 Complete Remission Partial Hematologic Recovery

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

5.3.2.3 Complete Remission with Incomplete Platelet Recovery

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

5.3.2.4 Complete Remission with Incomplete Hematological Recovery

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

5.3.2.5 Partial Remission

For subjects to be classified as being in PR, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25%.

5.3.2.6 Relapse

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

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

5.3.2.7 Treatment Failure (defined by lack of CRc)

Treatment failure is defined as lack of CRc (CR, CRp or CRi), and is determined at the end of treatment.

5.3.2.8 Best Response

Best response is defined as the best measured response (in the order of CR, CRp, CRi or treatment failure defined by lack of CRc) from all postbaseline visits.

5.3.2.9 Complete Remission Rate

Complete Remission Rate is defined as the rate of all complete CRs.

5.3.2.10 Composite Complete Remission Rate

CRc rate is defined as the remission rate of all complete and incomplete CRs (i.e., CR+ CRp + CRi).

5.3.2.11 Complete Remission with Partial Hematologic Recovery Rate

CRh rate 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.

5.3.2.12 Complete Remission and Complete Remission with Partial Hematologic Recovery Rate

CR/CRh rate 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.

5.3.3 Survival Time, Duration of Response and Other Efficacy Endpoints

5.3.3.1 Survival Status and Subsequent Antileukemic Treatments and Their Outcomes

Information on survival status, subsequent antileukemic treatments (including HSCT) and outcomes will be collected for all subjects during long-term follow-up.

The first survival status will occur at the 30-day follow-up. 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. Data may be supplemented by site records when available at the time of the contact (e.g., treatment records, outcomes). Follow-up for subjects no longer receiving treatment will continue until the implementation of version 13.0, at which time they will discontinue from the study as further survival data is no longer needed. Long-term follow-up is estimated to be up to 3 years of follow-up for some subjects. Additional contacts may be made to support key analyses (e.g., interim/final analysis or analyses by the IDMC).

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 related to study regimen (ASP2215 and/or azacitidine), then the associated AE with outcome of death will also be reported on the AE eCRF and SAE Worksheet. 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 the eCRF.

5.3.3.2 Overall Survival (OS)

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

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

5.3.3.3 Event-free Survival (EFS)

EFS is defined as the time from the date of randomization until the date of documented relapse from CR, treatment failure or death from any cause, whichever occurs first.

If a subject experiences relapse from CR 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.

A subject is defined as having an EFS event related to treatment failure and the event date is the date of randomization, if the subject is randomized and receives treatment, and

- fails to achieve CR after completing 6 cycles of study treatment or
- discontinues all study treatment permanently without achieving CR prior to completing 6 cycles of study treatment or
- has no post-baseline disease assessment.

5.3.3.4 Leukemia-free Survival (LFS)

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.

5.3.3.5 Duration of Remission

Duration of remission includes duration of CRc, CR, CR/CRh, CRh, CRi, CRp and response (CRc + PR).

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

The duration of CR, CR/CRh, CRh, CRp or CRi is defined similarly as duration of CRc.

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

5.3.3.6 Transplantation Rate

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

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), radial pulse rate (beats/minute) and temperature will be obtained and recorded at the times specified in the Schedules of Assessments [Table 1 and Table 2]. All vital sign measurements 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 eCRF. 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 (including SAE) collection will begin from time of informed consent and continue until 30 days after the last dose of study treatment (ASP2215 and/or azacitidine) or the subject is determined to be a screen failure. During the long-term follow-up period, only SAEs related to ASP2215 alone, azacitidine alone or the ASP2215 + azacitidine combination will be collected.

For subjects who plan to proceed to HSCT, AE (included SAE) collection will continue until the start of the HSCT conditioning regimen or until 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), whichever comes first. However, the following AE/SAEs will continue to be collected until 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), 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
- Adverse events leading to death

For subjects who resume ASP2215 treatment after HSCT, AE (including all SAE) collection will resume upon the resumption of ASP2215 treatment and continue until 30 days after the last dose of study drug.

AEs will be collected at any time. All AEs and SAEs will be reported on the SAE worksheet to the Sponsor. See [Section 5.5, Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

See [Section 12.7 Continuation of Study Drug Treatment with ASP2215 and/or ASP2215 Plus Azacitidine] for information regarding AE and SAE collection while subjects are receiving study drug treatment with ASP2215 and/or ASP2215 plus azacitidine until they meet discontinuation criteria.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.3, Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, and 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, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

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

5.4.3 Laboratory Assessments

[Appendix 12.4] contains the laboratory tests that will be performed centrally during the conduct of the study. Refer to the Schedules of Assessments [Table 1 and Table 2] for study visit collection dates. Local laboratory tests can be used at screening for eligibility for serum chemistry, hematology, urinalysis and coagulation only. 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

For the screening visit, 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 examinations are to be performed only if clinically indicated. Physical examinations will be conducted as per the institutional practice at the subsequent visits outlined in the Schedules of Assessments [Table 1 and Table 2]. Weight is required 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 eCRF. 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

A 12-lead ECG will be performed during the screening period, predose of cycle 1 day 1, cycle 1 day 8, cycle 1 day 15 and day 1 of each subsequent cycle and at the end-of-treatment visit. Predose assessments should be taken within 1 hour before administration of ASP2215 for subjects in Arm A and AC and within 1 hour before administration of azacitidine for subjects in Arm C. 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 of the triplicate ECG from central read should be used for all final treatment decisions and AE reporting. Triplicate 12-lead ECGs should be obtained after the subject has rested quietly and is awake in a fully supine position (or semirecumbent if supine is not tolerated) for 10 minutes before the first ECG from a triplicate and at least 5 minutes apart per time point.

For cycle 1 day 8 ECG, If the mean QTcF from cycle 1 day 1 to cycle 1 day 8 has increased > 30 ms with no other known etiology, a confirmatory ECG should be performed on cycle 1 day 9. 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. If the cycle 1 day 8 and 9 ECGs confirm the > 30 ms increase in QTcF from baseline (cycle 1 day 1), then the investigator should assess if ASP2215 dose modification should occur as per the dose interruption or reduction guideline in [Section 5.1.2.1].

If the mean triplicate QTcF is > 500 ms at any time point, the ECG will be repeated (within 2 hours if identified on machine read or as soon as possible if identified from central read). Cardiology consult will be obtained as medically indicated. If QTcF > 500 ms is confirmed, then the investigator will interrupt and reduce ASP2215 per the interruption or reduction guidelines in [Section 5.1.2.1].

