A Phase 1/2 Study of ASP2215 in Combination with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia

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Incorporating Substantial Amendment 7

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Sponsor:

Astellas Pharma Inc.

2-5-1, Nihonbashi-Honcho, Chuo-ku,
Tokyo 103-8411, Japan

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SIGNATURES

1. AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This study will be conducted in adherence to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable laws and regulatory requirements, as well as this protocol. As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement by signature or "printed name and seal."

2. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 14 Sponsor's Signatures].

3. INVESTIGATOR'S SIGNATURE

A Phase 1/2 Study of ASP2215 in Combination with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia

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29 Aug 2021

I have read all pages of this 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that (s) and other relevant members of my personnel 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: _____

<Insert name and qualification of the investigator>

Address: _____

_____

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See Section 12.4.5	**Please fax or email the serious adverse events (SAE)/special situations worksheet to:** For investigational sites in Japan, Sponsor Contact: Astellas Pharma Inc., Development, Japan-Asia Clinical Development 1 2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan TEL: 03-3244-1097 FAX: 03-3243-5737 Contract Research Organizer (CRO) Contact: PPD-SNBL K.K., Global Clinical Development St Luke's Tower 12F, 8-1 Akashi-cho, Chuo-ku, Tokyo, Japan TEL: 03-6821-0932 FAX:03-6740-7912 For investigational sites in countries except for Japan, Astellas Pharma Inc. – Japan Pharmacovigilance Email: safety-jp@astellas.com
Medical Monitor/Study Physician	PPD ASTELLAS PHARMA GLOBAL DEVELOPMENT 1 Astellas Way, Northbrook, IL USA 60062 PPD
Clinical Research Contact	Pharmaceutical Product Development, LLC (PPD) PPD PPD

1 PROTOCOL SUMMARY

1.1 Synopsis

Date and Version of Protocol Synopsis:	29 Aug 2021, Version 8.0
Sponsor: Astellas Pharma Inc. (API)	**Protocol Number:** 2215-CL-0104
Compound Name: ASP2215	**Phase of Development:** Phase 1/2

Title of Study:
A Phase 1/2 Study of ASP2215 in Combination with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia

Planned Study Period:
From August 2014 to 4Q 2022 (including long-term follow-up period).

Study Objective(s) and Endpoint(s):
[Phase 1 part]

Objective(s)	**Endpoint(s)**
Primary	
● Determine the maximum tolerated dose (MTD) and/or recommended expansion dose (RED) of ASP2215 concomitant with cytarabine/idarubicin as induction chemotherapy based on the status of the onset of dose-limiting toxicity (DLT)	● MTD ● RED ● Occurrence of DLT
● Evaluate the safety and tolerability of ASP2215 concomitant with cytarabine/idarubicin as induction chemotherapy and high-dose cytarabine as consolidation chemotherapy	● Adverse events (AEs), safety laboratory tests, vital signs, and electrocardiograms (ECGs)
● Evaluate the safety and tolerability of ASP2215 in maintenance therapy after induction and consolidation therapy	● AEs, safety laboratory tests, vital signs, and ECGs
Secondary	
● Characterize the pharmacokinetic (PK) parameters of ASP2215 concomitant with induction and consolidation chemotherapy	● PK parameters
● Evaluate the PK parameters of cytarabine concomitant with ASP2215	● PK parameters
● Evaluate the pharmacodynamic (PD) parameters of ASP2215	● PD parameters

Table continued on next page

Objective(s)	**Endpoint(s)**
Exploratory	
• Evaluate the efficacy of ASP2215 concomitant with induction and consolidation chemotherapy	• CR (Complete Remission) • CRp (CR with incomplete platelet recovery) • CRi (CR with incomplete hematologic recovery) • PR (Partial Remission) • CRc (Composite CR): CR + CRp + CRi • Overall response rate: CRc + PR • Duration of response

[Phase 2 part]

Objective(s)	**Endpoint(s)**
Primary	
• Evaluate the efficacy of ASP2215 in combination with induction therapy in newly diagnosed FLT3-mutated acute myeloid leukemia (AML) subjects	• Complete remission (CR) rate after induction therapy period for Phase 2 part subjects
Secondary	
• Characterize the pharmacokinetic (PK) parameters of ASP2215 concomitant with induction and consolidation chemotherapy	• PK parameters
• Evaluate the safety and efficacy of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy	• Overall survival (OS) • Event free survival (EFS) • Relapse free survival (RFS) • CR rate after each treatment therapy • CR rate without minimal residual disease (MRD) after each treatment therapy • Complete remission with partial hematological recovery (CRh) rate after each treatment therapy • Composite complete remission (CRc) rate after each treatment therapy • CR/CRh rate after each treatment therapy

Table continued on next page

Objective(s)	Endpoint(s)
● Evaluate the safety and efficacy of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy *(continued)*	● Duration of CR, CRh, CR/CRh and CRc ● Duration of response ● Adverse events (AEs), safety laboratory tests, vital signs, and electrocardiograms (ECGs)
Exploratory	
● Evaluate the additional efficacy measures for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy	● Transplantation rate ● Cumulative incidence of relapse (CIR) after 1st CR (CR1) ● Cumulative incidence of death (CID) after CR1 ● Time to hematopoietic recovery after each treatment cycle ● MRD ● MRD-negative CR rate after induction ● Overall MRD-negative CR rate for any treatment period

Planned Total Number of Study Sites and Location(s):
Phase 1 part: Approximately 6 centers in Japan
Phase 2 part: Approximately 50 centers in Asia Pacific

Study Population:
Phase 1 part: Newly diagnosed acute myeloid leukemia (AML) patients
Phase 2 part: Newly diagnosed FLT3-mutated AML patients

Number of Subjects to be Enrolled/Randomized:
Phase 1 part: approximately 6 subjects
- Dose-evaluation part: At least 3 subjects per cohort (which may be changed according to the status of the onset of DLT and the number of cohorts)
- Expansion part: At least 3 subjects

Phase 2 part: approximately 80 subjects

Study Design Overview:
This study is a Phase 1/2, open-label, single-arm study in patients with newly diagnosed AML. The Phase 1 part evaluates the dose of ASP2215 using the Bayesian-continual reassessment method (hereinafter, Bayesian-CRM) and the Phase 2 part evaluates the safety and the effect of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy in newly diagnosed FLT3-mutated AML patients. This study is composed of two Phase 1 parts and a Phase 2 part. The Phase 1 parts are composed of dose evaluation and expansion parts with the target population of patients

with newly-diagnosed AML, whereas the Phase 2 part is evaluated in patients with newly-diagnosed AML with FLT3 mutation.

[Phase 1 part (dose evaluation part and dose expansion part)]

The dose evaluation part and the expansion part are considered as the Phase 1 part. The primary objective of the Phase 1 part is to determine the maximum tolerated dose (MTD) and/or recommended expansion dose (RED) of ASP2215 administered concomitantly with chemotherapy drugs as induction therapy based on the status of the onset of dose-limiting toxicity (DLT). Dose evaluation part will first evaluate the tolerated dose and the expansion part will confirm the safety of the dose identified in the dose evaluation part. Subject enrollment and DLT assessment will be continued until the criterion for enrollment completion shown in the procedure for Bayesian-CRM is met.

Table 1 Phase 1 part Dose Evaluation flow chart

Dose Level	Cohort 1	Cohort 2	. . .
1 (120 mg)	3 subjects	3 subjects	. . .
-1 (80 mg)		3 subjects	. . .

The starting dose of ASP2215 in the dose-evaluation part is 120 mg. According to the table below, at least 3 subjects will receive ASP2215 at the assigned dose (120 mg, or 80 mg as necessary) for the determination of MTD and/or RED. The DLT assessment period for the dose evaluation part is until the end of induction therapy Cycle 1 and until the end of consolidation therapy Cycle 1 for the dose expansion part. Subjects who meet any of the following criteria will be considered unevaluable for DLT and will be replaced by another subject in the cohort.

- A subject that receives less than 80% of the assigned dose of ASP2215 during DLT assessment period specified in each part (e.g., subject in dose assessment part who misses ≥ 3 daily doses during DLT assessment period of dose evaluation part and interrupts the study for a reason other than a DLT)
- Unable to assess the safety adequately during DLT assessment period specified in each part such as due to the lack of required safety assessment(s)

Table 2 Dose level of ASP2215

Dose level	ASP2215 dose (mg/day)
−1*	80
1	120

* Dose level −1 represents a dose that may be considered if dose level 1 is poorly tolerated.

The decision of whether or not to proceed to the next dose of ASP2215 based on the table above will be made through discussion among the sponsor, principal investigators, and medical advisor with reference to the recommended dose level calculated using Bayesian-CRM, the safety data, etc., and after review by the sponsor's responsible person. The MTD

is defined as the highest dose of ASP2215 at which the posterior mean of the DLT incidence during Cycle 1 of induction therapy is estimated to be closest to 33%.

[Phase 2 part]

After achieving the objectives of the Phase 1 part, the Phase 2 part can be initiated. Subjects will receive ASP2215 at the recommended dose established in the Phase 1 part. The primary objective of the Phase 2 part is to evaluate the efficacy of ASP2215 in combination with induction therapy in newly diagnosed FLT3-mutated AML subjects. The target population will be limited to newly diagnosed FLT3-mutated AML. The primary analysis for the primary endpoint of the CR rate will be conducted when all registered subjects complete the induction therapy period.

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, relapse and survival (cause and date of death). During the long-term follow-up period, the subject will be followed for 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.

Inclusion/Exclusion Criteria:

[Phase 1 part]

Inclusion Criteria:

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

1. Written informed consent has been obtained (However, if the subject is underage, consent must also be obtained from the subject's legal guardian).
2. Subject is ≥ 18 and < 70 years of age at the time of obtaining informed consent.
3. Subject is defined as having previously untreated *de novo* AML according to the World Health Organization (WHO) criteria (2008) within 28 days prior to study enrollment.
4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2.
5. Subject must meet all of the following criteria in the laboratory test at screening:
   - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤ 2.5 × institutional upper limit of normal (ULN)
   - Total serum bilirubin level of ≤ 1.5 × institutional ULN
   - Serum creatinine level of ≤ 1.5 × institutional ULN or an estimated glomerular filtration rate (eGFR) of > 50 mL/min†
     †Calculating formula: eGFR (mL/min/1.73 m^2 = 194 × $Cr^{-1.094}$ × $Age^{-0.287}$ (× 0.739 for female subjects)
6. Subject is suitable for oral administration of ASP2215.
7. Female subject falls under the following:
   Of non-childbearing potential:
   - Post-menopausal (defined as at least 1 year with no menses without a medical reason such as drug administration) at screening, or
   - Documented surgically sterile or status post-hysterectomy (at least 1 month prior to screening)

Of childbearing potential:

- Agrees not to try to become pregnant during the study and for 60 days after the final study drug administration,
- Has a negative result for the serum or urine pregnancy test at screening, and
- If heterosexually active, agrees to consistently use two effective contraceptive methods (one of which must be the barrier method) per locally accepted standards starting at screening and throughout the study period and for 60 days after the final study drug administration.

8. Female subject agrees not to breastfeed starting at screening and throughout the study period and for 60 days after the final study drug administration.
9. Female subject agrees not to donate ova starting at screening and throughout the study period and for 60 days after the final study drug administration.
10. Male subject and his female spouse/partner who is of childbearing potential agrees to use two effective contraceptive methods (one of which must be the barrier method) per locally accepted standards starting at screening and throughout the study period, and for 120 days after the final study drug administration.
11. Male subject agrees not to donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
12. Subject agrees not to participate in another interventional study while on study treatment.
13. Subject can be admitted during the induction therapy period.

Exclusion Criteria:

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

1. Subject was diagnosed with acute promyelocytic leukemia (APL).
2. Subject has breakpoint cluster region-abelson (BCR-ABL)-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has active malignant tumors other than AML or myelodysplastic syndrome (MDS).
4. Subject has received prior AML treatment except for the following:
   - Urgent leukapheresis
   - Hydroxyurea administration for emergency treatment of hyperleukocytosis (≤ 7 days)
   - Administration of retinoic acid before the diagnosis to exclude APL (≤ 7 days)
   - Supportive care using growth factors or cytokines
   - Steroid administration to treat hypersensitivity or blood transfusion reactions
5. Subject has clinically active central nervous system leukemia.
6. Subject has disseminated intravascular coagulation (DIC).
7. Subject has had major surgery within 28 days prior to the first study drug administration.
8. Subject has had radiation therapy within 28 days prior to the first study drug administration.

9. Subject has congestive heart failure of New York Heart Association (NYHA) class 3 or 4, or subject with a past history of congestive heart failure of NYHA class 3 or 4 and in whom echocardiogram (ECHO) or Multiple Gate Acquisition (MUGA) scan performed within 3 months prior to screening or at screening showed a left ventricular ejection fraction (LVEF) of < 45%.
10. Subject has cardiac impairment or a clinically significant cardiac disease, including any one of the following:
    - Complete left bundle branch block
    - Obligate use of a cardiac pacemaker
    - Long QT syndrome
    - Prolongation of the mean QTc interval (> 450 ms) on electrocardiogram (ECG) at screening
    - Right bundle branch block + left anterior hemiblock (bifascicular block)
    - Angina pectoris within 3 months prior to study drug administration
    - Acute myocardial infarction within 3 months prior to study drug administration
11. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.
12. Subject requires treatment with concomitant drugs that target serotonin $5HT_1$ or $5HT_{2B}$ receptors or sigma nonspecific receptors, with the exception of drugs that are considered absolutely essential for treatment of the subject.
13. Subject has an active uncontrollable infection.
14. Subject is known to have human immunodeficiency virus (HIV) infection.
15. Subject has active hepatitis B or C or other active hepatic disorders.
16. Subject has any condition that, in the investigator's opinion, makes the subject unsuitable for study participation.
17. Subject has potassium and magnesium levels of below institutional lower limit of normal in the laboratory test at screening.
18. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) (with the exception of drugs that are considered absolutely essential for the care of the subject).

[Phase 2 part]

Inclusion Criteria:

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

1. Institutional Review Board-/Independent Ethics Committee-approved written informed consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing informed consent form (ICF).
3. Subject has a diagnosis of previously-untreated *de novo* AML according to World Health Organization (WHO) classification (2017) documented within 28 days prior to enrollment.

4. Subject is positive for FLT3-ITD and/or TKD mutation in bone marrow or whole blood as determined by the central lab. Registration by the local lab result is not acceptable.
5. Subject has an ECOG performance status (PS) 0 or 1 (see Section 12.5). Subject who has an ECOG PS 2 is eligible only if investigators suspect that the primary disease related symptoms such as pneumonia and febrile neutropenia are the causes of PS score.
6. Subject is suitable for oral administration of ASP2215.
7. Female subject is not pregnant (see Section 12.3) and at least 1 of the following conditions apply:
   a. Not a woman of childbearing potential (WOCBP) (see Section 12.3)
   b. WOCBP who agrees to follow the contraceptive guidance (see Section 12.3) from the time of informed consent through at least 180 days after final study treatment administration.
8. 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.
9. Female subject must not donate ova starting at screening and throughout the study period and for 180 days after the final study drug administration.
10. Male subject and their female partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 120 days after the final study drug administration.
11. Male subject must not donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
12. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 120 days after the final study treatment administration.
13. Subject agrees not to participate in another interventional study while on treatment.
14. Subject must meet the following criteria as indicated on the clinical laboratory tests:
    a. Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN), or if serum creatinine outside normal range, then glomerular filtration rate (GFR) > 50 mL/min/1.73 m^2 as calculated with the 4-parameter Modification of Diet in Renal Disease (MDRD) equation.
    b. Serum total bilirubin ≤ 2.5 mg/dL (43 µmol/L), except for subjects with Gilbert's syndrome.
    c. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 × ULN. If liver abnormality by the primary disease is suspected, subject may be pre-registered to initiate the chemotherapy. Prior to registration, AST/ALT values must meet the criteria to continue the study.
    d. Serum magnesium ≥ institutional lower limit of normal (LLN). Subject may pre-register without magnesium value, but subject must meet the criteria prior to the full registration on Day 8.
    e. Serum potassium ≥ institutional lower limit of normal (LLN).

Exclusion Criteria:
A subject will be excluded from participation in this clinical study if any of the following apply:

1. Subject was diagnosed with acute promyelocytic leukemia (APL).
2. Subject has known BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has therapy-related AML.
4. Subject has active malignant tumors other than AML.
5. Subject has received previous therapy for AML, with the exception of the following:
   - Emergency leukapheresis,
   - Emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 10 days,
   - Preemptive treatment with retinoic acid prior to exclusion of APL ≤ 7 days,
   - Growth factor or cytokine support, or
   - Steroids for the treatment of hypersensitivity or transfusion reactions.
6. Subject has QTcF interval > 450 ms (average of triplicate determinations based on central reading).
7. Subject with long QT syndrome.
8. Subject has clinically active central nervous system leukemia.
9. Subject has had major surgery within 4 weeks prior to the first study dose.
10. Subject has radiation therapy within 4 weeks prior to the first study dose.
11. Subject has immediate life-threatening, severe complications of leukemia such as severe uncontrolled bleeding and/or severe disseminated intravascular coagulation.
12. Subject is known to have human immunodeficiency virus infection.
13. Subject has active hepatitis B or C.
14. Subject has an uncontrolled infection. An infection controlled with an approved or closely monitored antibiotic/antiviral/antifungal treatment is allowed.
15. Subject has uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, congestive heart failure New York Heart Association (NYHA) class 3 or 4 or subject with a past history of congestive heart failure of NYHA class 3 or 4 and in whom echocardiogram (ECHO) or Multiple Gate Acquisition (MUGA) scan performed within 3 months prior to screening or at screening showed a left ventricular ejection fraction (LVEF) of < 45%.
16. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.
17. Subject requires treatment with concomitant drugs that target serotonin $5HT_{2B}$ receptors or sigma nonspecific receptors, with the exception of drugs that are considered absolutely essential for treatment of the subject.
18. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.
19. Subject has prior malignancies, except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.
20. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

Study Drugs and Concomitant Chemotherapy:
ASP2215, AS3329381/Cytarabine and idarubicin (if applicable)

Name and Use:
[Phase 1 part]

ASP2215	study drug
Cytarabine	concomitant chemotherapy
Idarubicin	concomitant chemotherapy

[Phase 2 part]

ASP2215	study drug
AS3329381/Cytarabine	study drug and/or concomitant chemotherapy (based on the local regulation)
Idarubicin	concomitant chemotherapy

Dose(s) and Mode(s) of Administration:
[Phase 1 part]
Induction therapy (per cycle)

ASP2215	The specified dose level (120 mg or 80 mg) QD from **Day 4-17**
Idarubicin	12 mg/m^2/day by intravenous injection from Day 1 to 3
Cytarabine	100 mg/m^2/day by intravenous injection from Day 1 to 7

Consolidation therapy (per cycle)

ASP2215	The specified dose level (120 mg or 80 mg) QD from Day 1-14
Cytarabine	1.5 g/m^2 twice a day by intravenous injection on Day 1, 3, 5

Maintenance therapy (per cycle)

ASP2215	The specified dose level (120 mg or 80 mg) QD

[Phase 2 part]
Induction therapy (per cycle)

ASP2215	The specified dose level (120 mg) QD from **Day 8-21**
Idarubicin	12 mg/m^2/day by intravenous injection from Day 1-3
Cytarabine	100 mg/m^2/day by intravenous injection from Day 1-7

Consolidation therapy (per cycle)

ASP2215	The specified dose level (120 mg) QD from Day 1-14
Cytarabine	1.5 g/m^2 twice a day by intravenous injection on Day 1, 3, 5

Maintenance therapy (per cycle)

ASP2215	The specified dose level (120 mg) QD

Study Treatment Period

[Phase 1 part]

Treatment of AML in this study is composed of 3 phases of therapy: induction therapy, consolidation therapy, and maintenance therapy. The decision of tolerability at ASP2215 dose levels will be made based on the occurrence of DLT during Cycle 1 of the induction therapy period for the evaluation part. In the expansion part, at least 3 subjects will receive ASP2215 at RED that has been recommended in the dose evaluation part and the safety will be assessed based on the onset of DLTs during Cycle 1 of the induction and consolidation therapy period. RED will finally be assessed based on DLT in the dose-evaluation part and that in the expansion part.

Induction therapy period (42 days per cycle):

During the induction therapy period, subjects will receive idarubicin (12 mg/m^2/day by intravenous injection) on 3 consecutive days beginning from Day 1 and cytarabine (100 mg/m^2/day by intravenous injection) on 7 consecutive days beginning from Day 1. Subjects will receive ASP2215 once daily on 14 consecutive days from Day 4 through Day 17. Subjects will be hospitalized during the induction therapy period. Induction therapy may be conducted up to 2 cycles based on the response to the 1st cycle of therapy.

Consolidation therapy period (28 days per cycle):

Subjects who received 1 or 2 cycles of induction therapy and achieved CR, CRp, or CRi will receive consolidation therapy. Consolidation therapy will be started without delay when a subject has reached remission by induction therapy with blood count recovery. Consolidation therapy can be started during a cycle of the induction therapy period. A subject who cannot start consolidation therapy by Day 57 of the last cycle of induction therapy will be withdrawn from the study. During the consolidation therapy period, subjects will receive cytarabine (1.5 g/m^2 by intravenous injection) twice daily at 12-hour intervals on Days 1, 3, and 5 of each cycle. Subjects will receive oral ASP2215 once daily on 14 consecutive days from Day 1 through Day 14. The subsequent cycle will be started after Day 22 of the previous cycle and recovery of the subject's blood count. Consolidation therapy may be conducted up to 3 cycles. Withdrawal from the study will be considered for a subject who cannot enter the subsequent cycle of consolidation therapy or start maintenance therapy by Day 36 of each cycle.

Maintenance therapy period (28 days per cycle):

Subjects who completed at least 1 cycle of consolidation therapy will receive maintenance therapy. Maintenance therapy is 28 days per cycle and will be conducted up to 26 cycles with once-daily oral administration of ASP2215.

Follow-up observation period:

After treatment discontinuation, subjects will have a 28-day follow-up visit for safety.

[Phase 2 part]

Induction therapy period:

The same chemotherapy regimen is applied as the Phase 1 part. Subjects will receive ASP2215 once daily on 14 consecutive days **from Day 8 through Day 21**. Induction therapy may be conducted up to 2 cycles based on the response to the 1st cycle of therapy. Upon the investigator's discretion, patients are allowed to proceed immediately to hematopoietic stem cell transplantation (HSCT) without receiving consolidation therapy. Postponing the initiation of consolidation therapy until blood recovery is preferred. The maximum number of days in 1 cycle for induction therapy period is not defined.

Consolidation therapy period:

The same chemotherapy regimen is applied as the Phase 1 part. Subjects will receive oral ASP2215 once daily on 14 consecutive days from Day 1 through Day 14. The maximum number of days in 1 cycle for the consolidation therapy period is not defined. Omission of consolidation therapy due to HCST is allowed. Consolidation therapy may be conducted up to 4 cycles.

Maintenance therapy period (28 days per cycle):

The same therapy is applied as the Phase 1 part. Maintenance therapy may be conducted up to 26 cycles.

Resuming the study after HSCT:

Subjects who have a donor identified and have achieved a response are allowed to undergo HSCT per each institution's assessment and continue to receive the protocol specified maintenance therapy without leaving the study. However, ASP2215 should be stopped and a pre-HSCT visit should be performed prior to starting the conditioning regimen for HSCT. ASP2215 can be resumed after HSCT if the following conditions are met:

- Subject is between 30 - 90 days post-HSCT
- Subject has had successful engraftment as demonstrated by absolute neutrophil count (ANC) $\geq 500/mm^3$ and platelets $\geq 20000/mm^3$ without transfusions
- Subject does not have ≥ Grade 2 acute graft-versus-host disease (GVHD)
- Subject is in composite complete remission (CRc)

For subjects resuming treatment, they will follow the procedures listed under initial or subsequent cycle day 1 of maintenance therapy in the Schedule of Assessments. Subjects who do not resume ASP2215 will be followed for the survival endpoints.

Long-term follow-up period:

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, relapse and survival (cause and date of death). During the long-term follow-up period, the subject will be followed for 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.

Dose Modifications:

[Phase 1 part]

ASP2215:

Intra-subject dose escalation of ASP2215 is not permitted. If DLT occurs during the DLT assessment period, the study treatment will be discontinued without dose reduction. The investigator may interrupt the administration of ASP2215 when the safety of patient needs to be ensured.

Interruption, discontinuation, or dose reduction of ASP2215 should be performed in accordance with the Table 3 if the study drug-related toxicities are observed in a subject in the maintenance period. Note that each dose reduction should be performed by 40 mg. After the initial dose reduction, additional dose reductions may be performed until the dosage reaches 40 mg. If no further dose reduction is possible, the study treatment will be discontinued. Dose re-escalation in subjects who had a dose reduction is not permitted.

In addition, the investigator may interrupt or reduce the dose of ASP2215 when it is considered necessary to ensure the safety of the patients for reasons other than those presented in the table below. The investigator must promptly notify the sponsor of the interruption or dose reduction for reasons not specified in the table.

Table 3 Guidelines for ASP2215 Dose Interruption or Reduction Event (for Phase 1)

Retinopathy	
Grade 2	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.
Grade 3/4	Treatment will be discontinued.
Non-hematological events	
Grade 3	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.
Grade 4	Treatment will be discontinued.
QTcF > 500 ms	If the mean triplicate QTcF is > 500 ms at any time point (according to values shown in an ECG chart or analyses in a central laboratory), the ECG will be repeated 3 times (within 2 hours if identified according to the ECG chart values or as soon as possible if identified from central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While the study drug may be interrupted temporarily based on ECG chart values, the central reading should be used for final treatment decisions. Cardiovascular medicine consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (Grade 1 or less severe) by central reading within 14 days, the subject may resume dosing from the reduced dose.
Myelosuppression	
Grade 4 neutropenia and thrombocytopenia	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.

Concomitant drugs (idarubicin and cytarabine):

Intra-subject dose escalation of idarubicin or cytarabine is not permitted.

Dose reduction of idarubicin and cytarabine will be conducted following the standard treatment method at each study site. If discontinuation, interruption, or dose reduction of idarubicin and/or cytarabine occurs during Cycle 1 of the induction period, the study sponsor will consider whether the subject is eligible for DLT assessment.

[Phase 2 part]

ASP2215:

The starting dose of ASP2215 is 120 mg, the RED which was determined in the Phase 1 part. Dose escalation of ASP2215 is not allowed and re-escalation after dose reduction is also not allowed in this study. The ASP2215 dose may be initially reduced to 80 mg per day. The ASP2215 dose can be further reduced to 40 mg per day if the subject has already experienced clinical benefit. Note that dose reductions should occur in a step-wise manner. Dose reduction can occur any time during the study drug treatment period based on the dose reduction guideline in Table 4 or any reason other than the ones listed on the table if the investigator deems it necessary to ensure subject safety. In the unusual circumstance that dosing is interrupted or reduced for reasons not specified in the tables, the investigator should promptly inform the Medical Monitor or his/her designee. 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. However, if no further dose reduction is possible, the study treatment should be discontinued.

Table 4 Guidelines for ASP2215 Dose Interruption or Reduction Event (for Phase 2)

ASP2215 Dosing Instructions	
Non-hematological 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 at the reduced dose.
Grade 4 toxicity at least possibly related to ASP2215	Treatment will be discontinued.
QTcF > 500 ms	If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less severe) by central reading within 14 days, the subject may resume dosing at the reduced dose.
Myelosuppression (Maintenance therapy only)	
Grade 4 neutropenia and thrombocytopenia	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.

ECG: electrocardiogram; QTcF: Fridericia-corrected QT interval

Concomitant drugs (idarubicin and cytarabine):

Intra-subject dose escalation of idarubicin or cytarabine is not permitted.

Dose reduction of idarubicin and cytarabine should not be performed. If discontinuation, interruption, or dose reduction of idarubicin and/or cytarabine occurs during Cycle 1 of the induction period, information should be reported to the sponsor. Based on the investigator decision, chemotherapy dosing of Induction Cycle 2 may be reduced after confirmation with the sponsor.

Concomitant Treatment (Medication and Non-Medication Therapy) Restrictions or Requirements:

- Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215 with the exception of hydroxyurea up to 6 g daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L, prophylactic intrathecal chemotherapy or cranial irradiation.
- Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited.
- Treatment with concomitant drugs that are strong inhibitors or inducers of P-gp and concomitant drugs that target serotonin $5HT_{2B}$ receptor 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 CYP3A 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.
- Intake of grapefruit juice should be avoided during the study to the greatest extent possible.

For chemotherapy drugs, the instructions in the local package insert under “Special warnings and precautions for use” section should be followed. The treatment mentioned in the specified section should be avoided or used with caution and closely monitored during idarubicin and cytarabine administration.

Duration of Treatment:

[Phase 1 part]

- Induction therapy period (maximum 2 cycles): Once-daily repeated oral administration from Day 4 through Day 17 of induction therapy in 42-day cycles.
- Consolidation therapy period (maximum 3 cycles): Once-daily repeated oral administration from Day 1 through Day 14 of consolidation therapy in 28-day cycles.
- Maintenance therapy period (maximum 26 cycles): Once-daily repeated oral administration in 28-day cycles until the end of Cycle 26, or a discontinuation criterion is met.

[Phase 2 part] ● Induction therapy period (maximum 2 cycles): Once-daily repeated oral administration from Day 8 through Day 21 of induction therapy. ● Consolidation therapy period (maximum 4 cycles): Once-daily repeated oral administration from Day 1 through Day 14 of consolidation therapy. ● Maintenance therapy period (maximum 26 cycles): Once-daily repeated oral administration in 28-day cycles until the end of Cycle 26, or a discontinuation criterion is met.
Treatment Discontinuation Criteria: [Phase 1 part] Subjects who meet any of the following criteria during the study will be withdrawn from study treatment. ● Withdrawal of consent ● Poor compliance (failure to make the scheduled visits and others) ● A serious protocol deviation is found ● Failure to achieve remission after 2 cycles of induction therapy ● Relapse after remission ● Occurrence of an unacceptable adverse event (AE) requiring discontinuation of treatment ● The investigator determines that continuation of study treatment will be detrimental to the subject. ● Subjects or their partners are found to be pregnant. [Phase 2 part] *Discontinuation Criteria from Treatment for Individual Subjects who completed registration*: ● 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 one 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 fails to achieve remission after 2 cycles of induction therapy. ● Subject relapses following remission. ● Subject develops an intolerable or unacceptable toxicity. ● Subject receives any antileukemic therapy other than the assigned treatment with the exception of hydroxyurea up to 6 g daily for up to 2 weeks, prophylactic intrathecal chemotherapy cranial irradiation or HSCT. ● Investigator determines that the continuation of the study treatment will be detrimental to the subject. ● Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject. ● Female subject becomes pregnant. ● Death.

Discontinuation Criteria from Post-Treatment 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.

[Only applies to Phase 2 part]

The study meets the criteria to complete the long-term follow-up (i.e., During the long-term follow-up period, the subject will be followed for 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.)

Statistical Methods:

Sample Size Justification:

[Phase 1 part]

For dose evaluation part: To assess MTD and RED of ASP2215 as induction therapy concomitant with cytarabine/idarubicin in newly diagnosed AML subjects, 3 DLT evaluable subjects per dose level for 1 dose level were assumed.

For dose expansion part: The sample size was set to 3 subjects to further assess the safety and efficacy of ASP2215 at the dose tested in the expansion part.

[Phase 2 part]

The sample size of Phase 2 part is approximately 80 subjects. An evaluable sample size of 70 subjects in Phase 2 part provides more than 80% power to detect a 15% increase in CR rate from 55% (historical benchmark based on the RATIFY study, Stone et al, 2017.) to 70% at one-sided significance level of 0.05. Assuming approximately 10% drop-out rate, a total of 80 subjects will be enrolled into Phase 2 part.

Efficacy:

[Phase 1 Part]

CR rate, CRp rate, CRi rate, CRc (CR + CRp + CRi) rate, PR rate, overall response rate, duration of response will be summarized using summary statistics.

[Phase 2 Part]

Primary Efficacy Analysis:

For the primary efficacy endpoint of CR rate after induction therapy period, the two-sided 90% exact confidence interval (CI) by Clopper-Pearson method will be calculated for 70 subjects who took at least one dose of ASP2215 and had at least one post-baseline bone marrow assessment. The lower limit of the CI will be used to compare with the benchmark of CR rate of 55%. Out of 70 evaluable subjects, at least 46 subjects who achieve CR after induction is necessary to exclude 55% based on the exact 90% CI of CR rate as summarized the Table 5 below.

Table 5 Observed CR with Exact 90% CI (N=70 in Phase 2 part)

Observed CR (n and %)	Exact 90% CI
56 (80.0%)	(70.5%, 87.5%)
49 (70.0%)	(59.7%, 78.9%)
48 (68.6%)	(58.3%, 77.7%)
47 (67.1%)	(56.8%, 76.4%)
46 (65.7%)	(55.3%, 75.1%)
45 (64.3%)	(53.8%, 73.8%)

Secondary Efficacy Analyses:

The statistical analyses on secondary efficacy endpoints include the following descriptive analyses for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy:

- Kaplan-Meier method for time-to-event endpoints including OS, EFS, RFS, duration of CR, CRh, CR/CRh, and CRc.
- The two-sided 95% exact confidence interval of the binary endpoints including CR rate, CRh rate, CR/CRh rate, and CRc rate.

Safety:

[Phase 1 part]

Posterior mean of DLT incidence will be estimated for each dosage.

- All AEs and AEs for which a causal relationship with the study drug and with the remission induction or consolidation therapy including the study drug cannot be ruled out will be summarized by frequency, by System Organ Class (SOC), and by Preferred Term (PT).
- Summary statistics will be calculated or a summary of frequency will be produced for the following parameters depending on the nature of the data.
- Laboratory parameters
- Vital signs
- Body weight
- 12-lead ECG (including QT assessment)

[Phase 2 part]

- All AEs and AEs for which a causal relationship with the study drug and with the remission induction or consolidation therapy including the study drug cannot be ruled out will be summarized by frequency, by System Organ Class (SOC), and by Preferred Term (PT).
- Summary statistics will be calculated or a summary of frequency will be produced for the following parameters depending on the nature of the data.
- Laboratory parameters
- Vital signs
- Body weight
- 12-lead ECG (including QT assessment)

Pharmacokinetics:

[Phase 1 part]

Using the plasma ASP2215 and cytarabine concentration measurements, pharmacokinetic parameters and summary statistics will be calculated.

[Phase 2 part]

Using the plasma ASP2215 concentration measurements, pharmacokinetic parameters and summary statistics will be calculated.

Pharmacodynamics | Immunogenicity:

[Phase 1 part]

Percent inhibition of phosphorylation of FLT3 and AXL as compared to those at baseline sampling will be summarized by cohort.

[Phase 2 part]

Not applicable

Interim Analyses:

[Phase 1 part]

Not applicable

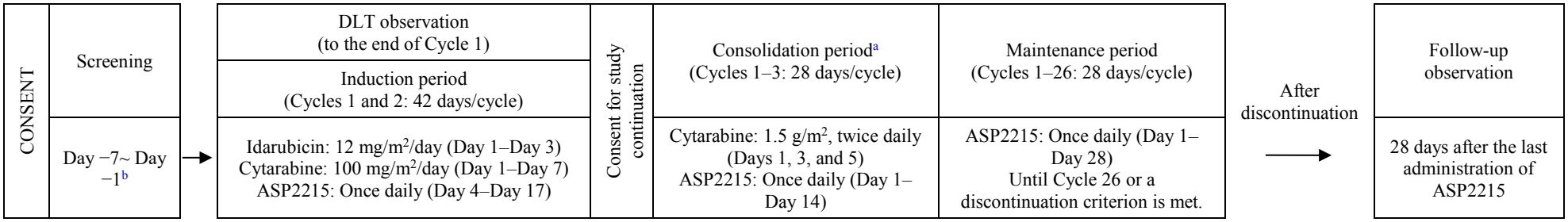
[Phase 2 part]

Not applicable

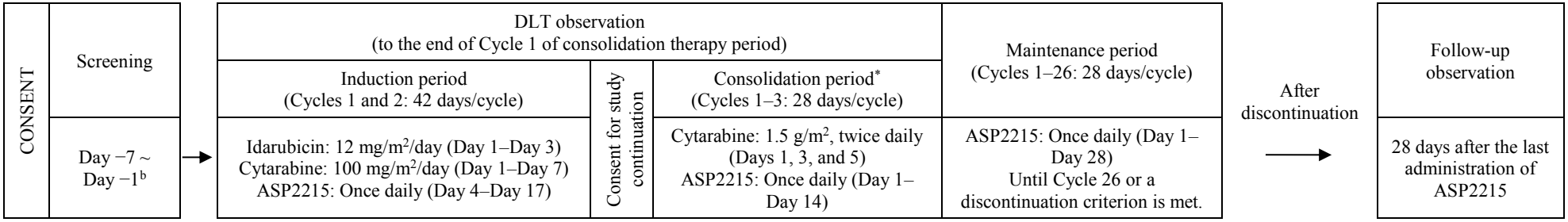
1.2 Study Schema

Figure 1 Study Schema

[Phase 1 part: Dose-evaluation]



[Phase 1 part: Expansion part]



[a] Cycle 1 will be started without delay when a subject has reached remission with blood count recovery (within 57 days from the start of the last cycle of induction chemotherapy). Subsequent cycles will be started after the completion of the assessment scheduled on Day 28 of the previous cycle, which is to be performed after Day 22 of the previous cycle, following recovery of the subject's blood count.

