STATISTICAL ANALYSIS PLAN

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

ISN: 2215-CL-0104

Sponsor: Astellas Pharma Inc. (API)

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
AESI	Adverse events of special safety interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
API	Astellas Pharma Inc.
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area under the plasma concentration-time curve
AUC_{24}	Area under plasma concentration-time curve from time 0 to 24
AUC_{inf}	AUC from the time of dosing extrapolated to time infinity
AUC_{last}	AUC from the Time of Dosing to the Last Measurable Concentration
AXL	AXL receptor tyrosine kinase
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CID	Cumulative Incidence of Death
CIR	Cumulative Incidence of Relapse
CL/F	Oral clearance
C_{max}	Maximum concentration
CR	Complete Remission
CR1	1st Complete Remission
CRc	Composite Complete Remission
CRF	Case Report Form
CRh	Complete Remission with Partial Hematological Recovery
CRi	Complete Remission with Incomplete Hematological Recovery
CRM	Continual Reassessment Method
CRp	Complete Remission with Incomplete Platelet Recovery
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DDAS	Dose-Determining Analysis Set
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFS	Event Free Survival

Abbreviations	Description of abbreviations
ELN	European LeukemiaNet
ESS	Effective Sample Size
FAB	French-American-British
FAS	Full Analysis Set
FLT3	FMS-like tyrosine kinase-3
FLT3-ITD	FLT3- Internal Tandem Duplication
FLT3-TKD	FLT3- Tyrosine Kinase Domain
GM	Geometric Mean
HLT	High Level Term
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
Lambda z	Terminal elimination rate constant
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MAS	MRD Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
MR	Molecular Response
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
MUGA	Multiple Gate Acquisition
NCI	National Cancer Institute
NE	Not Evaluable
NR	No Response
NYHA	New York Heart Association
OS	Overall Survival
PD	Pharmacodynamic
PDAS	Pharmacodynamic Analysis Set
PK	Pharmacokinetic
PKAS	Pharmacokinetics Analysis Set
PR	Partial Remission
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Preferred Term
QTc	Corrected Q-T Interval
QTcF	QT interval corrected for heart rate using Fridericia's factor
RBC	Red Blood Cell
RED	Recommended Expansion Dose
RFS	Relapse Free Survival
RR	Interval between 2 consecutive r waves on an ECG
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
$t_{1/2}$	Apparent terminal elimination half-life
TLF	Tables, Listings and Figures
t_{max}	Time of the Maximum concentration
TTE-FAS	Time-to-Event Full Analysis Set

Abbreviations	Description of abbreviations
ULN	Upper Limit of Normal
V_z/F	Apparent Volume of Distribution During the Terminal Elimination Phase after Oral Dosing
WHO	World Health Organization
WHODD	WHO Drug Dictionary
WHODD(B2)	WHO Drug Dictionary (B-2 Format)
WHODD(B3)	WHO Drug Dictionary (B-3 Format)
WOCBP	Women of childbearing potential

List of Key Terms

Terms	Definition of terms
Baseline	Last available 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).
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.
Registration failure	A subject who signed the ICF and met the pre-registration criteria but did not meet all inclusion and exclusion criteria by day 8. These subjects received chemotherapy but never received ASP2215.
Screening	A process of active consideration of potential subjects for enrollment in a study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This SAP contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to database lock for primary analysis for the primary endpoint.

This statistical analysis is coordinated by the responsible biostatistician of Development API (Global Development, API). Any changes from the analyses planned in the SAP will be justified in the CSR.

2 FLOW CHART AND VISIT SCHEDULE

Details of the schedule of clinical assessments are available in the protocol.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

3.1.1 Primary objectives

[Phase 1 part]

- To 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).
- To evaluate the safety and tolerability of ASP2215 concomitant with cytarabine/idarubicin as induction chemotherapy and high-dose cytarabine as consolidation chemotherapy.
- To evaluate the safety and tolerability of ASP2215 in maintenance therapy after induction and consolidation therapy.

[Phase 2 part]

- To evaluate the efficacy of ASP2215 in combination with induction therapy in newly diagnosed FLT3 (FMS-like tyrosine kinase-3) -mutated AML (Acute Myeloid Leukemia) subjects.

3.1.2 Secondary objectives

[Phase 1 part]

- To characterize the pharmacokinetic (PK) parameters of ASP2215 concomitant with induction and consolidation chemotherapy.
- To evaluate the PK parameters of cytarabine concomitant with ASP2215.

[Phase 2 part]

- To characterize the PK parameters of ASP2215 concomitant with induction and consolidation chemotherapy.
- To evaluate the safety and efficacy of ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy

3.1.3 Exploratory objectives

[Phase 1 part]

- To evaluate the efficacy of ASP2215 concomitant with induction and consolidation chemotherapy.
- To evaluate the pharmacodynamic (PD) parameters of ASP2215.