At a subset of sites, approximately 12 non-Japanese and 12 Japanese subjects will have additional ECGs as part of the dense PK sampling subset. On cycle 1 day 4 and day 15, ECGs will be performed at predose (within 1 hour before ASP2215 (Arm A and AC) and azacitidine (Arm C) administration) and within 30 minutes prior to 4 hours of postdose in triplicate and transmitted electronically for central reading.

ECGs are to be performed prior to obtaining the time-matched PK sample, therefore, the ECGs must be started at least 10 to 15 minutes before the PK draw.

For subjects participating in the dense PK sampling subset only, additional ECGs will be performed in triplicate and transmitted electronically for central reading on:

- Cycle 1 day 4 for Arm A and AC: Predose (within 1 hour before ASP2215 administration) and within 30 minutes prior to 4 hours of post dose
- Cycle 1 day 4 for Arm C: Predose (within 1 hour before azacitidine administration) and within 30 minutes prior to 4 hours of post dose
- Cycle 1 day 15 for Arm A and AC: within 30 minutes prior to 4 hours of post dose.

Table 3 provides the sampling time points for ECGs, PK and dense PK samples for subjects in each treatment arm of randomization cohort.

Whenever a study procedure coincides with the scheduled time point 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 is not mandatory and can be changed if required in order to accommodate PK time points.

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 a chest x-ray results performed within 2 weeks prior to start of screening is available to assess subject eligibility.

5.4.7 Multigated Acquisition Scan or Echocardiogram

A multigated acquisition scan (MUGA) or echocardiogram (ECHO) (as per standard of care) is to be performed at screening for subjects with a history of New York Heart Association Class 3 heart failure. MUGA scans are not applicable to sites in Germany.

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 SAE worksheet accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical examination) 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.

A summary of key laboratory test results by CTCAE grade will be part of the analysis plan.

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 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, 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 on the Special Situations 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 "AEs 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 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 SAE worksheet:

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 and will continue until 30 days after last dose of study treatment (ASP2215 and/or azacitidine). During the long-term follow-up period, all AEs and SAEs will be reported on the SAE worksheet to the Sponsor and the data will be reported in the safety database.

For subjects who plan to proceed to HSCT, AE (included SAE) collection will continue until the start of the HSCT conditioning regimen or until 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), whichever comes first. However, the following AE/SAEs will continue to be collected until 30 days after the last dose of study treatment (ASP2215 and/or azacitidine), 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 VOD of the liver, cardiac failure, grade 3 or higher QT prolongation, rhabdomyolysis, drug-induced liver injury, or PRES
- Adverse events leading to death

For subjects who resume ASP2215 treatment after HSCT, AE (including all SAE) collection will resume upon the resumption of ASP2215 treatment and continue until 30 days after the last dose of study drug.

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

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

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

Astellas Pharma Global Development, Inc.
Global 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:

For Japan, in the case of an SAE, the investigator or subinvestigator 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.

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE Worksheet to:

PAREXEL International
Global Monitoring Operations
Fax: 03-6888-1486

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 (exception Japan sites).

Full details of the SAE should be recorded on the medical records and on the eCRF.

The following minimum information is required:

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

The Sponsor or Sponsor's designee will submit expedited safety reports (Investigational New Drug [IND] Safety Reports, CIOMS-I) to the regulatory agencies (i.e., FDA, EMA) as necessary and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/ local IEC within timelines set by regional regulations (i.e., EU, electronic Common Technical Document, FDA). 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 contract research organization (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.

The investigators 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 12.3, 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 12.5, Common Serious Adverse Events]. The list does NOT change 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 SAEs” as specified in [Appendix 12.5, 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 180 days from the discontinuation of dosing, the investigator should report the information to the Sponsor as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

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

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

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

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

5.5.9 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 azacitidine, please refer to the approved Package Insert, Summary of Product Characteristics or local product information supplied by the manufacturer or by Sponsor.

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 Urgent Safety Measures and Deviations from the Protocol and Other Actions Taken to Avoid Life-threatening Risks to Subjects

An Urgent Safety Measure (USM) is an intervention, which is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant Competent Authorities, IRB/IEC, where applicable, in order to protect study participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate an USM. The cause of an USM can be safety, product or procedure related.

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.

1. 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.
2. 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.

5.5.12 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the Astellas Study Physician and/or Astellas team member (Japan only) (within 24 hrs of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be an USM the sponsor will take appropriate action to ensure the safety and welfare of the patients. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the trial, or stopping the study in its entirety. The sponsor or sponsor's designee will notify CA and cEC within the timelines required per current local regulations, and will inform the investigators as required.

When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

PK samples will be collected at predose for all subjects randomized into Arm A* and Arm AC to evaluate ASP2215 plasma concentrations as outlined in the Schedule of Assessments [Table 1] and sampling time points for PK and Dense PK [Table 3].

At sites participating in the dense PK subset, approximately 12 non-Japanese and 12 Japanese subjects on cycle 1 day 4, for all treatment arms, will have dense PK sampling for plasma concentrations of azacitidine and ASP2215 as outlined in the sampling time points for Dense PK [Table 11].

At least 6 Japanese and 6 non-Japanese subjects from each treatment arm will be included.

Table 11 Minimum Number of Subjects Required for Dense Pharmacokinetic Sub-group

	ARM AC	ARM C	TOTAL
Japanese Subjects	6	6	12
Non-Japanese Subjects	6	6	12

If sufficient dense PK sampling cannot be performed, the subject may be replaced.

Subjects in the dense PK sampling subset on Arms A* and AC only will also have samples collected on cycle 1 day 15 at 4 hours post dose for plasma concentrations of ASP2215.

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

Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a Sponsor-designated analytical laboratory. Please refer to the Laboratory 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 sores items will be assessed during the study period to report the subject's experience of symptoms/treatment and quality of life.

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

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 subjects with fatigue due to cancer and cancer treatment. The BFI inventory 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 patient reported outcome (PRO) device. The BFI will be administered at cycle 1 at day 1, cycle 1 at day 8 (± 1 day), day 15, cycle 2 at day 1 (± 2 days), day 15 (± 1 day) and all subsequent cycles at day 1 (± 2 days) as well as the end-of-treatment visit. If possible, PRO measures should be performed prior to any other assessments and administration of study treatment 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 to 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. The EQ-5D-5L will be administered at site visits directly to the subjects via an electronic PRO device during treatment through the end-of-treatment visit. It will be administered at cycle 1 at day 1, day 1 (± 2 days) of all subsequent cycles, end-of-treatment visit, the 30-day follow-up visit and during long-term follow-up. If possible, PRO measures should be performed prior to any other assessments and administration of study treatment on that visit day. During long-term follow-up or if a telephone visit is conducted for the 30-day 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 at day 1, at day 1 (± 2 days) of all subsequent cycles and the end-of-treatment visit. If possible, PRO measures should be performed prior to any other assessments and administration of study treatment 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 subjects. 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 at day 1, at day 1 (± 2 days) of all subsequent cycles and the end-of-treatment visit. If possible, PRO measures should be performed prior to any other assessments and administration of study treatment on that visit day.