[b] Treatment on Day 1 may be started on the day informed consent is obtained when the investigator or subinvestigator judges that immediate treatment is required due to rapid proliferative disease progression. In this case, among the test items specified in both screening and Day 1 of Cycle 1, tests to determine body height, body weight, vital signs, and ECOG-PS and laboratory tests are not required to be performed twice.

[Phase 2 part]

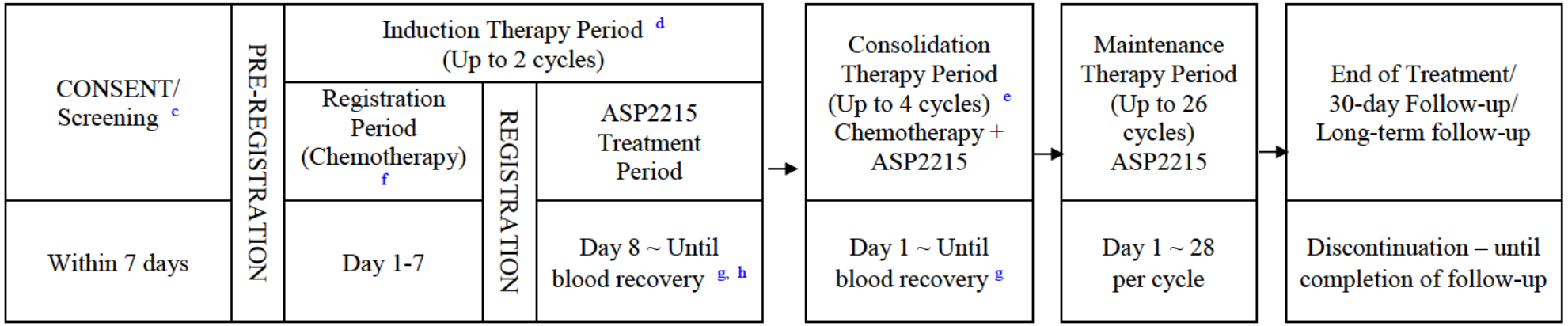
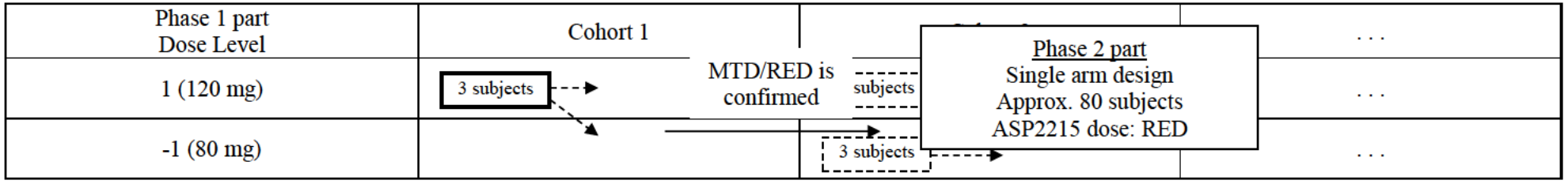


Figure 2 Study Design



[c] Consent, Screening, and Cycle 1 Day 1 may be performed on the same day if investigator(s) judges it is necessary due to rapid disease progression and subject meets all inclusion/exclusion criteria except for Inclusion criteria (IC) #4, #14-c, and #14-d for pre-registration. Cycle 1 Day 1 must be initiated within 7 days of consent.

[d] Number of days in one cycle is not defined in the Phase 2 part. Each cycle may be extended until blood recovery is observed. Timing to initiate the 2nd cycle or next treatment period is determined by investigators based on subject condition.

[e] Subjects who are eligible for HSCT may receive HSCT without consolidation therapy. Subjects who received HSCT may return to the study unless the conditions are met.

[f] Subjects must fulfill all inclusion and exclusion criteria by the end of Day 7 in order to complete Registration on Day 8.

[g] Preferably, the following cycle is started after full hematologic recovery (absolute neutrophil count [ANC] $\geq 1.0 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L), allowing formal assessment of response.

[h] Subjects who achieve full blood recovery prior to Day 42 is preferred to perform Day 42 scheduled visit for subject safety. If the subject achieves more than PR, the subjects may continue to the next therapy or proceed to HSCT. If refractory is confirmed, scheduled visits may be skipped to perform the Cycle 2 of induction therapy.

1.3 Schedules of Assessments

Table 6 Schedule of Assessments [Phase 1 part]

Assessments (Induction therapy)	Screening (Day −7–Day −1) [i]	Day 1 [i]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 15	Day 17	Day 28	Day 42
Visit window	-	0	0	0	0	0	0	0	0	0	±1	−1	±7	+14
Signed ICF	X													
Hospitalization		◄	—	—	—	—	—	—	—	—	—	—	—	►
Medical history/concurrent disease	X													
Physical examination	X	X							X		X		X	X
Height and weight [j]	X	X												
Vital signs	X	X							X		X		X	X
ECOG PS	X	X							X					
Prior and concomitant medications	X [k]	◄	—	—	—	—	—	—	—	—	—	—	—	►
Pregnancy test for WOCBP [l]	X													
Chest X-ray or chest CT [m]	X													
12-lead ECG [n]	X	X			X					X		X	X	
Table continued on next page														

[i] Cycle 1 Day 1 may be started on the day informed consent is obtained when the investigator or subinvestigator judges that immediate treatment is required due to rapid proliferative disease progression. In this case, among the test items specified in both screening and Cycle 1 Day 1 twice, tests to determine body height, body weight, vital signs, and ECOG-PS and laboratory tests are not required to be performed twice.
[j] Height will be measured only at screening. Body surface area will be calculated when body weight is measured.
[k] Includes medications taken within 28 days prior to Day 1 of remission induction.
[l] WOCBP must undergo a serum or urine pregnancy test.
[m] Not necessary to perform if chest X-ray or chest CTs were performed within 7 days prior to enrollment even before obtaining consent. Chest X-ray or chest CTs will be performed when they are determined to be clinically necessary.
[n] QT interval measurements will be performed at the central ECG laboratory on Day 1 (at pre-dose of idarubicin and cytarabine), Day 4 (at pre-dose and 4 hours post-dose), Day 11 (at pre-dose), Day 17 (at pre-dose and 4 hours post-dose), and Day 28. The 12-lead ECGs for QT interval measurement will be recorded in triplicate (3 separate ECGs with approximately 2-minute intervals) and transmitted electronically for central reading. When the timing for PK blood sampling and ECG is close, ECG will be performed prior to PK blood sampling.

Assessments (Induction therapy)	**Screening (Day −7–Day −1)** [i]	**Day 1** [i]	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 11**	**Day 15**	**Day 17**	**Day 28**	**Day 42**
Laboratory tests (hematology, biochemistry, thyroid function test, coagulation test and urinalysis) [o]	X	X			X				X		X		X	X
ECHO or MUGA [p]	X													
Sampling for FLT3 mutation test (bone marrow or whole blood) [q]	X													
Bone marrow test	X [r]												X	
AE assessment		◄	─	─	─	─	─	─	─	─	─	─	─	►
PK plasma sampling [s, t]		X		X	X	X			X	X		X	X	
Sampling for PGx banking [u, t]		X												
Idarubicin dosing		X	X	X										
Cytarabine dosing		X	X	X	X	X	X	X						
ASP2215 dosing					◄	─	─	─	─	─	─	►		

[o] To be performed at pre-dose of idarubicin and cytarabine during Cycle 1.
[p] To be performed on patients with a history of congestive heart failure of NYHA class 3 or 4 (however, not necessary to be repeated at screening if ECHO or MUGA performed within 3 months prior to enrollment showed LVEF of ≥ 45%).
[q] The bone marrow sample will be collected at screening for the FLT3 mutation test. If bone marrow samples cannot be obtained, whole blood samples will be collected at screening.
[r] Not necessary to perform if the bone marrow test was performed within 28 days prior to enrollment even before obtaining consent.
[s] Plasma PK samples for ASP2215 will be collected on Day 4 at pre-dose, 1, 2, 4, 6, 10, and 24 hours post-dose (on Day 5 at pre-dose), and on Days 8, 11, and 17 at pre-dose, and on Day 28. Plasma PK samples for cytarabine will be collected on Days 1 and 3 at pre-dose of idarubicin and cytarabine and on Day 8 at pre-dose.
[t] These samples will be collected only during Cycle 1.
[u] Buccal swab and blood will be collected from subjects who have consented to sampling for future PGx study.

Consolidation therapy

Assessments	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 14	Day 15	Day 28
Visit window	0	0	0	0	0	0	0	0	−1	±7
Signed ICF	X [v]									
Physical examination	X						X		X	X
Weight	X									
Vital signs	X						X		X	X
ECOG PS	X						X			
Concomitant medications	◄	─	─	─	─	─	─	─	─	►
Pregnancy test for WOCBP	X									
12-lead ECG [w]	X	X							X	
Laboratory tests (hematology, biochemistry, thyroid function test, coagulation test)	X			X			X		X	X
Sampling for FLT3 mutation test (bone marrow or whole blood) [x]	X									
Bone marrow test	X [y]									
AE assessment	◄	─	─	─	─	─	─	─	─	►
PK plasma sampling [z]	X	X				X			X	
Cytarabine dosing	X		X		X					
ASP2215 dosing	◄	─	─	─	─	─	─	►		

[v] Obtain written informed consent for continuous participation in the study before starting ASP2215 dosing for consolidation chemotherapy.
[w] QT interval measurements will be performed at the central ECG laboratory on Day 1 at pre-dose and 4 hours post-dose, Day 2 at pre-dose, and Day 15 (at pre-dose if performed on Day 14 within the allowed visit window [−1] for Day 15). The 12-lead ECGs for QT interval measurement will be recorded in triplicate (3 separate ECGs with approximately 2-minute intervals) and transmitted electronically for central reading. When the timing for PK blood sampling and ECG is close, ECG will be performed prior to PK blood sampling.
[x] The bone marrow sample will be collected on Day 1 for the FLT3 mutation test. If bone marrow samples cannot be obtained, whole blood samples will be collected on Day 1.
[y] The bone marrow test will be performed only for starting Cycle 1 of consolidation chemotherapy within 7 days prior to chemotherapy start. It is not necessary to repeat the test if the bone marrow test was performed during the induction therapy period within this period.
[z] Plasma sampling for PK will be performed only during Cycle 1. Plasma PK samples for ASP2215 will be collected on Day 1 at pre-dose, 1, 2, 4, 6, 10, and 24 hours post-dose (before dosing on Day 2), on Day 6 at pre-dose, and on Day 15 (at pre-dose if performed on Day 14 within the allowed visit window [−1] for Day 15). Plasma PK samples for cytarabine will be collected on Day 2 and Day 6 at pre-dose.

Maintenance therapy and End of Treatment

Assessments	Cycle 1		Cycle ≥ 2	At discontinuation or the end of Cycle 26	Follow-up observation [aa]
	Day 1	Day 15	Day 1	Day of judgment of discontinuation or Day 28 of Cycle 26	Last day of dosing +28 days
Allowed visit window	0	±3	±3	Day of judgment of discontinuation or Day 28 of Cycle 26 +7	±7
Physical examination	X	X	X	X	X
Weight	X			X [bb]	
Vital signs	X		X	X [bb]	
ECOG PS	X			X [bb]	
Concomitant medications	←	—	—	—	→
Pregnancy test for WOCBP	X			X [bb]	
12-lead ECG				X [bb]	
Laboratory tests (hematology, biochemistry, thyroid function test, coagulation test and urinalysis)	X		X	X [bb]	
Sampling for FLT3 mutation test (bone marrow or whole blood) [cc]	X				
Bone marrow test [dd]	X			X [bb]	
AE assessment	←	—	—	—	→
PK plasma sampling				X [ee]	
ASP2215 dosing	←	—	—	→	

[aa] Follow up observation will be skipped if it is difficult to be conducted due to initiation of a successive treatment after discontinuation or for another reason.
[bb] Not necessary to repeat these tests if they were performed at a scheduled visit after the last dosing of ASP2215.
[cc] The bone marrow sample will be collected on Day 1 for the FLT3 mutation test. If bone marrow samples cannot be obtained, whole blood samples will be collected on Day 1.
[dd] The bone marrow test will be performed within 7 days prior to the start of maintenance therapy. It will be also performed whenever it was determined to be clinically necessary during the period of ASP2215 dosing.
[ee] PK blood sampling for ASP2215 is strongly recommended even in the case of discontinuation.

Table 7 Schedule of Assessments [Phase 2 part]

Induction therapy

Assessments	Screening [ff]	D1 [ff]	D2-3	D4-7	D8	D9-14	D15	D16-20	D21	D28	D42 [h]	D56 [gg]
Visit window	Within 7 days	0	0	0	0	0	+/- 2	0	+/- 2	+7	+7	+7
Signed ICF	X											
Medical and Disease History												
MUGA or ECHO [hh]												
Pregnancy Test for WOCBP [ii]												
Chest X-ray (or CT of Chest) [jj]												
Idarubicin Administration		X	X									
Cytarabine Administration		X	X	X								
ASP2215 Administration					X	X	X	X	X [kk]			
Registration to the study [ll]	X				X							
Physical Examination	X [mm]	X			X		X		X	X	X	X
Vital Signs	X [mm]	X			X		X		X	X	X	X
Height, Weight and BSA [nn]	X [mm]	X			X							
ECOG Performance	X [mm]	X			X							
Prior and Concomitant Medications	X [oo]	X	X	X	X	X	X	X	X	X	X	X

Table continued on next page

[ff] Consent, Screening, and Cycle 1 Day 1 may be performed on the same day if investigator(s) judges it is necessary due to rapid disease progression and subject meets all inclusion/exclusion criteria except for Inclusion criteria (IC) #4, #14-c, and #14-d for pre-registration. Cycle 1 Day 1 must be initiated within 7 days of consent.

[gg] The end of induction therapy period is not defined. Peripheral blood sample at blood recovery should be submitted to a central lab. If full blood recovery has been observed, scheduled visit for Day 56 may be omitted as long as samples after blood recovery has been submitted to central labs.

[hh] ECHO or MUGA scans are to be performed at Screening for subjects with history of congestive heart failure NYHA Class 3 or 4. ECHO or MUGA performed prior to consent and within 3 months prior to screening may be used.

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

[jj] Chest X-ray/CT of Chest performed prior to consent and within 1 week prior to Screening may be used.

[kk] Administration of ASP2215 should not be more than 14 days even if the scheduled visit has been shifted within the visit window.

[ll] Pre-registration is required before the initiation of induction therapy (Day 1). Registration is required before initiation of ASP2215 treatment. For registration failure subjects, no follow up visits should be conducted.

[mm] If the Screening visit and Day 1 are performed on the same day, only Day 1 data is mandatory.

[nn] Height is only required at Screening. BSA will be calculated when the body weight is measured.

[oo] Includes medications taken within 28 days prior to Day 1.

Assessments	Screening [ff]	D1 [ff]	D2-3	D4-7	D8	D9-14	D15	D16-20	D21	D28	D42 [h]	D56 [gg]
Bone Marrow Aspiration/Biopsy [pp, qq]	X [rr]									X [ss]		
Response Assessment (including extramedullary leukemia)												
FLT3 Mutation Status (bone marrow aspirate or whole blood) [qq]	X [tt]											
PGx [uu]					X							
12-lead ECG [vv]	X [mm]	X			X		X		X	X		
Clinical Laboratory Tests (chemistry, hematology, thyroid function, coagulation, urinalysis) [ww]	X [mm, rr, xx]	X			X [yy]		X		X	X	X	X
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X
PK ASP2215 [zz]							X		X			

[pp] On days when a bone marrow is performed including unscheduled visits, hematology will also be sent to a central lab.
[qq] Remaining bone marrow aspirate will be used for MRD analysis in applicable countries.
[rr] 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 measureable 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 2-8°C and can be sent within 5 days of collection and testing can occur within 7 days of sample collection. Aspirate from initial diagnosis can be sent to Hematogenix if it was collected in EDTA or sodium heparin tube and can be shipped out on the same day of collection or within 1 day of collection. The most recent local bone marrow data before or after informed consent will be collected in eCRF if the central assessment result could not be obtained.
[ss] Bone marrow assessment will be performed any time after Day 28 for response assessment per institutional guidelines.
[tt] FLT3 mutation status will be assessed from bone marrow sample taken at the Screening Visit or at the visit prior to consent. If bone marrow sample is unavailable, the whole blood sample taken at the Screening Visit will be used. Cycle 1 only.
[uu] Buccal swab and/or peripheral blood on screening for optional pharmacogenetic study. Sample collection may be performed any time between registration and ASP2215 administration on Day 8.
[vv] ECG assessment will be evaluated at day 1 (pre-dose), day 8 (pre-dose and 4-hour post-dose [+/- 30 minutes]), day 15 (pre-dose), day 21 (pre-dose) and on day 28. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs 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, however in case of emergency, local ECG or central ECG paper printout results can be considered. Central ECG data should be submitted if urgent treatment decision was made based on the local ECG result.
[ww] All lab tests should be obtained pre-dose unless noted otherwise. Thyroid function test is only performed at Screening.
[xx] Eligibility criteria laboratory tests can be confirmed by the local lab. The values used for eligibility evaluation should be entered in eCRF and the central sample at the same timing of local lab tests should be submitted. Lab values prior to informed consent may be collected in the eCRF in case the local bone marrow assessment result before informed consent was collected.
[yy] Liver function values should be reconfirmed before registration if abnormality due to the primary disease was observed at pre-registration. Local lab assessment is allowed, but samples should be submitted to central lab.
[zz] PK samples for ASP2215 will be collected pre-dose on Day 15, and on Day 21. Pre-dose samples should be collected within 1 hour before ASP2215 administration. If Day 21 scheduled visit is performed within the visit window, PK sampling on Day 19 or 20 is preferred. Cycle 1 only.

Consolidation therapy

Assessments	**D1**	**D2**	**D3**	**D4**	**D5**	**D6-D7**	**D8**	**D9-D14**	**D15**	**D21** [aaa]
Visit window	0	0	0	0	0	0	0	0	+/- 2	+7
Cytarabine Administration	X		X		X					
ASP2215 Administration	X	X	X	X	X	X	X	X		
Physical Examination	X						X		X	X
Vital Signs	X						X		X	X
Weight and BSA	X									
ECOG Performance	X						X			
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Response Assessment (including extramedullary leukemia)	X[bbb]									
Bone Marrow Aspiration/Biopsy [pp, qq]										
12-lead ECG [ccc]	X						X		X	
Clinical Laboratory Tests (chemistry, hematology, coagulation, thyroid function, urinalysis) [ddd]	X						X		X	X [eee]
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X
PK ASP2215 [fff]							X		X	

[aaa] Initiation of the next cycle may be postponed until blood recovery is observed.
[bbb] May be done within 7 days prior to initiation of consolidation. First consolidation cycle only.
[ccc] ECG assessment will be evaluated at day 1 at pre-dose and 4-hour post-dose (+/- 30 minutes), day 8, and day 15. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs at least 5 minutes apart per time point) and transmitted electronically for central reading.
[ddd] All lab tests should be obtained pre-dose unless noted otherwise. Thyroid function test is only performed at Cycle 1 Day 1.
[eee] Peripheral blood sample should be sent to central lab when blood count recovery is observed any time after Day 21.
[fff] PK samples for ASP2215 will be collected at pre-dose on Cycle 1 Day 8 and anytime on Day 15.

Maintenance therapy

Assessments	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 15**	**Cycle X Day 1** [ggg]
Visit window		+/- 2	+/- 7	+/- 2	+/- 7
ASP2215 Administration [hhh]	X	X	X	X	X
Physical Examination	X				
Vital Signs and Weight					
ECOG Performance					
Prior and Concomitant Medications	X	X	X	X	X
Response Assessment (including extramedullary leukemia)	X [iii]	X [jjj]			
Bone Marrow Aspiration/Biopsy [pp, qq]					
Pregnancy Test for WOCBP	X				X
Clinical Laboratory Tests (chemistry, hematology, coagulation, thyroid function, urinalysis) [kkk]	X		X		X
AE/SAE Assessment	X	X	X	X	X
12-lead ECG	X		X		X

[ggg] One Scheduled visit for maintenance therapy is required every 3 cycle.
[hhh] ASP2215 should be administered in the clinic on scheduled visit days after laboratory assessment. All other days, ASP2215 will be taken at home. ASP2215 is administered daily.
[iii] May be done within 7 days prior to initiation of maintenance therapy.
[jjj] Frequency should be determined by clinical practice at each site.
[kkk] All lab assessments should be obtained pre-dose unless noted otherwise. Thyroid function test is only performed at Cycle 1 Day 1.

End of Treatment

Assessments	**Pre-HSCT Visit EOT Visit** [lll]	**30-Day Follow-up** [mmm]	**Long-term Follow-up** [nnn]
Visit window		+ 7 days	+/- 7 days
Physical Examination	X [ooo]	X	
Vital Signs	X [ooo]		
ECOG Performance	X [ooo]		
Concomitant Medications	X [ppp]	X [ppp]	
12-lead ECG	X		
Clinical Laboratory Tests (chemistry, hematology, thyroid function, urinalysis)	X [ooo]		X [qqq]
Response Assessment (including extramedullary leukemia)	X [rrr]		X [sss]
Bone Marrow Aspiration/Biopsy [pp, qq]			
AE/SAE Assessment	X [ttt]	X	X [uuu]
Survival and Subsequent Antileukemic Treatments and Their Outcomes		X	X [vvv]

EOT: End of Treatment, HSCT: Hematopoietic Stem Cell Transplant

[lll] In addition to the subjects who discontinued the study, subjects who complete the maintenance therapy will also perform the End of Treatment (EOT) visit.
[mmm] On-site visit is preferred for safety assessment, however, a phone call follow-up is acceptable.
[nnn] During the long-term follow-up period, the subject will be followed for 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer. The first follow-up will be performed 3 months after the 30-day follow-up visit. On site visit assessment will be performed at the timing of relapse.
[ooo] Does not need to be repeated if data are obtained at a regularly scheduled visit within 3 days of the scheduled Visit.
[ppp] All concomitant treatments administered from Induction Cycle 1 Day 1 to the EOT visit must be recorded. Concomitant medications used for reported AE/SAE should be collected during the AE reporting period (Section 7.3.1 and 7.3.2). Concomitant medications during the long-term follow-up do not need to be collected even if they are used for reported AEs.
[qqq] Only peripheral blood samples for hematology should be collected and submitted to central laboratory at the timing of relapse.
[rrr] Does not need to be repeated if collected at a regularly scheduled visit within 7 days of the Pre-HSCT visit or End of Treatment visit. If bone marrow aspirate is unobtainable (e.g., dry tap), the whole blood sample will be used.
[sss] Bone marrow sample (aspiration or biopsy) should be collected and submitted to central laboratory at the timing of relapse.
[ttt] ASP2215 related SAE should always be reported regardless of the time of the HSCT during the study participation. For subjects who plan to proceed to HSCT and resume ASP2215 treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen and will resume upon the resumption of ASP2215 treatment until 30-day follow-up visit. For subjects who do not plan to resume ASP2215 treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen or 30 days after the last dose of ASP2215, whichever comes first. However, the following AE/SAEs will continue to be collected until 30 days after the last dose of ASP2215, regardless of the time of the HSCT conditioning regimen, the HSCT, and the resumption of ASP2215 treatment:

- 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

Above AE/SAEs will be collected throughout the HSCT period for the subjects who plan to resume ASP2215.

2 INTRODUCTION

2.1 Background

Globally, over 90% of leukemia cases are diagnosed in adults 20 years of age and older, among whom the most common types are chronic lymphocytic leukemia (35%) and acute myeloid leukemia (AML) (32%) [American Cancer Society, 2014]. The median age at diagnosis is 67 years of age, with 54% of patients diagnosed at 65 years or older [O'Donnell et al., 2012]. In Japan, it was estimated that 5600 patients were diagnosed with AML in 2017 [Kantar Health, 2017]. It is estimated that 21450 people will be diagnosed with AML, and 10920 will die from the disease in 2019 in the US [American Cancer Society, 2019]. While 60% to 80% of younger patients achieve a complete remission (CR) with standard therapy, only about 30% to 40% of the overall patient population has long-term disease-free survival [Tallman, 2005]. Outcomes are worse for patients aged 60 years or over, with CR rates in the range of 40% to 55% and poor long-term survival rates.

In Japan, the standard method of induction chemotherapy for previously untreated adult patients with AML is a combination of cytarabine and anthracycline (idarubicin or daunorubicin) [Miyawaki S, et al., 2009]. Although approximately 80% of patients achieve CR with this therapy, nearly 70% of them experience relapse, and only about 30% maintains remission and survive for the long-term. Furthermore, roughly 15% of patients have AML that is resistant to the initial induction chemotherapy. Consequently, the current treatment for newly diagnosed AML is not yet satisfactory, and it is very important to develop new drugs to improve the prognosis of AML patients.

FLT3 is a member of the class III receptor tyrosine kinase family that is normally expressed on the surface of hematopoietic progenitor cells. FLT3 and its ligand play an important role in proliferation, survival, and differentiation of multipotent stem cells. FLT3 is over-expressed in the majority of AML cases. In addition, FLT3 constantly activated with ITD mutation at the juxtamembrane domain or tyrosine kinase domain (TKD) mutations at around D835 in the activation loop are present in 28% to 34% or 11% to 14% of AML cases, respectively [Schlenk & Dohner, 2009]. These mutations which constantly activate 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, and reduced disease-free survival and overall survival [Gale et al., 2008; Moreno et al., 2003; Patel et al., 2012; Yanada, Matsuo, Suzuki, Kiyoi, & Naoe, 2005].

AXL is a receptor tyrosine kinase. It has been suggested that AXL is overexpressed in AML patients who are FLT3-ITD mutation-positive and the activation of AXL is involved in the activation of FLT3 [Park et al., 2013]. Expression of AXL was also observed in FLT3 mutation-negative AML cells, and inhibition of AXL resulted in cell growth suppression [Ben-Batalla et al., 2013]. Moreover, it was reported that a high expression of AXL contributed to chemotherapy resistance of AML [Hong et al., 2008]. Mutation of the c-CBL,

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[uuu] Only SAE data that is related to ASP2215 will be collected.
[vvv] Telephone contact every 3 months until completion of the study.

E3 ubiquitin protein ligase has been noted in some AML cases, and it has been suggested that c-CBL is involved in the activation of FLT3 by suppressing the degradation of FLT3 [Sanada et al., 2009].

Gilteritinib hemifumarate, also referred to as ASP2215 and gilteritinib, is a new chemical entity discovered by Astellas Pharma Inc. in collaboration with Kotobuki Pharmaceutical Co., Ltd. It is a third-generation oral FLT3 inhibitor under development for the treatment of AML. ASP2215 also has inhibitory activities for AXL, leukocyte receptor tyrosine kinase (LTK) and anaplastic lymphoma kinase (ALK). ASP2215 demonstrated favorable efficacy in a nonclinical AML model, with complete regression of tumors in the xenograft model mice transplanted with MV4-11, human AML cell line expressing FLT3-ITD, by repeated oral doses. In addition, ASP2215 inhibited the growth of cells expressing either FLT3-ITD, FLT3-D835Y or FLT3-ITD-D835Y.

Based on the result of a phase 3 study which showed superior efficacy over salvage chemotherapy, XOSPATA (ASP2215) tablets have been approved by Food and Drug Administration (FDA) and Ministry of Health, Labor, and Welfare (MHLW) for the treatment of patients who have relapsed or refractory AML with an FLT3 mutation.

2.1.1 Nonclinical and Clinical Data

2.1.1.1 Nonclinical Pharmacology

ASP2215 inhibited the activity of FLT3, NPM1-ALK, LTK, ALK, and AXL at 1 and 5 nmol/L and of TRKA, ROS, RET, and MER at 5 nmol/L by over 50%. ASP2215 inhibited FLT3, EML4-ALK, and KIT with half maximal inhibitory concentration (IC_{50}) values of 0.291, 1.2, and 229 nmol/L, respectively.

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 receptor (rat), serotonin $5HT_1$ receptor (non-selective, rat), serotonin $5HT_{2B}$ receptor (human), and sigma nonspecific receptor (non-selective, guinea pig) with IC_{50} values of 4.57, 4.90, 0.190, and 0.615 µmol/L, respectively. Examination of the activity of ASP2215 on human $5HT_{2B}$ receptor function in a cell function assay revealed the inhibitory effect of ASP2215, with an IC_{50} value of 5.82 µmol/L; however, it showed no agonistic activity against the receptor to 10 µmol/L.

ASP2215 inhibited the cell growth of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y with IC_{50} values of 1.8, 1.6, and 2.1 nmol/L, respectively. ASP2215 inhibited the growth of MV4-11 cells, which endogenously express FLT3-ITD mutation, with an IC_{50} value of 0.92 nmol/L.

The activity of ASP2215 against MV4-11 cells was further examined in an *in vitro* study. ASP2215 suppressed FLT3 phosphorylation in the cells; treatment at 0, 0.1, 1, and 10 nmol/L resulted in phosphorylation of 100%, 86%, 19%, and 7%, respectively. In addition, ASP2215 suppressed phosphorylation of the signal transducer and activator of transcription 5 (STAT5), AKT, and extracellular signal-regulated kinase in the cells. Furthermore, treatment with

ASP2215 at 3 or 10 nmol/L considerably increased the population of the cells in the G1 phase, suggesting that ASP2215 arrests the cell growth cycle of the cells. In addition, treatment with ASP2215 at 10 or 30 nmol/L considerably increased the annexin V-positive population in the cells, thereby suggesting that ASP2215 induces the apoptosis of the cells.

The antitumor effect of ASP2215 was examined in mice to which MV4-11 tumor was transplanted. Once-daily oral administration of ASP2215 induced growth inhibition of MV4-11 tumors and tumor regression. In particular, its administration at 6 or 10 mg/kg/day induced complete tumor regression for 4 and 6 out of 6 mice, respectively. In this case, the body weight of the mice treated with ASP2215 was not affected at any tested dose. A single oral dose of ASP2215 at 1, 3, 6, and 10 mg/kg administered to mice xenografted with MV4-11 cells inhibited the phosphorylation of FLT3 and STAT5 in MV4-11 tumors. In a combined administration study in mice xenografted with MV4-11 cells, when ASP2215 alone (3 mg/kg/day, oral administration), or 2 drugs of cytarabine (50 mg/kg/day, intraperitoneal administration) and idarubicin (0.5 mg/kg/day, intravenous administration) were administered to mice xenografted with MV4-11 cells, no individual with tumor regression was found, whereas the combination of 3 drugs induced complete tumor regression in 6 of 8 mice [Ueno Y, 2014].

These results indicate that ASP2215 should exhibit antitumor response in patients with AML with FLT3-ITD mutation or FLT3 mutation at D835. ASP2215 in combination with cytarabine and daunorubicin or in combination with cytarabine and idarubicin showed superior antitumor efficacy in mice xenografted with MV4-11 cells compared to ASP2215 alone or to either chemotherapy combinations without ASP2215.

2.1.1.2 Safety Pharmacology and Toxicology

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.

Gilteritinib has a potential to induce genotoxicity in vivo.

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

Gilteritinib 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-Good Laboratory Practice (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 tract was suggested to be a target organ of toxicity at doses of 10 mg/kg per day or higher in juvenile rats, as well 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).

2.1.1.3 Non-Clinical Pharmacokinetics and Metabolism

After a single intravenous administration, terminal $t_{1/2}$ values for ASP2215 were 6.93 hours in rats and 25.4 hours in dogs. 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 most distributed to the liver and was detectable at 72-hour post-dose in many tissues. The concentration of [^{14}C]ASP2215-derived radioactivity administered to pigmented rats fell below the limit of detection by 4-week post-dose in many tissues. However, the elimination of radioactivity from the ciliary body and retina and choroid were notably slow, and Ct/C_{max} ratios at 17-week post-dose were 32.7% and 42.8%, respectively. 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 (HSA). Except one minor metabolite in human hepatocytes, no major human-specific ASP2215 metabolites were formed by liver microsomes or hepatocytes. The main enzyme involved in the metabolism of ASP2215 was estimated to be 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. After oral administration of [^{14}C]ASP2215 at 1 mg/kg to albino rats, the urinary and fecal excretion of radioactivity within 168-hour post-dose was 1.4% and 89.9% of the dose, respectively. The urinary and biliary excretion of radioactivity within 48-hour post-dose was 8.6% and 29.3% of the dose, suggesting that oral absorption was at least 37.9%. A part of biliary excretion is assumed to undergo enterohepatic circulation.

In Caco-2 cells, the permeability of ASP2215 was between that of known low and high permeability markers. ASP2215 is a substrate for P-glycoprotein (P-gp), but not for BCRP, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, or organic cation

transporter (OCT) 1. ASP2215 demonstrated a potential to inhibit BCRP and multidrug and toxin extrusion (MATE)1 at clinically relevant concentrations of ASP2215. However, preliminary results from the drug-drug interaction assessment of co-administration of ASP2215 and cephalexin, a MATE1 substrate, in patients with relapsed or refractory AML (Study 2215-CL-0101) indicate lack of a clinically-significant interaction between ASP2215 and MATE1 substrates (see Section 1.2.4.1). Based on EMA Guideline on the Investigation of Drug Interaction (Jun 2012), ASP2215 may also inhibit liver transporters OCT1 and OATP1B1 at clinically relevant drug exposures.

2.1.1.4 Clinical Studies

2.1.1.4.1 Clinical Pharmacokinetics and Pharmacodynamics

The pharmacokinetic parameters of unchanged drug after single and multiple doses of ASP2215 to AML patients were investigated in the dose escalation cohort of Study 2215-CL-0101. Assessment of C_{trough} over time for individual subjects (both dose escalation and dose expansion cohorts) showed that in most subjects, the trough concentration of ASP2215 appeared to reach steady state by Day 15 of multiple administrations of ASP2215 from 20 to 120 mg once daily. Plasma inhibitory assay from the samples collected pre-dose and post-dose on Days 1, 8, 15 and 29 demonstrated sustained inhibition of phospho-FLT3 at doses 80 mg and higher.

The effect of strong and moderate cytochrome P450(CYP)3A4 inhibitors and strong CYP3A4 inducers on ASP2215 exposure was assessed in patients with relapsed or refractory AML (Study 2215-CL-0101) and healthy subjects (Study 2215-CL-0108). In relapsed or refractory patients with AML, there was a less than 2-fold increase in ASP2215 exposure when ASP2215 was co-administered with moderate or strong CYP3A4 inhibitors. In healthy subjects, ASP2215 exposure increased approximately 2-fold when ASP2215 was co-administered with itraconazole, a strong CYP3A4 and P-glycoprotein (P-gp) inhibitor. Co-administration of ASP2215 with rifampicin, a strong CYP3A4 inducer, resulted in an approximate 70% decrease in ASP2215 exposure. Collectively, these data support monitoring subjects who require concomitant medications that are strong CYP3A4 inhibitors and restricting use of concomitant medications that are strong CYP3A4 inducers.

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

Primary analysis of the relationship between ASP2215 plasma concentration and Fridericia-corrected QT interval (QTcF) change from baseline (ΔQTcF) was performed on data from the 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 study. This assessment included 3344 observations from 487 patients. A concentration-related increase in ΔQTcF was observed; however, the mean ΔQTcF at the mean steady-state C_{max} at 120 mg was predicted to be less

than 10 msec and the upper one-sided 95% confidence interval was predicted to be less than 10 msec and not considered as clinically significant. In addition, less than 5% of relapse/refractory subjects had a maximum post baseline QTcF interval > 500 msec and approximately 7% of subjects had a > 60 msec change in their maximum QTc relative to baseline. Although these data indicate that clinically relevant QTc prolongation is not anticipated, the sponsor has implemented additional eligibility criteria for enrollment in ASP2215 clinical trials (exclusion of subjects with QTcF > 450 msec, long QT syndrome, hypokalemia or hypomagnesemia) and electrocardiogram (ECG) assessments at multiple time points. Astellas will continue to monitor for arrhythmias and clinically significant QT prolongation during the conduct of ASP2215 clinical trials.