[Phase 2 part]

- To evaluate the additional efficacy measures for ASP2215 in combination with induction and consolidation therapy followed by maintenance therapy

3.2 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 following table for Bayesian-CRM is met.

Table **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, 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). 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.

3.3 Randomization

Randomization is not performed in this study since this is an open-label, uncontrolled study.

4 SAMPLE SIZE

4.1.1 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

4.1.2 Justification of Sample Size

[Phase 1 part: 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. The sample size may increase depending on the occurrence of toxicities.

[Phase 1 part: 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]

A 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. To account for several subjects dropping out from the study, 80 subjects will be enrolled.

5 ANALYSIS SETS

In accordance with ICH recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

5.1 Full Analysis Set (FAS)

[Phase 1 part]

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

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

For the statistical analysis of some Time-to-Event efficacy variables, TTE-FAS will be used. TTE-FAS is defined similarly as the FAS, however, the criterion for bone marrow assessment is removed.

5.2 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the SAF will be used.

[Phase 1 part]

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

[Phase 2 part]

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

5.3 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.

5.4 Pharmacokinetics 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.

5.5 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.

5.6 MRD Analysis Set (MAS)

[Phase 1 part]

Not applicable.

[Phase 2 part]

Subjects who received at least one dose of study drug, were centrally confirmed as FLT3-ITD positive at screening and had a baseline and at least one post-baseline sample with MRD data.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Response Definition

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.

Antitumor response is defined per modified Cheson criteria (2003) or modified ELN recommendations (2017) as outlined below [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 both centrally and locally. 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 $\geq 1{,}000/mm^3$ and platelet count of $\geq 100{,}000/mm^3$, bone marrow myeloblasts < 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 myeloblasts < 5%, partial hematologic recovery neutrophil count$\geq 500/mm^3$ and platelet count $\geq 50{,}000/mm^3$, 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).

Partial Remission (PR):

At a post-baseline visit, PR is defined as a condition with regeneration of normal hematopoietic cells in the bone marrow.

If bone marrow myeloblasts between 5% and 25% and a decrease from baseline of at least 50% in the marrow myeloblasts, no detectable (or trace of residual) blasts, and no evidence of extramedullary leukemia, the response is classified as PR.

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 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% myeloblasts in the bone marrow 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 myeloblasts in the bone marrow to > 25% or >2% blast in peripheral blood not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Best Response:

Best response is defined as the best measured response to treatment for all visits (in the order of CR, CRp, CRi, PR, NR and NE) post-baseline. Subjects who achieve the best responses of CR, CRp, CRi, or PR will be classified as responders. Subjects who do not achieve at least PR will be classified as non-responders.

6.1.2 Primary Efficacy Endpoint

[Phase 1 part]

Not applicable.

[Phase 2 part]

- CR rate after induction therapy period

Defined as the number of subjects who achieve the best response of CR divided by the number of subjects in the analysis population during induction therapy period. Subjects with unknown or missing response, or who provide no information on response will be treated as non-responders and will be included in the denominator when calculating rates.

6.1.3 Secondary Efficacy Endpoints

[Phase 1 part]

Not applicable.

[Phase 2 part]

- Overall survival (OS)

OS is defined as the time from start date of the first treatment until the date of death due to any cause. For a subject who is not known to have died by the end of long-term follow-up, OS is censored at the date of last known alive.

As a sensitivity analysis, OS is defined similarly as the above, however, subjects who undergo HSCT will be censored at the time of HSCT.

- Event free survival (EFS)

The time from the date of start date of the first treatment until the date of documented relapse after CR, 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. Subject without post-treatment disease assessment will be censored at the start date of the treatment.

Treatment failure includes those subjects who failed to achieve CRc by the end of consolidation period, or who discontinued the treatment due to "lack of efficacy" without a previous response.

Treatment failure date refers to the end of treatment date for subjects with treatment failure.

- Relapse free survival (RFS)

The time from the date of achievement of first CRc until relapse or death from any cause, whichever comes first for subjects who achieve CRc. 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.

Last relapse-free disease assessment date refers to the subject's last disease assessment date.

- CR rate after each treatment therapy

Defined as the number of subjects who achieve the best response of CR divided by the number of subjects in the analysis population after each treatment therapy period.
Subjects with unknown or missing response, or who provide no information on response will be treated as non-responders and will be included in the denominator when calculating rates.

- CR rate without MRD after each treatment therapy

Defined similarly as CR rate after each treatment therapy. Responders achieve that the best response is CR and MRD status is negative. CRc rate without MRD after each treatment therapy will also be defined similarly.

- CRh rate after each treatment therapy

Defined similarly as CR rate after each treatment therapy.