5.7.1.5 Dizziness and Mouth Sores Items

Two additional items evaluating commonly reported impacts of AML on subjects, dizziness and mouth sores, will be administered to subjects. The dizziness and mouth sores items will be administered at site visits directly to the subjects via an electronic PRO device. These 2 items will be administered at cycle 1 at day 1, at day 1 (± 2 days) of all subsequent cycles and the end-of-treatment visit. If possible, PRO measures should be performed **prior to** any other assessments and administration of study treatment on that visit day.

5.7.2 Resource Utilization

Resource utilization in this study population will include analysis of data on hospitalization, blood transfusion, antibiotic intravenous infusions, medication for AEs and opioid usage. Details on hospitalizations and other relevant resource utilization will be collected at each study visit as indicated in the Schedules of Assessments [Table 1 and Table 2].

For each hospitalization, reason, admission and discharge dates, ward type (normal vs intensive care unit) and type and reason for hospitalization will be recorded in the eCRF.

The following other resource utilization will be recorded in the eCRF: number of blood transfusions, number of units of each transfusion, number of antibiotic intravenous infusions, type of antibiotic, start/end dates of antibiotic treatment, type of medication for AEs, mode of administration of medication for AEs (oral, intravenous, etc.), start/end dates of medication for AEs, type of opioid medication, mode of administration of opioids, (oral, intravenous, etc.), start/end dates of opioids.

5.7.3 Exploratory Biomarker Analyses

5.7.3.1 FLT3 Mutation Status

FLT3 mutation status will be assessed from bone marrow samples taken at the screening visit and end-of-treatment and may be assessed from bone marrow or blood samples at other time points during the study. Additional protein or genetic biomarkers related to AML and ASP2215 activity may be analyzed. If a bone marrow sample is unavailable, the whole blood samples taken at the visit will be used.

The FLT3 mutation assay is an approved 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 with ASP2215.

Bone marrow/blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a Sponsor-designated

analytical laboratory. All biomarker samples collected will be stored for a period up to 15 years following study database hard lock. Please refer to the Laboratory Manual for more detailed information on this topic.

5.7.3.2 Minimal Residual Disease Assessment

FLT3 MRD may be measured from bone marrow samples taken at the screening visit, end of treatment/disease progression and from bone marrow samples taken at other time points during the study. FLT3 mutation will be measured in relation to total FLT3. Changes in FLT3 mutation to total FLT3 will be compared with baseline/screening samples.

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

Pharmacogenomic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, PK and toxicity/safety issues. After randomization, a whole blood and buccal swab sample 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-0201)
- Subject number and
- Purpose and biological matrix (i.e., “biobanking,” “buccal sample”)

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate Laboratory Manual

See [Appendix 12.6, Retrospective PGx Substudy] 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, if results are needed before central laboratory results are available or for disease assessment, then additional blood may be drawn for monitoring.

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

The maximum amount of blood collected for study specific assessments during the screening and cycle 1 period is approximately 105 mL.

The maximum amount of blood collected for study specific assessments in cycle 2 is approximately 27 mL.

The maximum amount of blood collected for study specific assessments in cycle 3 and beyond is approximately 21 mL per cycle.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled or randomized 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.

Based on the planned interim analysis in Dec 2020, an IDMC recommended terminating the study based on protocol-specified boundaries for futility, concluding results are unlikely to show a statistically significant increase in overall survival, Astellas made decision to stop enrollment for the study.

Subjects can continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine upon reconsent until they meet discontinuation criteria. Subjects will be managed per the local institution’s standard of care for safety and efficacy assessments while on study drug treatment. No data will be collected in the eCRFs after subjects reconsent under this protocol Version 13.0, as the clinical database will be locked. Only AEs and SAEs (as defined in [Section 5.5.2 Definition of Serious Adverse Events]) will be collected and reported to Astellas Pharma Global Development Product Safety & Pharmacovigilance (Japan will continue reporting to PAREXEL International). AE and SAE data will be reported in the safety database. Once subjects receiving treatment meet the study discontinuation criteria, subjects will be discontinued from the study. AE and SAE collection will continue until 30 days after last dose of study treatment (ASP2215 and/or azacitidine). IRT notification is required when subjects discontinue from study drug treatment. See [Section 12.7 Continuation of Study Drug Treatment with ASP2215 and/or ASP2215 Plus Azacitidine].

Subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until the implementation of protocol version 13.0, at which time they will discontinue from the study as further survival data is no longer needed.

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 (including HSCT for Arm C) other than the assigned treatment, with the exception of hydroxyurea up to 6 g daily for up to 2 weeks, intrathecal chemotherapy, prophylactic cranial irradiation and leukapheresis.
- Investigator/subinvestigator 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.
- Female subject becomes pregnant.
- Death
- Subject is receiving ASP2215, azacitidine, or the combination of ASP2215+ azacitidine and has progressive disease, recurrence under treatment, or no response, and in the opinion of the investigator the subject is no longer deriving clinical benefit.

Discontinuation Criteria from Posttreatment Follow-up for Individual Subjects:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death
- More than 3 years has passed from the subject's 30 day follow up visit

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor (*for 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-US. A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the clinical study report.

Prior to database lock, a Final Review of Data and Tables, Listings and Figures 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.

Separate summary will be provided for safety cohort by dose level evaluated.

7.1 Sample Size

This is an open-label, randomized study. One interim analysis and one final analysis are planned. This is a group sequential design based on OS using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha/beta spending method (East®). The interim analysis will occur when approximately 50% (i.e., death events = 70) of the planned total number of deaths (i.e., death events = 140) by any cause have occurred. The IDMC will evaluate the test of OS and inform the sponsor the result if Arm AC has favorable outcome (i.e., P value < 0.003) or unfavorable outcome (i.e., P value ≥ 0.724, non-binding futility boundary) compared to Arm C with respect to OS, the study may be stopped due to efficacy or futility, respectively. Otherwise, the study will continue without impact and the final analysis will be performed after the planned 140 death events have been observed. Additionally, OS will be tested at 2-sided 0.049 significant level for efficacy.