An exposure-related increase was observed between ASP2215 plasma concentration and creatine phosphokinase (CK) change from baseline (ΔCK) in patients with relapsed/refractory AML based on pharmacokinetic/pharmacodynamic modeling that included 3361 time-matched data points (n = 497 patients). In addition, the incidence of higher Common Terminology Criteria for Adverse Events (CTCAE) grades related to elevated CK appears to have increased with an increasing ASP2215 dose. However, almost all of the observed elevations in CK laboratory values were Grade 1 and Grade 2, and the incidence of Grade ≥ 3 related adverse events reported in the study population was low. The preferred term of blood creatine phosphokinase increased has been identified as an expected adverse drug reaction (ADR) of ASP2215.

There was a trend toward an increasing incidence of AEs and shifts in laboratory values related to hepatotoxicity with increasing ASP2215 doses as well. Similar to ΔCK, an exposure-related increase was observed between ASP2215 plasma concentration and AST change from baseline (ΔAST) based on pharmacokinetic/pharmacodynamic modeling that included 1517 time-matched data points (n = 243) with low incidence of Grade ≥ 3 related adverse events observed (6.0%). The preferred terms of alanine aminotransferase increased and aspartate aminotransferase increased have been identified as expected ADRs.

2.1.1.4.2 Clinical Studies

Clinical studies of ASP2215 are conducted as a monotherapy in relapsed or treatment-refractory patients with AML as a phase 1/2 clinical study in the US (Protocol No.: 2215-CL-0101) and a phase 1 clinical study in Japan (Protocol No.: 2215-CL-0102), and currently ongoing in relapsed or treatment-refractory FLT3 mutation-positive patients with AML as a phase 3 global study (Protocol No.: 2215-CL-0301) as a validation upon determining the recommended dose in the subsequent phase as 120 mg.

In addition, a phase 1 study in the US (Protocol No.: 2215-CL-0103) in newly diagnosed AML patients is currently ongoing as a combination study with the initial dose of 40 mg.

[Phase 1/2 monotherapy study in the US: 2215-CL-0101]

In 2215-CL-0101, the safety of ASP2215, including ≥ Grade 2 AEs and DLTs, was evaluated at each dose level, and the recommended dose for the next phase in the study was determined to be 120 mg.

2215-CL-0101 consists of dose-escalation and expansion parts. The dose levels examined in each part are as follows:

- Dose-escalation part (20, 40, 80, 120, 200, 300, and 450 mg)
- Expansion part (20, 40, 80, 120, 200, and 300 mg)

As of the data cutoff date of 07 Mar 2018, a total of 265 patients were enrolled in Study 2215-CL-0101 and 252 received at least 1 dose of ASP2215.

A total of 189 (75.0%) of patients experienced at least 1 TEAE considered by the investigator to be possibly or probably related to study drug. Common drug-related TEAEs (occurring in at least 5% of patients) included diarrhea (17.1%); fatigue (14.7%), AST increased (13.5%); ALT increased (11.5%); blood creatine phosphokinase increased (9.9%); anemia (9.1%); constipation and edema peripheral (8.7% each); nausea and platelet count decreased (8.3% each); dysgeusia (7.5%); dizziness (7.1%); thrombocytopenia and vomiting (6.7% each); ECG QT prolonged (6.3%); neutrophil count decreased, transaminases increased and decreased appetite (5.6% each); and neutropenia (5.2%).

The majority of patients (229 [90.9%]) experienced at least 1 grade 3 or higher TEAE. Common grade 3 or higher TEAEs (occurring in at least 5% of patients) included febrile neutropenia (39.7%); anemia (25.4%); AML disease progression (19.0%); platelet count decreased and sepsis (15.1% each); thrombocytopenia (13.1%); pneumonia (14.3%); neutrophil count decreased (8.7%); neutropenia (8.3%); hypoxia (7.5%); hypotension, bacteremia and hypophosphatemia (7.1% each); AST increased (6.7%); fatigue, white blood cell count decreased, hypocalcemia, dyspnea and, respiratory failure (6.0% each); ALT increased (5.6%); and leukocytosis, diarrhea, pyrexia and syncope (5.2% each). Overall, 53 (21.0%) patients experienced a TEAE of maximum grade 3, 71 (28.2%) experienced a TEAE of maximum grade 4 and 105 (41.7%) patients experienced a TEAE of maximum grade 5. The incidence of grade 3 or higher TEAEs in the 20 mg, 40 mg, 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups was 70.6%, 93.8%, 91.7%, 87.0%, 98.1%, 80.0% and 100%, respectively.

Overall, 105 (41.7%) patients experienced TEAEs with an outcome of death, 6 of which occurred more than 28 days after the last dose of ASP2215. The incidence of deaths in the 20 mg, 40 mg, 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups was 29.4%, 37.5%, 45.8%, 34.8%, 48.5%, 40.0% and 33.3%, respectively. The majority of the deaths were attributed to disease progression. Six of the deaths were possibly attributed to ASP2215 administration (1 case each of hemorrhage intracranial, pulmonary embolism, hemoptysis, septic shock, neutropenia and ventricular fibrillation) and 1 death was probably attributed to ASP2215 administration (respiratory failure).

The majority of patients (210 [83.3%]) experienced a serious TEAE. The incidence of serious TEAEs in the 20 mg, 40 mg, 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups was 58.8%, 87.5%, 87.5%, 76.8%, 91.3%, 80.0% and 66.7%, respectively. The most frequent serious TEAEs (occurring in at least 10% of patients overall) were febrile neutropenia (31.7%); AML disease progression (19.0%); sepsis (15.5%), pneumonia (13.1%) and acute kidney injury (10.7%).

Overall, 76 (30.2%) patients experienced a serious TEAE that was considered related to the study drug by the investigator. The incidence of drug-related serious TEAEs in the 20 mg, 40 mg, 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups was 11.8%, 6.3%, 41.7%, 29.0%, 35.9%, 20.0% and 66.7%, respectively. Drug-related serious TEAEs that occurred in 2 or more patients included febrile neutropenia, blood creatine phosphokinase increased and acute kidney injury (2.0% each); AST increased; diarrhea, and pyrexia (1.6% each); gastrointestinal hemorrhage, blood bilirubin increased and hypotension (1.2% each); and neutropenia, myocarditis, supraventricular tachycardia, lower gastrointestinal hemorrhage, nausea, small intestinal obstruction, vomiting, mucosal inflammation, streptococcal bacteremia, ALT increased, liver function test increased, transaminases increased, muscular weakness, posterior reversible encephalopathy syndrome (PRES) and hypoxia (0.8% each).

As of 07 Mar 2018, 31 (14.0%) patients experienced DLTs; most (29/31) patients were in the dose expansion cohort. The following DLTs were experienced in each of the dose groups (number of patients with DLTs in dose group):

- 20 mg dose group (1 patient): grade 5 hemorrhage intracranial.
- 40 mg dose group (1 patient): grade 3 toxic shock syndrome.
- 80 mg dose group (2 patients): grade 3 conjunctival edema and grade 5 septic shock.
- 120 mg dose group (7 patients): grade 3 events of hypoxia, pleural effusion, hematochezia, lower gastrointestinal hemorrhage, hyperbilirubinemia, blood lactate dehydrogenase increased and liver function test increased; grade 4 renal tubular necrosis; and grade 5 ventricular fibrillation.
- 200 mg dose group (15 patients): grade 2 events of dysgeusia, nausea, fatigue and decreased appetite; grade 3 events of transaminases increased, abdominal pain, hematochezia, intestinal perforation, ALT increased, blood creatine phosphokinase increased, ECG QT prolonged, acute promyelocytic leukemia differentiation syndrome, gamma-glutamyl transferase increased, hypotension, dizziness, myalgia, and acidosis and pelvic pain; grade 4 events of hypoxia and PRES. The grade 3 events of transaminases increased and hypotension and grade 4 events of hypoxia were experienced by 2 patients each. All other events occurred in 1 patient each.
- 300 mg dose group (3 patients): grade 3 events of disseminated intravascular coagulation (DIC), gastrointestinal hemorrhage, hypertension, AST increased and rhabdomyolysis; grade 4 blood creatine phosphokinase increased; and grade 5 pulmonary embolism.
- 450 mg dose group (2 patients): grade 3 events of diarrhea and AST increased.

The maximum tolerated dose (MTD) in Study 2215-CL-0101 is considered to be 300 mg.

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 overall survival (OS) from Kaplan-Meier estimates in FLT3 mutation positive patients in ≥ 80 mg dose levels were 218.0 days, with survival probabilities of 56.2% at 26 weeks and 24.9% at 1 year.

[Phase 1 monotherapy study in JP: 2215-CL-0102]

Twenty-seven Japanese patients with AML were enrolled in Study 2215-CL-0102. Of these, 24 received the study drug and 3 discontinued before the start of study drug.

Overall, all patients receiving the study drug experienced at least 1 AE and 91.7% (22/24) of patients experienced a drug-related AE. Common AEs, occurring in ≥ 20% of all patients, were hepatic function abnormal and blood creatine phosphokinase increased (37.5%, 9/24), blood lactate dehydrogenase increased (33.3%, 8/24), diarrhea and pyrexia (29.2%, 7/24) and febrile neutropenia, stomatitis, renal impairment and hypertension (20.8%, 5/24). Of these common AEs, hepatic function abnormal, blood creatine phosphokinase increased and diarrhea appeared to have increased incidence with increasing doses. Blood creatine phosphokinase and diarrhea have been identified as expected adverse reactions for ASP2215.

Overall, AEs with maximum National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher were reported in 66.7% (16/24) of all patients, including 100% (1/1) of patient in 20 mg dose group, 50.0% (2/4) of patients in the 40 mg, 80 mg and 120 mg dose groups, 77.8% (7/9) of patients in the 200 mg dose group and 100% (2/2) of patients in the 300 mg dose group.

The NCI-CTCAE grade 3 or higher AEs reported in ≥ 10% of all patients were platelet count decreased (16.7%, 4/24) and disseminated intravascular coagulation, febrile neutropenia, pneumonia and blood creatine phosphokinase increased (12.5%, 3/24). In the 200 mg dose group, the most common (occurring in 2 or more patients) AEs of NCI-CTCAE grade 3 or higher were platelet count decreased (33.3%, 3/9) and blood creatine phosphokinase increased (22.2%, 2/9).

The majority of the common AEs, including hepatic function abnormal, blood creatine phosphokinase increased and diarrhea, were considered by the investigator to be related to study drug. Drug-related AEs were reported in 91.7% (22/24) of all patients, including 75.0% (3/4) of patients in the 40 mg and 80 mg dose groups and 100.0% of patients in all of the remaining dose groups (n = 1 to 9). The most common SOC that included drug-related AEs

was Investigations (50.0%, 12/24), followed by Gastrointestinal Disorders (37.5%, 9/24) and Hepatobiliary Disorders (33.3%, 8/24).

One patient in the 80 mg dose group died due to an SAE (subdural hematoma possibly related to study drug). Seven patients (29.2%) experienced a serious TEAE, including 25.0% (1/4) of patients in the 40 mg and 80 mg dose groups, and 55.6% (5/9) of patients in the 200 mg dose group. No SAE was reported in the 20 mg, 120 mg or 300 mg dose groups. The only SAE reported in ≥ 2 patients was subdural hematoma (8.3%, 2/24).

Within the 24 DLT-evaluable patients, 3 patients experienced a DLT during cycle 0 and cycle 1, specifically 1 patient (25.0%) in the 120 mg dose group and 2 patients (100%) in the 300 mg dose group. All 3 patients had a dose interruption due to DLT.

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.

[Phase 1 combination study in the US: 2215-CL-0103]

In Study 2215-CL-0103, 5 patients were enrolled before the change of dosing schedule of the study drug. One patient was found to have decrease ejection fraction (Grade 3), which was transient. The other patient was found to have low ANC and platelets by Day 42. Both of the events are considered as DLTs. The dosing schedule of the study drug had been as follows: In the induction phase, idarubicin (12 mg/m^2/day, intravenous administration) is administered for 3 days from Day 1, cytarabine (100 mg/m^2/day, intravenous administration) is administered for 7 days from Day 1, and ASP2215 is administered once daily for 28 days from Day 1 repeatedly until proceeding to the subsequent treatment cycle; in the consolidation phase, cytarabine (1.5 g/m^2, intravenous administration) is administered twice daily on Days 1, 3, and 5 in each cycle and ASP2215 is administered once daily for 28 days from Day 1 repeatedly; and in the maintenance phase, ASP2215 is orally administered once daily for 28 days from Day 1 repeatedly. However, based on the abovementioned facts, this schedule was changed as follows: In the induction phase, idarubicin (12 mg/m^2/day, intravenous administration) is administered for 3 days from Day 1, cytarabine (100 mg/m^2/day, intravenous administration) is administered for 7 days from Day 1, and ASP2215 is administered for 14 days from Day 4, when idarubicin administration has ended, to Day 17, which should be completed after the end of idarubicin administration and 25 days prior to the start of consolidation therapy; in the consolidation phase, cytarabine (1.5 g/m^2, intravenous administration) is administered twice daily on Days 1, 3, and 5 in each cycle and ASP2215 administration is limited to 14 days from Day 1 to Day 14; and in the maintenance period, ASP2215 is orally administered once daily for 28 days from Day 1 repeatedly.

As of the data cutoff date of 23 Oct 2017, 98.0% (48/49) of patients reported at least 1 TEAE. The most frequently reported TEAEs occurring in ≥ 20% of patients in the gilteritinib total

group included febrile neutropenia (65.3% [32/49]); diarrhea (63.3% [31/49]); nausea (42.9% [21/49]); edema peripheral (36.7% [18/49]); pyrexia (34.7% [17/49]) constipation; stomatitis (30.6% [15/49]); abdominal pain, ALT increased, fatigue and vomiting (26.5% [13/49]); AST increased, blood ALP increased and headache (24.5% [12/49]); drug eruption (22.4% [11/49]); and blood creatine increased, dizziness, hypertension, hypokalaemia, mucosal inflammation and thrombocytopenia (20.4% [10/49]).

Overall, 91.8% (45/49) of patients reported at least 1 drug-related TEAE. The most frequently reported drug-related TEAEs occurring in ≥ 10% of patients in the gilteritinib total group included diarrhea (44.9% [22/49]), febrile neutropenia and nausea (36.7% [18/49], each), ALT increased (22.4% [11/49]) and AST increased (20.4% [10/49]).

As of the data cutoff date of 23 Oct 2017, no TEAEs leading to death were reported.

Overall, 42.9% (21/49) of patients reported at least 1 drug-related serious TEAE. The most frequently reported drug-related serious TEAE was febrile neutropenia (16.3% [8/49]); the other drug-related serious TEAEs were reported in ≤ 2 patients in the gilteritinib total group.

As of the data cutoff date of 23 Oct 2017, 16.3% (8/49) of patients experienced a DLT during the induction period. Ejection fraction decreased and small intestinal obstruction were experienced by 4.1% (2/49) of patients, each; all other DLTs during the induction period were experienced by 2.0% (1/49) of patients each.

DLTs were experienced by more patients in the gilteritinib 120 mg group (16.7% [6/36]) compared with the gilteritinib 40 mg group (22.2% [2/9]); 1 patient experienced neutropenia and thrombocytopenia and 1 patient experienced ejection fraction decreased; no patients in the gilteritinib 80 mg group experienced a DLT during the induction period.

During the consolidation period, 7.7% (1/13) of patients in the gilteritinib 120 mg group experienced a DLT of febrile neutropenia; no patients in the gilteritinib 40 mg or the gilteritinib 80 mg group experienced a DLT.

As of the data cutoff date of 23 Oct 2017, there were 22 evaluable patients with a positive FLT3 mutation status in Study 2215-CL-0103. 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).

[Phase 1 part of combination study in JP: 2215-CL-0104]

Similar to the 2215-CL-0103 study, the dosing schedule of the study drug was also changed in this study. Although one patient was enrolled in the ASP2215 40 mg group prior to the change of the dosing schedule of the study drug and has received the study drug, no serious TEAE or DLT, which was considered to be related to the study drug by the investigator, was found.

A total of 13 patients were enrolled after the change of the dosing schedule of the study drug. As of Mar 4, 2019, among the 13 patients who received at least one dose of ASP2215, 13 patients (100.0%) had at least one drug-related TEAE. Drug-related TEAEs that were

found in at least 3 patients were as follows: anemia (61.5%), febrile neutropenia (61.5%), alopecia, diarrhea, platelet count decreased, white blood cell count decreased (38.5% each), neutropenia, neutrophil count decreased, pneumonia (30.8% each), electrocardiogram QT prolonged, leukopenia, and thrombocytopenia (23.1% each).

At least one serious TEAE was found in 3 patients (23.1%). Serious TEAEs that were found were hepatic function abnormal (7.7%) and liver function test abnormal (15.4%).

At least one more than Grade 3 TEAE was found in 11 patients (84.6%). More than Grade 3 TEAEs that were found in 2 or more patients were as follows: anemia (53.8%), febrile neutropenia (76.9%), leukopenia (30.8%), neutropenia (46.2%), thrombocytopenia (30.8%), diarrhea (23.1%), device related infection (15.4%), liver function test abnormal (23.1%), neutrophil count decreased (15.4%), platelet count decreased (38.5%), white blood cell count decreased (38.5%), decreased appetite (15.4%). At least one more than Grade 3 TEAE that was considered related to the study drug by the investigator was found in 8 patients (61.5%). More than Grade 3 TEAEs that were considered related to the study drug by the investigator were found in 2 or more patients were as follows: anemia (38.5%), febrile neutropenia (46.2%), leukopenia (23.1%), neutropenia (30.8%), thrombocytopenia (23.1%), diarrhea (23.1%), platelet count decreased (15.4%), white blood cell count decreased (15.4%).

One patient was found DLT (Grade3 Diarrhea). No TEAE resulting in death was found.

7 patients completed DLT evaluation period, so 7 patients are evaluable for efficacy assessment. Based on the efficacy at the end of the induction phase, 7 patients (100.0%) achieved CRc overall, 4 patients (57.1%) achieved CR, 2 patients (28.6%) achieved CR with incomplete hematologic recovery (CRi) and 1 patient (14.3%) achieved CR with incomplete platelet recovery (CRp). No patients achieved PR.

[Phase 3 monotherapy study in the US: 2215-CL-0301]

Study 2215-CL-0301 is a phase 3, open-label, multicenter, randomized study of ASP2215 versus salvage chemotherapy in patients with relapsed or refractory AML with FLT3 mutation. As of the data cutoff date of 04 Jan 2018, 219 patients had received at least 1 dose of ASP2215 120 mg in Study 2215 CL 0301. The majority of patients (63.9% [140/219]) had ended treatment. The most common reasons for end of treatment (occurring in ≥ 10% of discontinued patients) were progressive disease (37.1% [52/219]), death (20.0% [28/219]), disease relapse (11.4% [16/219]) and AEs (10.7% [15/219]).

As of the data cutoff date of 04 Jan 2018, 219 patients have received at least 1 dose of ASP2215 120 mg. A total of 213 (97.3%) patients experienced at least 1 TEAE and 173 (79.0%) patients experienced at least 1 drug related TEAE. Common TEAEs, occurring in ≥ 10% of all patients, were febrile neutropenia (45.7%), anemia (41.6%), pyrexia (35.2%), ALT increased (34.7%), AST increased (33.3%), diarrhea (30.6%), constipation (30.1%), nausea (28.3%), fatigue (26.0%), cough (25.6%), hypokalemia (25.6%), headache (22.4%), platelet count decreased (21.9%), dyspnea (21.5%), edema peripheral (21.5%), thrombocytopenia (21.5%), blood ALP increased (19.6%), vomiting (19.2%), hypotension

(17.8%), neutrophil count decreased (16.9%), dizziness (16.9%), hypocalcemia (16.4%), insomnia (15.5%), decreased appetite (15.1%), epistaxis (15.1%), abdominal pain (14.6%), pneumonia (14.6%), hypophosphatemia (14.2%), stomatitis (14.2%), hypomagnesemia (13.7%), hyperglycemia (13.2%), myalgia (13.2%), white blood cell count decreased (12.8%), pain in extremity (12.8%), AML disease progression (12.3%), asthenia (11.9%), hyponatremia (11.9%), hypoalbuminemia (11.9%), rash (11.9%), blood creatinine increased (11.4%), blood creatine phosphokinase increased (11.4%), neutropenia (10.5%), back pain (10.5%), arthralgia (10.0%) and pruritus (10.0%). Diarrhea, blood creatine phosphokinase increased, ALT increased and AST increased and edema peripheral and myalgia have been identified as expected adverse reactions for ASP2215.

Common drug-related TEAEs, occurring in ≥ 10% of all patients, were ALT increased (24.7%), AST increased (24.2%), anemia (18.3%), febrile neutropenia (15.1%), thrombocytopenia (13.2%), platelet count decreased (12.8%), nausea (11.9%), blood ALP increased (11.0%), neutrophil count decreased (11.0%), white blood cell count decreased (11.0%), diarrhea (10.5%) and fatigue (10.0%).

The NCI-CTCAE grade 3 or higher TEAEs reported in ≥ 10% of patients were febrile neutropenia (45.7%), anemia (34.2%), platelet count decreased (20.5%), thrombocytopenia (18.7%), neutrophil count decreased (16.9%), AST increased (13.2%), AML disease progression (12.3%), white blood cell count decreased (12.3%), ALT increased (11.4%), hypokalemia (11.4%) and neutropenia (10.5%).

As of the data cutoff date of 04 Jan 2018, 25.6% (56/219) of patients experienced TEAEs leading to death. 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. TEAEs leading to death were considered drug-related for 4.1% (9/219) of patients.

The majority of patients (76.7% [168/219]) experienced at least 1 serious TEAE. The most frequently reported serious TEAEs, occurring in ≥ 10% of all patients, were febrile neutropenia (29.2% [64/219]) and AML disease progression and pyrexia (12.3% [27/219], each). Drug-related serious TEAEs were experienced by 35.2% (77/219) of patients. The most frequently reported drug-related serious TEAEs were febrile neutropenia (7.8% [17/219]), ALT and AST increased (3.7% [8/219], each) and pneumonia (3.2% [7/219]).

In the final analysis for this study, the co-primary study objective of OS was achieved (HR: 0.637; 95% CI: 0.490, 0.830; 1-sided P-value: 0.0004); the median OS was 9.3 months in the ASP2215 arm versus 5.6 months in the salvage chemotherapy arm. The survival probability was higher in the ASP2215 arm compared with the salvage chemotherapy arm at 6 months and 12 months. When censoring patients at the time of HSCT, OS was also significantly longer in the ASP2215 arm compared with the salvage chemotherapy arm (median OS: 8.3 months versus 5.3 months) (HR: 0.575; 95% CI: 0.434, 0.762; 1-sided P-value: < 0.0001). The key secondary study objective of EFS was not achieved, but showed a favorable trend in the ASP2215 arm (HR: 0.793; 95% CI: 0.577, 1.089; 1-sided P-value: 0.0415). The median

EFS duration was 2.8 months in the ASP2215 arm versus 0.7 months in the salvage chemotherapy arm. Another key secondary study objective was to determine the overall efficacy in CR rate of ASP2215 compared to salvage chemotherapy. The treatment difference of CR rate between the ASP2215 and the salvage chemotherapy arms was 10.6% (95% CI: 2.8, 18.4; 1-sided nominal P-value: 0.0053).

2.1.2 Summary of Key Safety Information for Study Drug(s)

Overall, ASP2215 has a nonclinical safety pharmacology and toxicology profile that is acceptable for the treatment of patients with relapsed or refractory FLT3 mutation positive AML at the proposed therapeutic dose. The integrated relapsed and refractory (R/R) AML safety population consisted of FLT3 mutation positive and negative patients from phase 1/2 studies 2215-CL-0101 and 2215-CL-0102 and the phase 3 study 2215-CL-0301.

The safety profile of ASP2215 was similar for the integrated ASP2215 120 mg group in both the R/R AML safety population and the subset of the integrated R/R AML safety population that was positive for FLT3 mutation. Based on an assessment of TEAE by subpopulations of demographic variables, no specific safety precautions are warranted by sex, age, or other demographic factors. The tolerability profile of ASP2215 in these ongoing studies appears to be similar to the integrated R/R AML safety population. Important identified risks associated with ASP2215 treatment, based on the clinical data, include PRES and QT prolongation. Pancreatitis is an important potential risk associated with treatment with ASP2215.

The safety evaluation of ASP2215 is based on 319 patients (including 246 patients in the ADMIRAL trial) with relapsed or refractory AML who received at least one dose of 120 mg ASP2215 daily. At the time of final analysis cutoff, the median duration of exposure to ASP2215 was 111 days (range 4 to 1320 days).

The most common adverse reactions (≥10%) were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, diarrhea, fatigue, nausea, constipation, cough, peripheral edema, dyspnea, blood alkaline phosphatase increased, dizziness, hypotension, pain in extremity, asthenia, blood creatine phosphokinase increased, arthralgia and myalgia.

The most frequent serious adverse reactions (≥2%) reported in patients were ALT increased, diarrhea, AST increased, hypotension and dyspnea.

For the most updated information, see the latest “ASP2215 Investigator’s Brochure.”

2.2 Study Rationale

Mutations in FLT3 (either ITD or TKD) are observed in approximately 30% of patients with newly diagnosed AML. FLT3 mutations have oncogenic potential and most patients carrying these mutations in their leukemic cells have a particular dismal prognosis. Treatment results of patients with FLT3-mutated AML are still unsatisfactory with the majority of patients succumbing from their disease. Treatment using compounds that specifically target mutant cells may be beneficial in improving outcome of patients with these subtypes of AML. ASP2215 is a third-generation oral FLT3 inhibitor that has been approved by FDA and MHLW for the treatment of patients who have relapsed or refractory AML with an FLT3

mutation. In 2215-CL-0301 study, ASP2215 demonstrated prolonged OS, supported by improved CR rate with durable responses, and improved transfusion dependencies in patients with FLT3-mutated R/R AML, as compared to salvage chemotherapy. Non-clinical data suggest that addition of ASP2215 to the intensive chemotherapy induced superior antitumor efficacy compared to standard chemotherapy alone.

Despite advances in AML therapy, the majority of patients die of their disease. The first hurdle to achieve on the road to potential curative therapy in AML is achievement of remission with induction therapy. Pharmacologic targeting of FLT3 (both ITD and TKD) represents an important potential approach for improving these outcomes. While midostaurin, which is a small molecule that inhibits multiple receptor tyrosine kinases including FLT3, demonstrated an improvement in CR and in survival in FLT3-mutated AML patients in RATIFY trial [Stone et al., 2017], ASP2215, as a more selective/potent FLT3 inhibitor, may induce higher CR rate and Minimal Residual Disease (MRD) negative CRs and decreased risk of relapse after CR for FLT3-mutated AML. Together, the data provide a strong rationale to evaluate whether addition of ASP2215 to standard chemotherapy improves clinical benefit in newly diagnosed FLT3-mutated AML patients, comparing with historical benchmark of standard chemotherapy.

2.3 Risk Benefit Assessment

The potential undesirable effects of ASP2215 in humans based on toxicities observed in the nonclinical studies and in the recent clinical study in patients with AML are summarized in previous sections. As with any investigational agent, subjects may experience side effects that are more severe than those observed in the nonclinical and clinical studies or may experience side effects not observed in nonclinical and clinical studies. Findings of potential concern for clinical trials with ASP2215 include effects on the gastrointestinal tract, immune system, hematopoietic system, eye, liver and kidney. ASP2215 has the potential to induce genotoxicity *in vivo*. In the embryo-fetal development toxicity study in rats, ASP2215 showed teratogenic effects and embryo-fetal lethal effects.

In vitro, ASP2215 inhibited the cell growth of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y. In addition, ASP2215 induced complete regression of tumors in the xenograft tumor bearing model mice transplanted with a human AML cell line expressing FLT3-ITD. Furthermore, ASP2215 has shown anti-leukemic activity in an ongoing trial in FLT3 mutation-positive patients with AML.

When a combination of ASP2215 (at a low dose), cytarabine, and idarubicin was tested in mice xenografted with MV4-11 cells, tumor regression was not induced in groups receiving ASP2215 alone or dual drug administration of cytarabine/idarubicin, whereas complete tumor regression was induced in the group receiving triple drug administration.

These nonclinical study results suggest that ASP2215 will show antitumor responses in AML patients, and concomitant administration of ASP2215 with cytarabine and idarubicin will enhance the antitumor effect of these chemotherapy drugs.

Tolerability and efficacy of ASP2215 has been shown in the previous monotherapy studies conducted. Currently available therapy for FLT3-mutated R/R AML consists of intensive salvage chemotherapy, which is generally associated with severe AEs and poor survival outcomes. Additionally, a large number of these patients are over the age of 60 with multiple comorbidities and are therefore not eligible for intensive chemotherapy. In 2215-CL-0301 Study, ASP2215 demonstrated prolonged OS, supported by improved CR/CRh rate with durable responses, and improved transfusion dependencies in patients with FLT3-mutated R/R AML, as compared to salvage chemotherapy. 2215-CL-0101 study provides further evidence, which includes prolonged survival and deep molecular responses in this patient population [Levis et al., 2018]. ASP2215 was well tolerated, associated risks are manageable, and only a small fraction of patients discontinued treatment due to ADRs. Although the safety profile of ASP2215 concomitant with cytarabine and idarubicin has not yet been fully investigated, the safety information obtained from the 2215-CL-0103 study shows good tolerability in the dosage up to 120 mg. Therefore, the benefits of ASP2215 treatment outweigh the risks in patients with FLT3 mutation positive newly diagnosed AML.

3 STUDY OBJECTIVE(S) AND ENDPOINT(S)

Table 8 Study Objective(s) and Endpoint(s)

[Phase 1 part]

Objective(s)	**Endpoint(s)**
Primary	
● Determine the maximum tolerated dose (MTD) and/or recommended expansion dose (RED) of ASP2215 concomitant with cytarabine/idarubicin as induction chemotherapy based on the status of the onset of dose-limiting toxicity (DLT)	● MTD ● RED ● Occurrence of DLT
● Evaluate the safety and tolerability of ASP2215 concomitant with cytarabine/idarubicin as induction chemotherapy and high-dose cytarabine as consolidation chemotherapy	● Adverse events (AEs), safety laboratory tests, vital signs, and electrocardiograms (ECGs)
● Evaluate the safety and tolerability of ASP2215 in maintenance therapy after induction and consolidation therapy	● AEs, safety laboratory tests, vital signs, and ECGs
Secondary	
● Characterize the pharmacokinetic (PK) parameters of ASP2215 concomitant with induction and consolidation chemotherapy	● PK parameters
● Evaluate the PK parameters of cytarabine concomitant with ASP2215	● PK parameters
Table continued on next page	

Objective(s)	**Endpoint(s)**
Exploratory	
● Evaluate the pharmacodynamic (PD) parameters of ASP2215	● PD parameters
● Evaluate the efficacy of ASP2215 concomitant with induction and consolidation chemotherapy	● CR (Complete Remission) ● CRp (CR with incomplete platelet recovery) ● CRi (CR with incomplete hematologic recovery) ● PR (Partial Remission) ● CRc (Composite CR): CR + CRp + CRi ● Overall response rate: CRc + PR ● Duration of response

[Phase 2 part]

Objective(s)	**Endpoint(s)**
Primary	
● Evaluate the efficacy of ASP2215 in combination with induction therapy in newly diagnosed FLT3-mutated acute myeloid leukemia (AML) subjects	● Complete remission (CR) rate after induction therapy period for Phase 2 part subjects
Secondary	
● Characterize the pharmacokinetic (PK) parameters of ASP2215 concomitant with induction and consolidation chemotherapy	● PK parameters
● Evaluate the safety and efficacy of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy	● Overall survival (OS) ● Event free survival (EFS) ● Relapse free survival (RFS) ● CR rate after each treatment therapy ● CR rate without minimal residual disease (MRD) after each treatment therapy ● Complete remission with partial hematological recovery (CRh) rate after each treatment therapy
Table continued on next page	

Objective(s)	**Endpoint(s)**
● Evaluate the safety and efficacy of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy *(continued)*	● Composite complete remission (CRc) rate after each treatment therapy ● CR/CRh rate after each treatment therapy ● Duration of CR, CR/CRh, CRh, and CRc ● Duration of response ● Adverse events (AEs), safety laboratory tests, vital signs, and electrocardiograms (ECGs)
Exploratory	
● Evaluate the additional efficacy measures for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy	● Transplantation rate ● Cumulative incidence of relapse (CIR) after 1st CR (CR1) ● Cumulative incidence of death (CID) after CR1 ● Time to hematopoietic recovery after each treatment cycle ● MRD ● MRD-negative CR rate after induction ● Overall MRD-negative CR rate for any treatment period

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Study Design

This study is a Phase 1/2, open-label, single-arm study in patients with newly diagnosed AML. The phase 1 part evaluates the dose of ASP2215 using the Bayesian-continual reassessment method (hereinafter, Bayesian-CRM) and the Phase 2 part evaluates the safety and the effect of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy in newly diagnosed FLT3-mutated AML patients. This study is composed of two Phase 1 parts, which are the dose-evaluation part and the expansion part, and the Phase 2 part; the target population for each part is newly diagnosed AML patients and newly diagnosed AML patients with FLT3 mutation, respectively. Phase 1 part will be conducted in Japan and Phase 2 part will be conducted in Asia Pacific countries.

[Phase 1 part (dose-evaluation part and dose expansion part)]

The dose evaluation part and the expansion part are considered as the Phase 1 part. The primary objective of the Phase 1 part is to determine the MTD and/or recommended

expansion dose (RED) of ASP2215 concomitant with chemotherapy drugs as induction therapy based on the status of the onset of dose-limiting toxicity (DLT). Dose-evaluation part will first evaluate the tolerated dose and the expansion part will confirm the safety of the dose identified in the dose-evaluation part. Subject enrollment and DLT assessment will be continued until the criterion for enrollment completion shown in the Table 9 for Bayesian-CRM is met.

Table 9 Phase 1 Part Dose Evaluation Flow Chart

Dose Level	Cohort 1	Cohort 2	. . .
1 (120 mg)	3 subjects	3 subjects	. . .
-1 (80 mg)		3 subjects	. . .

The starting dose of ASP2215 in the dose-evaluation part is 120 mg. According to the Table 9, at least 3 subjects will receive ASP2215 at the assigned dose (120 mg, or 80 mg as necessary) for the determination of MTD and/or RED. The DLT assessment period for the dose-evaluation part is until the end of induction therapy Cycle 1 and until the end of consolidation therapy Cycle 1 for the dose-expansion part. Subjects who meet any of the following criteria will be considered unevaluable for DLT and will be replaced by another subject in the cohort.

- A subject that receives less than 80% of the assigned dose of ASP2215 during DLT assessment period specified in each part (e.g., subject in dose assessment part who misses ≥ 3 daily doses during DLT assessment period of dose evaluation part and interrupts the study for a reason other than a DLT)
- Unable to assess the safety adequately during DLT assessment period specified in each part such as due to the lack of required safety assessment(s)

The decision of whether or not to proceed to the next dose of ASP2215 will be made through discussion among the sponsor, principal investigators, and medical advisor with reference to the recommended dose level calculated using Bayesian-CRM, the safety data, etc., and after review by the sponsor's responsible person. The MTD is defined as the highest dose of ASP2215 at which the posterior mean of the DLT incidence during Cycle 1 of induction therapy is estimated to be closest to 33%.

[Phase 2 part]

After achieving the objectives of the Phase 1 part, the Phase 2 part can be initiated. Subjects will receive ASP2215 at the recommended dose established in the Phase 1 part. The primary objective of the Phase 2 part is to evaluate the efficacy of ASP2215 in combination with induction therapy in newly diagnosed FLT3-mutated AML subjects. The target population will be limited to newly diagnosed FLT3-mutated AML. The primary analysis for the

primary endpoint of the CR rate will be conducted when all registered subjects complete the induction therapy period.

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, relapse and survival (cause and date of death). During the long-term follow-up period, the subject will be followed for 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.

4.1.1 Administration Plan

[Phase 1 part]

In the Phase 1 part of this study, the next dose level to which subjects are enrolled is determined sequentially using Bayesian-CRM (O'Quigley, Pepe, & Fisher, 1990). The starting dose level of ASP2215 in this study will be 120 mg per day, and the study should examine dose levels as the safety is assessed. To assess the safety of the dose levels determined to be administered, 3 subjects, in principle, will be enrolled to receive each dose level, which will be considered as 1 cohort. The procedure for determining the dose levels for subject enrollment is as follows. The details of the procedure will be specified separately.