- CRc (Composite CR) rate after each treatment therapy

CRc: CR + CRp + CRi
Defined similarly as CR rate after each treatment therapy.

- CR/CRh rate after each treatment therapy

CR/CRh: CR or CRh.
Defined similarly as CR rate after each treatment therapy.

- Duration of CR, CR/CRh, CRh, CRc, response

Duration of CR is defined as the time from the date of achieving first CR until the date of first documented relapse for subjects who achieve CR. Subjects who die without report of

relapse are considered non-events and censored at their last relapse-free disease assessment date. Subjects who come off the study for HSCT will be considered non-events and censored at the time of HSCT. Other subjects who do not relapse on study are considered non-events and censored at the last relapse-free assessment date. Duration of CRh, Duration of CR/CRh, Duration of CRc and Duration of response are defined similarly as Duration of CR.

6.1.4 Exploratory Efficacy Endpoints

[Phase 1 part]

- CR rate
  Defined as the number of subjects with CR divided by the number of subjects in the analysis population. Subjects with unknown or missing response, or who provide no information on response at the end of study will be treated as non-responders and will be included in the denominator when calculating rates.
- CRp rate
  Defined similarly as CR rate.
- CRi rate
  Defined similarly as CR rate.
- CRc rate
  Defined similarly as CR rate.
- PR rate
  Defined similarly as CR rate.
- Overall response rate: CRc + PR
  Defined similarly as CR rate.
- Duration of response – Duration of response is defined as the period from the first date of achieving CR, CRp, CRi, or PR to the first date of documented relapse for subjects who achieve CR, CRp, CRi, or PR. Subjects who die without report of relapse are considered non-events and censored at their last relapse-free disease assessment date. Other subjects who do not relapse on study are considered non-events and censored at the last relapse-free disease assessment date.
- Duration of CR is defined similarly as duration of response for subjects who achieved CR.
- Duration of CRc is defined similarly as duration of response for subjects who achieved CRc.

[Phase 2 part]

- Transplantation rate

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

- Cumulative incidence of relapse (CIR) after 1st CR (CR1)

Defined as the time from the date of achieving CR1 until relapse. When calculating this variable, only subjects who achieved CR1 are included. Subjects alive without relapse will be censored on the date of last relapse-free disease assessment date. Although subjects who died without relapse should be treated as the subjects who occurred competing event, those

subjects will be censored at the date of death.

- Cumulative incidence of death (CID) after CR1

Defined as the time from the date of achieving CR1 until death. When calculating this variable, only subjects who achieved CR1 are included. Subjects who are alive without death will be censored at the date of last known alive.

- Time to hematopoietic recovery after each treatment cycle

Defined as the time from the date of start date of the treatment until the date of having a neutrophil count of ≥ 1,000/ mm^3 and platelet count of ≥ 100,000/ mm^3. Subjects with none of these events are censored at the date of last assessment within each treatment cycle.

- MRD

MRD is defined as binary endpoint, negative or positive. More detail of the definition is in Section 6.5. MRD rate is defined as the percentage of subjects whose MRD is negative.

- MR

MR is defined as binary endpoint, MR or no MR. More detail of the definition is in Section 6.5. MR rate is defined as the percentage of subjects who achieve MR.

- MRD-negative CR rate after induction

Defined as the number of subjects who achieve the best response of CR and whose MRD is negative during induction period divided by the number of subjects in the analysis population during induction therapy period. Subjects with unknown or missing response, or who provide no information on response will be treated as non-responders and will be included in the denominator when calculating rates.

- Overall MRD-negative CR rate for any treatment period

Defined as the number of subjects who achieve the best response of CR and at least one post-baseline MRD is negative divided by the number of subjects in the analysis population. If subjects have multiple MRD samples collected across different timepoints, the overall MRD status is negative if there is at least one MRD sample is negative and the overall MRD status is positive if all available MRD samples are positive. Subjects with unknown or missing post-baseline MRD status, or who provide no information on post-baseline MRD status will be treated as MRD positive and will be included in the denominator when calculating rates.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Occurrence of DLTs (Phase 1 part only)
- Adverse events (AEs)

A treatment-emergent adverse event (TEAE) is defined as an AE observed after starting administration of the study drug. If the adverse event occurs on first administration date of the study drug and the onset check box is marked “Onset after first ASP2215 taken” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on first administration date of the study drug and the onset check box is marked “Onset before first ASP2215 taken”, then the adverse event will not be considered treatment emergent. If a subject experience an event both before starting administration of the study drug and after starting administration of the study drug, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new

start date). All adverse events collected that begin within 30 days after taking the last dose of the study drug will also be counted as TEAE, except for subjects that undergo HSCT without leaving the study and plan to resume ASP2215 treatment after HSCT. For these subjects, TEAE is defined as adverse events observed after starting administration of the study drug until the last dose before pre-HSCT visit plus 30 days, and adverse events that begin after resumption of ASP2215 and within 30 days after the last dose of ASP2215 will also be counted as TEAE. Any AEs with onset dates completely missing will be considered TEAEs in summaries. AEs with partially missing onset dates will be assumed TEAEs unless the available portion of the date indicates that the onset was strictly before start of study drug or 30 days after the last dose of study drug. Missing or partial AE onset date will be imputed per Section 7.11.1.