The planned sample size of approximately 250 subjects (note: enrollment has stopped with a total of 183 subjects) will be randomized in a 2:1 ratio to receive ASP2215 plus azacitidine (AC) or azacitidine (C). The study will provide at least 80% power to detect a difference in OS between AC and C, assuming 16.7 months median survival time from AC and 10 months median survival time from C (hazard ratio = 0.6) at the overall 2-sided 0.05 significance level.

Based on the planned sample size and final OS analysis timing, 176 EFS events are expected, which will provide above 80% power to detect a hazard ratio of 0.6 in EFS (11.2 months median EFS for Arm AC and 6.7 months for Arm C). The EFS will be evaluated at the time of OS interim analysis, only if the OS result is positive at the interim analysis. By the time of OS interim analysis with 70 events, 88 EFS events are expected (the actual number of events may vary). An O'Brien-Fleming stopping boundary based on Lan-DeMets alpha spending

method will be used for EFS. Based on a projected number of events of 88 at the interim, the efficacy stopping boundary is 2-sided nominal alpha of 0.003 for interim analysis and 0.049 for the final analysis. The actual rejection boundary for EFS may vary according to the actual number of EFS events that occur at the interim analysis.

The sample size for the safety cohort is not based on a statistical power calculation. The planned number of subjects up to 12 would provide adequate information for the objectives of the safety cohort.

7.2 Analysis Set

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

7.2.1 Full Analysis Set

The full analysis set (FAS) is defined as the intention to treat set, which will consist of all subjects who are randomized and will be used for efficacy analyses. Subjects will be analyzed based on the randomized treatment.

7.2.2 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 analyses for the primary and key secondary endpoints will be performed on the PPS. Select demographic and baseline characteristics will also be summarized for the PPS.

7.2.3 Safety Analysis Set

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all randomized subjects who took at least 1 dose of study drug (ASP2215 or azacitidine) and will be used for safety analyses. The subjects will be analyzed based on the actual treatment received.

7.2.4 Safety Cohort Analysis Set

The safety cohort analysis set (SAFSC) consists of all subjects who enrolled in safety cohort and took at least 1 dose of study drug (ASP2215 or azacitidine). The SAFSC will be used for safety analyses of safety cohort subjects. The subjects will be analyzed based on the treatment regimen initially received.

7.2.5 Pharmacokinetic Analysis Set

The PK 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 in the Classification Specifications and determined at 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 for the SAF. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints and frequency and percentage for categorical endpoints.

7.3.2 Medical History

A detailed medical history for each subject will be obtained during screening period and will be summarized by treatment group for the SAF.

7.3.3 Disease History

Each subject's complete cancer history will be listed. The number and percentage of subjects will be used to summarize the AML subtype and 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 for various disposition parameters including analysis sets, reason for treatment discontinuation, reason for study discontinuation, lost to follow-up, and protocol deviation.

7.3.6 Treatment Compliance

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

7.3.7 Extent of Exposure

Exposure to treatment, measured by the duration of treatment in number of days will be summarized by treatment group on SAF. Duration of exposure to a study drug is defined as: (the last date that subject took study drug – the first dose date + 1 – number of days without drug administration in between). The total dose administered, number and proportion of subjects with dose reduction, dose escalation and dose interruption will be tabulated.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

The primary efficacy endpoint of OS for Arm AC and Arm C will be analyzed on the FAS using the stratified log-rank test with strata of age and risk groups and FLT3 mutation status.

The variables used as stratification factors in the model are described below:

- Age Group
  - Age ≥ 75 years
  - Age < 75 years
- Risk Group
  - Favorable or intermediate cytogenetic risk
  - Unfavorable cytogenetic risk or secondary AML (regardless of cytogenetic risk)
- FLT3 Mutation Status
  - FLT3-TKD
  - FLT3-ITD low allelic ratio (< 0.5, LAR)
  - FLT3-ITD high allelic ratio (≥ 0.5, HAR)

Patients with FLT3-ITD mutations will be classified based on low allelic ratio (< 0.5, LAR) or high allelic ratio (≥ 0.5, HAR). Allelic ratio will be determined by the LeukoStrat CDx FLT3 Mutation Assay and calculated as the ratio of the peak area of the FLT3-ITD mutant signal, if present, divided by the peak area of the FLT3 wild type signal, if present.

Cytogenetic risk groups used for stratification are defined by the presence of cytogenetic abnormalities and based on common clinical criteria [National Comprehensive Cancer Network, 2015] and presented in [Table 12].

Table 12 Cytogenetic Risk

Cytogenetic Risk Category	Definitions
Favorable	• Core binding factor: inv(16) or t(16;16) or t(8;21). Other cytogenetic abnormalities in addition to these do not alter better risk status.

Intermediate	• Normal cytogenetics
	  • +8 alone
	  • t(9;11)
	  • Other non-defined cytogenetic abnormality

Unfavorable	• Complex (≥ 3 clonal chromosomal abnormalities) • Monosomal karyotype • -5, 5q-, -7, 7q- • 11q23 – non t(9;11) • inv(3), t(3;3) • t(6;9)

t(15;17) and t(9;22) are not included in the table as they are not eligible for this trial.

Using the same notation of AC and C, as in [Section 7.1], the hypothesis testing on the primary endpoint will be performed at the overall 2-sided 0.05 significance level to test the null hypothesis that OS of Arm AC is equal to that of Arm C versus the alternative hypothesis that OS of Arm AC is different from that of Arm C. The interim analysis will occur when approximately 50% (i.e., death events = 70) of the planned total number of deaths (i.e., death events = 140) by any cause have occurred. If Arm AC has favorable outcome (i.e., P value < 0.003) or unfavorable outcome (i.e., P value ≥ 0.724, non-binding futility boundary) compared to Arm C with respect to OS, the study may be stopped due to efficacy or futility, respectively. Otherwise, the study will continue without impact. The final analysis will be performed after the planned 140 death events have been observed. OS will be tested at 2-sided 0.049 significant level for efficacy.

- The sensitivity analyses for the primary efficacy endpoint will be performed as described below:

- Stratified Cox proportional hazard model on the FAS
- Stratified log-rank test/Cox proportional hazard model on the FAS with subjects who are censored at the time of HSCT
- Stratified log-rank test/Cox proportional hazard model with strata of age group on the FAS
- Unstratified log-rank test/Cox proportional hazard model on the FAS
- Stratified log-rank test/Cox proportional hazard model with strata of age and risk group and FLT3 mutation status on the PPS, which includes all subjects in FAS and do not have any major protocol deviations (PDs)

KM survival plots will be used to describe the OS in each treatment group. Median OS and 95% Confidence Interval (CI), survival rates at 6, 12 and 24 months and 95% CI will be estimated from KM plots. Median follow-up time and 95% CI will be obtained from reverse KM method.