1. The sponsor will obtain the safety information for Cycle 1 from 3 subjects, in principle, in the same cohort.
2. The sponsor, the medical expert, and the investigator (or the when assigned by the investigator) will review the safety information submitted by the study site and confirm whether or not the reported DLT events meet the definition in Section 4.1.2.
3. At the end of the Cycle 1 assessment for the given cohort, the sponsor will use all of the DLT data obtained to date from the study, and using Bayesian-CRM, calculate the posterior mean of the DLT incidence for each dose level. Then, the sponsor will propose the next recommended dose level for subject enrollment.
4. If there is safety information from Cycle 1 and from prior cohorts, if any, the sponsor, the medical expert and the investigator (or the when assigned by the investigator) will comprehensively assess the safety information from Cycles subsequent to 1, and by referring to the recommended dose indicated by Bayesian-CRM, discuss the next dose level for subject enrollment (dose escalation by 1 level, continue with the same dose level without escalation, dose reduction or, if necessary, addition of an intermediate dosage) or the end of enrollment. Based on the outcome of the discussion, the sponsor will make the final decision on the next dose level.
5. When the next dose level is finalized, in principle, 3 subjects will be enrolled to receive that dosage, and the same assessment procedure will be repeated.

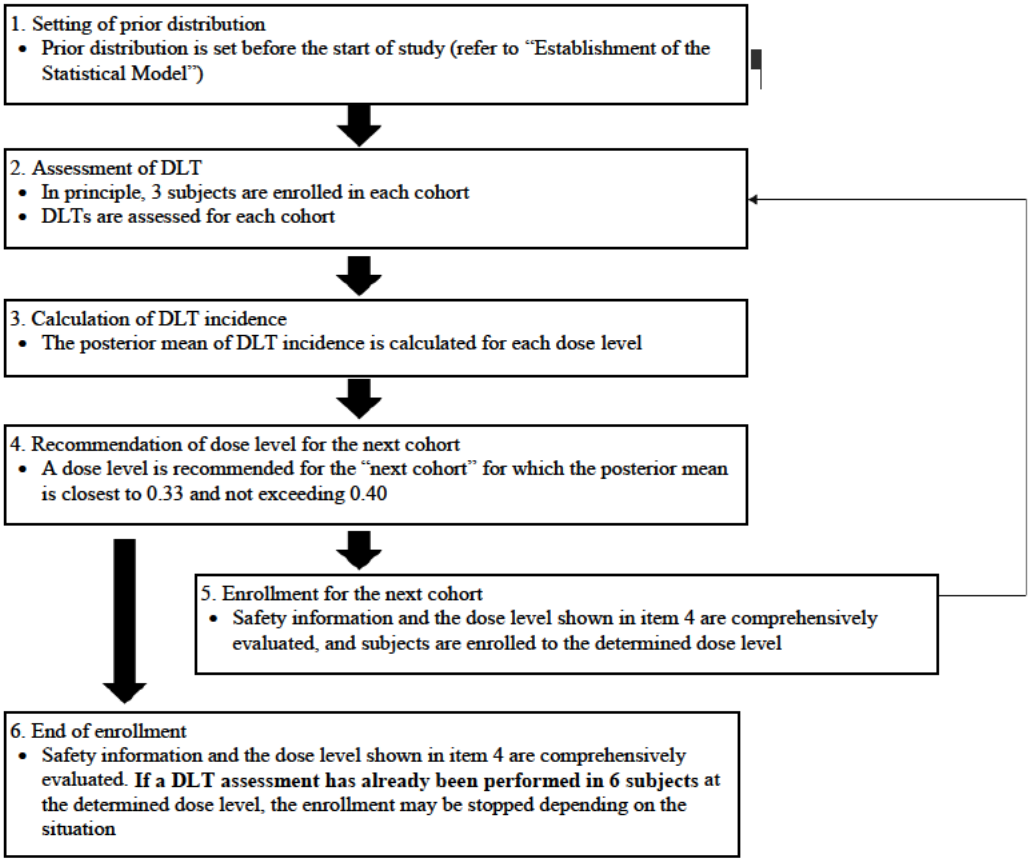
Subject enrollment and DLT assessment will be continued until the criterion for ending enrollment shown in the Table 9 for Bayesian-CRM is met.

Procedures for the Transition of Cohorts using Bayesian-CRM:

The transition of cohorts will be performed by the following procedure.

Procedures

1. Set the prior distribution before the start of the study.
2. Assess the DLTs in each cohort.
3. Estimate the posterior mean of the DLT incidence for each dose level based on the incidence of DLTs accumulated up to the latest cohort assessment.
4. The dosage for which the posterior mean is closest to 0.33 but not exceeding 0.40 will be the "recommended dose level for the next cohort." However, the recommended dose level must be no more than 1 step higher/lower than the dose level of the latest cohort (for dose escalation/reduction, there will be no skipping of dosage between cohorts).
5. Comprehensively assess the safety information and the "recommended dose level for the next cohort" in item 4 to determine the dose level for the next cohort. Newly enrolled subjects to the determined dose level.
6. Comprehensively assess the safety information and "recommended dose level for the next cohort" in item 4 to determine the dose level for the next cohort. However, if a DLT assessment has already been performed in 6 subjects at the determined dose level, enrollment may be stopped depending on the situation.



Establishment of the Statistical Model

The dose-response relationship against DLT occurrence assumes a power model (O'Quigley & Shen, 1996), as shown below.

The occurrence of DLTs for each patient should follow the Bernoulli distribution.

Power model:

$$\Pr(Y_i = 1 | dose = d_i) = \pi(x_i, \alpha) = {x_i}^{\exp(\alpha)},$$

where α is the parameters, x_k is the skeleton of DLT incidence probability in the dose for number k used in the statistical model, Y_j is the presence/absence of DLT in subject j (1 is present), d_j is the administered dose of subject j, and π(•) is the probability of DLT occurrence under given conditions.

Prior distribution of parameters assumed a normal distribution with the mean as 0 and variance as 1.26. Using the Effective Sample Size (ESS) (Morita, Thall, & Muller, 2008), the variance of the prior distribution of a parameter α was set so that the information content of prior distribution in the power model is approximately 1 subject (Takeda & Morita, 2015).

The skeletons to be used in the statistical model are $x_1 = 0.08$ and $x_2 = 0.17$.

[Phase 2 part]

Not applicable

4.1.2 Definition of DLT

[Phase 1 part]

A DLT is defined as any of the following events that occurs during the DLT assessment period, and that is considered to be possibly, probably, or definitely related to induction or consolidation therapies including the study drugs. The DLT assessment period for making a decision of whether or not to proceed to the next dose is defined as the shorter of the following 2 periods: 39 days from the start of the treatment with ASP2215 in the induction period or days between the start of induction therapy and the start of the first consolidation therapy. For safety assessment during the expansion part, the DLT assessment period includes Cycle 1 of consolidation therapy in addition to the period defined above.

Any Grade ≥ 3 non-hematologic or extramedullary toxicity or any events that require dose reduction of ASP2215. However, the following exceptions are noted:

- Anorexia, or fatigue
- Grade 3 nausea and/or vomiting that do not require tube feeding or total parenteral nutrition (TPN), and Grade 3 diarrhea that does not require prolonged hospitalization. However, they are limited to the ones that can be managed to Grade ≤ 2 with standard antiemetic or antidiarrheal medications used at the prescribed dose within 7 days of onset
- Grade 3 mucositis that resolves to Grade ≤ 2 within 7 days of onset

- Grade 3 pyrexia with neutropenia, with or without infection
- Grade 3 infection

The following hematologic toxicities that occur after the first dose of ASP2215 that does not resolve by Day 42 of the last induction therapy cycle or before the start of the first consolidation cycle, whichever is sooner, will be considered a DLT. However, hematologic toxicity in subjects who did not achieve remission is not included in assessment.

- Peripheral neutrophil count < 500/mm^3 (Grade 4)
- Platelet count < 20,000/mm^3 due to bone marrow hypoplasia (except for cases caused by leukemic infiltration or other causes). Bone marrow hypoplasia is defined as bone marrow cellularity less than 20%.
- Platelet count < 50,000/mm^3 accompanying bleeding (≥ Grade 3)
- Platelet count < 25,000/mm^3 requiring platelet transfusion (Grade 4)

[Phase 2 part]

Not applicable

4.1.3 Determination of Maximum Tolerated Dose and Recommended Expansion Dose

[Phase 1 part]

Determination of MTD:

The dose at which the posterior mean of DLT incidence is estimated to be closest to 33% when calculated using Bayesian-CRM from the status of DLT occurrence accumulated from this study during Cycle 1 of the induction period will be the candidate MTD. Through discussion with the medical expert, investigator, and advisor of medical statistics, the sponsor will comprehensively review the data obtained from Cycle 1, and decide the final MTD. The detailed procedure will be specified separately.

Determination of RED:

The sponsor will decide the RED considering the MTD, safety, pharmacokinetic, and efficacy of ASP2215. The final RED will be decided by the sponsor's responsible person by comprehensively assessing the data obtained from the study, and taking into account the discussion held between the sponsor, the medical expert, the investigator, and the advisor of medical statistics. The detailed procedure will be specified separately.

[Phase 2 part]

Not applicable

4.2 Dose Rationale

The starting dose of ASP2215 of 120 mg in this clinical study was established because good tolerability had been found in the phase 1 combination study in the US (Protocol No.: 2215-

CL-0103) in the newly diagnosed patients with AML and the dose had been set as a recommended dose.

Good tolerability was also found at a dose of 120 mg in dose-escalation clinical studies of ASP2215 monotherapy, which are currently ongoing in patients with relapsed or treatment-refractory AML in the US as Phase 1/2 study (Protocol No.: 2215-CL-0101) and domestic Phase 1 study (Protocol No.: 2215-CL-0102), and a phase 3 global study in relapsed or treatment-refractory FLT3 mutation-positive patients with AML (Protocol No.: 2215-CL-0301) is currently ongoing as a validation study upon determining the recommended dose in the subsequent phase as 120 mg.

As a result of comparison and evaluation of the safety, efficacy, and pharmacokinetics of ASP2215 in the 2215-CL-0101 and 2215-CL-0102 study, no substantial ethnical difference was considered between Westerners and Japanese. In addition, there was no substantial racial difference in pharmacokinetics of cytarabine, the dosing period of which overlaps that of ASP2215, in the induction and consolidation phases. Furthermore, because the metabolic and elimination pathways are different between ASP2215 and cytarabine, it is estimated to be less likely to have pharmacokinetic interactions. Because the dosing period of idarubicin does not overlap, the effect on the pharmacokinetics is considered to be small. Based on these discussions in the monotherapy, no substantial ethnical difference is assumed in the pharmacokinetics at the combined administration; therefore, it is appropriate to set the 120 mg, in which tolerability was found in the 2215-CL-0103 study, as the starting dose of the 2215-CL-0104 study.

The ASP2215 dosage in the expansion part will be RED that has been recommended based on the results of the dose-evaluation part.

Chemotherapy regimen dose will not be changed to ensure that each subject is able to receive the minimum standard therapy for Phase 1 part (For Phase 2 part, based on the investigator decision, chemotherapy dosing of Induction Cycle 2 may be reduced after confirmation with the sponsor). The ASP2215 dosing schedule was changed in order to avoid concomitant administration with idarubicin, an anthracycline agent that should be carefully administered.

4.3 End of Study Definition

Study completion is defined as the conclusion of data collection for the defined study endpoints. The study may be closed within a participating country per local regulations once the study has been completed and if all subjects enrolled in the country are no longer receiving study drug. Study will continue until all long-term follow-ups are completed.

A discontinuation is a subject who enrolled in the study and for whom study treatment is terminated 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.

5 STUDY POPULATION

All screening assessments must be completed and reviewed to confirm the potential subject meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

[Phase 1 part]

Newly diagnosed AML patients

[Phase 2 part]

Newly diagnosed FLT3-mutated AML patients

5.1 Inclusion Criteria

[Phase 1 part]

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

1. Written informed consent has been obtained (However, if the subject is underage, consent must also be obtained from the subject's legal guardian).
2. Subject is ≥ 18 and < 70 years of age at the time of obtaining informed consent.
3. Subject is defined as having previously untreated *de novo* AML according to the World Health Organization (WHO) criteria (2008) within 28 days prior to study enrollment.
4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (refer to Section 12.5).
5. Subject must meet all of the following criteria in the laboratory test at screening:
    - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤ 2.5 × institutional upper limit of normal (ULN)
    - Total serum bilirubin level of ≤ 1.5 × institutional ULN
    - Serum creatinine level of ≤ 1.5 × institutional ULN or an estimated glomerular filtration rate (eGFR) of > 50 mL/min†

†Calculating formula: eGFR (mL/min/1.73 m^2 = 194 × $Cr^{-1.094}$ × $Age^{-0.287}$ (× 0.739 for female subjects)

6. Subject is suitable for oral administration of ASP2215.
7. Female subject falls under the following:

    Of non-child bearing potential:

    - Post-menopausal (defined as at least 1 year with no menses without a medical reason such as drug administration) at screening, or
    - Documented surgically sterile or status post-hysterectomy (at least 1 month prior to screening)

Of childbearing potential:

- Agrees not to try to become pregnant during the study and for 60 days after the final study drug administration,
- Has a negative result for the serum or urine pregnancy test at screening, and
- If heterosexually active, agrees to consistently use two effective contraceptive methods (one of which must be the barrier method) per locally accepted standards starting at screening and throughout the study period and for 60 days after the final study drug administration.

8. Female subject agrees not to breastfeed starting at screening and throughout the study period and for 60 days after the final study drug administration.
9. Female subject agrees not to donate ova starting at screening and throughout the study period and for 60 days after the final study drug administration.
10. Male subject and his female spouse/partner who is of childbearing potential agrees to use two effective contraceptive methods (one of which must be the barrier method) per locally accepted standards starting at screening and throughout the study period, and for 120 days after the final study drug administration.
11. Male subject agrees not to donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
12. Subject agrees not to participate in another interventional study while on study treatment.
13. Subject can be admitted during the induction period.

[Phase 2 part]

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

1. Institutional Review Board-/Independent Ethics Committee-approved written informed consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing informed consent form (ICF).
3. Subject has a diagnosis of previously-untreated *de novo* AML according to World Health Organization (WHO) classification (2017) documented within 28 days prior to enrollment.
4. Subject is positive for FLT3-ITD and/or TKD mutation in bone marrow or whole blood as determined by the central lab. Registration by the local lab result is not acceptable.
5. Subject has an ECOG performance status (PS) 0 to 1 (see Section 12.5). Subject who has an ECOG PS 2 is eligible only if investigators suspect that the primary disease related symptoms such as pneumonia and febrile neutropenia are the causes of PS score.
6. Subject is suitable for oral administration of ASP2215.

7. Female subject is not pregnant (see Section 12.3) and at least 1 of the following conditions apply:
   a. Not a woman of childbearing potential (WOCBP) (see Section 12.3)
   b. WOCBP who agrees to follow the contraceptive guidance (see Section 12.3) from the time of informed consent through at least 180 days after final study treatment administration.
8. 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.
9. Female subject must not donate ova starting at screening and throughout the study period and for 180 days after the final study drug administration.
10. Male subject and their female partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 120 days after the final study drug administration.
11. Male subject must not donate sperm starting at screening and throughout the study period and for 120 days after the final study drug administration.
12. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 120 days after the final study treatment administration.
13. Subject agrees not to participate in another interventional study while on treatment.
14. Subject must meet the following criteria as indicated on the clinical laboratory tests:
   a. Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN), or if serum creatinine outside normal range, then glomerular filtration rate (GFR) > 50 mL/min/1.73 m^2 as calculated with the 4-parameter Modification of Diet in Renal Disease (MDRD) equation.
   b. Serum total bilirubin ≤ 2.5 mg/dL (43 µmol/L), except for subjects with Gilbert's syndrome.
   c. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN. If liver abnormality by the primary disease is suspected, subject may be pre-registered to initiate the chemotherapy. Prior to registration, AST/ALT values must meet the criteria to continue the study.
   d. Serum magnesium ≥ institutional lower limit of normal (LLN). Subject may pre-register without magnesium value, but subject must meet the criteria prior to the full registration on Day 8.
   e. Serum potassium ≥ institutional lower limit of normal (LLN).

5.2 Exclusion Criteria

[Phase 1 part]

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

1. Subject was diagnosed with acute promyelocytic leukemia (APL).
2. Subject has breakpoint cluster region-abelson (BCR-ABL)-positive leukemia (chronic myelogenous leukemia in blast crisis).

3. Subject has active malignant tumors other than AML or myelodysplastic syndrome (MDS).
4. Subject has received prior AML treatment except for the following:
    - Urgent leukapheresis
    - Hydroxyurea administration for emergency treatment of hyperleukocytosis (≤ 7 days)
    - Administration of retinoic acid before the diagnosis to exclude APL (≤ 7 days)
    - Supportive care using growth factors or cytokines
    - Steroid administration to treat hypersensitivity or blood transfusion reactions
5. Subject has clinically active central nervous system leukemia.
6. Subject has disseminated intravascular coagulation (DIC).
7. Subject has had major surgery within 28 days prior to the first study drug administration.
8. Subject has had radiation therapy within 28 days prior to the first study drug administration.
9. Subject has congestive heart failure of NYHA class 3 or 4 (see Section 12.5), or subject with a past history of congestive heart failure of NYHA class 3 or 4 and in whom echocardiogram (ECHO) or Multiple Gate Acquisition (MUGA) scan performed within 3 months prior to screening or at screening showed a left ventricular ejection fraction (LVEF) of < 45%.
10. Subject has cardiac impairment or a clinically significant cardiac disease, including any one of the following:
    - Complete left bundle branch block
    - Obligate use of cardiac pacemaker
    - Long QT syndrome
    - Prolongation of the mean QTc interval (> 450 ms) on electrocardiogram (ECG) at screening
    - Right bundle branch block + left anterior hemiblock (bifascicular block)
    - Angina pectoris within 3 months prior to study drug administration
    - Acute myocardial infarction within 3 months prior to study drug administration
11. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.
12. Subject requires treatment with concomitant drugs that target serotonin $5HT_1$ or $5HT_{2B}$ receptors or sigma nonspecific receptors, with the exception of drugs that are considered absolutely essential for treatment of the subject.
13. Subject has an active uncontrolled infection.
14. Subject is known to have human immunodeficiency virus (HIV) infection.
15. Subject has active hepatitis B or C or other active hepatic disorders.
16. Subject has any condition that, in the investigator's opinion, makes the subject unsuitable for study participation.
17. Subject has potassium and magnesium levels of below institutional lower limit of normal in the laboratory test at screening.

18. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) (with the exception of drugs that are considered absolutely essential for the care of the subject).

[Phase 2 part]

A subject will be excluded from participation in this clinical study if any of the following apply:

1. Subject was diagnosed with acute promyelocytic leukemia (APL).
2. Subject has known BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has therapy-related AML.
4. Subject has active malignant tumors other than AML.
5. Subject has received previous therapy for AML, with the exception of the following:
   - Emergency leukapheresis,
   - Emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 10 days,
   - Preemptive treatment with retinoic acid prior to exclusion of APL ≤ 7 days,
   - Growth factor or cytokine support, or
   - Steroids for the treatment of hypersensitivity or transfusion reactions.
6. Subject has QTcF interval > 450 ms (average of triplicate determinations based on central reading).
7. Subject with long QT syndrome.
8. Subject has clinically active central nervous system leukemia.
9. Subject has had major surgery within 4 weeks prior to the first study dose.
10. Subject has radiation therapy within 4 weeks prior to the first study dose.
11. Subject has immediate life-threatening, severe complications of leukemia such as severe uncontrolled bleeding and/or severe disseminated intravascular coagulation
12. Subject is known to have human immunodeficiency virus infection.
13. Subject has active hepatitis B or C.
14. Subject has an uncontrolled infection. An infection controlled with an approved or closely monitored antibiotic/antiviral/antifungal treatment is allowed.
15. Subject has uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, congestive heart failure New York Heart Association (NYHA) class 3 or 4 or subject with a past history of congestive heart failure of NYHA class 3 or 4 and in whom echocardiogram (ECHO) or Multiple Gate Acquisition (MUGA) scan performed within 3 months prior to screening or at screening showed a left ventricular ejection fraction (LVEF) of < 45%.
16. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.
17. Subject requires treatment with concomitant drugs that target serotonin $5HT_{2B}$ receptors or sigma nonspecific receptors, with the exception of drugs that are considered absolutely essential for treatment of the subject.

18. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.
19. Subject has prior malignancies, except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.
20. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

5.3 Restrictions during the Study

The investigator and study coordinators will instruct the subjects on the following during the study:

1. General precautions

Subjects must visit the study site on the scheduled examination dates. If a subject cannot visit the study site for any reason, they must immediately contact the investigator, or study coordinator and ask for their instruction.

2. Behavior

If any symptom has occurred, the subject should contact the investigator or study coordinator as soon as possible.

3. Treatment compliance

Subjects must follow the instructions of the investigator or study coordinator and comply with the study treatment.

The study drug must not be chewed or dissolved in the mouth before swallowing.

If a subject vomits after taking the study drug, no more drugs should be taken to replace it.

During the outpatient period, the subject must comply with the above, as well as the following:

- Any remaining study drugs that the subject has forgotten to take should be brought in at the next visit, and after confirmation by the investigator or study coordinator, the status of treatment compliance should be reported. Any study drugs that the subject is not scheduled to take must be returned and should never be disposed of by the subjects themselves.
- If the study treatment is discontinued at the subject's discretion, the subject must visit the study site as soon as possible and undergo examination by the investigator.

4. Communications about concomitant drugs and therapies

Subjects must not take any prescription drugs or OTC drugs at their own discretion without talking first with the investigator or study coordinator. Subjects must consult the investigator or study coordinator in advance if they wish to take such medication.

If a subject is consulting or planning to consult another department of the study site or a different hospital, they should contact the investigator or study coordinator beforehand whenever possible. If the subject cannot contact the investigator or study coordinator beforehand, they should do so afterward as soon as possible.

5. Other

Subjects must use contraception throughout the study period, and male subjects for 120 days and female subjects for 180 days following the final study drug administration.

Subjects must not donate blood during the study period (See Section 12.3).

5.4 Screen Failures

A screen failure is defined as a potential subject who signed the ICF but did not meet 1 or more criteria required for participation in the study and was not pre-registered.

For screen failures, the minimum data (the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure) will be collected in the screening failure log (SFL). This information can be entered into the study database.

5.4.1 Rescreening

[Phase 1 part]

Not applicable

[Phase 2 part]

Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, ECG, etc.) may be repeated within the 7-day screening period without the need to register the subject as a screen failure. The registration criteria described in Section 5.5 should be met before Day 8 and assessments may be repeated. If more than 7 days elapse from the date of signing the ICF or did not meet all registration criteria by Day 8, the subject must be documented as a screen failure. In order to re-screen, a new ICF must be signed and the subject entered into screening with a new subject identification number. Rescreening is only allowed once for an individual subject.

5.5 Pre-Registration, Registration and Registration Failures

[Phase 1 part]

Not applicable

[Phase 2 part]

Pre-registration occurs when a subject meets all eligibility criteria except for Inclusion criteria #4, #14-c, and #14-d and is prepared for Day 1. Subjects must meet all criteria by the planned administration of ASP2215 on Day 8 in order to be registered and to continue the study. Confirmation of criteria and the process of registration by Day 8 by investigator should be documented. If the subject did not meet all criteria by planned administration of ASP2215 on Day 8, the subject should be considered as registration failure. For Inclusion criteria #14-c, and #14-d, the most recent value prior to registration should meet the criterion.

5.6 Subject Replacement

[Phase 1 part]

If a subject is found to meet any of the following criteria, the subject will be considered unevaluable for DLT, and a new subject will be added to this cohort.

- The subject has received less than 80% of the intended dose of ASP2215 during DLT assessment period specified in each part (e.g., subject in the dose-evaluation part who misses ≥ 3 daily doses during DLT assessment period and interrupts the study treatment for reasons other than a DLT).
- The safety of the subject cannot be assessed adequately during DLT assessment period specified in each part such as due to the lack of required safety assessment(s).

[Phase 2 part]

Not applicable

6 STUDY DRUGS AND CONCOMITANT CHEMOTHERAPY

6.1 Study Drugs and Concomitant Chemotherapy

Table 10 Study Drugs and Concomitant Chemotherapy

Name	**ASP2215 (gilteritinib fumarate)**	**Cytarabine**	**Idarubicin**
Code name	ASP2215	AS3329381 (*unique to JP region*)	Not applicable
Use	Study drug	Study drug/Concomitant chemotherapy (based on the local regulation)	Concomitant chemotherapy
Dosage Formulation	Tablet	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.
Table continued on next page			

Name	**ASP2215 (gilteritinib fumarate)**	**Cytarabine**	**Idarubicin**
Physical Description	Round light yellow film-coated tablet	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.
Unit Dose Strength	40 mg tablet	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.
Packaging and Labeling	HDPE bottle containing 30 tablets	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.	Refer to the country Package Insert or equivalent information provided by the manufacturer or the Sponsor.
Route of Administration	Oral	IV infusion	IV infusion
Administration Instruction	Once daily with water	Administered intravenously and duration of infusion can be determined based on site clinical practice and the local package insert	Administered intravenously and duration of infusion can be determined based on site clinical practice and the local package insert
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor or supplied locally by investigational site	Provided centrally by Sponsor or supplied locally by investigational site

IV: intravenous

Refer to the pharmacy manual, product label and package insert for detailed information regarding preparation, handling and storage of the study drug and concomitant chemotherapy.

6.1.1 Dose/Dose Regimen and Administration Period

Dose/Dose Regimen:

[Phase 1 part]

Subjects will receive the specified dose of ASP2215 shown in Table 11 once a day orally with water. The study drug should be taken as close as possible to the same time each day. The daily dose in the dose expansion part will be RED recommended in the dose-evaluation part.

Table 11 Dose level of ASP2215

Dose level	ASP2215 dose (mg/day)
−1	80
1	120

[Phase 2 part]

The daily dose in the Phase 2 part will be the RED determined in the Phase 1 part.

Administration Period:

ASP2215

[Phase 1 part]

- Induction period (maximum of 2 cycles): Once-daily repeated oral administration on 14 consecutive days from **Day 4 through Day 17**. One cycle lasts for 42 days or from the start of induction chemotherapy to the start of the subsequent chemotherapy regimen.
- Consolidation period (maximum of 3 cycles): Once-daily repeated oral administration on 14 consecutive days from Day 1 through Day 14. One cycle lasts for 28 days or until the start of the subsequent consolidation or maintenance therapy.
- Maintenance period (maximum of 26 cycles): Once-daily repeated oral administration in 28-day cycles until the end of Cycle 26 or a discontinuation criterion is met.

[Phase 2 part]

- Induction period (maximum of 2 cycles): Once-daily repeated oral administration on 14 consecutive days from **Day 8 through Day 21**. One cycle lasts until investigator judges to proceed to next cycle or consolidation therapy. Postponing the initiation of consolidation therapy until blood recovery is preferred.
- Consolidation period (maximum of 4 cycles): Once-daily repeated oral administration on 14 consecutive days from Day 1 through Day 14. One cycle lasts until investigator judges to proceed to next cycle or maintenance therapy.
- Maintenance period (maximum of 26 cycles): Once-daily repeated oral administration in 28-day cycles until the end of Cycle 26 or a discontinuation criterion is met.

Concomitant Chemotherapy

Idarubicin and cytarabine will be intravenously administered using the dosage and regimen below. Ideal body weight with correction may be used for chemotherapy calculation per Institutional standard of care.

Induction period:

- Once-daily intravenous injection of 12 mg/m^2 idarubicin on 3 consecutive days beginning from Day 1.
- Once-daily intravenous injection of 100 mg/m^2 cytarabine on 7 consecutive days beginning from Day 1.

Consolidation period:

- Twice-daily intravenous injection of 1.5 g/m^2 cytarabine at 12-hour intervals on Day 1, 3, and 5.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All study drugs supplied by the sponsor in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at API or sponsor's designee in accordance with API or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

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

Refer to the pharmacy manual, product label and package insert for detailed information regarding packaging and labeling of the study drug and concomitant chemotherapy.

6.2.1.1 ASP2215

All medications used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person at API in accordance with API Standard Operation Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Packaging form:

Thirty ASP2215 Tablets 40 mg are packaged in a HDPE bottle with a deoxidizing agent.

Labeling:

The following items should be stated on the package of the study drugs:

- That the drugs are intended "for investigational use"
- Study number
- Name of the study drug
- Lot number, package unit, storage method, and other precautions
- Name and address of the sponsor

6.2.1.2 Concomitant Chemotherapy (Idarubicin, Cytarabine)

[Phase 1 part]

Commercially available idarubicin hydrochloride for injection (brand name: Idamycin for Intravenous Use) and cytarabine for injection (brand names: Cylocide Injection/Cylocide N Injection/Cytarabine Intravenous Infusion) will be used at each study site.

[Phase 2 part]

All chemotherapy drugs provided by the Sponsor will be packaged and labeled under the responsibility of API in accordance with API's designee SOP, GMP guidelines, ICH GCP guidelines.

6.2.2 Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only subjects enrolled in the study may receive study drug and only authorized study site personnel may supply or administer study drug. Only study drug with appropriate expiry/retest dating may be dispensed.
3. All study drug must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel.
4. The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records).
5. Further guidance and instruction on final disposition of used and unused study drug is provided in the pharmacy manual.

Refer to the pharmacy manual for detailed information regarding handling, storage and accountability of the study drug and concomitant chemotherapy.

[UNIQUE to JP REGION]

The head of the study site or the study drug storage manager will take responsibility for the following tasks related to the study drugs.

- The study drug storage manager will store and manage the study drugs in accordance with the procedures for handling the study drugs written by the sponsor.
- The study drug storage manager will prepare and retain records of the receipt of study drugs, the inventory at the study site, use by each subject, and return of unused study drugs to the sponsor or alternative disposal of unused study drugs. These records should include dates, quantities, batch/serial numbers or codes, expiration dates (if applicable), and the subject identification codes.
- The study drug storage manager will prepare and retain records that document adequately that the subjects were provided the doses specified by the protocol, and that the number and quantity of all the study drugs supplied from the sponsor were properly managed.

6.3 Randomization and Blinding

This is an open-label study. For Phase 2 part, subject enrollment and dispensation of study drug and concomitant chemotherapy will be performed via the interactive response technology (IRT) system. Specific IRT procedures will be described in the respective study manual.

6.3.1 Assignment and Allocation

Since this is an open-label, uncontrolled study, allocation of the study drugs will not be performed.

6.4 Study Drug and Concomitant Chemotherapy Compliance

During hospitalization, the treatment compliance of subjects will be confirmed by the investigator and the study drug storage manager. For outpatients, the treatment compliance will be confirmed from the information provided by subjects at each visit or the amount of returned study drugs. If there are any unreturnable study drugs, the reason should be confirmed and entered into the study drug storage management table. Even if a subject is failing to visit and it becomes difficult to ask about the status of treatment compliance, the subject should be contacted by phone or letter and every effort should be made to confirm their treatment compliance and collect the unused study drugs. Treatment compliance should be monitored closely and deviation in compliance should be reported to the sponsor.

If the study treatment has been interrupted, the duration and reason for the interruption, deviations from the prescribed dose regimen will be recorded in the electronic case report form (eCRF).

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

6.5.1 Previous Medication (Drugs and Therapies)

All previous Medication (except for the medications for the purpose other than treatment such as contrast agent, laboratory examination, etc.) administered from 28 days prior to Induction Cycle 1 Day 1 must be recorded in the eCRF. The period of evaluation for previous medications and the items to be entered into the eCRF are as follows.

Table 12 Evaluation Period for Previous Medications and eCRF Entry Items

Previous medication	Evaluation period	eCRF entry item
All drugs	28 days before Day 1 of induction therapy period – before Day 1 of induction therapy period	Drug name, route of administration, treatment duration, reason(s) for treatment
All therapies		Therapy name, treatment duration, reason(s) for treatment

6.5.2 Concomitant Medication (Drugs and Therapies)

All concomitant treatments (except for the medications for the purpose other than treatment such as contrast agent, laboratory examination, etc.) administered from Induction Cycle 1 Day 1 to the EOT visit must be recorded in the Case Report Form (CRF) for registered subjects. Concomitant medications used for reported AE/SAE should be collected during the AE reporting period (Section 7.3.1 and 7.3.2). Concomitant medications during the long-term follow-up do not need to be collected even if they are used for reported AEs. For screen/registration failure subjects, collection should can be terminated when failure from the study is confirmed.

The period of evaluation for concomitant medications and the items to be entered into the eCRF are as follows.

Table 13 Evaluation Period for Concomitant Medications/Therapies and eCRF Entry Items

Concomitant medication	Evaluation period	eCRF entry items
All drugs	Day 1 of induction therapy period – EOT From EOT to 30-day follow-up, only medications/therapies for reported AE/SAE will be collected.	Drug name, route of administration, treatment duration, reason(s) for treatment
All therapies		Therapy name, treatment duration, reason(s) for treatment

Prohibited concomitant medications:

- Any treatments of AML except for the ones specified in this study (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy, or cellular therapy) are prohibited during treatment with ASP2215, except for hydroxyurea (6 g/day, up to 14 days) to keep the absolute blast count below 50 x 10^9/L, intrathecal chemotherapy, and cranial irradiation used as prophylaxis.
- Drugs that are strong inducers of CYP3A.
- Drugs that are strong inhibitors or inducers of P-gp, those that target serotonin $5HT_{2B}$ receptors or sigma nonspecific receptors (except drugs that are considered absolutely essential for treatment of the subject).

Concomitant medications requiring caution:

- Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals, and antivirals, which are used as the standard of care to prevent or treat infections. If strong CYP3A inhibitors are used concomitantly, subjects should be closely monitored for AEs.
- Precaution should be taken in the use of ASP2215 with concomitant drugs that are known to prolong QT intervals or QTc.
- Intake of grapefruit juice should be avoided during the study to the greatest extent possible.

For chemotherapy drugs, the instructions in the local package insert under “Special warnings and precautions for use” section should be followed. The treatment mentioned in the specified section should be avoided or used with caution and closely monitored during idarubicin and cytarabine administration.

6.6 Dose Modification

[Phase 1 part]

ASP2215

Intra-subject dose escalation of ASP2215 is not permitted. If DLT occurs during the DLT assessment period, the study treatment will be discontinued without dose reduction. The investigator may interrupt the administration of ASP2215 when the safety of patient needs to be ensured.

If a study drug-related AE occurs in the maintenance period, interruption, discontinuation, or dose reduction of ASP2215 should be performed in accordance with Table 14. Each dose reduction should be performed by 40 mg. Additional dose reductions are permitted until the dosage reaches 40 mg. However, if no further dose reduction is possible, the study treatment should be discontinued. Dose re-escalation in subjects who had a dose reduction is not permitted.

In addition, the investigator may interrupt or reduce the dose of ASP2215 when it is considered necessary to ensure the safety of the patients for reasons other than those presented in Table 14. The investigator must promptly notify the sponsor of the interruption or dose reduction for reasons not specified in the table.

Table 14 Treatment Criteria in Event of a Study Drug-related Adverse Event

Retinopathy	
Grade 2	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at a reduced dose.
Grade 3/4	Treatment will be discontinued.
Non-hematological Events	
Grade 3	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at a reduced dose.
Grade 4	Treatment will be discontinued.
QTcF > 500 ms	If the mean triplicate QTcF is > 500 ms at any time point (according to values shown in an ECG chart or analyses in a central laboratory), the ECG will be repeated 3 times (within 2 hours if identified according to the ECG chart values or as soon as possible if identified from central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While the study drug may be interrupted temporarily based on ECG chart values, central reading should be used for final treatment decisions. Cardiovascular medicine consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (Grade 1 or less severe) by central reading within 14 days, the subject may resume dosing from the reduced dose.
Myelosuppression	
Grade 4 neutropenia and thrombocytopenia	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.

Concomitant drugs (idarubicin and cytarabine):

Intra-subject dose escalation of idarubicin or cytarabine is not permitted.

Dose reduction of idarubicin and cytarabine will be conducted following the standard treatment method at each study site. If discontinuation, interruption, or dose reduction of idarubicin and/or cytarabine occurs during Cycle 1 of the induction period, the study sponsor will consider whether the subject is eligible for DLT assessment.

[Phase 2 part]

ASP2215

Dose escalation of ASP2215 is not allowed and re-escalation after dose reduction is also not allowed in this study.

The ASP2215 dose may be initially reduced to 80 mg per day. The ASP2215 dose can be further reduced to 40 mg per day if the subject has already experienced clinical benefit. Note that dose reductions should occur in a step-wise manner. Dose reduction can occur any time during the study drug treatment period based on the dose reduction guideline in Table 15 or any reason other than the ones listed on the table if the investigator deems it necessary to ensure subject safety. In the unusual circumstance that dosing is interrupted or reduced for reasons not specified in the tables, the investigator should promptly inform the study Medical Monitor or his/her designee. Any subjects that have been off treatment for more than 14 days other than for HSCT or a study drug related AE, may only resume treatment after discussion with the Medical Monitor. However, if no further dose reduction is possible, the study treatment should be discontinued.

Table 15 should be followed if the specified events occurred during the ASP2215 dosing period. If the events occurred outside the ASP2215 dosing period, reduction of ASP2215 dosing may be determined upon the investigator's discretion.

Table 15 Guidelines for ASP2215 Dose Interruption or Reduction Event (for Phase 2)

ASP2215 Dosing Instructions	
Non-hematological 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 at the reduced dose.
Grade 4 toxicity at least possibly related to ASP2215	Treatment will be discontinued.
Table continued on next page	

ASP2215 Dosing Instructions	
QTcF > 500 ms	If the mean of the triplicate QTcF is > 500 ms at any time point (by either value on ECG tracing printout or central reading), then triplicate ECGs will be repeated (within 2 hours if based on value on ECG tracing printout and as soon as possible if based on central reading). If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of ASP2215 will be interrupted for up to 14 days. While ASP2215 may be interrupted temporarily based on value on ECG tracing printout, the central reading should be used for final treatment decisions. Cardiology consult will be obtained as medically indicated. If QTcF resolves to ≤ 480 ms (grade 1 or less severe) by central reading within 14 days, the subject may resume dosing at the reduced dose.
Myelosuppression (Maintenance therapy only)	
Grade 4 neutropenia and/or thrombocytopenia	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.

ECG: electrocardiogram; QTcF: Fridericia-corrected QT interval

Concomitant drugs (idarubicin and cytarabine):

Intra-subject dose escalation of idarubicin or cytarabine is not permitted.

Dose reduction of idarubicin and cytarabine should not be performed. If discontinuation, interruption, or dose reduction of idarubicin and/or cytarabine occurs during Cycle 1 of the induction period, information should be reported to the sponsor. Based on the investigator decision, chemotherapy dosing from Cycle 2 of the induction period may be reduced after confirmation with the sponsor.

6.7 Resumption of Treatment After Hematopoietic Stem Cell Transplantation

Subjects who have a donor identified and achieve a response allowing them to undergo HSCT per each institution's assessment can undergo HSCT without leaving the study. However, ASP2215 should be stopped and a pre-HSCT visit should be performed prior to starting the conditioning regimen for HSCT. ASP2215 can be resumed after stem cell transplantation if the following conditions are met:

- Subject is between 30 - 90 days post HSCT
- Subject has had successful engraftment as demonstrated by ANC ≥ 500/mm^3 and platelets ≥ 20000/mm^3 without transfusions
- Subject does not have ≥ grade 2 acute GVHD
- Subject is in CRc

For subjects resuming treatment, they will follow the procedures listed under initial or subsequent cycle day 1 of maintenance therapy in the Schedules of Assessments. Subjects who do not resume ASP2215 will be followed for the survival endpoints.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Efficacy Assessments

7.1.1 Bone Marrow Aspirate and Biopsy

[Phase 1 part]

Bone marrow samples will be analyzed locally according to Table 6. Bone marrow aspirate is required and bone marrow biopsy in addition is preferred. In case of inadequate aspirate, bone marrow biopsy is required.

[Phase 2 part]

Bone marrow samples will be analyzed centrally and/or locally according to Table 7. Bone marrow aspirate is required and bone marrow biopsy in addition is preferred. In case of inadequate aspirate, bone marrow biopsy is required. If bone marrow aspirate is unavailable, then collection 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. All local bone marrow assessment along with local hematology results will also be collected on the eCRF.

7.1.1.1 Minimal Residual Disease (MRD)

[Phase 1 part]

Left-over samples (bone marrow aspirate) sent for central laboratory may be used for assessment of MRD.

[Phase 2 part]

MRD will be analyzed by a central laboratory according to Table 7. Bone marrow aspirate will be collected and sent by overnight courier to the central laboratory for assessment of MRD. A peripheral blood sample is not acceptable for MRD assessment.

7.1.2 Antitumor Response

Antitumor response will be assessed on the days of bone marrow sampling based on the bone marrow findings, and peripheral blast count, neutrophil count, and platelet count. Preferably, samples from both bone marrow aspiration and biopsy should be obtained, but if the bone marrow aspiration was determined to be sufficient, biopsy may be omitted. The bone marrow samples will be collected on the dates shown in Table 6 and Table 7.

Antitumor response is defined per modified Cheson criteria (2003) or modified European LeukemiaNet (ELN) recommendations (2017) as outlined below and samples are evaluated at central laboratories [Döhner et al, 2017; Cheson et al, 2003].

[Phase 1 part]

The assessment will be performed by the investigator. The results of bone marrow findings and peripheral blast count will be entered into the eCRF.

[Phase 2 part]

Bone marrow aspiration and/or biopsy samples and hematology samples are evaluated centrally. If bone marrow samples were obtained for unscheduled visits, those samples along with hematology samples should be submitted for central assessment. All local bone marrow assessments along with local hematology results should be collected in the eCRF.

Definitions

Complete Remission (CR):

CR is defined as a morphologically leukemia-free state at the post-baseline visit, having a neutrophil count of ≥ 1,000/mm^3 and platelet count of ≥ 100,000/mm^3, bone marrow blasts < 5%. There must be no evidence of Auer rods and no evidence of extramedullary leukemia. The blast counts in peripheral blood must be ≤ 2%.

Complete Remission with Partial Hematologic Recovery (CRh):

CRh is defined as a condition at the post baseline visit, having bone marrow blasts < 5%, partial hematologic recovery neutrophil count≥ 500/mm^3 and platelet count ≥ 50,000/mm^3, no evidence of extramedullary leukemia and cannot be classified as CR. The blast counts in peripheral blood must be ≤ 2%.

Complete Remission with Incomplete Platelet Recovery (CRp):

CRp is defined as a condition that meets all of the CR criteria at the post-baseline visit, except for the unrecovered platelet count (< 100,000/mm^3).

Complete Remission with Incomplete Hematological Recovery (CRi):

CRi is defined as a condition that meets all of the CR criteria at the post-baseline visit, except for the unrecovered neutrophil count (< 1,000/mm^3; whether or not having unrecovered platelet counts).

Composite Complete Remission (CRc):

To be classified as being in CRc at a post-baseline visit, a subject must either achieve CR, CRp or CRi at the visit.

Partial Remission (PR):

At a post-baseline visit, PR is defined as a condition with regeneration of normal hematopoietic cells in the bone marrow, no detectable (or trace of residual) blasts, ≥ 50% decrease of blasts in the bone-marrow aspirate and total bone marrow blasts of 5–25%. There should be no evidence of extramedullary leukemia.

Not Evaluable (NE)/No Response (NR):

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

Relapse:

Relapse after CR, CRh, CRp or CRi is defined as a reappearance of leukemic blasts in the peripheral blood (>2%) or ≥ 5% blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia. Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

7.1.2.1 Best Response

Best response is defined as the best assessment (CR, CRp, CRi, or PR) obtained at each efficacy assessment time point after the start of treatment.

7.1.3 Survival Time, Duration and Other Efficacy Endpoints

Information on survival status, remission and relapse status, subsequent anti-leukemic treatments 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).

For the Phase 1 part, follow-up will continue until when the last subject enrolled reaches the 28-day follow-up visit. For the Phase 2 part, follow-up will continue until 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.

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

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

7.1.3.1 Overall Survival

[Phase 1 part]

Not applicable.

[Phase 2 part]

Overall survival (OS) is defined as the time from the date of first dose of day 1 to the date of death due to any cause. Patients still alive or lost to follow up will be censored at the time they were last known to be alive.

7.1.3.2 Event-free Survival

[Phase 1 part]

Not applicable.

[Phase 2 part]

Event-free survival (EFS) is defined as the time from the date of first dose of study regimen (day 1) until the date of documented relapse, treatment failure or death from any cause, whichever occurs first. For a subject with none of these events, EFS is censored at the date of last disease assessment.

7.1.3.3 Relapse-free Survival

[Phase 1 part]

Not applicable.

[Phase 2 part]

Relapse-free survival (RFS) is defined as time from the date of achievement of first CRc until relapse or death from any cause, whichever comes first. For a subject who is not known to have relapsed or died, RFS is censored on the date of last relapse-free disease assessment date.

7.1.3.4 Transplantation Rate

[Phase 1 part]

Not applicable.

[Phase 2 part]

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

7.1.3.5 Duration of Response

Duration of response is defined as the period from the first day of achieving CR, CRp, CRi, or PR to the first day of confirmed relapse.

7.2 Safety Assessments

Study procedures and their timing is summarized in the schedule of assessments. Protocol waivers or exemptions are not allowed unless mentioned in the protocol.

Procedures conducted as part of a subject's routine clinical management (i.e., standard of care) obtained before signing the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame, as defined in the schedule of assessments.

7.2.1 Adverse Events

See Section 12.4 for information regarding AE collection and data handling.

7.2.2 Laboratory Assessments

A list of laboratory test items is shown in Section 12.8. Samples (blood and urine) will be collected at the times shown in Table 6 and Table 7. The date of sampling and the test results will be entered into the eCRF. The investigator will compare the test results with the baseline values and if any clinically significant abnormalities are found, will enter them into the eCRF as AEs. Baseline laboratory values are defined as the laboratory values obtained on Induction Day 1.

[Phase 1 part]

Measurements will be performed locally at each study site. No central laboratory assessment is performed.

[Phase 2 part]

Measurements will be performed centrally for both scheduled and unscheduled visits. Local lab assessments can be performed. The local hematology assessment will be recorded in the eCRF if the central assessment was not evaluable.

7.2.3 Vital Signs

Systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, and arterial oxygen saturation will be measured after rest at the times shown in Table 6 and Table 7. Each of the measurements will be recorded and entered into the eCRF. The investigator will compare the measurements with the baseline values, and if any clinically significant abnormalities are found, will enter them into the eCRF as AEs. Baseline vital signs are defined as the vital signs measured on Day 1.

7.2.4 Height and Weight

The weight of the subjects will be measured at the times shown in Table 6 and Table 7. Each of the measurements will be recorded and entered into the eCRF. Body surface area will be calculated when the body weight is measured. The investigator will compare the measurements with the baseline values, and if any clinically significant abnormalities are found, will enter them into the eCRF as AEs. Baseline body weight is defined as the body weight measured on Induction Day 1.

The height of the subjects will be measured at screening, and the measurements will be entered into the eCRF as subject demographics.

7.2.5 Physical Examination

Standard, full physical examinations will be performed to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems. Genitourinary and rectal system examinations are to be performed only if clinically indicated. Physical examinations will be conducted at the visits outlined in Table 6 and Table 7. If clinically significant worsening of findings from pre-dose (Cycle 1 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.

The investigator will assess the subject's ECOG Performance Status from among the 5 stages (see Section 12.5) at the times shown in Table 6 and Table 7, and enter the results into the eCRF.

7.2.6 Electrocardiogram

The 12-lead ECG will be measured at the times shown in Table 6 and Table 7. 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.

Assessments scheduled at the same times as the pharmacokinetic plasma sampling should be performed before the sampling.

<u>QT interval and other interval measurements:</u>

The ECG chart measured at the times shown in Table 6 and Table 7 will be sent to the central ECG laboratory for measuring the QT interval and other intervals. The sent ECG charts will be analyzed at the central ECG laboratory to measure the QT, PR, RR, and QRS intervals.

[Phase 1 part]

The investigator will confirm the ECG chart, and enter the result of the assessment as either "normal," "abnormal (not clinically significant)," or "abnormal (clinically significant)" into the eCRF. If the ECG chart was assessed as "abnormal (clinically insignificant abnormality)" or "abnormal (clinically significant abnormality)," the abnormal finding will be entered into the eCRF.

[Phase 2 part]

The investigator will confirm the central ECG chart and assess whether any AEs should be reported. Confirmation by an investigator should be documented.

7.2.7 Chest X-ray or Computed Tomography Scan

Chest X-ray or computed tomography (CT) scan is to be performed at screening. A chest X-ray (or CT of chest) does not need to be repeated if performed within 1 week prior to consent.

7.2.8 Multigated Acquisition Scan or Echocardiogram

A MUGA or ECHO is to be performed at screening for subjects with a history of NYHA Class 3 or 4 congestive heart failure (unless MUGA or ECHO performed within 3 months prior to screening revealed left ventricular ejection fraction ≥ 45%).

7.2.9 Pregnancy Tests

If the subject is a woman of childbearing potential, a pregnancy test will be performed locally on serum or urine samples, and the results will be entered into the eCRF.

7.2.10 DLT

See Section 4.1.2.

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in Section 12.4.

The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an AE or SAE.

7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information

[Phase 1 part]

AE monitoring will begin from the start of induction therapy through to the end of the follow-up observation.

[Phase 2 part]

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug. AE collection begins after the signing of the ICF and will be collected until 30-day follow-up visit or when the subject is determined to be a screen/registration failure. In case the chemotherapy is provided from the sponsor, AE collection will continue until the drug administration is completed. During the long-term follow-up period, only SAE data that the investigator assesses as possibly or probably related to study drug will be collected.

7.3.2 Adverse Event and Serious Adverse Event during HSCT

ASP2215 related SAE should always be reported regardless of the time of the HSCT during the study participation. For subjects who plan to proceed to HSCT and resume ASP2215 treatment after HSCT, AE collection will continue until the start of the HSCT conditioning

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

- 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

Above AE/SAEs will be collected throughout the HSCT period for the subjects who plan to resume ASP2215.

7.3.3 Method of Detecting Adverse Events and Serious Adverse Events

The methods of recording, evaluating and assessing seriousness, causality and severity of AEs and SAEs are described in Section 12.4. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

If the severity/ National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) grade of an AE changes, the event should be relisted on eCRF with the new severity/NCI-CTCAE grade and new onset date.

If the severity/NCI-CTCAE grade decreases, the AE should be relisted on eCRF with the new severity/NCI-CTCAE grade and new onset date. The exception is ongoing pre-dose events that continue post-dose and improve post-dose. Such events should not be re-listed.

If the severity of an SAE reduces, then also provide the details of the AE on the SAE worksheet for the medical assessor to be able to assess the course of the event.

7.3.4 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 by the investigator.

If after the protocol-defined AE collection period, an AE progresses to an SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug or study participation, the investigator must promptly notify the sponsor.

7.3.5 Reporting of Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential, so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

Procedures for reporting SAEs to the sponsor are described in Section 12.4.5.

7.3.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Under this protocol, the following event(s) will not be considered as an(S)AE:

- Disease progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study drug and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of study drug must be reported as an SAE, even if attributed to disease progression.
- Pre-planned and elective hospital/clinical procedures/interventions or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the study. These procedures are collected per the eCRF's completion guidelines.

7.3.7 Special Situations

[Phase 1 part]

Not applicable.

[Phase 2 part]

Certain special situations observed in association with the study drug, such as incorrect administration (e.g., wrong dose of study drug or background therapy) are collected in the eCRF, as protocol deviation or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in the electronic data source. If the AE meets the definition of an SAE, the SAE is to be reported as described in Section 12.4.5 and the details of the associated special situation are to be included in the clinical description on the SAE worksheet. Cases of pregnancy is reported to the sponsor (the reporting procedure is the same as SAE reporting) using the Pregnancy Form provided by the sponsor.

The special situations are:

- Pregnancy
- Medication error, overdose and "Off-label Use" (i.e., use outside of what is stated in the protocol)
- Misuse/abuse
- Occupational exposure
- Suspected drug-drug interaction

Instructions and procedures for reporting special situations are provided in Section 12.4.6.

7.3.8 Supply of New Information Affecting the Conduct of the Study

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

The investigator will also inform the subjects, who will be required to sign an updated ICF in order to continue in the study.

[UNIQUE to JP REGION]

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 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 Pharmaceutical Affairs Law, the sponsor should inform all investigators involved in the study, head of the study site and appropriate regulatory authorities of such information. The head of the study site who receives such information will decide whether the 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 12.1.4.2.
2. In addition, when the head of the study site receives the revisions of the investigator's brochure, protocol, written information, information on the matters covering the quality of the test product, efficacy and safety, information necessary for conducting the study properly or documents to be examined by the IRB, these documents should be sent to the IRB.

7.3.9 Urgent Safety Measures <*For JP Region:* Deviations from the Protocol and Other Actions Taken to Avoid Life-threatening Risks to Subjects>

[Phase 1 part]

[UNIQUE to JP REGION]

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.

[Phase 2 part]

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

[UNIQUE to JP REGION]

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.

7.3.10 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the study physician and Astellas team member within 24 hours 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 a USM, the sponsor will take appropriate action to ensure the safety and welfare of the subjects. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

7.4 Pharmacokinetics

7.4.1 Pharmacokinetic Assessment

Samples will be collected to measure plasma ASP2215 and cytarabine concentrations at the times shown in Table 6 and Table 7. The dates and times of sampling will be recorded in the eCRF.

[Phase 1 part]

Table 16 Evaluation time point for Plasma ASP2215 Concentration

Induction period	
Cycle 1 Day 4	Pre-dose 1, 2, 4, 6, and 10 hours post-dose
Cycle 1 Day 5	Pre-dose (24 hours post-dose of Day 4 administration)
Cycle 1 Day 8	Pre-dose
Cycle 1 Day 11	Pre-dose
Cycle 1 Day 17	Pre-dose
Cycle 1 Day 28	
Consolidation period	
Cycle 1 Day 1	Pre-dose 1, 2, 4, 6, and 10 hours post-dose
Cycle 1 Day 2	Pre-dose (24 hours post-dose of Day 1 administration)
Cycle 1 Day 6	Pre-dose
Cycle 1 Day 15	Pre-dose

[Phase 2 part]

Induction period	
Cycle 1 Day 15	Pre-dose
Cycle 1 Day 21	Pre-dose
Consolidation period	
Cycle 1 Day 8	Pre-dose
Cycle 1 Day 15	Pre-dose

[Phase 1 part]

Table 17 Evaluation time point for Plasma Cytarabine Concentration

Induction period	
Cycle 1 Day 1	Pre-dose
Cycle 1 Day 3	Pre-dose
Cycle 1 Day 8	Pre-dose
Consolidation period	
Cycle 1 Day 2	Pre-dose
Cycle 1 Day 6	Pre-dose

[Phase 2 part]

Not applicable.

7.4.2 Test Drug Concentration

7.4.2.1 Measurement of Plasma ASP2215 Concentration

Sample collection will be performed as follows. The plasma ASP2215 concentration will be measured for all samples collected, even for discontinuations. The drug concentration laboratory will perform the measurements in accordance with the separately prepared measurement plan.

1. Plasma sample processing
   To obtain 0.5 mL of plasma, 1 mL of blood will be collected from the cutaneous vein of the forearm or the cubital fossa using a sampling tube containing EDTA-2K as an anticoagulant. The blood samples will be stored at room temperature until centrifugation. The blood samples will be centrifuged (at room temperature for 10 minutes at approximately 1700 *g*) within 2 hours of sampling. The plasma obtained will be divided into 2 polypropylene tubes (0.25 mL into the primary, and the rest into the back-up), then immediately freeze stored (at ≤ −20°C) to be used as samples for measuring test drug concentration. The sampling date and time will be recorded for each subject into the medical record or other source document, and entered into the eCRF.
2. Sample shipment
   Samples for measuring test drug concentration will be shipped to the drug concentration laboratory by a sample collection/transport organization in a frozen state cooled by dry ice.
3. Concentration measurement
   Measurement of plasma test drug concentrations will be performed at the drug concentration laboratory by an LC-MS/MS method established through a validation test (ISN No.: 2215-ME-0015 and 2215-ME-0033). When 0.05 mL of plasma is used, the lower limit of quantification of the test drug concentration is 0.5 and 10 ng/mL respectively (ISN No.: 2215-ME-0015 and 2215-ME-0033).
4. Precision control of measured data
   The person responsible at the drug concentration laboratory will confirm that there are no quality problems. If a quality problem is detected, the necessity of re-measuring or improving measurement methods should be discussed.
5. Obtaining the measurement results
   The sponsor will obtain the measurement report and the electronic files of the concentration measurements from the drug concentration laboratory, and a record of the receipt will be prepared.
6. Handling of remaining plasma
   Plasma samples for concentration measurement will be stored frozen (at ≤ −20°C or lower) at the drug concentration laboratory until the measurement report is finalized. Thereafter, the samples will be discarded after contacting the sponsor.

7.4.2.2 Measurement of Plasma Cytarabine Concentration

[Phase 1 part]

Sample collection for measurement of the plasma cytarabine concentration will be performed at the times shown in Table 6 and Table 7. A blood sample of 2 mL will be collected at each time point. The plasma cytarabine concentration will be measured for all samples collected, even for discontinuations. The drug concentration laboratory will perform the measurements in accordance with the separately prepared measurement plan.

1. Plasma sample processing
   Blood of 2 mL will be collected from the cutaneous vein of the forearm or the cubital fossa using a syringe without any additive such as anticoagulant. The collected blood will be promptly transferred to a blood collection tube containing EDTA-2K as anticoagulant and tetrahydrouridine as stabilizer, gently mixed and stored at room temperature. The blood samples will be centrifuged (at room temperature for 10 minutes at 1500 to 2000 *g*) within 30 minutes of sampling. The plasma obtained will be divided into 2 polypropylene tubes (0.75 mL into the primary, and the rest into the back-up), then freeze stored (at ≤ −20°C) as promptly as possible to be used as samples for measuring concentration. The sampling date and time will be recorded for each subject into the medical record or other source document, and entered into the eCRF.
2. Sample shipment
   Samples for measuring concentration will be shipped to the drug concentration laboratory by a sample collection/transport organization in a frozen state cooled by dry ice.
3. Concentration measurement
   Measurement of plasma cytarabine concentrations will be performed at the drug concentration laboratory by an LC-MS/MS method established through a validation test. When 0.050 mL of plasma is used, the lower limit of quantification of cytarabine concentration is 0.5 ng/mL.
4. Precision control of measured data
   The person responsible at the drug concentration laboratory will confirm that there are no quality problems. If a quality problem is detected, the necessity of remeasuring or improving measurement methods should be discussed.
5. Obtaining the measurement results
   The sponsor will obtain the measurement report and the electronic files of the concentration measurements from the drug concentration laboratory, and a record of the receipt will be prepared.
6. Handling of remaining plasma
   Plasma samples for concentration measurement will be stored frozen (at ≤ −20°C) at the drug concentration laboratory until the measurement report is finalized. Thereafter, the samples will be discarded after contacting the sponsor.

[Phase 2 part]

Not applicable.

7.5 Pharmacodynamics | Immunogenicity

[Phase 1 part]

The inhibitory effect of ASP2215 on blood FLT3 and AXL phosphorylation will be investigated to assess the pharmacodynamics of a single or repeated oral administration of ASP2215. This investigation will be terminated after assessment in some subjects in this study, taking into account that qualitative pharmacodynamic assessment has been completed in the domestic phase I study (Protocol No.: 2215-CL-0102).

The pharmacodynamic measurement organization will perform the measurements in accordance with a separately prepared measurement procedure by the organization. The sponsor will obtain the measurement results and records whose quality has been assured from the pharmacodynamic measurement organization.

Samples will be collected and processed using the following procedures. The exact sampling time for each subject will be recorded.

2 mL of blood will be sampled from the vein using a blood collection tube containing sodium heparin as an anti-coagulant. The sample obtained will be immediately frozen for storage (approximately –70°C or lower) to be used as a sample for pharmacodynamic measurement. The samples will be sent to the pharmacodynamic measurement organization by a sample collection/transport organization in a frozen state cooled by dry ice. After the pharmacodynamic measurement organization performs the pharmacodynamic assessments, the remaining blood samples will be stored frozen (approximately –70°C or lower) until the measurement records are finalized. Thereafter, the samples will be discarded after contacting the sponsor.

[Phase 2 part]

Not applicable.

7.6 Exploratory Biomarker(s)

7.6.1 FLT3 Mutation Assessment

In order to investigate the presence/absence of the ITD mutation of FLT3 and point mutation at D835/I836 residues, samples will be collected on the dates shown in Schedule of Assessment.

[Phase 1 part]

Subjects' consent for sample collection for the FLT3 mutation test will be obtained at the same time as informed consent for this study. 1 mL of bone marrow aspirate will be collected before the start of Cycle 1 of the induction period (at screening) and on Day 1 of Cycle 1 of the consolidation and maintenance periods, from each subject who provided consent. If

collection of bone marrow aspirate is difficult, blood may be collected instead (4 mL in the case of blood). The bone marrow aspirate or peripheral blood collected will be stored refrigerated at the study site until sample collection. The samples will be collected by the sample collection/transport organization, and analyzed for the presence or absence of the following FLT3 mutations at the FLT3 mutation testing laboratory. Details will be specified in a separate procedure.

- FLT3-ITD mutation
- FLT3 point mutation (D835, I836)

The sponsor will obtain the test results from the FLT3 mutation testing laboratory as a separate report. This test is an exploratory analysis to investigate the relationship between the efficacy of the study drug and the FLT3 gene. Therefore, the results of the genetic analysis will not be disclosed. (Analysis results of the FLT3-mutation test obtained for the screening test will be disclosed to the study sites.)

[Phase 2 part]

FLT3 mutation status will be assessed from bone marrow samples taken at the screening visit and may be assessed from bone marrow or blood samples at other time points during the study.

The FLT3 companion diagnostic being used to determine a subject's FLT3 mutation status is approved by the PMDA and FDA. The manufacturer of the assay will analyze the samples collected from this study and utilize it to seek regulatory approval of the FLT3 mutation assay companion diagnostic that will be used with ASP2215.

Bone marrow/blood sampling, processing, storage and shipment instructions will be provided in the 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.

7.6.2 Minimal Residual Disease (MRD) 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.

7.6.3 Other Biomarker Assessment

If leftover bone marrow samples are available, FLT3 sequencing analysis can be performed at the screening visit, and end of treatment/disease progression. Samples at other time points and/or peripheral blood samples can also be provided for FLT3 sequencing analysis. In addition, samples may be analyzed for mutations in AML related genes (e.g., IDH1, NPH1) and changes in proteins in relation to treatment effects at the screening visit, and end of

treatment/disease progression with using appropriate method (e.g. Archer VariantPlex Core Myeloid Kit etc.).

7.6.4 Sample for Banked Pharmacogenomic Sample Analysis

PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues. After registration, buccal swab and blood will be collected from subjects who have consented to sampling for future PGx study. Samples will be shipped to a Sponsor designated banking CRO.

Labels should uniquely identify each sample and contain at least:

- Protocol number (2215-CL-0104)
- 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.

7.7 Total Amount of Blood and Bone Marrow Fluid

[Phase 1 part]

The test parameters, the number of samplings, and the approximate sampling amounts for blood and bone marrow fluid in this study are as follows. If a follow-up of a laboratory test becomes necessary, blood sampling will be performed whenever necessary.

Table 18 Approximate Amounts of Blood and Bone Marrow Fluid

	Screening	Induction period (1 cycle)	Consolidation period (1 cycle)	Maintenance period		End of treatment
				Cycle 1	Cycle 2 and beyond	
Blood	13.5 mL or 17.5 mL*	100 mL	78.5 mL or 82.5 mL*	13.5 mL or 17.5 mL*	13.0 mL	14.5 mL
Bone marrow fluid	3 mL or 4 mL*	3 mL	3 mL or 4 mL*	3 mL or 4 mL*	-	3 mL

* If blood or bone marrow fluid was collected for FLT3 mutation test

The approximate amounts of blood and bone marrow fluid to be sampled for each purpose are as follows:

- Hematology: 2 mL/test
- Biochemistry: 7 mL/test
- Thyroid function test: 2 mL/test
- Coagulation test: 2 mL/test
- Pregnancy test: 0.5 mL/test (blood)
- Plasma drug concentrations: 1 mL/test (ASP2215), 2 mL/test (cytarabine)

- Bone marrow test: 3 mL/test (bone marrow fluid)
- Blood sample for biobanking: 5 mL
- FLT3 mutation test: 4 mL (blood), 1 mL (bone marrow fluid)

[Phase 2 part]

The test parameters, the number of samplings, and the approximate sampling amounts for blood and bone marrow fluid in this study are as follows. If a follow-up of a laboratory test becomes necessary, blood sampling will be performed whenever necessary.

Table 19 Approximate Amounts of Blood and Bone Marrow Fluid

	Screening	Induction period (1 cycle)	Consolidation period (1 cycle)	Maintenance period		End of treatment	At relapse (during the long term follow up)
				Cycle 1	Cycle 2 and beyond		
Blood	13 - 19.5 mL*	81-86 mL	50-52 mL	13 - 15.5 mL**	13 - 17 mL	13 – 17 mL*	13 mL
Bone marrow fluid	3 - 4 mL*	3 mL	3 mL	3 mL	0 - 3 mL	3 - 4 mL*	3 mL

* If blood or bone marrow fluid was collected for FLT3 mutation test.

** If blood sample was used for pregnancy test.

The approximate amounts of blood and bone marrow fluid to be sampled for each purpose are as follows:

- Hematology: 2 mL/test
- Biochemistry: 7 mL/test
- Thyroid function test: 2 mL/test
- Coagulation test: 2 mL/test
- Pregnancy test: 0.5 mL/test (blood)
- Plasma drug concentrations: 1 mL/test (ASP2215)
- Bone marrow test: 3 mL/test (bone marrow fluid)
- Blood sample for biobanking: 3 mL
- FLT3 mutation test: 4 mL (blood), 1 mL (bone marrow fluid)

8 DISCONTINUATION

8.1 Discontinuation of Individual Subject(s) from Study Treatment

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

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

The reason for discontinuation from study treatment must be documented in the subject's medical records.

For withdrawn cases, the date of the final study drug administration, date of the end of treatment (discontinuation; date the investigator decided the discontinuation), and the reason for the discontinuation will be entered into the eCRF.

When discontinuing the treatment, the investigator will take appropriate measures/treatment as required, and perform the tests/assessments scheduled at the end of treatment (discontinuation). At 30 days after the final study drug administration, tests and assessments scheduled as follow-up observation will be performed. However, if the setting up of follow-up observation is difficult, such as when another treatment must be started after study discontinuation, the follow-up observation may be omitted or shortened.

A subject must discontinue study treatment for any of the following reasons:

[Phase 1 part]

- Withdrawal of consent
- Poor compliance (failure to make the scheduled visits and others)
- A serious protocol deviation is found
- Failure to achieve remission after 2 cycles of induction therapy
- Relapse after remission
- Occurrence of unacceptable AE requiring discontinuation of treatment
- The investigator determines that continuation of the study treatment will be detrimental to the subject
- Subjects or their partners are found to be pregnant

[Phase 2 part]

- 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 one 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 fails to achieve remission after 2 cycles of induction therapy.
- Subject relapses following remission.
- Subject develops an intolerable or unacceptable toxicity.
- Subject receives any antileukemic therapy other than the assigned treatment, with the exception of hydroxyurea up to 6 g daily for up to 2 weeks, HSCT, prophylactic intrathecal chemotherapy or cranial irradiation.
- Investigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.

- Female subject becomes pregnant.
- Death.

8.2 Discontinuation of Individual Subject(s) from Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in Schedules of Assessments. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

For the Phase 2 part, all subjects who discontinue study treatment are to be followed for survival status until completion of the study.

Discontinuation Criteria from Post-Treatment 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.

[Only applies to Phase 2 part]

- The study meets the criteria to complete the long-term follow-up (i.e., During the long-term follow-up period, the subject will be followed for 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.).

8.2.1 Lost to Follow-up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data and retrieve study drug.

8.3 Discontinuation of the Study Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor (***UNIQUE to JP Region***: and the head of the study site.)

8.4 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.

9 STATISTICAL METHODOLOGY

[Phase 1 part]

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures (TLFs) to be produced. Statistical analysis will be performed based on the following principles. In principle, the analysis will be separately performed for the dose-evaluation and expansion parts. In addition, when necessary, the analysis of RED will be performed for the dose-evaluation and expansion parts as a whole.

[Phase 2 part]

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures (TLFs) to be produced. The SAP will be finalized before the database lock at the latest. Changes from the planned analyses in the final SAP that impact the statistical analyses will be justified in the clinical study report (CSR).

In general, continuous data will be summarized with descriptive statistics, frequency and percentage for categorical data.

9.1 Sample Size

9.1.1 Target Sample Size

[Phase 1 part]

6 subjects

Dose-evaluation part: At least 3 subjects per cohort (which may be changed according to the status of the onset of DLT and the number of cohorts)

Expansion part: At least 3 subjects

[Phase 2 part]

Approximately 80 subjects

9.1.2 Justification of Sample Size

[Phase 1 part]

<u>Dose-evaluation part:</u>

To assess MTD and RED of ASP2215 as induction therapy concomitant with cytarabine/idarubicin in newly diagnosed AML subjects, 3 DLT evaluable subjects per dose level for 1 dose level were assumed. The sample size may increase depending on the occurrence of toxicities.

<u>Expansion part:</u>

The sample size was set to 3 subjects to further assess the safety and efficacy of ASP2215 at the dose tested in the expansion part.

[Phase 2 part]

The sample size of Phase 2 part is approximately 80 subjects. An evaluable sample size of 70 subjects in phase 2 part provides more than 80% power to detect a 15% increase in CR rate from 55% (historical benchmark based on the RATIFY study, Stone et al, 2017.) to 70% at one-sided significance level of 0.05. Assuming approximately 10% drop-out rate, a total of 80 subjects will be enrolled into Phase 2 part.

9.2 Analysis Sets

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

In principle, the analysis sets will be selected as in from Section 9.2.1 to 9.2.6. However, when necessary, the analysis sets will be determined considering the cases by referring to the opinions and advice from medical experts and statistical advisors.

9.2.1 Full Analysis Set (FAS)

[Phase 1 part]

Subjects who meet all of the following criteria will be included:

- Received at least 1 dose of the study drug
- Assessed for at least 1 efficacy variable after study drug administration

[Phase 2 part]

Subjects who meet all of the following criteria will be included:

- Received at least 1 dose of ASP2215
- Had at least one post-baseline bone marrow assessment

9.2.2 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the Safety Analysis Set (SAF) will be used.

[Phase 1 part]

All subjects who received at least 1 dose of ASP2215 will be included.

[Phase 2 part]

The SAF will be defined as the same as phase 1 part.

9.2.3 Pharmacokinetic Analysis Set (PKAS)

Subjects who received the study drug, from whom samples for drug concentration measurement have been collected for at least 1-time point after the study drug administration, and from whom drug concentration measurement has been obtained will be included.

9.2.4 Pharmacodynamic Analysis Set (PDAS)

[Phase 1 part]

Subjects who received the study drug, from whom samples for pharmacodynamic assessment have been collected for at least 1-time point after the study drug administration, and from whom pharmacodynamic measurement has been obtained will be included.

[Phase 2 part]

Not applicable.

9.2.5 Dose-Determining Analysis Set (DDAS)

[Phase 1 part]

Subjects who do not fall under any of the following criteria will be included:

- Received less than 80% of the intended dose of ASP2215 during DLT assessment period specified in each part (e.g., subject in dose evaluation part who misses ≥ 3 daily doses during DLT assessment period and interrupts the study for a reason other than a DLT)
- Unable to assess safety adequately during DLT assessment period specified in each part such as due to the lack of required safety assessment(s).

[Phase 2 part]

Not applicable.

9.2.6 MRD Analysis Set (MAS)

[Phase 1 part]

Not applicable.

[Phase 2 part]

The MRD Analysis Set (MAS) consists of all subjects who were enrolled and received at least 1 dose of study drug, were centrally confirmed as FLT3-ITD positive and had a baseline and at least post-baseline sample with MRD data.

9.3 Demographics and Baseline Characteristics

9.3.1 Demographics

[Phase 1 part]

The following analyses will be performed in the FAS, SAF, DDAS, PKAS, and PDAS. Analyses will be performed by dosage for the dose-evaluation part.

- The discrete variables will be summarized by frequency.
- Summary statistics will be calculated for the continuous variables.

[Phase 2 part]

Descriptive statistics will include number of subjects, mean, standard deviation, minimum, Q1, median, Q3 and maximum for continuous endpoints and frequency and percentage for categorical endpoints. The analyses will be performed in the FAS, SAF, PKAS, and MAS.