The proportional hazards assumption will be evaluated graphically using the plots of the LOG(–LOG) survival function versus time and scaled Schoenfeld residuals versus time, and by testing the interaction term between the treatment arm and log(time) in the Cox proportional hazard model. If the hazards appear to be non-proportional, piecewise Cox proportional hazard models will be used to explore the changes in hazard ratio over time.

No hypothesis testing of OS will be done for Arm A.* Descriptive summary statistics will be done for the OS data of Arm A.*

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Key Secondary Endpoint

The key secondary efficacy endpoint of EFS for Arm AC and Arm C will be analyzed on the FAS using the stratified log-rank test with strata of age and risk group and FLT3 mutation status. The null hypothesis for the key secondary endpoint is EFS of Arm AC is not different from that of Arm C. To control for overall type I error at the 2-sided 0.05 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 interim analysis or final analysis. The rejection boundary of EFS will be based on the actual number of events at the interim and final analyses and the group sequential testing method as described in [Section 7.8].

The sensitivity analyses for the key secondary efficacy endpoint will be performed as described below:

- With strata of age and risk groups and FLT3 mutation status
  - Stratified Cox proportional hazard model on the FAS
  - Stratified log-rank test\Cox proportional hazard model on the FAS with subjects who are censored at the time of HSCT
  - Stratified log-rank test\Cox proportional hazard model on the PPS
  - Stratified interval-censored survival analysis [Wellner and Zhan, 1997] on the FAS to evaluate the impact of different assessment schedules for response and non-response subjects
- Other sensitivity analyses
  - Stratified log-rank test\Cox proportional hazard model with strata of age group on the FAS
  - Unstratified log-rank test\Cox proportional hazard model on the FAS
- Sensitivity analyses on different timing and censoring for EFS
  - Defining EFS as the time from randomization to relapse from CR (for subjects who achieved CR), or death from any cause, whichever comes first
  - Setting time to treatment failure as the date of permanent discontinuation of all study treatment or the end of 6 cycles of therapy, whichever is earlier

No hypothesis testing of EFS will be done for Arm A.[*] Descriptive summary statistics will be done for the EFS data of Arm A.[*]

7.4.2.2 Other Secondary Endpoints

The statistical analyses on other secondary efficacy endpoints for Arm AC and Arm C include:

- Stratified log-rank test\Cox proportional hazard model on duration of remission and LFS

[*] Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

- Cochran-Mantel-Haenszel (CMH) method on the CR rate, CRc rate, CR/CRh rate, CRh rate, transfusion conversation rate and transfusion maintenance rate
- Analysis of variance (ANOVA) model to analyze the change in the BFI global fatigue score (average of all 9 items) from baseline to post-baseline visits

Only descriptive summary statistics will be done for Arm A.*

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 and D835/I836 TKD mutations, will be analyzed.

ANOVA model will be used to analyze the change from baseline of MRD for post-baseline visits. CMH method will be used for the cumulative proportion of subjects with undetectable MRD by visit.

CMH method will be used for transplantation rate and resource utilization status (hospitalization, blood transfusion, antibiotic intravenous infusions, medication for AEs and opioid medication).

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

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

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

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

Due to limited number of subjects in Arm A,* only descriptive summary statistics will be done for Arm A.*

7.4.4 Subgroup Analysis

Subgroup analysis for Arm AC and Arm C will be performed on primary and key secondary efficacy endpoint for age group (≥ 75 and < 75 years), sex, baseline ECOG performance status scores, race, cytogenetic risk, FLT3 mutation status and region (North America, South America, Europe and Asia/Pacific).

* Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (ASP2215 monotherapy), AC or C. Randomization to Arm A was removed in protocol version 7.0. Subjects previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.

7.5 Analysis of Safety

The safety evaluation will be based mainly on AEs, clinical laboratory results, vital sign measurements, ECGs, physical examination findings and ECOG performance scores. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment received and the analyses will be performed on the SAF.

7.5.1 Adverse Events

All AEs recorded on treatment including within 30 days from the last study treatment will be summarized. AEs will be categorized by SOC and PT using the MedDRA dictionary 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.

SAE information may be added to updated patient narratives for subjects who continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine upon reconsent until they meet discontinuation criteria.

7.5.2 Laboratory Assessments

Clinical laboratory evaluations (including serum chemistry, hematology, coagulation and urinalysis) 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 laboratory 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 point.

7.5.4 Physical Examination

Physical examination findings will be listed by treatment group. All clinically significant abnormal findings will be recorded as medical history or AEs and graded using NCI-CTCAE version 4.03 guidelines.

7.5.5 ECGs

The 12-lead ECG results will be summarized by treatment group and time point. Overall ECG interpretation will be summarized for each time point. A shift analysis table showing shifts from baseline in overall ECG (normal, abnormal) will be provided. ECG parameters and their change from baseline will be summarized by treatment group using descriptive statistics.

7.5.6 ECOG Performance Scores

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

7.6 Analysis of Pharmacokinetics

Based on PK data obtained within this study, a separate population PK 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 PK analysis plan.

In a subset of non-Japanese and Japanese subjects with dense PK sampling, plasma concentrations and PK parameters will be summarized for ASP2215 and azacitidine by treatment arm using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) of the mean and geometric mean. Time-course of mean drug plasma concentrations will be plotted as appropriate.

Subjects with sufficient PK samples will have PK parameter estimates for ASP2215 to include calculation of AUC_t, C_{max}, C_{trough} and t_{max} and for azacitidine AUC_t, C_{max}, C_{trough} and t_{max} using standard noncompartmental analysis. For assessment of drug interactions, the 90% CI will be constructed for the geometric mean ratio (GMR) of C_{max} and AUC_t for azacitidine + ASP2215 to azacitidine alone (denominator) based on a mixed-effects model on the natural logarithm transformed PK parameters with treatment as the fixed-effect factor. In addition, the GMRs for azacitidine and ASP2215 PK will be compared in Japanese and non-Japanese subjects for each of the following treatments: azacitidine alone and azacitidine + ASP2215.

7.7 Protocol Deviations and Other Analyses

Protocol deviations as defined in [Section 8.1.6, Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

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

PD1 - Entered into the study even though they did not satisfy entry criteria,
PD2 - Developed withdrawal criteria during the study and was not withdrawn,
PD3 - Received wrong treatment or incorrect dose,
PD4 - Received excluded concomitant treatment.