9.3.2 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented. All disposition details and dates of first and last evaluations for each subject will be listed.

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

All previous and concomitant treatment will be listed.

9.3.4 Medical History

Medical history for each subject will be listed.

9.3.5 Study Drug Exposure

The number and percentage of subjects exposed to study drug will be summarized.

All study drug exposure data will be listed.

9.4 Analysis of Efficacy

[Phase 1 part]

The following analyses will be performed in the FAS. Analyses will be performed by dosage for the dose-evaluation part.

The following endpoints will be summarized by the Bruce D. Cheson standard (2003) or modified ELN recommendations (2017).

- CR (Complete Remission) rate
- CRp (CR with incomplete platelet recovery) rate
- CRi (CR with incomplete hematologic recovery) rate
- PR (Partial Remission) rate
- CRc (Composite CR) rate: CR + CRp + CRi
- Overall response rate: CRc + PR

Summary statistics will be calculated for the duration of response.

[Phase 2 part]

Efficacy analysis will be conducted on the FAS. The interpretation of statistical results will be based on the FAS.

9.4.1 Analysis of Primary Endpoint

9.4.1.1 Primary Analysis

[Phase 1 part]

Not applicable.

[Phase 2 part]

For the primary efficacy endpoint of CR rate after induction therapy period, the two-sided 90% exact confidence interval (CI) by Clopper-Pearson method will be calculated for 70 subjects who took at least one dose of ASP2215 and had at least one post-baseline bone marrow assessment. The lower limit of the CI will be used to compare with the benchmark of CR rate of 55%. Out of 70 evaluable subjects, at least 46 subjects who achieve CR after induction is necessary to exclude 55% based on the exact 90% CI of CR rate as summarized in Table 20.

Table 20 Observed CR with Exact 90% CI (N=70 in phase 2 part)

Observed CR (n and %)	Exact 90% CI
56 (80.0%)	(70.5%, 87.5%)
49 (70.0%)	(59.7%, 78.9%)
48 (68.6%)	(58.3%, 77.7%)
47 (67.1%)	(56.8%, 76.4%)
46 (65.7%)	(55.3%, 75.1%)
45 (64.3%)	(53.8%, 73.8%)

9.4.1.2 Subgroup Analysis

[Phase 1 part]

Not applicable.

[Phase 2 part]

Subgroup analysis will be conducted using the FAS. Subgroups are defined on the basis of the categorized variables such as sex, age group, country and FLT3 mutation status.

9.4.2 Analysis of Secondary Endpoints

[Phase 1 part]

Not applicable.

[Phase 2 part]

The statistical analyses on secondary efficacy endpoints include the following descriptive analyses for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy:

- Kaplan-Meier method for time-to-event endpoints including OS, EFS, RFS, duration of CR, CRh, CR/CRh, CRc and response.
- The two-sided 95% exact confidence interval of the binary endpoints including CR rate, CRh rate, CR/CRh rate, and CRc rate.

For each of the secondary responder endpoints, analyses are conducted after each treatment therapy.

9.4.3 Analysis of Exploratory Endpoints

[Phase 1 part]

The statistical analyses on exploratory endpoints include the following descriptive analyses for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy:

- Kaplan-Meier method for time-to-event endpoints duration of response, CR and CRc.
- The 2-sided 95% exact confidence interval of the binary endpoints CR rate, CRp rate, CRi rate, PR rate, CRc rate and response rate.

[Phase 2 part]

The statistical analyses on exploratory endpoints include the following descriptive analyses for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy:

- Kaplan-Meier method for time-to-event endpoints including Cumulative incidence of relapse (CIR) after CR1, Cumulative incidence of death (CID) after CR1, and time to hematopoietic recovery after each treatment cycle.
- The two-sided 95% exact confidence interval of the binary endpoints including transplantation rate, MRD, MRD-negative CR rate and overall MRD-negative CR rate. Transplantation rate and MRD is analyzed after each treatment therapy. MRD-negative CR rate is analyzed after induction therapy period. Overall MRD-negative CR rate is analyzed at any treatment period.

Exploratory biomarker analysis of MRD will be performed using MAS.

9.5 Analysis of Safety

The analyses in Section 9.5.1 will be performed in the DDAS, and the analyses in Sections 9.5.2 to 9.5.6 will be performed in the SAF. Analyses will be basically performed for Phase 1 part and Phase 2 part. Some analyses that do not depend on the measurement time point such as the summary of adverse events will be performed for Phase 1/Phase 2 part totally.

9.5.1 Occurrence of DLTs

- The posterior mean of DLT incidence will be estimated using Bayesian-CRM.
- The occurrence of DLTs will be summarized by frequency.

9.5.2 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and graded using NCI-CTCAE. A treatment-emergent adverse event (TEAE) is defined as an AE observed after starting administration of the study drug and within 30 days (for phase 1 part, 28 days) after the last administration of study drug. A drug-related TEAE is defined as any TEAE with a causal relationship assessed as YES by the investigator.

The number and percentage of subjects with TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to withdrawal of treatment and drug-related TEAEs leading to withdrawal of treatment will be summarized by System Organ Class (SOC), Preferred Term (PT). The number and percentage of TEAEs by severity will also be summarized.

9.5.3 Laboratory Assessments

- For continuous variables, summary statistics will be calculated using measured values by measurement time point.
- For continuous variables, a case plot of measured values will be prepared.
- The discrete variables will be summarized by frequency by measurement time point.

9.5.4 Vital Signs

- For each parameter, summary statistics of the measured values will be calculated by measurement time point.
- For each parameter, a case plot of measured values will be prepared.

9.5.5 12-lead Electrocardiogram

The result of assessment will be summarized by frequency for each measurement time point.

9.5.6 Body Weight

Summary statistics of measured values will be calculated for each measurement time point.

9.6 Analysis of Pharmacokinetics

In the PKAS, pharmacokinetic parameters and summary statistics will be calculated using the plasma drug concentration measurements. If any measured values are BQL, their drug concentration will be handled as 0 (zero). Details of the analytical method including the figures and tables to be prepared in the pharmacokinetic analysis will be described in the pharmacokinetic analysis plan.

9.6.1 Estimation of Pharmacokinetic Parameters

The following pharmacokinetic parameters will be calculated using the plasma drug concentrations:

[Phase 1 part]

- ASP2215: C_{max}, t_{max}, AUC_{24}, CL/F, AUC_{last}, $t_{1/2}$, V_z/F, and C_{trough}
- Cytarabine: C_{trough}

[Phase 2 part]

Not applicable.

9.6.2 Statistical Analysis of Pharmacokinetic Parameters

Calculation of Summary Statistics:

The number of subjects (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV), minimum (Min), median (Median), maximum (Max), and geometric mean (GM) will be calculated for the plasma drug concentrations and the pharmacokinetic parameters calculated in Section 7.4 by dosage and assessment time point.

9.7 Analysis of Pharmacodynamics | Immunogenicity

[Phase 1 part]

The calculated amount of phosphorylated protein relative to total protein for each sampling time point for FLT3 and AXL will be obtained, and the rate of variability from the pre-dose value on Day 1 during the induction period will be calculated. Whenever possible, the relationship between the rate of variability and the pharmacokinetic parameters should be investigated.

[Phase 2 part]

Not applicable.

9.8 Other Analyses

9.8.1 Analysis of Exploratory Biomarker(s)

The presence/absence of the following FLT3 mutations will be summarized by frequency.

- FLT3-ITD mutation
- FLT3 point mutation (D835, I836)

9.8.2 Retrospective Pharmacogenomic Study

The content of analysis for the retrospective pharmacogenomic investigation has not been determined at this point. An exploratory investigation to determine whether there is a relationship between the results of genetic analysis and the results of this trial (clinical information; for example, drug reaction, toxicity, survival rate, pharmacokinetics, etc.) may be conducted in the future. The sponsor will begin the study once the specific content of the investigation has been determined, at which point the sponsor will prepare the study plan, the appropriateness of conducting the study will be assessed from ethical and scientific viewpoints by the sponsor's IEC, and approval will be obtained prior to the study. The results of this study will not be included in the clinical study report; a separate report will be prepared instead.

9.9 Major Protocol Deviations

Major protocol deviations as defined in Section 10.3 will be summarized for all subjects who received study drug by study site.

Major protocol deviation data will be listed by study site and subject.

The major protocol deviation criteria will be uniquely identified in the summary table and listing.

9.10 Interim Analysis (and Early Discontinuation of the Study)

[Phase 1 part]

Not applicable.

[Phase 2 part]

Not applicable.

9.11 Additional Conventions

The handling of missing data, outliers, and visit windows in the final analysis will be decided before the data hard lock, as necessary, by referring to the opinions and advice from medical experts and statistical advisors. For standards for handling the visit windows, refer to the acceptable time ranges described in Section 12.9. If any subjects or data are excluded from analysis, they should be included in lists but excluded from summaries such as summary statistics.

If the start and stop dates of AEs and concomitant medications are incomplete, imputed dates will be used to determine whether an AE is/is not treatment emergent or to allocate a concomitant medication to the study period it was taken.

See the SAP for details of the definition for analysis windows to be used for analyses by visit.

Study sites that do not enroll at least 1 subject will be pooled for analyses by study site. The pooling decisions will be made and documented prior to study hard lock.

10 OPERATIONAL CONSIDERATIONS

10.1 Procedure for Clinical Study Quality Control

10.1.1 Data Collection

The investigator or site designee will enter data using an Electronic Data Capture (EDC) system. The investigator is responsible for ensuring that all data in the eCRFs and queries are accurate and complete. The source documents should be appropriately maintained by the site.

For screening failures, the minimum data (the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure) will be collected in the SFL. This information can be entered into the study database.

The Data Science department of API will obtain the test results from the following organizations in the form of an electronic file.

[Phase 1 part]

- Assessments of QT interval and other intervals: Central ECG laboratory
- Pharmacodynamic assessments: Pharmacodynamics laboratory
- FLT3 mutation test: FLT3 mutation testing laboratory
- Plasma drug concentration assessments: Drug concentration laboratory

[Phase 2 part]

- Assessments of QT interval and other intervals: Central ECG laboratory
- FLT3 mutation test: FLT3 mutation testing laboratory
- Plasma drug concentration assessments: Drug concentration laboratory
- Assessment of peripheral blood, urine, bone marrow aspirate/biopsy: Central laboratories
- Registration information: Interactive Response Technology (IRT)

10.1.2 Specification of Source Documents

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

In this study, the following study-related records will be used as source documents, and these records will contain the source information (source data) entered into the eCRFs.

- Medical record
- Records attached to the medical record
- Subject registration record
- Participation in study and signed and dated informed consent forms
- Demographic data (birth date, sex, race, height, etc.)
- Results of relevant examinations (ECG chart, X-ray films, and photographs)
- Laboratory test slip
- Detailed records of dispensing and return of study drug such as a study drug storage management table, and dispensing of concomitant medications

For the following data, the data entered into the eCRF will be considered the source document. However, if they are described in the medical record or records that are attached or stored together, or can be determined from the source document, data described in the source document will be used as source data.

- Time of vital signs measurements
- Blood sampling time, performing blood sampling
- Route of administration of prior and concomitant medications, administration periods
- Treatment duration of prior and concomitant medications
- Date, reason, and details of discontinuation

- Severity and seriousness, assessment of causal relationship with the study drug and with the induction or consolidation therapy including the study drug, reason for assessment, measures taken, and the outcome of AEs
- Time, measured value, and contents of the diagnosis and assessment of ECG measurement
- Comments in the eCRF

10.2 Demographics and Baseline Characteristics

10.2.1 Demographics

The following demographics will be confirmed at screening and entered into the eCRF.

- Date of informed consent
- Date of birth
- Sex
- Race
- Height
- Target disease information
- Medical history
- ECOG Performance Status
- Chest X-ray or chest CT (if performed)
- ECHO or MUGA (if performed)
- Pregnancy test (for WOCBP)

10.2.2 Medical History and Concurrent Diseases

Medical history is any disease from which the subject has recovered before the start of study drug administration.

The diagnosis and the duration of circulatory disease, hematologic disease, and malignant tumors (excluding AML, which is the target disease of this study) will be investigated and entered into the eCRF.

Any medical conditions from which the subject has not recovered before the start of study drug administration should also be collected as concurrent diseases in the eCRF.

The following disease related events if present at baseline (ongoing at the time of Informed Consent) should be reported on the Medical History eCRF as ongoing and with the highest grade:

- Leukocytosis / Elevated white blood cells (WBC)
- Leucopenia / Decreased WBC
- Neutropenia / Decreased ANC
- Anemia / Low RBC / Low hemoglobin
- Thrombocytopenia / Decreased platelets

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

The diagnosis and findings of AML, which is the target disease of this study, will be confirmed at screening, and the following items will be entered into the eCRF.

- Date of diagnosis
- Bone marrow findings (FAB classification, WHO classification, classification of prognosis)
- FLT3 mutation

10.3 Major Protocol Deviations

[Phase 1 part]

Not applicable.

[Phase 2 part]

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. All deviations from the protocol are to be recorded. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

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 well-being 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 subjects.

A major protocol deviation is 1 that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject. Major protocol deviations will have additional reporting requirements.

When a major 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.

The major protocol deviation criteria that will be summarized at the end of the study are as follows:

- PD1 - Entered into the study even though the subject 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

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

10.4 STUDY ORGANIZATION

10.4.1 Efficacy and Safety Evaluation Committee

[Phase 1 part]

The Efficacy and Safety Evaluation Committee will be comprised of members of a third party who are not directly involved in the clinical study. The committee will be responsible for evaluating safety issues submitted by the sponsor in accordance with the SOP primarily from the viewpoint of the subjects. In the case of an event that poses a safety issue, the committee will discuss and recommend to the sponsor whether to continue, modify, or stop the trial.

[Phase 2 part]

Not applicable.

10.4.2 Other Study Organization

Please refer to the Attachment.

10.5 Registration of Subjects

[Phase 1 part]

The investigator will confirm each subject's eligibility to participate in this study at screening. Once the subject's eligibility is confirmed, the investigator will enter the necessary information into the subject registration form and inform the sponsor. Administration of the study drug will start within 7 days of registration.

Similarly, the investigator will enter the necessary information into the subject registration form for screen failures and inform the sponsor.

The registration procedure will be specified separately.

[Phase 2 part]

The investigator will confirm each subject's eligibility to participate in this study at screening. Pre-registration occurs when a subject meets all eligibility criteria except for Inclusion criteria #4, #14-c, and #14-d and is prepared for Day 1. Subjects must meet all criteria by the planned administration of ASP2215 on Day 8 in order to be registered and to continue the study. Confirmation of criteria and the process of registration by Day 8 by investigator should be documented. If the subject did not meet all criteria by planned administration of ASP2215 on Day 8, the subject should be considered as registration failure. For Inclusion criteria #14-c, and #14-d, the most recent value prior to registration should meet the criterion.

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12 APPENDICES

12.1 Ethical, Regulatory and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

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

The pharmacogenomic study will be conducted in accordance with the "Ethical Guidelines for Human Genome and Genetic Analysis Research" (MECSST/MHLW/METI Notification No. 1 of 2004) and "Use of Pharmacogenomics in Clinical Trials of Medicinal Products" (PFSB Notification dated September 30, 2008) in addition to the above.

12.1.2 Institutional Review Board/Independent Ethics Committee

GCP requires that the protocol, any protocol amendments, investigator's brochure, ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB/IEC. The IRB/IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB/IEC approval of the protocol, ICF and subject information and/or advertising, as relevant, will be obtained prior to initiation of any study-specific procedures.

Any substantial amendments to the protocol will require competent authority and IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU Regulation No. 536/2014 for studies (if applicable), and all other applicable local regulations.

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC or competent authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, investigator, IRB/IEC and appropriate regulatory authorities (if applicable).

Amendments to this protocol must be signed by the sponsor and investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented.

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 ICF, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new ICF must also be forwarded to the sponsor.

12.1.4 Informed Consent of Subjects

12.1.4.1 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 (if applicable) and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed, signed (***UNIQUE to JP Region:*** place a personal seal) and dated by the subject or his/her guardian or legal representative (if applicable), the person who administered the ICF and any other signatories according to local requirements. A copy of the signed (***UNIQUE to JP Region:*** 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 the ICF was signed prior to any study-related procedures and that the subject received a signed copy of the ICF.

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

Prior to execution of the clinical study, the investigator should prepare the written informed consent form and other written information in collaboration with the sponsor and revise the information whenever necessary. The written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

The investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will. However, if the subject is underage, informed consent must also be obtained from the subject's legal guardian besides the subject.

The investigator or other responsible personnel should note the following when obtaining consent from subjects:

- No subject may be subjected to undue influence, such as compulsory enrollment in a study.
- The language and expression used in the written information should be as plain and understandable as possible. Subjects should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal

rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator, study coordinators, or the sponsor from liability for negligence.

[Phase 1 part]

Informed consent for continuing ASP2215 treatment must be obtained before the start of study drug administration in the consolidation period.

[Phase 2 part]

No consent is required to at the beginning of consolidation therapy.

12.1.4.2 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 verbally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participating in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update the subject's ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided verbally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF (***UNIQUE to JP Region:*** place a personal seal). A copy of the signed (***UNIQUE to JP Region:*** 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 re-consent process.

12.1.4.3 Subject Information and Consent for Retrospective Pharmacogenomic Study

In addition to the informed consent for participation in the study, a written informed consent form must be obtained from subjects who also consent to the collection and storage of samples for retrospective pharmacogenomic study. The process of subject information and consent for the retrospective pharmacogenomic study should also follow Section 12.1.4.1.

The informed consent for retrospective pharmacogenomic study can be obtained only from subjects who have consented to participate in this study. Subjects who have consented to the retrospective pharmacogenomic study may withdraw only their consent to the retrospective pharmacogenomic study without withdrawing their consent to participate in this study. The pharmacogenomic samples of subjects who withdraw their consent to retrospective pharmacogenomic study will be destroyed except in the case where the samples have already been irreversibly anonymized.

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

12.1.5 Source Documents

Source data must be available at the study site to document the existence of the 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 investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, and/or drug accountability.

Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information, if applicable). All printed records must be kept in the subject file and be available for archiving.

12.1.6 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data CRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. The sponsor will notify the study site/investigator if the NDA/MAA/J-NDA is approved or if the IND/investigational medicinal product dossier (IMPD)/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subject’s medical records and/or study progress notes.

[UNIQUE to JP Region]

The records to be retained at the study sites are those 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 appropriate 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 (1) or (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, 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 study selected from those verified in other departments or hospitals.
2. Study contracts, written ICFs, written information and other documents or their copies prepared by the study personnel. A letter of request for study (including a request for continuation/amendment), letter of request for review, notice of study contract, 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 signatures and print of seals (copy) and eCRF (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the 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 study whose period exceeds 1 year or the adequacy of continuously conducting the study from which information on adverse drug reactions is obtained, and other documents obtained. A finalized protocol (including revisions), finalized 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 drug and other duties related to the study. Procedure for controlling the study drug, drug inventory and accountability record, vouchers for the receipt and return of the study drug, and the prescriptions for concomitant medications

[Phase 1 part]

(If applicable) The documents of the efficacy and safety evaluation committee (minutes and SOPs and others) and the judgment committee outside the study sites (minutes and SOPs and others) shall be retained by the sponsor.

[Phase 2 part]

Not applicable.

12.1.7 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator 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 study without justifiable reasons.

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

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number 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 agrees to comply and process personal data 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 Data Protection Directive (DPD), and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. 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 DPD.

12.1.8 Arrangement for Use of Information and Publication of the Study

Information concerning the test product, 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 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 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 may be discussed in the study agreement.

12.1.9 Insurance of Subjects and Others *(UNIQUE to JP)*

If a subject suffers any study-related injury, the sponsor will compensate the subject appropriately according to the severity and duration of the damage. However, if the injury 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 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 a compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the study contract.
4. The sponsor shall make an arrangement for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

12.1.10 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final CSR that 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 the coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database hard-lock.

12.2 Procedure for Study Quality Control

12.2.1 Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP. The sponsor is responsible for assigning the study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 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 appropriate regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the CRO, the IRB/IEC or appropriate regulatory authorities. The confidentiality of the subject's identity shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 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 the data management team. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and the WHO Drug Dictionary, respectively.

12.3 Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the schedule of assessments. Pregnancy test results must confirm that the subject is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Females in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal with 1 of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

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

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than 1 follicle-stimulating hormone (FSH) measurement 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 1 of the non-estrogen 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.

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

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 180 days after the final study drug administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- 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
- Other combined (estrogen- and progesterone-containing) methods
  - Vaginal ring
  - Injectable
  - Implantable
  - Intrauterine hormone-releasing system or 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 test product. 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 subject. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] 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 subjects participating in clinical studies.

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

Male subjects with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 120 days after final drug administration.[a]

- 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
- Use a condom
- Female partners of male subjects who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

12.4.1 Definition of Adverse Events

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

12.4.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g. hematology, biochemistry or urinalysis) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease, does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

12.4.1.2 Potential Cases of Drug-induced Liver Injury

Refer to Section 12.6 for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in Section 12.6, in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per Section 12.4.5.

12.4.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, the event:

- 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 inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE)
- Other medically important events (defined in paragraph below)

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

12.4.3 Criteria for Causal Relationship to Study Drug

A medically qualified investigator is obligated to assess the relationship between study drug/concomitant chemotherapy and each occurrence of each (S)AE. This investigator will use medical judgment as well as the reference safety information to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the study drug/concomitant chemotherapy and each (S)AE will be assessed by answering “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the study drug/concomitant chemotherapy?” For this study, causality of with each study drug/concomitant chemotherapy (ASP2215, cytarabine, and idarubicin) should be determined and reported by investigator.

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a “reasonable possibility” that an (S)AE may have been caused by the study drug/concomitant chemotherapy (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the subject been administered study drug/concomitant chemotherapy?
- Plausibility (i.e., could the event have been caused by the suspect drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- Dechallenge/dose reduction/rechallenge:
    - Dechallenge: Did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?

  - Dose reduction: Did the (S)AE resolve or improve after reducing the dose of the suspect drug?
  - Rechallenge: Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results: a specific lab investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of IP exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible temporal relationship between exposure to the IP and (S)AE onset and/or resolution will be provided. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor contact personnel (Section 12.4.5). However, it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor contact personnel (Section 12.4.5). With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of "no" is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship with the study drugs could not be ruled out."

Table 21 Criteria for Determining Causal Relationship with the Study Drug

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

12.4.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute-common terminology criteria for adverse event (NCI-CTCAE) guidelines version 4.0. The items that are not stipulated in the NCI-CTCAE version 4.0 will be assessed according to the criteria below and entered into the eCRF:

Table 22 Grading Scale Defining the Severity of an Adverse Event

Grade	Assessment Standard
1 - Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2 - Moderate	Minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL†
3 - Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization indicated; disabling; limiting self-care ADL‡
4 - Life-threatening	Life threatening consequences, urgent intervention indicated
5 - Death	Death related to AE

ADL: activities of daily living; AE: adverse event

†Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

‡Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

12.4.5 Reporting Procedures for Serious Adverse Events

[Non-Japanese clinical sites]

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the Sponsor contact personnel by fax or email immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on delegation of authority log). Signature confirms accuracy and completeness of the SAE data

as well as the investigator causality assessment including the explanation for the causality assessment.

For contact details, see [Contact Details of Sponsor's Key Personnel]. Email the SAE/special situations worksheet to:

Astellas Pharma Inc. – Japan
Pharmacovigilance
Email: safety-jp@astellas.com

[UNIQUE to JP Region]

In the case of a SAE, the investigator must report to the head of the study site and must contact the sponsor via the delegated CRO by fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the appropriate regulatory authorities to the sponsor via the delegated CRO by fax or email immediately (within 24 hours of awareness) and to the head of the hospital.

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE/special situations worksheet to:

Sponsor Contact:

Astellas Pharma Inc., Development, Japan-Asia Clinical Development 1
Location: 2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan
TEL: 03- 3244-1097

Sponsor Contact [Contract Research Organizer (CRO) Contact]:

PPD-SNBL K.K., Global Clinical Development
St Luke's Tower 12F, 8-1 Akashi-cho, Chuo-ku, Tokyo, Japan
TEL: 03-6821-0932
FAX:03-6740-7912

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or their designee [Contact Details of Sponsor's Key Personnel].

Follow-up information for the event should be sent promptly (as soon as available, but no longer than within 7 days of the initial notification [***UNIQUE to JP Region***: within 2 days for the initial notification]).

Full details of the SAE should be recorded on the medical records, SAE/special situation worksheet and on the eCRF.

The following minimum information is **required**:

- International study number/study number
- Subject number, sex and age

- Date of report
- Description of the SAE (event and seriousness criteria)
- Causal relationship to the IP (including reason)
- Drug provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., SUSAR reporting) according to current local/regional regulatory requirements. The sponsor or sponsor's designee will submit expedited safety reports to competent authorities and concerned ethics committee per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/ IEC of expedited safety reports should be retained by the study site. In the US, FDA expedited IND reporting guidelines will be followed.

The sponsor will notify all investigators responsible for ongoing clinical studies with the test product of all SUSARs, which require submission per local requirements.

The investigators (***UNIQUE to JP REGION:*** the heads of the study sites) should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the rights, safety or well-being of the subject.

12.4.6 Reporting Procedures for Special Situations

12.4.6.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 120 days from the discontinuation of dosing, the investigator is to report the information to the Sponsor contact personnel according to the timelines in Section 12.4.5 using the SAE worksheet as a special situation and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period and report the information to the Sponsor contact personnel according to the timelines in Section 12.4.5 using the Pregnancy form provided by the sponsor as a special situation.

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.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female subject as an AE in the eCRF or SAE per Section 12.4.5. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the SAE worksheet.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the IP.
- If an infant dies more than 1 month after the birth, it is to be reported if a relationship between the death and intrauterine exposure to the IP is judged as "possible" by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

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 or other means as appropriate. (S)AEs experienced by the newborn/infant should be reported via the pregnancy reporting form. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date.

12.4.6.2 Medication Error, Overdose and "Off-label Use"

If a medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the subject), overdose or "off-label use" (i.e., use outside of what is stated in the protocol) is suspected, refer to Section 10.3. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in Section 12.4.5 together with the details of the medication error, overdose and/or "off-label use."

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

12.4.6.3 Misuse/Abuse

Definition of misuse: Situations where the IP is/are intentionally and inappropriately used not in accordance with the intended use as defined in the protocol.

Definition of abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

If misuse or abuse of the IP is suspected, the investigator must forward the special situation worksheet to the Sponsor contact personnel (Section 12.4.5) by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the *eCRF*. If the AE meets the definition of an SAE, the SAE is also to be reported as described in Section 12.4.5 together with details of the misuse or abuse of the IP.

12.4.6.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the subject) to the IP occurs, the investigator must forward the special situation worksheet to the Sponsor contact personnel (Section 12.4.5) by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the

individual associated with or resulting from the special situation are to be reported on the special situations worksheet.

12.4.6.5 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situation worksheet to the Sponsor contact personnel (Section 12.4.5) by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in Section 12.4.5 together with details of the suspected drug-drug interaction.

12.4.7 Monitoring of Common Serious Adverse Events

The following is a list of SAEs commonly anticipated to occur in the study population independent of drug exposure that will be monitored by the Sponsor 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 (Section 12.4.5).

SAEs associated with the primary disease (AML)	**Grade commonly seen in AML**
Hematologic AEs	
Anemia	0–4
Hypocellular marrow	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
Leukopenia	0–4
Infection AEs	
Bacterial infection (regardless of the organ or cause by specific bacteria)	0–3
Chills	0–3
Cough	0–3
Febrile neutropenia (without infection)	0–4
Pyrexia	0–5
Flu–like symptoms	0–3
Fungal infection (regardless of the organ or cause)	0–3
Mucositis	0–4
Periodontal disease	0–3
Pneumonia	0–5
Sepsis/bacteraemia (any cause)	0–5
Sinusitis	0–4
Pharyngeal pain	0–3
Table continued on next page	

SAEs associated with the primary disease (AML)	**Grade commonly seen in AML**
Psychiatric and neurological AEs	
Anxiety	0–2
Cognitive disorder	0–3
Confusion	0–5
Depressed level of consciousness	0–5
Depression	0–3
Libido decreased	0–2
Meningism	0–5
Seizure	0–5
Somnolence	0–5
Syncope	3
Other AEs	
Activated partial thromboplastin time prolonged	0–2
Alanine aminotransferase increased	0–2
Alkaline phosphatase increased	0–2
Inappetence	0–2
Aspartate aminotransferase increased	0–2
Blood bilirubin increased	0–2
Bone and joint pain	0–2
Contusion	0–2
Hemorrhage	0–5
Diarrhea	0–2
Dyspnea	0–5
Fatigue	0–3
Flushing	0–2
Gamma–glutamyltransferase increased	0–1
Graft versus host disease (GVHD) acute and chronic	0–2
Gingiva hypertrophia	0–1
Hyperuricemia	0–1
Hypokalemia	0–2
Hypotension	0–2
Hypoxia	0–3
INR increased	0–1
Lactate dehydrogenase increased	0–2
Malaise	0–2
Multi–organ failure	0–5
Nausea	0–2
Oral dysesthesia	0–2
Petechiae	0–2
Pruritus	0–3
Skin and subcutaneous tissue disorders	0–3
Transient ischemic attack	0–2
Tumor lysis syndrome	3–5
Vasculitis	0–5
Vomiting	0–2
Weight decreased	0–2

12.5 Special terms

Table 23 ECOG Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, 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.

Common Toxicity Criteria, Version 2.0 Publication Date April 30, 1999

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf

http://www.jcog.jp/doctor/tool/C_150_0050.pdf

Table 24 NYHA (New York Heart Association) Functional Classification

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Slight limitation of physical activity. Patient is asymptomatic at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Marked limitation of physical activity. Patient is asymptomatic at rest. Less than ordinary activity will lead to fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Inability to carry out any physical activity without discomfort. Symptoms of heart failure and anginal pain are present at rest. Any physical activity will aggravate these symptoms.

12.6 Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of drug-induced liver injury during the course of the study. It should be noted that this section does not specify the End of Study analyses of liver enzymes. The end of study liver enzymes analyses will be described in the SAP. Any subject enrolled in a study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALP, ALT, AST and TBL). Testing should be repeated within 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 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 is as shown below.

Table 25 Definition of Liver Abnormalities

	ALT or AST		TBL
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and†	> 2 × ULN

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

†Samples taken simultaneously or within maximum 24 hours.

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† and* TBL > 2 × ULN or 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%)

† Samples taken simultaneously or within a maximum of 24 hours.

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 clinical laboratory tests. The study site personnel are to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests should be repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the IP 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 IP 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 are to be recorded as "AEs" within 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 AT 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 are to be entered in 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 clinical laboratory tests, including INR and 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 Treatment Discontinuation

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study 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† TBL > 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%)

† Samples taken simultaneously or within a maximum of 24 hours.

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

Hy's Law definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant).

The two "requirements" for Hy's Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in AT elevations > 3 × ULN ("2 × ULN elevations are too common in treated and untreated subjects to be discriminating").
2. Cases of increased total bilirubin (at least 2 × ULN) with concurrent AT elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome (Temple, 2006).

FDA Guidance for Industry titled, "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by the FDA on July 2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
2. Among subjects showing such AT elevations, often with ATs much greater than 3 × ULN, 1 or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

12.7 List of Excluded Concomitant Medications

For strong CYP3A inhibitors and strong CYP3A inducers, refer to the below link for details.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

12.8 Laboratory Assessments

Table 26 Laboratory Materials and Parameters (Phase 1)

	Collecting tube	Parameters to be analyzed
Hematology	Blood: EDTA tube	Erythrocytes (RBC) Reticulocytes Hemoglobin Hematocrit Leukocytes (WBC) Differential WBC (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Platelets MCV MCH MCHC Blast count
Biochemistry	Blood: Serum tube	CK Triglyceride Total cholesterol Albumin A/G ratio ALP ALT AST BUN Serum creatinine Na Ca Cl Glucose LDH Mg P K Total bilirubin Total protein
Thyroid function test	Blood: Serum tube	TSH FT4
Coagulation test	Blood: Na Citrate tube	PT PT/INR APTT Fibrinogen (only at screening) D-Dimer (only at screening)
Urinalysis	Urine test strips	Gravity pH Bilirubin Occult blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen

Table continued on next page

	Collecting tube	**Parameters to be analyzed**
Pregnancy test	Serum or urine sample: Serum tube or urine test strips	hCG
Bone marrow test	Bone marrow fluid: Na heparin tube or tissue biopsy	Blast count and cell count
FLT3 mutation	Bone marrow fluid: Tube containing heparin sodium, or Blood: Tube containing heparin sodium	FLT3 mutation

[Phase 2 part]

Laboratory tests will be performed according to the schedule of assessments and sent to a central laboratory for analysis.

Table 27 Laboratory Materials and Parameters (Phase 2)

	Collecting tube	Parameters to be analyzed
Hematology	EDTA tube	White Blood Cell Count White Blood Cell Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Hemoglobin Blast count
Biochemistry	Serum tube	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Uric Acid 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 test	Serum tube	Thyroid Function Tests including TSH and Free T4
Coagulation test	Na Citrate tube	INR (with PT if reported) aPTT Fibrinogen (only at screening) D-Dimer (only at screening)
Table continued on next page		

	Collecting tube	Parameters to be analyzed
Urinalysis	Urine test strips	Color Appearance Specific Gravity pH Bilirubin Blood Glucose Ketones Leukocyte Esterase Nitrite Protein Urobilinogen
Pregnancy test	Serum or urine sample: Serum tube or urine test strips	hCG
Bone marrow test	Aspirate 3-mL EDTA (disease assessment/MRD) and a 3-mL Heparin (FLT3 status), 2 to 3 bedside smear slides and/or biopsy (or whole blood)	Blast Count and Cell Counts Flow Cytometry for Blasts FLT3 Mutation Status Minimal Residual Disease (FLT3 allelic frequency) Future biomarkers (protein or genetic) related to ASP2215 and/or AML
FLT3 mutation	Bone marrow fluid: Tube containing heparin sodium, or Blood: Tube containing heparin sodium	FLT3 mutation
Pharmacokinetic	2 mL blood into dipotassium EDTA tube, processed to 1 mL plasma in transfer tube	Plasma ASP2215 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; PGx: pharmacogenomics; PT: prothrombin time; T4: thyroxine; THU: tetrahydrouridine; TSH: thyroid stimulating hormone.

12.9 Acceptable Range of Schedule of Assessments

[Phase 1 part]

The acceptable time ranges of the examinations, observations, etc., specified in the schedule are as follows.

[Acceptable Time Ranges of Safety and Efficacy Tests]

Laboratory Tests (Hematology, Biochemistry, Coagulation Test, Thyroid Function Test, Urinalysis):

Table 28 Acceptable Time Ranges for Laboratory Tests

Induction period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	Treatment on Day 1 may be started on the day informed consent is obtained when the investigator or subinvestigator judges that immediate treatment is required due to rapid proliferative disease progression. In this case, among the test items specified in both screening and Day 1 of Cycle 1 are not required to be performed twice.
Day 1	Day 1	Before dosing on the scheduled date	Same as above
Day 4	Day 4	Scheduled date	
Day 8	Day 8	Scheduled date	
Day 15	Day 15	Scheduled date ± 1 day	
Day 28	Day 28	Scheduled date ± 7 days	
Day 42	Day 42	Scheduled date + 14 days	

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1	Day 1	Scheduled date	
Day 4	Day 4	Scheduled date	
Day 8	Day 8	Scheduled date	
Day 15	Day 15	Scheduled date – 1 day	
Day 28	Day 28	Scheduled date ± 7 days	

Table continued on next page

Maintenance period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1	Day 1	Scheduled date	
Cycle X Day 1	Day 28 (X − 1) + 1	Scheduled date ± 3 days	X = Cycle 2 and subsequent cycles
End of treatment (for any period) or at the end of Cycle 26 of the maintenance period	Date of judgment of discontinuation or Cycle 26 Day 28 of the maintenance period	Scheduled date + 7 days	If the scheduled tests at discontinuation have been performed after the final study drug administration, the tests do not have to be repeated even if they were performed before the date of judgment of discontinuation.

Table 29 Acceptable Time Ranges for Vital Signs

Induction period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	Treatment on Day 1 may be started on the day informed consent is obtained when the investigator or subinvestigator judges that immediate treatment is required due to rapid proliferative disease progression. In this case, among the test items specified in both screening and Day 1 of Cycle 1 are not required to be performed twice.
Day 1	Day 1	Before dosing on the scheduled date	Same as above
Day 8	Day 8	Scheduled date	
Day 15	Day 15	Scheduled date ± 1 day	
Day 28	Day 28	Scheduled date ± 7 days	
Day 42	Day 42	Scheduled date + 14 days	
Table continued on next page			

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1	Day 1	Scheduled date	
Day 8	Day 8	Scheduled date	
Day 15	Day 15	Scheduled date − 1 day	
Day 28	Day 28	Scheduled date ± 7 days	

Maintenance period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1	Day 1	Scheduled date	
Cycle X Day 1	Day 28 (X − 1) + 1	Scheduled date ± 3 days	X = Cycle 2 and subsequent cycles
End of treatment (for any period) or at the end of Cycle 26 of the maintenance period	Date of judgment of discontinuation or Cycle 26 Day 28 of the maintenance period	Scheduled date + 7 days	If the scheduled tests at discontinuation have been performed after the final study drug administration, the tests do not have to be repeated even if they were performed before the date of judgment of discontinuation.

Table 30 Acceptable Time Ranges for 12-lead ECG (Including assessment of QT interval)

Induction period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	QT interval assessments will not be performed at the central ECG laboratory
Day 1 pre-dose	Day 1	Scheduled date, within 30 minutes before dosing	Performed prior to PK blood sampling
Day 4 pre-dose	Day 4	Scheduled date, within 30 minutes before dosing	
Day 4 4 hours post-dose	Day 4	Scheduled date, within ± 30 minutes of the scheduled time	
Day 11 pre-dose	Day 11	Scheduled date, within 30 minutes before dosing	
Day 17 pre-dose	Day 17	Scheduled date – 1 day, within 30 minutes before dosing	
Day 17 4 hours post-dose	Day 17	Scheduled date – 1 day, within ± 30 minutes of the scheduled time	
Day 28	Day 28	Scheduled date ± 7 days	

Table continued on next page

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1 pre-dose	Day 1	Scheduled date, within 30 minutes before dosing	Performed prior to PK blood sampling
Day 1 4 hours post-dose	Day 1	Scheduled date, within ± 30 minutes of the scheduled time	
Day 2 pre-dose	Day 2	Scheduled date, within 30 minutes before dosing	
Day 15	Day 15	Scheduled date − 1 day	Performed prior to PK blood sampling. If performed on Day 14 within the allowed visit window [−1] for Day 15, 12-lead ECG will be performed at pre-dose.
End of treatment (for any period) or at the end of Cycle 26 of the maintenance period	Date of judgment of discontinuation or Cycle 26 Day 28 of the maintenance period	Scheduled date + 7 days	QT interval assessments will not be performed at the central ECG laboratory. If the scheduled tests at discontinuation have been performed after the final study drug administration, the tests do not have to be repeated even if they were performed before the date of judgment of discontinuation.

Table 31 Acceptable Time Ranges for ECOG Performance Status

Induction period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	Treatment on Day 1 may be started on the day informed consent is obtained when the investigator or subinvestigator judges that immediate treatment is required due to rapid proliferative disease progression. In this case, among the test items specified in both screening and Day 1 of Cycle 1 are not required to be performed twice.
Day 1	Day 1	Before dosing on the scheduled date	Same as above
Day 8	Day 8	Scheduled date	

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1	Day 1	Scheduled date	
Day 8	Day 8	Scheduled date	

Maintenance period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1	Day 1	Scheduled date	
End of treatment (for any period) or at the end of Cycle 26 of the maintenance period	Date of judgment of discontinuation or Cycle 26 Day 28 of the maintenance period	Scheduled date + 7 days	If the scheduled tests at discontinuation have been performed after the final study drug administration, the tests do not have to be repeated even if they were performed before the date of judgment of discontinuation.

Table 32 Acceptable Time Ranges for ECHO or MUGA

Assessment timing	Scheduled date	Acceptable time range	Remarks
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	To be performed on patients with a history of congestive heart failure of NYHA class 3 or 4 (however, not necessary to be repeated at screening if ECHO or MUGA performed within 3 months prior to enrollment showed LVEF of ≥ 45%).

Table 33 Acceptable Time Ranges for Chest X-Ray or Chest CT

Assessment timing	Scheduled date	Acceptable time range	Remarks
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	

Table 34 Acceptable Time Ranges for Body Height/Weight

Induction period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	Height is measured only at screening. Treatment on Day 1 may be started on the day informed consent is obtained when the investigator or subinvestigator judges that immediate treatment is required due to rapid proliferative disease progression. In this case, among the test items specified in both screening and Day 1 of Cycle 1 are not required to be performed twice.
Day 1	Day 1	Before dosing on the scheduled date	Same as above

Table continued on next page

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1	Day 1	Scheduled date	

Maintenance period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1	Day 1	Scheduled date	
End of treatment (for any period) or at the end of Cycle 26 of the maintenance period	Date of judgment of discontinuation or Cycle 26 Day 28 of the maintenance period	Scheduled date + 7 days	If the scheduled tests at discontinuation have been performed after the final study drug administration, the tests do not have to be repeated even if they were performed before the date of judgment of discontinuation.

Table 35 Acceptable Time Ranges for Pregnancy Test

Induction period			
Assessment timing	**Scheduled date**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1	Day 1	Scheduled date	
Table continued on next page			

Maintenance period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1	Day 1	Scheduled date	
End of treatment (for any period) or at the end of Cycle 26 of the maintenance period	Date of judgment of discontinuation or Cycle 26 Day 28 of the maintenance period	Scheduled date + 7 days	If the scheduled tests at discontinuation have been performed after the final study drug administration, the tests do not have to be repeated even if they were performed before the date of judgment of discontinuation.

Table 36 Acceptable Time Ranges for Bone Marrow Tests

Induction period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	Not necessary to repeat if the test was performed within 28 days prior to study enrollment even before obtaining consent.
Day 28	Day 28	Scheduled date ± 7 days	

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Day 1 of each cycle Start of treatment)**	**Acceptable time range**	**Remarks**
Day 1	Day 1	Scheduled date – 7 days	Performed only at the start of Cycle 1 of consolidation period

Table continued on next page

Maintenance period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1	Day 1	Scheduled date – 7 days	
End of treatment (for any period) or at the end of Cycle 26 of the maintenance period	Date of judgment of discontinuation or Cycle 26 Day 28 of the maintenance period	Scheduled date + 7 days	If the scheduled tests at discontinuation have been performed after the final study drug administration, the tests do not have to be repeated even if they were performed before the date of judgment of discontinuation.

Table 37 Acceptable Time Ranges for Blood Sampling for PK Analysis of ASP2215 and Cytarabine

Induction period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1 pre-dose	Day 1	Scheduled date, within 30 minutes before dosing	Blood sampling for cytarabine
Cycle 1 Day 3 pre-dose	Day 3	Scheduled date, within 30 minutes before dosing	Blood sampling for cytarabine
Cycle 1 Day 4 pre-dose	Day 4	Scheduled date, within 30 minutes before dosing	Blood sampling for ASP2215
Cycle 1 Day 4 1 hour post-dose	Day 4	Scheduled date, scheduled time ± 10 minutes	
Cycle 1 Day 4 2 hours post-dose	Day 4	Scheduled date, scheduled time ± 10 minutes	
Cycle 1 Day 4 4 hours post-dose	Day 4	Scheduled date, scheduled time ± 20 minutes	
Cycle 1 Day 4 6 hours post-dose	Day 4	Scheduled date, scheduled time ± 20 minutes	
Cycle 1 Day 4 10 hours post-dose	Day 4	Scheduled date, scheduled time ± 20 minutes	
Cycle 1 Day 4 24 hours post-dose	Day 5	Scheduled date, scheduled time ± 60 minutes and prior to Day 5 dosing	
Cycle 1 Day 8 pre-dose	Day 8	Scheduled date, within 30 minutes before dosing	Blood sampling for ASP2215 and cytarabine
Cycle 1 Day 11 pre-dose	Day 11	Scheduled date, within 30 minutes before dosing	Blood sampling for ASP2215
Cycle 1 Day 17 pre-dose	Day 17	Scheduled date − 1 day, within 30 minutes before dosing	
Cycle 1 Day 28	Day 28	Scheduled date ± 7 days	

Table 38 Acceptable Time Ranges for FLT3 Mutation Test (Sampling)

Induction period			
Assessment timing	**Scheduled date**	**Acceptable time range**	**Remarks**
Screening	—	7 days before dosing – 1 day before dosing* * Before dosing if the screening and Day 1 of Cycle 1 overlap.	

Consolidation period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1	Day 1	Scheduled date + 7 days	Performed only for Cycle 1 of consolidation period

Maintenance period			
Assessment timing	**Scheduled date (Day 1: Cycle 1 Day 1 Start of treatment)**	**Acceptable time range**	**Remarks**
Cycle 1 Day 1	Day 1	Scheduled date	

[Phase 2 part]

The definitions for windows to be used by visit will be outlined in Table 7 (Schedule of Assessments [Phase 2 Part]).

12.10 Pharmacogenomic Analysis with Banked Sample (Optional)

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring differences in a subject's gene and/or expression of genes based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

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

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 the PGx sub-study. Subjects must provide written consent prior to providing any blood samples that may be used at a later time for PGx analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide 4 to 6 mL sample of whole blood/buccal swab per Astellas' instructions. Each sample will be identified by the unique subject number. Samples will be shipped to a designated banking CRO as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis if evidence suggests that genetic variants may be influencing the drug's pharmacokinetics, efficacy and/or safety.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database 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 unless otherwise specified by local regulation.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the study, if applicable. The results of the PGx 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.

12.11 Clinical Study Continuity

INTRODUCTION

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

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study subjects and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated schedules of assessments [Table 6 and Table 7] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the subject, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 7 Study Procedures and Assessments] due to a crisis.

INFORMED CONSENT

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

SUBJECT PROCEDURES ASSESSMENT

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

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

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

Adherence to the original protocol as reflected in the schedules of assessments [Table 6 and Table 7] is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 39] below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate measures. This is to allow for continuity of receiving study drug and maintaining critical safety and efficacy assessments for subjects in the study at a time of crisis.

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

Table 39 Alternative Schedule of Assessments in Response to a Crisis [Phase 2 part]

Assessments	Alternate Approach(es)	Treatment phase			EOT/Pre-HSCT	Follow-up (30-day and Long-term)
		Screening/Induction	Consolidation	Maintenance		
Informed consent	Not applicable	X				
Eligibility criteria	Not applicable	X				
Medical and disease history	Not applicable	X				
Vital Signs	• No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period. • For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X	X	
Height and Weight	• No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period. • For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X		
ECOG Performance Status	• No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period. • For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X	X	

Table continued on next page

Assessments	Alternate Approach(es)	Treatment phase			EOT/Pre-HSCT	Follow-up (30-day and Long-term)
		Screening/Induction	Consolidation	Maintenance		
Physical examination	• No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period. • For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X	X	X
Pregnancy test for WOCBP (serum)	• No alternative approach during screening period and both cytarabine and idarubicin/HIDAC treatment period within consolidation treatment period. • For the maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X		X		
Pregnancy test for WOCBP (urine)	• No alternative approach during screening period and both cytarabine and idarubicin/HIDAC treatment period within consolidation treatment period. • For the maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X		X		
Chest x-ray (or chest CT)	No alternative approach	X				
12-lead ECG	• No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period. • For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X	X	

Table continued on next page

Assessments	Alternate Approach(es)	Treatment phase			EOT/Pre-HSCT	Follow-up (30-day and Long-term)
		Screening/Induction	Consolidation	Maintenance		
Clinical laboratory tests (chemistry, hematology, coagulation, urinalysis)	• No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within induction treatment period and consolidation treatment period. • For the remaining visits including maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X	X	X
Thyroid function tests	• No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the consolidation treatment period. • For the maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X	X	
MUGA or ECHO	No alternative approach	X				
PK Sample Collection	No alternative approach	X	X			
PGx	No alternative approach	X				
FLT3 mutational status	No alternative approach	X				
Bone marrow aspirate/biopsy and MRD analysis	• No alternative approach during the screening period and HIDAC treatment period within the consolidation treatment period. • For the remaining visits including maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.	X	X	X	X	X
AE/SAE assessment	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X

Table continued on next page

Assessments	Alternate Approach(es)	Treatment phase			EOT/Pre-HSCT	Follow-up (30-day and Long-term)
		Screening/Induction	Consolidation	Maintenance		
Prior and concomitant medications	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X
Subsequent anti-leukemic treatments/outcomes	Remote/Virtual/Telemedicine Visits allowed					X
Survival	Remote/Virtual/Telemedicine Visits allowed					X
Cytarabine administration	No alternative approach	X	X			
Idarubicin administration	No alternative approach	X				
ASP2215 administration	If necessary, ASP2215 could be delivered from the hospital to the patient	X	X	X		

AE: adverse event; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; EOT: end of treatment; FLT3: FMS-like tyrosine kinase 3; HIDAC: high-dose cytarabine; HSCT: hematopoietic stem cell transplant; PGx: pharmacogenomic; MRD: minimal residual disease; MUGA: multigated acquisition; PI: principal investigator; PK: pharmacokinetic; SAE: serious adverse event; SOC: standard of care; WOCBP: woman of childbearing potential.

STUDY DRUG SUPPLY

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

- Increase stock of study drug on site to reduce number of shipments required, if site space will allow.
- Direct-to-Subject shipments of study drug from the site to the subject's home.

DATA COLLECTION REQUIREMENTS

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

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

12.12 List of Abbreviations and Definition of Key Study Terms

Table 40 List of Abbreviations

Abbreviations	Description of abbreviations
ADL	Activities of Daily Living
AE	Adverse Event
AML	Acute Myeloid Leukemia
ALK	Anaplastic lymphoma receptor tyrosine kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANCOVA	Analysis of Covariance
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase (GOT)
AUC	Area under the plasma concentration-time curve
AUC_{24}	Area under plasma concentration-time curve from time 0 to 24
AXL	AXL receptor tyrosine kinase
BCR-ABL	Breakpoint cluster region-Abelson
BCRP	Breast cancer resistant protein
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
Ca	Calcium
c-CBL	Cbl proto-oncogene, E3 ubiquitin protein ligase
CCSI	Company Core Safety Information
CI	Confidence interval
C_{max}	Maximum concentration
Cl	Chloride
CL/F	Oral clearance
CR	Complete remission
CRc	Composite complete remission (antitumor response criterion)
CRi	CR with incomplete hematologic recovery
CRp	CR with incomplete platelet recovery
CRF	Case Report Form
CRM	Continual Reassessment Method
CRO	Contract Research Organizer
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Plasma trough concentration
CYP	Cytochrome P450
CV	Coefficient of Variation
DDAS	Dose-Determining Analysis Set
DIC	Disseminated Intravascular Coagulation
DILI	Drug-induced Liver Injury
DLT	Dose-Limiting Toxicity

Abbreviations	Description of abbreviations
DPD	Data Protection Directive
ECG	Electrocardiogram
eCOA	electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
ECHO	Echocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FLT3	FMS-like tyrosine kinase-3, fms-related tyrosine kinase 3
FLT3-ITD	FLT3- Internal Tandem Duplication
FT4	Free T4
GCP	Good Clinical Practice
GM	Geometric mean
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GGT	Gamma-Glutamyltransferase
GVHD	Graft versus host disease
hERG	Human ether-à-go-go related gene
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-severely Toxic Dose
HSA	Human serum albumin
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IC_{50}	Half Maximal (50%) Inhibitory Concentration
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVR	Interventional Radiology
ISN	International Study Number
K	Potassium
LA-CRF	Liver Abnormality Case Report Form
LDH	Lactate Dehydrogenase
LTK	Leukocyte receptor tyrosine kinase
LVEF	Left Ventricular Ejection Fraction
MAS	MRD Analysis Set

Abbreviations	Description of abbreviations
MATE	Multidrug and toxin extrusion protein
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MER	c-mer proto-oncogene tyrosine kinase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gate Acquisition Scan
NASH	Nonalcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PD	Pharmacodynamic
PDAS	Pharmacodynamic Analysis Set
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	Partial Remission
PS	Performance Status
PT	Preferred term
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
RED	Recommended Expansion Dose
RET	ret proto-oncogene tyrosine kinase
ROS	c-ros oncogene 1, receptor tyrosine kinase
RSI	Reference Safety Information
(S)AE	Serious Adverse Event or Adverse Event
SAE	Serious adverse event
SAF	Safety Analysis Set
SDV	Source Data Verification
SFL	Screening Failure Log
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics

Abbreviations	**Description of abbreviations**
STD_{10}	Severely Toxic Dose in 10% of the Animals
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{½}$	terminal elimination half-life
TBL	Total Bilirubin
TEAE	Treatment-emergent adverse event
t_{max}	time of maximum concentration
TPN	Total Parenteral Nutrition
TRKA	Neurotrophic tyrosine kinase, receptor, type 1
TSH	Thyroid Stimulating Hormone
QT	QT interval
QTc	QT interval corrected
$t_{1/2}$	Apparent terminal elimination half-life
t_{max}	Time to attain C_{max}
ULN	Upper Limit of Normal
V_z/F	Apparent Volume of Distribution During the Terminal Elimination Phase after Oral Dosing
WBC	White Blood Cell
WOCBP	Woman of childbearing potential

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of subjects as they enter a study before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a study. Note: Once a subject has received the IP or placebo, the protocol applies to the subject.
Intervention	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a subject, and continues until the last assessment after completing administration of the test product or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening	A process of active consideration of potential subjects for enrollment in a study.
Screen failure	Potential subject who signed the ICF, but did not meet 1 or more criteria required for participation in the study and was not enrolled.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

13 ATTACHMENT 1 – SUBSTANTIAL AMENDMENT 7

I. The purpose of this amendment is:

Substantial Changes
1. Remove Interim Analysis
DESCRIPTION OF CHANGE:
The Phase 2 part interim analysis is removed from the protocol.
RATIONALE:
This revision is made to ensure consistency in the assessment of efficacy endpoints (e.g., response definitions) between ASP2215 studies in de novo acute myeloid leukemia (AML) patients who are eligible for intensive chemotherapy. Given the timing of the interim analysis and enrollment status, the sponsor decided to remove the planned interim analysis and perform the primary analysis with the revised response definitions based on the targeted enrollment of approximately 80 subjects in the Phase 2 part. There are no potential new safety signals or lack of efficacy for subjects who are in the ASP2215 studies; therefore, the removal of the interim analysis does not affect the safety of subjects.
2. Update Definition of Complete Response (CR)
DESCRIPTION OF CHANGE:
The definition of CR is updated and 'transfusion dependency' is removed. Antitumor response is defined per modified Cheson criteria or modified European LeukemiaNet recommendations.
RATIONALE:
The Response definition for de novo AML population was aligned at the program level to avoid the differences between studies potentially leading to inconclusive interpretation.

Nonsubstantial Changes
1. Update Key Study Personnel
DESCRIPTION OF CHANGE:
Contact details for medical monitor/study physician and clinical research contact are updated.
RATIONALE:
Contact details of medical monitor/study physician and clinical research contact are updated based on changes to study personnel.

2. Update Study Period
DESCRIPTION OF CHANGE:
The planned study period is updated from 1Q 2022 to 4Q 2022.
RATIONALE:
This revision is made due to an extension of the study duration.
3. Add Extramedullary Leukemia to Response Assessment
DESCRIPTION OF CHANGE:
In the Schedules of Assessments, extramedullary leukemia is added as part of the response assessment.
RATIONALE:
This revision is made for clarification
4. Update Nonclinical Pharmacology and Toxicology
DESCRIPTION OF CHANGE:
Section 2.1.1.2, Safety Pharmacology and Toxicology section is updated.
RATIONALE:
This update is made based on the latest information made to the Investigator's Brochure, Version 8.0.
5. Provide Timing of Primary Analysis for Primary Endpoint
DESCRIPTION OF CHANGE:
Text is added to clarify when the primary analysis for the primary endpoint will be conducted.
RATIONALE:
This revision is made for clarification.
6. Remove the Per Protocol Set (PPS) and Add MRD Analysis Set (MAS)
DESCRIPTION OF CHANGE:
PPS is removed and a MAS is added for analysis of the Phase 2 Part.
RATIONALE:
This revision is made for consistency with other 2215 studies.

7. Update Reporting Information for Serious Adverse Events (SAEs)
DESCRIPTION OF CHANGE:
The reporting information for SAEs is updated to clarify that SAEs must be reported to the sponsor via the delegated contract research organization.
RATIONALE:
This revision is made for clarification of the SAE reporting information.
8. Add Appendix for Clinical Study Continuity
DESCRIPTION OF CHANGE:
A Clinical Study Continuity appendix is added to the protocol. This appendix contains procedures for continuity of care during a crisis. An alternative schedule of assessments is provided.
RATIONALE:
This appendix is added to provide acceptable alternate methods to assess safety and efficacy parameters in the event the clinical study is interrupted at the country, state, site or subject level during any crisis (e.g., natural disaster or pandemic).
9. Update Study Monitoring
DESCRIPTION OF CHANGE:
The term ‘verifiable’ and related language is removed from the protocol.
RATIONALE:
Monitoring strategy is updated due to COVID-19 and the sponsor’s policy.
10. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering AND consistency throughout the protocol). The term ‘investigational product’ is replaced with ‘study drug’ and ‘concomitant chemotherapy.’ The word ‘drug’ is removed from ‘concomitant chemotherapy drugs.’ The link to the FDA’s Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers is updated. Correct symbol errors in Table 7. A reference for Döhner et al, 2017 is added to the reference list. Duration of response is added to study objective sections. Definition of ‘Duration of Response’ is corrected (Section 7.1.3.5) and missing information for ‘Analysis of Exploratory Endpoints’ is added (Section 9.4.3).
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

IIA. Substantial Changes

1 Protocol Summary *1.1 Synopsis, Interim Analysis*
WAS:
[Phase 2 part] At the timing when 35 subjects (50%) in Phase 2 part are evaluable for the primary endpoint of CR rate after induction therapy period, the interim analysis for futility stopping of Phase 2 part will be conducted. Predictive probability that 46 or more subjects will achieve CR at the final analysis of 70 evaluable subjects will be calculated as futility criteria. When the predictive probability is less than 10%, further enrollment into Phase 2 part may be stopped, taking into account other efficacy and safety results.
IS AMENDED TO:
[Phase 2 part] **Not applicable** ~~At the timing when 35 subjects (50%) in Phase 2 part are evaluable for the primary endpoint of CR rate after induction therapy period, the interim analysis for futility stopping of Phase 2 part will be conducted. Predictive probability that 46 or more subjects will achieve CR at the final analysis of 70 evaluable subjects will be calculated as futility criteria. When the predictive probability is less than 10%, further enrollment into Phase 2 part may be stopped, taking into account other efficacy and safety results.~~

7 Study Procedures and Assessments *7.1.2 Antitumor Response*
WAS:
Antitumor response is defined by the following revised standard by Bruce D. Cheson (2003) and samples are evaluated at central laboratories [Cheson et al., 2003]. [Phase 2 part] Bone marrow aspiration and/or biopsy samples and hematology samples are evaluated centrally. If bone marrow samples were obtained for unscheduled visits, those samples along with hematology samples should be submitted for central assessment. Definitions Complete Remission (CR): CR is defined as a morphologically leukemia-free state at the post-baseline visit, having a neutrophil count of ≥ 1,000/mm3 and platelet count of ≥ 100,000/mm3, bone marrow blasts < 5%, not being dependent on red blood cell (RBC) and platelet transfusion. There must be no presence of Auer rods and moreover being free of extramedullary leukemia. The blast counts in peripheral blood must be ≤ 2%. Complete Remission with Incomplete Hematological Recovery (CRi):

CRi is defined as a condition that meets all of the CR criteria at the post-baseline visit, except for the unrecovered neutrophil count (< 1,000/mm3; whether or not having unrecovered platelet counts, or receiving RBC and platelet transfusion).
IS AMENDED TO:
Antitumor response is defined **per modified Cheson criteria** ~~by the following revised standard by Bruce D. Cheson~~ (2003) **or modified European LeukemiaNet (ELN) recommendations (2017) as outlined below** and samples are evaluated at central laboratories [**Döhner et al, 2017;** Cheson et al~~.~~, 2003]. [Phase 2 part] Bone marrow aspiration and/or biopsy samples and hematology samples are evaluated centrally. If bone marrow samples were obtained for unscheduled visits, those samples along with hematology samples should be submitted for central assessment. **All local bone marrow assessments along with local hematology results should be collected in the eCRF.** Definitions Complete Remission (CR): CR is defined as a morphologically leukemia-free state at the post-baseline visit, having a neutrophil count of ≥ 1,000/mm3 and platelet count of ≥ 100,000/mm3, bone marrow blasts < 5%~~, not being dependent on red blood cell (RBC) and platelet transfusion~~. There must be no **evidence of Auer rods and no evidence of extramedullary leukemia** ~~presence of Auer rods and moreover being free of extramedullary leukemia~~. The blast counts in peripheral blood must be ≤ 2%. Complete Remission with Incomplete Hematological Recovery (CRi): CRi is defined as a condition that meets all of the CR criteria at the post-baseline visit, except for the unrecovered neutrophil count (< 1,000/mm3; whether or not having unrecovered platelet counts~~, or receiving RBC and platelet transfusion)~~. **Composite Complete Remission (CRc):** **To be classified as being in CRc at a post-baseline visit, a subject must either achieve CR, CRp or CRi at the visit.**

7 Study Procedures and Assessments *7.1.2.1 Best Response*
WAS:
Best response is defined as the best assessment (CR, CRh, CRp, CRi, or PR) obtained at each efficacy assessment time point after the start of treatment.
IS AMENDED TO:
Best response is defined as the best assessment (CR, ~~CRh,~~ CRp, CRi, or PR) obtained at each efficacy assessment time point after the start of treatment.

9 Statistical Methodology
9.4 Analysis of Efficacy

WAS:

[Phase 1 part]
The following classifications according to the Bruce D. Cheson standard (2003) will be summarized by frequency after each treatment period.
[Phase 2 part]
Efficacy analysis will be conducted on the FAS and PPS. The interpretation of statistical results will be based on the FAS. The PPS will be used to assess the robustness of statistical results based on the FAS.

IS AMENDED TO:

[Phase 1 part]
The following **endpoints will be summarized by** ~~classifications according to~~ the Bruce D. Cheson standard (2003) **or modified ELN recommendations (2017)**~~will be summarized by frequency after each treatment period~~.
[Phase 2 part]
Efficacy analysis will be conducted on the FAS ~~and PPS~~. The interpretation of statistical results will be based on the FAS. ~~The PPS will be used to assess the robustness of statistical results based on the FAS.~~

9 Statistical Methodology
9.10 Interim Analysis (and Early Discontinuation of the Study)

WAS:

[Phase 2 part]
At the timing when 35 subjects (50%) in Phase 2 part are evaluable for the primary endpoint of CR rate after induction therapy period, the interim analysis for futility stopping of Phase 2 part will be conducted. The interim analysis is based on Bayesian predictive probability approach. Binomial distribution is assumed to the number of responders among 35 subjects at the interim analysis and Jeffreys prior is assigned to the prior distribution as follows:

$$\mathrm{Y} \sim \mathrm{Bin}(35, \mathrm{p}), 0 \leq p \leq 1,$$
$$\mathrm{p} \sim \mathrm{Beta}(0.5,0.5)$$

Where Y is the number of responders at the interim analysis and p is the CR rate. Consequently, the posterior distribution of the CR rate follows a beta distribution

$$\mathrm{p|y} \sim \mathrm{Beta}(0.5 + \mathrm{y}, 0.5 + 35 - \mathrm{y}).$$

Thus, let X denote the number of responders after the interim analysis, the posterior predictive distribution of X given Y=y is a beta-binomial distribution as follows:

$$\Pr(\mathrm{x|y}) = \binom{35}{x} \frac{\mathrm{Beta}\ (0.5 + \mathrm{y} + \mathrm{x}, 0.5 + 70 - \mathrm{y} - \mathrm{x})}{\mathrm{Beta}\ (0.5 + \mathrm{y}, 0.5 + 35 - \mathrm{y})}$$

The predictive probability is defined as the probability that 46 or more subjects will achieve CR at the final analysis of 70 evaluable subjects. Thus the predictive probability can be expressed as $\Pr(x + y \geq 46|y)$.

This will be calculated as futility criteria at the interim analysis. When the predictive probability is less than 10%, further enrollment into phase 2 part may be stopped, taking into account other efficacy and safety results.

For the interim analysis, an Independent Data Monitoring Committee (IDMC) will not be organized.

IS AMENDED TO:

[Phase 2 part]

Not applicable.~~At the timing when 35 subjects (50%) in Phase 2 part are evaluable for the primary endpoint of CR rate after induction therapy period, the interim analysis for futility stopping of Phase 2 part will be conducted. The interim analysis is based on Bayesian predictive probability approach. Binomial distribution is assumed to the number of responders among 35 subjects at the interim analysis and Jeffreys prior is assigned to the prior distribution as follows:~~

$$\cancel{Y \sim \mathrm{Bin}(35, p), 0 \leq p \leq 1,}$$
$$\cancel{p \sim \mathrm{Beta}(0.5, 0.5)}$$

~~Where Y is the number of responders at the interim analysis and p is the CR rate. Consequently, the posterior distribution of the CR rate follows a beta distribution~~

$$\cancel{p|y \sim \mathrm{Beta}(0.5 + y, 0.5 + 35 - y).}$$

~~Thus, let X denote the number of responders after the interim analysis, the posterior predictive distribution of X given Y=y is a beta-binomial distribution as follows:~~

$$\cancel{\Pr(x|y) = \binom{35}{x} \frac{\mathrm{Beta}\,(0.5 + y + x, 0.5 + 70 - y - x)}{\mathrm{Beta}\,(0.5 + y, 0.5 + 35 - y)}}$$

~~The predictive probability is defined as the probability that 46 or more subjects will achieve CR at the final analysis of 70 evaluable subjects. Thus the predictive probability can be expressed as $\Pr(x + y \geq 46|y)$.~~

~~This will be calculated as futility criteria at the interim analysis. When the predictive probability is less than 10%, further enrollment into phase 2 part may be stopped, taking into account other efficacy and safety results.~~

~~For the interim analysis, an Independent Data Monitoring Committee (IDMC) will not be organized.~~

IIB. Nonsubstantial Changes

Contact Details of Sponsor's Key Personnel	
WAS:	
Medical Monitor/Study Physician	PPD ASTELLAS PHARMA GLOBAL DEVELOPMENT 1 Astellas Way, N6-163, Northbrook, IL USA 60062 PPD
Clinical Research Contact	Pharmaceutical Product Development, LLC (PPD) PPD
IS AMENDED TO:	
Medical Monitor/Study Physician	PPD ASTELLAS PHARMA GLOBAL DEVELOPMENT 1 Astellas Way, ~~N6-163,~~ Northbrook, IL USA 60062 PPD
Clinical Research Contact	Pharmaceutical Product Development, LLC (PPD) PPD

1 Protocol Summary *1.1 Synopsis, Planned Study Period*
WAS:
From August 2014 to 1Q 2022 (including long-term follow-up period).
IS AMENDED TO:
From August 2014 to **4Q**~~1Q~~ 2022 (including long-term follow-up period).

1 Protocol Summary *1.1 Synopsis, Study treatment period*
WAS:
[Phase 1 part] [Phase 2 part] Consolidation therapy period: The same chemotherapy regimen is applied as the Phase 1 part. Omission of consolidation therapy due to HCST is allowed. Consolidation therapy may be conducted up to 4 cycles. Maintenance therapy period: The same therapy is applied as the Phase 1 part. Maintenance therapy may be conducted up to 26 cycles. After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, relapse and survival (cause and date of death). Duration of long-term follow-up is until 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.
IS AMENDED TO:
[Phase 1 part] **Follow-up observation period:** **After treatment discontinuation, subjects will have a 28-day follow-up visit for safety.** [Phase 2 part] Consolidation therapy period: The same chemotherapy regimen is applied as the Phase 1 part. **Subjects will receive oral ASP2215 once daily on 14 consecutive days from Day 1 through Day 14. The maximum number of days in 1 cycle for the consolidation therapy period is not defined.** Omission of consolidation therapy due to HCST is allowed. Consolidation therapy may be conducted up to 4 cycles. Maintenance therapy period **(28 days per cycle)**:

The same therapy is applied as the Phase 1 part. Maintenance therapy may be conducted up to 26 cycles.

Long-term follow-up period:
After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, relapse and survival (cause and date of death). **During the long-term follow-up period, the subject will be followed for** ~~Duration of long-term follow-up is until~~ 3 years after the last subject**'s** first treatment or completion of 30-day follow-up of the last subject, whichever is longer.

1 Protocol Summary
1.1 Synopsis, Investigational Products (Study drugs and concomitant drugs)

WAS:

Name and Use:
[Phase 1 part]

ASP2215	study drug
Cytarabine	concomitant chemotherapy drug
Idarubicin	concomitant chemotherapy drug

[Phase 2 part]

ASP2215	study drug
AS3329381/Cytarabine	study drug and/or concomitant chemotherapy drug (based on the local regulation)
Idarubicin	concomitant chemotherapy drug

IS AMENDED TO:

Name and Use:
[Phase 1 part]

ASP2215	study drug
Cytarabine	concomitant chemotherapy ~~drug~~
Idarubicin	concomitant chemotherapy ~~drug~~

[Phase 2 part]

ASP2215	study drug
AS3329381/Cytarabine	study drug and/or concomitant chemotherapy ~~drug~~ (based on the local regulation)
Idarubicin	concomitant chemotherapy ~~drug~~

1 Protocol Summary
1.1 Synopsis, Treatment Discontinuation Criteria

WAS:

Discontinuation Criteria from Post-Treatment 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.
- The study meets the criteria to complete the long term follow-up (i.e., Duration of long-term follow-up is until 3 years after the last subject first treatment or completion of 30-day follow-up of the last subject, whichever is longer.)

IS AMENDED TO:

Discontinuation Criteria from Post-Treatment 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.

[Only applies to Phase 2 part]

- The study meets the criteria to complete the long-term follow-up (i.e., **During the long-term follow-up period, the subject will be followed for** ~~Duration of long-term follow-up is until~~ 3 years after the last subject**'s** first treatment or completion of 30-day follow-up of the last subject, whichever is longer.)

1 Protocol Summary
1.3 Schedule of Assessments, Table 7 [Phase 2 part], Induction Therapy

WAS:

Response Assessment

xx Eligibility criteria laboratory tests can be confirmed by the local lab. The values used for eligibility evaluation should be entered in eCRF and the central sample at the same timing of local lab tests should be submitted.

IS AMENDED TO:

Response Assessment **(including extramedullary leukemia)**

xx Eligibility criteria laboratory tests can be confirmed by the local lab. The values used for eligibility evaluation should be entered in eCRF and the central sample at the same timing of local lab tests should be submitted. **Lab values prior to informed consent**

may be collected in the eCRF in case the local bone marrow assessment result before.

1 Protocol Summary
1.3 Schedule of Assessments, Table 7 [Phase 2 part], Consolidation Therapy

WAS:

Assessments	D1
Response Assessment	X
Bone Marrow Aspiration/Biopsy [pp, qq, bbb]	

IS AMENDED TO:

Assessments	D1
Response Assessment **(including extramedullary leukemia)**	X[bbb]
Bone Marrow Aspiration/Biopsy [pp, qq, ~~bbb~~]	

1 Protocol Summary
1.3 Schedule of Assessments, Table 7 [Phase 2 part], Maintenance Therapy

WAS:

Assessments	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle X Day 1 [a]
Response Assessment	X				
Bone Marrow Aspiration/Biopsy [pp, qq]	X [iii]	X [jjj]			

IS AMENDED TO:

Assessments	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle X Day 1 [a]
Response Assessment **(including extramedullary leukemia)**	~~X~~ X [iii]	X [jjj]			
Bone Marrow Aspiration/Biopsy [pp, qq]					

1 Protocol Summary
1.3 Schedule of Assessments, Table 7 [Phase 2 part], End of Treatment

WAS:

Assessments	Pre-HSCT Visit EOT Visit m	30-Day Follow-Up [mmm]	Long-term Follow-Up [nnn]
Visit window		+/- 7 days	+/- 7 days
Response Assessment	X [rrr]		X [sss]
Bone Marrow Aspiration/Biopsy [pp, qq]			

[nnn] Duration of long-term follow-up is until 3 years after the last subject first treatment or completion of 30-day follow-up of the last subject, whichever is longer. The first follow-up will be performed 3 months after the 30-day follow-up visit. On site visit assessment will be performed at the timing of relapse.

[rrr] Does not need to be repeated if collected at a regularly scheduled visit within 7 days of the End of Treatment Visit. If bone marrow aspirate is unobtainable (e.g., dry tap), the whole blood sample will be used.