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

A formal interim analysis for the randomized study is planned when approximately 50% (i.e., death events = 70) of the planned total number of deaths (i.e., death events = 140) by any cause have occurred. The IDMC will evaluate the test of OS and inform the Sponsor the result if Arm AC has favorable outcome (i.e., P value < 0.003) or unfavorable outcome (i.e., P value ≥ 0.724) compared to Arm C with respect to OS, the study may be stopped due to efficacy or futility, respectively. Otherwise, the study will continue without impact.

If the study is not stopped after the interim analysis, a final analysis will occur after 100% of planned death events have been observed.

If the trial is stopped early, provisions will be made for subjects who continue to derive benefit on their assigned treatment arm based on the investigator's assessment.

The EFS will be evaluated at the time of OS interim analysis, only if the OS result is positive at the interim analysis. By the time of OS interim analysis with 70 events, 88 EFS events are expected (the actual number of events may vary). An O'Brien-Fleming stopping boundary based on Lan-DeMets alpha spending method will be used for EFS. Based on a projected number of events of 88 at the interim, the efficacy stopping boundary is 2-sided nominal alpha of 0.003 for interim analysis and 0.049 for the final analysis. The actual rejection boundary for EFS may vary according to the actual number of EFS events that occur at the interim analysis.

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 5 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.

Certain laboratory tests are performed at a central laboratory per the Schedules of Assessments [Table 1 and Table 2]. Laboratory data performed at a central laboratory 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 will be read 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.

Electronic PRO (ePRO):

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

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

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

- Entered into the study even though they did not satisfy entry criteria
- Developed withdrawal criteria during the study and not withdrawn

- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment

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

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

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

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 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, partial ICFs) 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 SAEs 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 BV (APEB)/Astellas Pharma Europe Ltd. (APEL)-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 (***Specific to Japan:*** place a personal seal), 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 (***Specific to Japan:*** or sealed) 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.

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

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

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must 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 (*Specific to Japan:* place a personal seal). A copy of the signed (*Specific to Japan:* or sealed) 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).

Specific to Germany:

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to a participant's privacy due to direct access to source documents, or from other sources, they may not disclose the content to third parties.

The sponsor agrees to comply and process personal data obtained during a research study in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the sponsor shall serve as the controller of such data, as defined by the EU General Data Protection Regulation (GDPR). If the sponsor is not based in the EEA, the sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the GDPR.

The Sponsor has performed a privacy impact assessment to describe the data processing activities, assess their necessity and proportionality and manage the risks to the rights and freedoms of data subjects resulting from the processing of personal information by assessing them and determining the measures or mitigation actions to address them. The Sponsor has assessed, among others, how the data is collected and the purposes they are used, the impact on data subject rights, the security mechanisms including the safeguards of potential transfer of data outside the European Union and the access rights to data. The Sponsor will take

actions to mitigate the risks to the rights and freedoms of data subjects resulting from the processing of their data as part of their participation in the study.

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.

Specific 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 (***Specific to Japan***– the JUTOKUNA YUUGAIJISHOU HOUKOKUSHO)
- 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 US federal regulation 21CFR Part 54
- Signed and dated FDA form 1572
- 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)
- In Japan only: Instruction and decision of the head of the study site
- 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:

- Unused study documentation,
- Unused study drug

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 US sites, 2 years after approval of the New Drug Application (NDA) or discontinuation of the IND). The Sponsor will notify the site/investigator if the NDA/Marketing Authorisation Application/J-NDA is approved or if the IND/Investigational Medicinal Product Dossier/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 investigator and Sponsor will mutually agree upon the storage format for the retention of electronic data.

The following 2 paragraphs are specific to 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 number 1 or number 2 below, whichever comes later.

1. 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)
2. Until 3 years after discontinuation or termination of the study.

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

1. Source documents (clinical data, documents and records for preparing the eCRF) hospital records, medical records, test records, memoranda, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the Sponsor, records of clinical coordinators and records related to the clinical study selected from those verified in other departments or hospitals.

2. Contracts, written ICFs, written information and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), Curriculum Vitae of investigators, list of subinvestigators, list of signatures and print of seals (copy) and CRFs (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), 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.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation) and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs and the prescriptions for concomitant medications.

8.3.3 Protocol Amendment and/or Revision

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

The following paragraph is 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:

1. 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.
2. 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.
3. The Sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. 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 EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

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

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

10 STUDY ORGANIZATION

10.1 Independent Data Monitoring Committee

The IDMC will be responsible for the review of subject safety, enrollment rates, response rates, and event (death) rates during periodic review and interim analysis as defined in the IDMC charter. The IDMC may recommend terminating the trial for favorable or unfavorable results at the interim analysis.

The IDMC will evaluate safety data on the first 6 subjects from investigational sites in Japan enrolled or randomized to combination therapy of ASP2215 and azacitidine (either in safety cohort or Arm AC of randomization portion of the study) after all 6 subjects either discontinue treatment or complete 1 cycle of treatment. The IDMC may recommend terminating enrollment for subjects from investigational sites in Japan based on safety evaluation.

Members of the independent 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 in the independent IDMC charter.

10.2 Other Study Organization-

10.2.1 Japan Site Contact List

The Japan site contact list is kept as a separate attachment to the protocol.

10.2.2 Dose Escalation Committee

A Dose Escalation Committee (DEC) comprising of the sponsor, principal investigators and, if appropriate, expert consultants will be set-up only for the safety cohort of this study. The DEC will review safety data through the DLT observation period in the safety cohort.

At each meeting, individual subject data in safety cohort will be reviewed for dose escalation or de-escalation decisions. Additional details regarding responsibilities and membership requirements will be included in the Subject Enrollment and Dose Escalation Plan.

11 REFERENCES

American Cancer Society. Cancer facts & figures 2018. Atlanta: American Cancer Society; 2018.

ASP2215 Investigator's Brochure, 2018.

Astellas Pharma Inc. [Internet]. Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan [Cited 2019 Oct 03]. Available from: www.astellas.com/en/news/14666.

Cella D, Jensen SE, Webster K, Hongyan D, Lai JS, Rosen S, et al. Measuring health-related quality of life in leukemia: the Functional Assessment of Cancer Therapy--Leukemia (FACT-Leu) questionnaire. Value Health. 2012;15:1051-8.

Chang E, Ganguly S, Rajkhowa T, Gocke CD, Levis M, Konig H. The combination of FLT3 and DNA methyltransferase inhibition is synergistically cytotoxic to FLT3/ITD acute myeloid leukemia cells. Leukemia. 2016;30:1025-32.

Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-9.