IS AMENDED TO:

Assessments	Pre-HSCT Visit EOT Visit m	30-Day Follow-Up [mmm]	Long-term Follow-Up [nnn]
Visit window		~~+/-~~ + 7 days	+/- 7 days
Response Assessment **(including extramedullary leukemia)**	X [rrr]		X [sss]
Bone Marrow Aspiration/Biopsy [pp, qq]			

[nnn] ~~Duration of~~ **During the** long-term follow-up **period, the subject will be followed for** ~~is until~~ 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer. The first follow-up will be performed 3 months after the 30-day follow-up visit. On site visit assessment will be performed at the timing of relapse.

[rrr] Does not need to be repeated if collected at a regularly scheduled visit within 7 days of the **Pre-HSCT visit or** End of Treatment ~~V~~visit. If bone marrow aspirate is unobtainable (e.g., dry tap), the whole blood sample will be used.

2 Introduction

2.1.1.2 Safety Pharmacology and Toxicology

WAS:

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-Good Laboratory Practice (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).

IS AMENDED TO:

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-Good Laboratory Practice (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 tract was suggested to be a target organ of toxicity at doses of 10 mg/kg per day or higher in juvenile rats, as well as in adult rats** ~~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).

2 Introduction
2.1.2 Summary of Key Safety Information for Investigational Product(s)

WAS:

2.1.2 Summary of Key Safety Information for Investigational Product(s)

IS AMENDED TO:

2.1.2 Summary of Key Safety Information for **Study Drug**~~Investigational Product(s)~~

1 Protocol Summary and 3 Study Objective(s) and Endpoint(s)
1.1 Synopsis, Table 8 Study Objective(s) and Endpoints [Phase 1 part]

WAS:

Exploratory	
• Evaluate the efficacy of ASP2215 concomitant with induction and consolidation chemotherapy	• CR (Complete Remission) • CRp (CR with incomplete platelet recovery) • CRi (CR with incomplete hematologic recovery) • PR (Partial Remission) • CRc (Composite CR): CR + CRp + CRi • Overall response rate: CRc + PR

IS AMENDED TO:

Exploratory	
• Evaluate the efficacy of ASP2215 concomitant with induction and consolidation chemotherapy	• CR (Complete Remission) • CRp (CR with incomplete platelet recovery) • CRi (CR with incomplete hematologic recovery) • PR (Partial Remission) • CRc (Composite CR): CR + CRp + CRi

	• Overall response rate: CRc + PR • **Duration of response**

1 Protocol Summary and 3 Study Objective(s) and Endpoints *1.1 Synopsis, Table 8 Study Objective(s) and Endpoints [Phase 2 part]*	
WAS:	
• Evaluate the safety and efficacy of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy	• Overall survival (OS) • Event free survival (EFS) • Relapse free survival (RFS) • CR rate after each treatment therapy • CR rate without MRD after each treatment therapy • Complete remission with partial hematological recovery (CRh) rate after each treatment therapy • CRc rate after each treatment therapy • Duration of CR, CRh, CR/CRh and CRc • Adverse events (AEs), safety laboratory tests, vital signs, and electrocardiograms (ECGs)
IS AMENDED TO:	
• Evaluate the safety and efficacy of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy	• Overall survival (OS) • Event free survival (EFS) • Relapse free survival (RFS) • CR rate after each treatment therapy • CR rate without **minimal residual disease (**MRD**)** after each treatment therapy • Complete remission with partial hematological recovery (CRh) rate after each treatment therapy • **Composite complete remission (**CRc**)** rate after each treatment therapy • **CR/CRh rate after each treatment therapy** • Duration of CR, CRh, CR/CRh and CRc

	● **Duration of response** ● Adverse events (AEs), safety laboratory tests, vital signs, and electrocardiograms (ECGs)

1 Protocol Summary and 4 Study Design and Dose Rationale *1.1 Synopsis, Study Design Overview, 4.1 Study Design*
WAS:
[Phase 2 part] After achieving of objectives of the Phase 1 part, the Phase 2 part can be initiated. Subjects will receive ASP2215 at the recommended dose established in Phase 1 part. The target population will be limited to newly diagnosed FLT3-mutated AML and the sample size is approximately 80 subjects. An evaluable sample size of 70 subjects in Phase 2 part provides more than 80% power to detect a 15% increase in CR rate from 55% (historical benchmark) to 70% at one-sided significance level of 0.05. Interim analysis for futility stopping of the Phase 2 part will be performed at the timing when 35 subjects are evaluable for the primary endpoint of CR rate after induction therapy period. Predictive probability that 46 or more subjects will achieve CR at the final analysis of 70 evaluable subjects will be calculated as futility criteria.
IS AMENDED TO:
[Phase 2 part] After achieving **the**~~of~~ objectives of the Phase 1 part, the Phase 2 part can be initiated. Subjects will receive ASP2215 at the recommended dose established in **the** Phase 1 **part**. **The primary objective of the Phase 2 part is to evaluate the efficacy of ASP2215 in combination with induction therapy in newly diagnosed FLT3-mutated AML subjects.** The target population will be limited to newly diagnosed FLT3-mutated AML. **The primary analysis for the primary endpoint of the CR rate will be conducted when all registered subjects complete the induction therapy period** ~~and the sample size is approximately 80 subjects~~. ~~An evaluable sample size of 70 subjects in Phase 2 part provides more than 80% power to detect a 15% increase in CR rate from 55% (historical benchmark) to 70% at one-sided significance level of 0.05.~~ ~~Interim analysis for futility stopping of the Phase 2 part will be performed at the timing when 35 subjects are evaluable for the primary endpoint of CR rate after induction therapy period. Predictive probability that 46 or more subjects will achieve CR at the final analysis of 70 evaluable subjects will be calculated as futility criteria.~~ **After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, relapse and survival (cause and date of death). During the long-term follow-up period, the subject will be followed for 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.**

4 Study Design and Dose Rationale *4.3 End of Study Definition*
WAS:
Study completion is defined as the conclusion of data collection for the defined study primary endpoints. The study may be closed within a participating country per local regulations once the study has been completed and if all subjects enrolled in the country are no longer receiving IP. Study will continue until all long-term follow-ups are completed.
IS AMENDED TO:
Study completion is defined as the conclusion of data collection for the defined study ~~primary~~ endpoints. The study may be closed within a participating country per local regulations once the study has been completed and if all subjects enrolled in the country are no longer receiving **study drug**~~IP~~. Study will continue until all long-term follow-ups are completed.

5 Study Population *5.4.1 Rescreening*
WAS:
[Phase 1 part] Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, ECG, etc.) may be repeated within the 7-day screening period without the need to register the subject as a screen failure. If more than 7 days elapse from the date of signing the ICF, the subject must be documented as a screen failure. In order to re-screen, a new ICF must be signed and the subject entered into screening with a new subject identification number.
IS AMENDED TO:
[Phase 1 part] **Not applicable** ~~Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, ECG, etc.) may be repeated within the 7-day screening period without the need to register the subject as a screen failure. If more than 7 days elapse from the date of signing the ICF, the subject must be documented as a screen failure. In order to re-screen, a new ICF must be signed and the subject entered into screening with a new subject identification number.~~

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs)
WAS:
6 INVESTIGATIONAL PRODUCTS (STUDY DRUGS AND CONCOMITANT CHEMOTHERAPY DRUGS) 6.1 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) Table 10 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs)

Use	Study drug	Study drug/Concomitant chemotherapy drug (based on the local regulation)	Concomitant chemotherapy drug

Refer to the pharmacy manual, product label and package insert for detailed information regarding preparation, handling and storage of the IP and concomitant chemotherapy drugs.

IS AMENDED TO:

6 ~~INVESTIGATIONAL PRODUCTS (~~STUDY DRUGS AND CONCOMITANT CHEMOTHERAPY ~~DRUGS)~~

6.1 ~~Investigational Products (~~Study Drugs and Concomitant Chemotherapy ~~Drugs)~~

Table 10 ~~Investigational Products (~~Study Drugs and Concomitant Chemotherapy ~~Drugs)~~

Use	Study drug	Study drug/Concomitant chemotherapy ~~drug~~ (based on the local regulation)	Concomitant chemotherapy ~~drug~~

Refer to the pharmacy manual, product label and package insert for detailed information regarding preparation, handling and storage of the **study drug**~~IP~~ and concomitant chemotherapy ~~drugs~~.

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs)
6.1.1 Dose/Dose Regimen and Administration Period

WAS:

[Phase 2 part]
Concomitant chemotherapy drugs

IS AMENDED TO:

[Phase 2 part]
Concomitant chemotherapy ~~drugs~~

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) *6.2.1 Packaging and Labeling*
WAS:
All IPs supplied by the Sponsor in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at API or sponsor's designee in accordance with API or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations. Each IP will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug. Refer to the pharmacy manual, product label and package insert for detailed information regarding packaging and labeling of the IP and concomitant chemotherapy.
IS AMENDED TO:
All **study drugs**~~IPs~~ supplied by the ~~S~~**s**ponsor in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at API or sponsor's designee in accordance with API or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations. Each **study drug**~~IP~~ will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug. Refer to the pharmacy manual, product label and package insert for detailed information regarding packaging and labeling of the **study drug**~~IP~~ and concomitant chemotherapy.

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) *6.2.1.1 ASP2215*
WAS:
• Study title
IS AMENDED TO:
• Study **number**~~title~~

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) *6.2.1.2 Concomitant Chemotherapy Drugs (Idarubicin, Cytarabine)*
WAS:
6.2.1.2 Concomitant Chemotherapy Drugs (Idarubicin, Cytarabine)

IS AMENDED TO:
6.2.1.2 Concomitant Chemotherapy ~~Drugs~~ (Idarubicin, Cytarabine)

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) *6.2.2 Handling, Storage and Accountability*
WAS:
1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP. 2. Only subjects enrolled in the study may receive IP and only authorized study site personnel may supply or administer IP. Only IP with appropriate expiry/retest dating may be dispensed. 3. All IP must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel. 4. The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records). 5. Further guidance and instruction on final disposition of used and unused IP is provided in the pharmacy manual. Refer to the pharmacy manual for detailed information regarding handling, storage and accountability of the IP and concomitant chemotherapy.
IS AMENDED TO:
1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all **study drug**~~IP~~ received and any discrepancies are reported and resolved before use of the **study drug**~~IP~~. 2. Only subjects enrolled in the study may receive **study drug**~~IP~~ and only authorized study site personnel may supply or administer **study drug**~~IP~~. Only **study drug**~~IP~~ with appropriate expiry/retest dating may be dispensed. 3. All **study drug**~~IP~~ must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel. 4. The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records). 5. Further guidance and instruction on final disposition of used and unused **study drug**~~IP~~ is provided in the pharmacy manual. Refer to the pharmacy manual for detailed information regarding handling, storage and accountability of the **study drug**~~IP~~ and concomitant chemotherapy.

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) *6.3 Randomization and Blinding*
WAS:
This is an open-label study. For Phase 2 part, subject enrollment and dispensation of IP and concomitant chemotherapy will be performed via the interactive response technology (IRT) system. Specific IRT procedures will be described in the respective study manual.
IS AMENDED TO:
This is an open-label study. For Phase 2 part, subject enrollment and dispensation of **study drug**~~IP~~ and concomitant chemotherapy will be performed via the interactive response technology (IRT) system. Specific IRT procedures will be described in the respective study manual.

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) *6.4 Investigational Product and Concomitant Chemotherapy Drug Compliance*
WAS:
6.4 Investigational Product and Concomitant Chemotherapy Drug Compliance
IS AMENDED TO:
6.4 **Study Drug**~~Investigational Product~~ and Concomitant Chemotherapy ~~Drug~~ Compliance

6 Investigational Products (Study Drugs and Concomitant Chemotherapy Drugs) *6.6 Dose Modification*
WAS:
[Phase 2 part] ASP2215: Table 15 Guidelines for ASP2215 Dose Interruption or Reduction Event (for Phase 2)

Myelosuppression (Maintenance therapy only)	
Grade 4 neutropenia and thrombocytopenia	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.

IS AMENDED TO:
[Phase 2 part] ASP2215: **Table 15 should be followed if the specified events occurred during the ASP2215 dosing period. If the events occurred outside the ASP2215 dosing period, reduction of ASP2215 dosing may be determined upon the investigator's discretion.** Table 15 Guidelines for ASP2215 Dose Interruption or Reduction Event (for Phase 2)

Myelosuppression (Maintenance therapy only)

Grade 4 neutropenia and/**or** thrombocytopenia	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ Grade 1 within 14 days, the subject may resume dosing at the reduced dose.

7 Study Procedures and Assessments *7.1.3 Survival Time, Duration and Other Efficacy Endpoints*
WAS:
Follow-up will continue until the final database lock, which is estimated to occur when the last subject enrolled reaches the 30-day follow-up visit.
IS AMENDED TO:
For the Phase 1 part, ~~F~~**f**ollow-up will continue until ~~the final database lock, which is estimated to occur~~ when the last subject enrolled reaches the **28**~~30~~-day follow-up visit. **For the Phase 2 part, follow-up will continue until 3 years after the last subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.**

7 Study Procedures and Assessments *7.1.3.3 Relapse-free Survival*
WAS:
[Phase 2 part] Relapse-free survival (RFS) is defined as time from the date of achievement of remission until relapse or death from any cause, whichever comes first. For a subject who is not known to have relapsed or died, RFS is censored on the date of last relapse-free disease assessment date.
IS AMENDED TO:
[Phase 2 part] Relapse-free survival (RFS) is defined as time from the date of achievement of **first CRc**~~remission~~ until relapse or death from any cause, whichever comes first. For a subject who is not known to have relapsed or died, RFS is censored on the date of last relapse-free disease assessment date.

7 Study Procedures and Assessments *7.1.3.4 Transplantation rate*
WAS:
Transplantation rate is defined as the percentage of subjects undergoing HSCT during the study period.

IS AMENDED TO:
[Phase 1 part] **Not applicable.** **[Phase 2 part]** Transplantation rate is defined as the percentage

7 Study Procedures and Assessments *7.1.3.5 Duration of Response*
WAS:
Duration of response is defined as the period from the first day of achieving CR, CRh, CRp, CRi, or PR to the first day of confirmed relapse.
IS AMENDED TO:
Duration of response is defined as the period from the first day of achieving CR, ~~CRh,~~ CRp, CRi, or PR to the first day of confirmed relapse.

7 Study Procedures and Assessments *7.2.2 Laboratory Assessments*
WAS:
[Phase 2 part] Measurements will be performed centrally for both scheduled and unscheduled visits. Local lab assessments can be performed. The local hematology assessment will be recorded in the eCRF if the central assessment was not evaluable.
IS AMENDED TO:
[Phase 2 part] Measurements will be performed centrally for both scheduled and unscheduled visits. Local lab assessments can be performed. **The local hematology assessment will be recorded in the eCRF if the central assessment was not evaluable.**

7 Study Procedures and Assessments *7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information*
WAS:
[Phase 2 part] In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received IP.

IS AMENDED TO:
[Phase 2 part] In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received **study drug~~IP~~**.

7 Study Procedures and Assessments *7.3.4 Follow-up of Adverse Events*
WAS:
If after the protocol-defined AE collection period, an AE progresses to an SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the IP or study participation, the investigator must promptly notify the sponsor.
IS AMENDED TO:
If after the protocol-defined AE collection period, an AE progresses to an SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the **study drug~~IP~~** or study participation, the investigator must promptly notify the sponsor.

7 Study Procedures and Assessments *7.3.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events*
WAS:
• Disease progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the IP and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of study drugIP must be reported as an SAE, even if attributed to disease progression.
IS AMENDED TO:
• Disease progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the **study drug~~IP~~** and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of study drugIP must be reported as an SAE, even if attributed to disease progression.

7 Study Procedures and Assessments *7.3.7 Special Situations*
WAS:
[Phase 2 part] Certain special situations observed in association with the IP, such as incorrect administration (e.g., wrong dose of IP or background therapy) are collected in the eCRF, as protocol deviation or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.
IS AMENDED TO:
[Phase 2 part] Certain special situations observed in association with the **study drug**~~IP~~, such as incorrect administration (e.g., wrong dose of **study drug**~~IP~~ or background therapy) are collected in the eCRF, as protocol deviation or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

7 Study Procedures and Assessments *7.6.1 FLT3 Mutation Assessment*
WAS:
[Phase 2 part] 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.
IS AMENDED TO:
[Phase 2 part] 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.

8 Discontinuation *8.1 Discontinuation of Individual Subject(s) From Study Treatment, 8.2 Discontinuation of Individual Subject(s) From Study*
WAS:
8.1 Discontinuation of Individual Subject(s) From Study Treatment [Phase 2 part] Discontinuation Criteria from Post-Treatment 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.
- The study meets the criteria to complete the long term follow-up (i.e. Duration of long-term follow-up is until 3 years after the last subject first treatment or completion of 30-day follow-up of the last subject, whichever is longer.).

8.2 Discontinuation of Individual Subject(s) From Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in Schedules of Assessments. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

All subjects who discontinue study treatment are to be followed for survival status until completion of the study.

IS AMENDED TO:

8.1 Discontinuation of Individual Subject(s) From Study Treatment

[Phase 2 part]

~~Discontinuation Criteria from Post-Treatment 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.~~
- ~~The study meets the criteria to complete the long term follow-up (i.e. Duration of long-term follow-up is until 3 years after the last subject first treatment or completion of 30-day follow-up of the last subject, whichever is longer.).~~

8.2 Discontinuation of Individual Subject(s) From Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in Schedules of Assessments. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

For the Phase 2 part, ~~A~~all subjects who discontinue study treatment are to be followed for survival status until completion of the study.

Discontinuation Criteria from Post-Treatment 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.**

[Only applies to Phase 2 part]

- **The study meets the criteria to complete the long-term follow-up (i.e., During the long-term follow-up period, the subject will be followed for 3 years after the last**

subject's first treatment or completion of 30-day follow-up of the last subject, whichever is longer.).

8 Discontinuation *8.2.1 Lost to Follow-up*
WAS:
Every reasonable effort is to be made to contact any subject lost to follow up during the course of the study to complete study related assessments, record outstanding data and retrieve IP.
IS AMENDED TO:
Every reasonable effort is to be made to contact any subject lost to follow up during the course of the study to complete study related assessments, record outstanding data and retrieve **study drug**~~IP~~.

9 Statistical Methodology *9.2.2 Per Protocol Set (PPS)*
DELETED:
~~9.2.2 Per Protocol Set (PPS)~~ ~~[Phase 1 part]~~ ~~Not applicable.~~ ~~[Phase 2 part]~~ ~~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 non-adherence to the protocol, in a manner that might reasonably impact the primary analysis, and will be defined in the SAP. The PPS will be a secondary analysis set for efficacy analyses. Selected demographic and baseline characteristics may also be summarized for the PPS.~~

9 Statistical Methodology *9.2.5 Pharmacodynamic Analysis Set (PDAS)*
WAS:
9.2.5 Pharmacodynamic Analysis Set (PDAS) [Phase 2 part] Subjects who received the study drug, from whom samples for pharmacodynamic assessment have been collected for at least 1-time point after the study drug administration, and from whom pharmacodynamic measurement has been obtained will be included. Exploratory biomarker analysis of MRD will be performed using PDAS.
IS AMENDED TO:

9.2.4~~9.2.5~~ Pharmacodynamic Analysis Set (PDAS)

[Phase 2 part]

Not applicable.~~Subjects who received the study drug, from whom samples for pharmacodynamic assessment have been collected for at least 1 time point after the study drug administration, and from whom pharmacodynamic measurement has been obtained will be included. Exploratory biomarker analysis of MRD will be performed using PDAS.~~

9 Statistical Methodology

ADDED:

9.2.6 MRD Analysis Set (MAS)

[Phase 1 part]

Not applicable.

[Phase 2 part]

The MRD Analysis Set (MAS) consists of all subjects who were enrolled and received at least 1 dose of study drug, were centrally confirmed as FLT3-ITD positive and had a baseline and at least post-baseline sample with MRD data.

9 Statistical Methodology
9.3.1 Demographics

WAS:

Descriptive statistics will include number of subjects, mean, standard deviation, minimum, Q1, median, Q3 and maximum for continuous endpoints and frequency and percentage for categorical endpoints. The analyses will be performed in the FAS, PPS, SAF, PKAS, and PDAS.

IS AMENDED TO:

Descriptive statistics will include number of subjects, mean, standard deviation, minimum, Q1, median, Q3 and maximum for continuous endpoints and frequency and percentage for categorical endpoints. The analyses will be performed in the FAS, ~~PPS,~~ SAF, PKAS, and **MAS**~~PDAS~~.

9 Statistical Methodology
9.3.2 Subject Disposition

WAS:

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all subjects who received IP. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented for all subjects who received IP. All disposition details and dates of first and last evaluations for each subject will be listed.

IS AMENDED TO:
The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented ~~for all subjects who received IP~~. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented ~~for all subjects who received IP~~. All disposition details and dates of first and last evaluations for each subject will be listed.

9 Statistical Methodology *9.3.5 Investigational Product Exposure*
WAS:
9.3.5 Investigational Product Exposure The number and percentage of subjects exposed to IP will be summarized. All IP exposure data will be listed.
IS AMENDED TO:
9.3.5 **Study Drug**~~Investigational Product~~ Exposure The number and percentage of subjects exposed to **study drug**~~IP~~ will be summarized. All **study drug**~~IP~~ exposure data will be listed.

9 Statistical Methodology *9.4.1.2 Sensitivity Analysis of Primary Endpoint*
DELETED:
~~9.4.1.2 Sensitivity Analysis of Primary Endpoint~~ ~~[Phase 1 part]~~ ~~Not applicable.~~ ~~[Phase 2 part]~~ ~~The same analysis of the primary endpoint as described in Section 9.4.1 will be conducted using the PPS.~~

9 Statistical Methodology *9.4.2 Analysis of Secondary Endpoints*
WAS:
[Phase 2 part] The statistical analyses on secondary efficacy endpoints include the following descriptive analyses for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy:

- Kaplan-Meier method for time-to-event endpoints including OS, EFS, RFS, duration of CR, CRh, CR/CRh, and CRc.
- The two-sided 95% exact confidence interval of the binary endpoints including CR rate, CRh rate, CR/CRh rate, and CRc rate.

For each of the secondary responder endpoints, analyses are conducted are analyzed after each treatment therapy.

IS AMENDED TO:

[Phase 2 part]

The statistical analyses on secondary efficacy endpoints include the following descriptive analyses for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy:

- Kaplan-Meier method for time-to-event endpoints including OS, EFS, RFS, duration of CR, CRh, CR/CRh, ~~and~~ CRc **and response**.
- The two-sided 95% exact confidence interval of the binary endpoints including CR rate, CRh rate, CR/CRh rate, and CRc rate.

For each of the secondary responder endpoints, analyses are conducted ~~are analyzed~~ after each treatment therapy.

9 Statistical Methodology

9.4.3 Analysis of Exploratory Endpoints

WAS:

[Phase 1 part]

Not applicable.

[Phase 2 part]

Exploratory biomarker analysis of MRD will be performed using PDAS.

IS AMENDED TO:

[Phase 1 part]

~~Not applicable.~~ **The statistical analyses on exploratory endpoints include the following descriptive analyses for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy:**

- **Kaplan-Meier method for time-to-event endpoints duration of response, CR and CRc.**
- **The 2-sided 95% exact confidence interval of the binary endpoints CR rate, CRp rate, CRi rate, PR rate, CRc rate and response rate.**

[Phase 2 part]

Exploratory biomarker analysis of MRD will be performed using **MAS**~~PDAS~~.

9 Statistical Methodology *9.5.2 Adverse Events*
WAS:
AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and graded using NCI-CTCAE. A treatment-emergent adverse event (TEAE) is defined as an AE observed after starting administration of the IP and within 30 days (for phase 1 part, 28 days) after the last administration of IP. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as YES by the investigator. The number and percentage of subjects with TEAEs, IP-related TEAEs, serious TEAEs, IP-related serious TEAEs, TEAEs leading to withdrawal of treatment and IP-related TEAEs leading to withdrawal of treatment will be summarized by System Organ Class (SOC), Preferred Term (PT). The number and percentage of TEAEs by severity will also be summarized.
IS AMENDED TO:
AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and graded using NCI-CTCAE. A treatment-emergent adverse event (TEAE) is defined as an AE observed after starting administration of the **study drug**~~IP~~ and within 30 days (for phase 1 part, 28 days) after the last administration of **study drug**~~IP~~. An **drug**~~IP~~-related TEAE is defined as any TEAE with a causal relationship assessed as YES by the investigator. The number and percentage of subjects with TEAEs, **drug**~~IP~~-related TEAEs, serious TEAEs, **drug**~~IP~~-related serious TEAEs, TEAEs leading to withdrawal of treatment and **drug**~~IP~~-related TEAEs leading to withdrawal of treatment will be summarized by System Organ Class (SOC), Preferred Term (PT). The number and percentage of TEAEs by severity will also be summarized.

9 Statistical Methodology *9.7 Analysis of Pharmacodynamics | Immunogenicity*
WAS:
[Phase 2 part] Not applicable. (PDAS is used for exploratory biomarker analysis of MRD.)
IS AMENDED TO:
[Phase 2 part] Not applicable. ~~(PDAS is used for exploratory biomarker analysis of MRD.)~~

9 Statistical Methodology *9.9 Major Protocol Deviations*
WAS:
Major protocol deviations as defined in Section 10.3 will be summarized for all subjects who received IP by study site.
IS AMENDED TO:
Major protocol deviations as defined in Section 10.3 will be summarized for all subjects who received **study drug**~~IP~~ by study site.

10 Operational Considerations *10.1.1 Data Collection*
WAS:
The investigator or site designee will enter data using an Electronic Data Capture (EDC) system. The investigator is responsible for ensuring that all data in the electronic Case Report Forms (eCRFs) and queries are accurate and complete and that all entries are verifiable with source documents. The source documents should be appropriately maintained by the site. The monitor should verify the data in the eCRF with the source documents and confirm that there are no inconsistencies between them.
IS AMENDED TO:
The investigator or site designee will enter data using an Electronic Data Capture (EDC) system. The investigator is responsible for ensuring that all data in the ~~electronic Case Report Forms (~~eCRFs~~)~~ and queries are accurate and complete ~~and that all entries are verifiable with source documents~~. The source documents should be appropriately maintained by the site. ~~The monitor should verify the data in the eCRF with the source documents and confirm that there are no inconsistencies between them.~~

10 Operational Considerations *10.2.2 Medical History and Concurrent diseases*
WAS:
Medical history is any disease from which the subject has recovered before the start of investigation product administration. Any medical conditions from which the subject has not recovered before the start of investigational product administration should also be collected as concurrent diseases in the eCRF.

IS AMENDED TO:
Medical history is any disease from which the subject has recovered before the start of ~~investigation product~~**study drug** administration. Any medical conditions from which the subject has not recovered before the start of **study drug**~~investigational product~~ administration should also be collected as concurrent diseases in the eCRF.

11 References
ADDED:
Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424-47.

12 Appendices *12.1.6 Record Retention*
WAS:
[UNIQUE to JP Region] 4. Records of control for IP and other duties related to the study. Procedure for controlling the IP, drug inventory and accountability record, vouchers for the receipt and return of the IP, and the prescriptions for concomitant medications.
IS AMENDED TO:
[UNIQUE to JP Region] 4. Records of control for **study drug**~~IP~~ and other duties related to the study. Procedure for controlling the **study drug**~~IP~~, drug inventory and accountability record, vouchers for the receipt and return of the **study drug**~~IP~~, and the prescriptions for concomitant medications.

12 Appendices *12.2.1 Study Monitoring*
WAS:
The sponsor or delegated CRO is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP and the study data reported by the investigators are accurate, complete and verifiable with the source. The sponsor is responsible for assigning the study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

IS AMENDED TO:
The sponsor or delegated CRO is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP ~~and the study data reported by the investigators are accurate, complete and verifiable with the source~~. The sponsor is responsible for assigning the study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12 Appendices *12.3 Contraception Requirements*
WAS:
Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 180 days after the final IP administration.[a]
IS AMENDED TO:
Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 180 days after the final **study drug**~~IP~~ administration.[a]

12 Appendices *12.4.1 Definition of Adverse Events*
WAS:
An AE is any untoward medical occurrence in a subject administered an investigational product (IP), and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IP whether or not considered related to the IP.
IS AMENDED TO:
An AE is any untoward medical occurrence in a subject administered a~~n~~ **study drug**~~investigational product (IP)~~, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of **study drug**~~IP~~ whether or not considered related to the **study drug**~~IP~~.

12 Appendices

12.4.3 Criteria for Causal Relationship to Investigational Product

WAS:

Criteria for Causal Relationship to Investigational Product

A medically qualified investigator is obligated to assess the relationship between IP and each occurrence of each (S)AE. This investigator will use medical judgment as well as the reference safety information to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the IP and each (S)AE will be assessed by answering "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IP?" For this study, causality of with each IP (ASP2215, cytarabine, and idarubicin) should be determined and reported by investigator.

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a "reasonable possibility" that an (S)AE may have been caused by the IP (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the subject been administered IP?

Table 21 Criteria for Determining Causal Relationship with the Investigational Product

IS AMENDED TO:

Criteria for Causal Relationship to **Study Drug**~~Investigational Product~~

A medically qualified investigator is obligated to assess the relationship between **study drug/concomitant chemotherapy**~~IP~~ and each occurrence of each (S)AE. This investigator will use medical judgment as well as the reference safety information to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the **study drug/concomitant chemotherapy**~~IP~~ and each (S)AE will be assessed by answering "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the **study drug/concomitant chemotherapy**~~IP~~?" For this study, causality of with each **study drug/concomitant chemotherapy**~~IP~~ (ASP2215, cytarabine, and idarubicin) should be determined and reported by investigator.

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a "reasonable possibility" that an (S)AE may have been caused by the **study drug/concomitant chemotherapy**~~IP~~ (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the subject been administered **study drug/concomitant chemotherapy**~~IP~~?

Table 21 Criteria for Determining Causal Relationship with the **Study Drug**~~Investigational Product~~

12 Appendices

12.4.5 Reporting Procedures for Serious Adverse Events

WAS:

[UNIQUE to JP Region]

In the case of a SAE, the investigator must report to the head of the study site and must contact the delegated CRO by fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the appropriate regulatory authorities to the delegated CRO by fax or email immediately (within 24 hours of awareness) and to the head of the hospital.

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE/special situations worksheet to:

Sponsor Contact:

Astellas Pharma Inc., Development, Japan-Asia Clinical Development 1

Location: 2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan

TEL: 03- 3244-1097

FAX: 03-3243-5737

Contract Research Organizer (CRO) Contact:

IS AMENDED TO:

[UNIQUE to JP Region]

In the case of a SAE, the investigator must report to the head of the study site and must contact **the sponsor via the** delegated CRO by fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the appropriate regulatory authorities to **the sponsor via the** delegated CRO by fax or email immediately (within 24 hours of awareness) and to the head of the hospital.

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE/special situations worksheet to:

Sponsor Contact:

Astellas Pharma Inc., Development, Japan-Asia Clinical Development 1

Location: 2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan TEL: 03- 3244-1097 ~~FAX: 03-3243-5737~~ **Sponsor Contact [**Contract Research Organizer (CRO) Contact**]**:

12 Appendices *12.7 List of Excluded Concomitant Medications*
WAS:
For strong CYP3A inhibitors and strong CYP3A inducers, refer to the below link for details. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-study-design-data-analysis-and-clinical-implications-guidance
IS AMENDED TO:
For strong CYP3A inhibitors and strong CYP3A inducers, refer to the below link for details. **https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers** ~~https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-study-design-data-analysis-and-clinical-implications-guidance~~

12 Appendices *12.9 Acceptable Range of Schedule of Assessments*
WAS:
[Phase 2 part] The definitions for windows to be used for analyses by visit will be outlined in the SAP.
IS AMENDED TO:
[Phase 2 part] The definitions for windows to be used ~~for analyses~~ by visit will be outlined in **Table 7 (Schedule of Assessments [Phase 2 Part])**~~the SAP~~.

12 Appendices
ADDED:
12.11 Clinical Study Continuity **INTRODUCTION**

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

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study subjects and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated schedules of assessments [Table 6 and Table 7] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the subject, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 7 Study Procedures and Assessments] due to a crisis.

INFORMED CONSENT

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

SUBJECT PROCEDURES ASSESSMENT

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

- **Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes subject travel to/from the study site nearly impossible.**
- **Site facilities have been closed for clinical study conduct.**
- **Site has been restricted to treating patients with conditions outside of the scope of the study.**
- **Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the subject with respect to time and travel.**
- **Subject(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the subject with respect to travel.**
- **Subject(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel.**
- **Subject has risk factors for which traveling to the site poses an additional risk to the subject's health and safety.**

Adherence to the original protocol as reflected in the schedules of assessments [Table 6 and Table 7] is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 37] below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate measures. This is to allow for continuity of receiving study drug and maintaining critical safety and efficacy assessments for subjects in the study at a time of crisis.

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

Alternative Schedule of Assessments in Response to a Crisis [Phase 2 part]

Assessments	Alternate Approach(es)	Treatment phase			EOT/Pre-HSCT	Follow-up (30-day and Long-term)
		Screening /Induction	Consolidation	Maintenance		
Informed consent	**Not applicable**	**X**				
Eligibility criteria	**Not applicable**	**X**				
Medical and disease history	**Not applicable**	**X**				
Vital Signs	• **No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period.** • **For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**	**X**	**X**	**X**	
Height and Weight	• **No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period.** • **For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**	**X**	**X**		
ECOG Performance Status	• **No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the**	**X**	**X**	**X**	**X**	

	induction treatment period and consolidation treatment period. • **For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**					
Physical examination	• **No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period.** • **For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**	**X**	**X**	**X**	**X**
Pregnancy test for WOCBP (serum)	• **No alternative approach during screening period and both cytarabine and idarubicin/HIDAC treatment period within consolidation treatment period.** • **For the maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**		**X**		
Pregnancy test for WOCBP (urine)	• **No alternative approach during screening period and both cytarabine and idarubicin/HIDAC treatment period within consolidation treatment period.** • **For the maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**		**X**		

Chest x-ray (or chest CT)	**No alternative approach**	**X**				
12-lead ECG	• **No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the induction treatment period and consolidation treatment period.** • **For the remaining visits including maintenance phase, this exam can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**	**X**	**X**	**X**	
Clinical laboratory tests (chemistry, hematology, coagulation, urinalysis)	• **No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within induction treatment period and consolidation treatment period.** • **For the remaining visits including maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**	**X**	**X**	**X**	**X**
Thyroid function tests	• **No alternative approach during the screening period and both cytarabine and idarubicin/HIDAC treatment period within the consolidation treatment period.** • **For the maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**	**X**	**X**	**X**	
MUGA or ECHO	**No alternative approach**	**X**				
PK Sample Collection	**No alternative approach**	**X**	**X**			

PGx	**No alternative approach**	**X**				
FLT3 mutational status	**No alternative approach**	**X**				
Bone marrow aspirate/biopsy and MRD analysis	• **No alternative approach during the screening period and HIDAC treatment period within the consolidation treatment period.** • **For the remaining visits including maintenance phase, these exams can be performed at a local clinic per SOC and results can be submitted to PI for evaluation.**	**X**	**X**	**X**	**X**	**X**
AE/SAE assessment	**Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.**	**X**	**X**	**X**	**X**	**X**
Prior and concomitant medications	**Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.**	**X**	**X**	**X**	**X**	**X**
Subsequent anti-leukemic treatments/outcomes	**Remote/Virtual/Telemedicine Visits allowed**					**X**
Survival	**Remote/Virtual/Telemedicine Visits allowed**					**X**
Cytarabine administration	**No alternative approach**	**X**	**X**			
Idarubicin administration	**No alternative approach**	**X**				
ASP2215 administration	**If necessary, ASP2215 could be delivered from the hospital to the patient**	**X**	**X**	**X**		

AE: adverse event; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; EOT: end of treatment; FLT3: FMS-like tyrosine kinase 3; HIDAC: high-dose cytarabine; HSCT: hematopoietic stem cell transplant; PGx: pharmacogenomic; MRD: minimal residual disease; MUGA: multigated acquisition; PI: principal investigator; PK: pharmacokinetic; SAE: serious adverse event; SOC: standard of care; WOCBP: woman of childbearing potential.

STUDY DRUG SUPPLY

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

- **Increase stock of study drug on site to reduce number of shipments required, if site space will allow.**
- **Direct-to-Subject shipments of study drug from the site to the subject's home.**

DATA COLLECTION REQUIREMENTS

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

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

14 SPONSOR SIGNATURE