Choi SW, Victorson DE, Yount S, Anton S, Cella D. Development of a conceptual framework and calibrated item banks to measure patient-reported dyspnea severity and related functional limitations. Value Health. 2011;14:291-306.

Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood. 2015;126(3):291-9.

Gale RE, Green C, Allen C, Mead AJ, Burnett AK, Hills RK, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008;111:2776-84.

Larrosa-Garcia M, Baer MR. FLT3 Inhibitors in Acute Myeloid Leukemia: Current Status and Future Directions. Mol Cancer Ther. 2017 Jun;16(6):991-1001.

Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999;85:1186-96.

Moreno I, Martín G, Bolufer P, Barragán E, Rueda E, Román J, et al. Incidence and prognostic value of FLT3 internal tandem duplication and D835 mutations in acute myeloid leukemia. Haematologica. 2003;88:19-24.

Mori M, Kaneko N, Ueno Y, Tanaka R, Cho K, Saito R, et al. ASP2215, a novel FLT3/AXL inhibitor: Preclinical evaluation in acute myeloid leukemia (AML). J Clin Oncol. 32:15, 2014 (suppl; abstr 7070).

National Cancer Institute. Common Terminology Criteria for Adverse Events v4.03. NCI, NIH, DHHS. NIH Publication #09-5410. June 14, 2010.

National Comprehensive Cancer Network. Acute Myeloid Leukemia (Version 1.2015). https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed 01/14/2015.

O'Donnell MR, Abboud CN, Altman J, Appelbaum FR, Arber DA, Attar E, et al. Acute myeloid leukemia. J Natl Compr Canc Netw. 2012;10:984-1021.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. AM J Clin Oncol. 1982;5:649-55.

Patel JP, Gönen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366:1079-89.

Ravandi F, Alattar ML, Grunwald MR, Rudek MA, Rajkhowa T, Richie MA, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood. 2013;121(23):4655-62.

Samson K. Prolonged Survival Possible in FLT3 Acute Myeloid Leukemia. Oncol Times. 2019:41(10):28.

Schlenk RF, Döhner K. Impact of new prognostic markers in treatment decisions in acute myeloid leukemia. Curr Opin Hematol. 2009;16(2):98-104.

Short NJ, Kantarjian H, Ravandi F, Daver N. Emerging treatment paradigms with FLT3 inhibitors in acute myeloid leukemia. Ther Adv Hematol. 2019 Feb 15;10:1-10.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press; 2008.

Tallman MS. New strategies for the treatment of acute myeloid leukemia including antibodies and other novel agents. Hematology Am Soc Hematol Educ Program. 2005:143-50.

Tiesmeier J, Müller-Tidow C, Westermann A, Czwalinna A, Hoffmann M, Krauter J, et al. Evolution of FLT3-ITD and D835 activating point mutations in relapsing acute myeloid leukemia and response to salvage therapy. Leuk Res. 2004;28:1069-74.

Wellner JA, Zhan Y. Hybrid algorithm for computation of the nonparametric maximum likelihood estimator from censored data. J Am Stat Assoc. 1997:92:945–59.

Yap GY, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89:1363-1372.

Yamamoto Y, Kiyoi H, Nakano Y, Suzuki R, Kodera Y, Miyawaki S, et al. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood. 2001;97(8):2434-9.

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

12 APPENDICES

12.1 Contraception Requirements

WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in [Table 1] and [Table 2].

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

Documentation of any of these categories can come from the site personnel's review of the female subject's medical records, medical examination or medical history interview.

A postmenopausal state is defined as at least 12 months after last regular menstrual bleeding without an alternative medical cause.

- In case the last regular menstrual bleeding cannot be clearly determined, confirmation with repeated follicle-stimulating hormone (FSH) measurements of at least > 40 IU/L (or higher per local institutional guidelines), is required.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required at the time of signing the ICF and until the end of relevant systemic exposure, defined as 180 days after the final study drug administration.*****

Highly Effective Contraceptive Methods (Failure rate of < 1% per year when used consistently and correctly)[a]

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- oral

- intravaginal
- transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation

- oral
- injectable
- implantable

Hormonal methods of contraception containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system

- intrauterine device
- bilateral tubal occlusion

Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*

Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected.*

***** Local laws and regulations may require use of alternative and/or additional contraception methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

UK only: Highly effective forms of birth control include:
- Consistent and correct usage of established oral contraception
- Established intrauterine device or intrauterine system
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during treatment and until the end of relevant systemic exposure defined as 120 days after final drug administration.*****

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom during treatment and until end of relevant systemic exposure defined as 180 days after final drug administration.

- Female partners of male participants who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 180 days after final drug administration.

UK only: Highly effective forms of birth control include:

- Consistent and correct usage of established oral contraception
- Established intrauterine device or intrauterine system
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository)

12.2 List of Excluded and Cautionary Concomitant Medications

Strong CYP3A Inhibitors

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.

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.

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

Source: FDA Draft Guidance for Industry – Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Recommendations (October 2017)
http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.

Strong CYP3A Inducers

Treatment with concomitant drugs that are strong inducers of CYP3A are **prohibited** in combination with ASP2215. The following list describes medications and foods that 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.

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

Source: FDA Draft Guidance for Industry – Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Recommendations (October 2017)
http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.

Drugs Targeting Serotonin Receptors

Treatment with concomitant drugs that target serotonin 5HT2B receptor are to be **avoided** with the exception of drugs that are considered absolutely essential for the care of the subject.

The following list describes medications that 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.

Drug Type	Generic Drug Name
Affinity or function to $5HT_{2B}R$	Eletriptan Hydrobromide

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

P-gp Inhibitors or Inducers

Treatment with strong inhibitors of P-gp are to be **avoided** with the exception of drugs that are considered absolutely essential for the care of the subject.

Treatment with strong inducers of P-gp are **prohibited**.

The following list describes medications and foods that 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.

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

Drugs Targeting Sigma (nonspecific) Receptor (sigma R)

Treatment with concomitant drugs that target non-sigma specific receptor are to be **avoided** with the exception of drugs that are considered absolutely essential for the care of the subject.

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

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

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
Azole antifungals	Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole
Table continued on next page	

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

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

Substrates of P-gp, BCRP and OCT1

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

12.3 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 or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase and total bilirubin). Testing should be repeated within 48 to 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

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

	ALT or AST		Total Bilirubin
Moderate	> 3 × ULN	or	> 2 × ULN
Severe[a]	> 3 × ULN	and	> 2 × ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal

[a] See definition of Hy's Law later in this appendix.

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
- ALT or AST > 3 × ULN and international normalized 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) that has been developed globally and can be activated for any study or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 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 the 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 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
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or 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%).

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

[a] 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% to 50% mortality (or transplant). The 2 "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 times the upper limit of normal ("2 × ULN elevations are too common in treated and untreated subjects to be discriminating"). 2) Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intrahepatic or extrahepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome [Temple 2006].

References

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

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

12.4 Laboratory Tests

Panel/Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Hematology	3 mL into EDTA tube 2 to 3 smear slides in addition to the sample	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 Uric Acid[b] Glucose Calcium Phosphate Magnesium Albumin Total Protein Alkaline Phosphatase Lactate Dehydrogenase Creatine Kinase Aldolase Triglycerides Total Cholesterol Phospholipid Globulin Liver Function Tests including: Total Bilirubin Alanine Aminotransferase Aspartate Aminotransferase Thyroid Function Tests including TSH and Free T4
Serum Pregnancy Test	1 mL serum or urine[c]	Human Chorionic Gonadotropin
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	2.5 mL into sodium citrate tube	INR (with PT if reported) aPTT Fibrinogen (screening Only) D-dimer (screening Only)

Table continued on next page

Panel/Assessment	Matrix/Collecting Tube	Parameters to be Analyzed
Urinalysis	Dipstick	Color Appearance Specific Gravity pH Bilirubin Blood Glucose Ketones Leukocyte Esterase Nitrite Protein Urobilinogen
Bone Marrow for disease assessment/MRD	Aspirate in 1 to 3-mL EDTA tube. If aspirate is unavailable, then biopsy and whole blood is required. 2 to 3 bedside smear slides in addition to the sample (aspirate/biopsy and whole blood).	Blast Count and Cell Counts[a] Flow Cytometry for Blasts FLT3 Mutation Status MRD
Bone Marrow for FLT3 mutation	Aspirate 3-mL Sodium Heparin tube. If aspirate is unavailable then whole blood in 3-mL in Sodium Heparin tube.	FLT3 Mutation Status (Screening Only)
Pharmacokinetic	2 mL blood into dipotassium EDTA tube, processed to 1 mL plasma in transfer tube	ASP2215 concentration
	2 mL blood into THU tube, processed to 1 mL plasma in transfer tube	Azacitidine concentration
Pharmacogenomics (For subjects who provide separate PGx consent)	3 mL into EDTA tube Buccal swab	PGx Analyses to be determined.

aPTT: activated partial thromboplastin time; FLT3: FMS-like tyrosine kinase; INR: international normalized ratio; MRD: minimal residual disease; PGx: pharmacogenomics; PT: prothrombin time; T4: thyroxine; THU: tetrahydrouridine; TSH: thyroid stimulating hormone.

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

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

c. Please refer to the Schedules of Assessments [Table 1 and Table 2].

12.5 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 the reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in [Section 5.5.2, Definition of Serious Adverse Events]**. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs." Investigators are required to follow the requirements detailed in [Section 5.5.5, Reporting of Serious Adverse Events].

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

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
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
Abdominal Pain	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
Constipation	0 - 2
Diarrhea	0 - 2
Dyspnea	0 - 5
Fatigue	0 - 3
Febrile neutropenia	0 - 4
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
Multiorgan failure	0 - 5
Nausea	0 - 2
Oral dysesthesia	0 - 2
Petichiae	0 - 2
Pruritus	0 - 3
Skin and subcutaneous tissue disorders	0 - 3
Table continued on next page	

Serious Adverse Events Caused by AML	**Grades Usually Observed with AML**
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

12.6 Retrospective Pharmacogenomics Substudy (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 and/or buccal swab is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, PK and toxicity/safety issues.

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

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study will participate in this PGx substudy. As part of this substudy, subjects must provide written consent prior to providing any blood and buccal swab 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 substudy. As part of this substudy, 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 substudy will provide one optional 3-mL tube of whole blood and 1 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 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. 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.

12.7 Continuation of Study Drug Treatment with ASP2215 and/or ASP2215 Plus Azacitidine

Based on the planned interim analysis in Dec 2020, an IDMC recommended terminating the study based on protocol specified boundaries for futility, concluding results are unlikely to show a statistically significant increase in overall survival, Astellas made decision to stop enrollment for the study.

Subjects can continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine until they meet a discontinuation criterion as outlined in [Section 6 Discontinuation] or applicable reimbursement becomes available in the country of residence.

ASP2215 and/or ASP2215 plus azacitidine will be supplied every 3 months via IRT as applicable. Subjects will be managed per the local institution's standard of care for safety and efficacy assessments while on study drug treatment. Subjects will follow the Schedule of Assessments in [Table 13]. No data will be collected in the eCRFs after subjects reconsent under this protocol Version 13.0, as the clinical database will be locked. Only AEs and SAEs (as defined in [Section 5.5.2 Definition of Serious Adverse Events]), will be collected and reported to Astellas Pharma Global Development Product Safety & Pharmacovigilance (Japan will continue reporting to PAREXEL International). All AEs and SAEs will be reported on the SAE worksheet to the Sponsor and the data will be reported in the safety database. Once subjects receiving treatment meet the study discontinuation criteria, subjects will be discontinued from the study. AE and SAE collection will continue until 30 days after last dose of study treatment (ASP2215 and/or azacitidine). IRT notification is required when subjects discontinue from study drug treatment.

Subjects in long-term follow-up who are no longer receiving treatment will be followed every 3 months for survival until the implementation of protocol version 13.0, at which time they will discontinue from the study as further survival data is no longer needed.

Table 13 Continuation of Study Drug Treatment with ASP2215 and/or ASP2215 Plus Azacitidine Schedule of Assessments

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

AE: adverse events; ICF: informed consent form; IRT: interactive response technology; SAE: serious adverse event

Footnotes continued on next page

a. AE and SAE collection will continue until 30 days after last dose of study treatment (ASP2215 and/or azacitidine). Subjects who complete treatment with an AE or SAE for which the relationship to ASP2215 alone, azacitidine alone or the ASP2215 plus azacitidine combination is plausibly related should be followed until the event stabilizes or returns to baseline. AEs and SAEs will be reported to Astellas Pharma Global Development Product Safety & Pharmacovigilance (Japan will continue reporting to PAREXEL International).
b. IRT notification is required when subjects discontinue from study drug treatment.

Discontinuation Criteria for Subjects who Reconsent Under This Protocol Version 13.0

Subjects will continue to receive study drug treatment with ASP2215 and/or ASP2215 plus azacitidine until one of the following occurs:

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

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

13 SPONSOR'S SIGNATURES