ASP2215-related TEAE is defined as any TEAE with at least possible relationship (possibly or probably related) to ASP2215 as assessed by the investigator or with missing assessment of the causal relationship

A regimen-related TEAE is defined as any TEAE with at least possible relationship (possibly or probably related) to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

Serious adverse events (SAEs) include adverse events that are flagged as serious by the investigator on eCRF or upgraded by the Sponsor based on review of the Sponsor's list of Always Serious term.

- Laboratory parameters
- Vital signs
- 12-lead ECG: including QT assessment

6.3 Pharmacokinetic Variables

- Plasma concentration of ASP2215 and Cytarabine
- Pharmacokinetic parameters of ASP2215

6.4 Pharmacodynamic Variables

[Phase 1 part]

- Total FLT3 concentration
- Total AXL concentration

[Phase 2 part]

Not applicable.

6.5 Other Variables

- FLT3-ITD mutation status
- FLT3-TKD mutation status
- FLT3 mutation status
  Either of FLT3-ITD mutation status or FLT3-TKD mutation status is positive, this variable shows positive.
- MRD
  MRD negative is defined as summed FLT3-ITD signal ratio of any post-baseline sample $\leq 10^{-4}$. MRD positive is defined as summed FLT3-ITD signal ratio of any post-baseline sample$> 10^{-4}$.

- MR
  MR is defined as summed FLT3-ITD signal ratio of any post-baseline sample $\leq 10^{-2}$.
  No MR is defined as summed FLT3-ITD signal ratio of any post-baseline sample$> 10^{-2}$.
- FLT3-ITD signal ratio

  FLT3-ITD signal ratio is defined as the ratio of FLT3-ITD sequence reads divided by the total number of FLT3 sequence reads. This is being calculated by central laboratory. For subjects with more than one FLT3-ITD variant, the FLT3-ITD signal ratio will be summed at each timepoint.

- Duration of exposure (days)
  Duration of exposure to each treatment will be calculated in days, using the following formula:

  - Duration of exposure for each treatment cycle is defined as Last dose date – First dose date + 1 – (on-study HSCT period for subjects undergo on-study HSCT) for each cycle. For Phase1 part, last dose date of study drug exposure = (initial dose date of the cycle + 14 – 1) if last dose date of the cycle is not captured on dosing CRF.
  - Duration of exposure for each treatment period is calculated as sum of the duration of exposure for each treatment cycle.
  - Duration of exposure during study for study drug =

    (Duration of exposure for Induction period) + (Duration of exposure for Consolidation period) + (Duration of exposure for Maintenance period).

  When the last date of exposure is beyond cutoff date, the cutoff date will be used as the last date of exposure. When the start or stop date is missing, then the exposure will be treated as missing.

- Number of dosing days (days)

  Defined as number of days with non-zero dosing.

  Number of dosing days is calculated for each treatment period.

- Cumulative dose (mg or g)

  Defined as total amount of drug given to a patient, which calculated as follows:

  - ASP2215: Sum of (actual dose level * number of dosing days within each dose level)
  - Chemotherapy: Sum of actual dose across the days when administered.

    Actual dose is calculated as:

    (Actual volume administered / Total volume prepared)* Intended dose * Body surface area.

If number of doses taken is unknown, it will be treated as missing.

Cumulative dose is calculated for each treatment period.

- Average of daily dose (mg/day or g/day)

  Defined as cumulative dose divided by number of dosing days.

  Average of daily dose is calculated for each treatment period.

- Dose intensity (mg/day or g/day)

  Represents unit of dose given to a patient per unit of time, calculated as cumulative dose divided by duration of exposure.

  Dose intensity is calculated for each treatment period.

- Relative dose intensity (%)

  Defined as dose intensity divided by planned dose intensity * 100%.

  Relative dose intensity is calculated for each treatment period.

  Where planned dose intensity (mg/day or g/day) will be calculated as follows:

  - ASP2215: 120 mg
  - Cytarabine, Induction for Phase 1 part: Calculated Dose in mg on CRF
  - Cytarabine, Induction for Phase 2 part: 100 mg/m^2 * BSA
  - Cytarabine, Consolidation for Phase 1 part: Calculated Dose (sum of Infusion 1 and 2) in g on CRF
  - Cytarabine, Consolidation for Phase 2 part: 1.5 g/m^2 * BSA * 2 times
  - Idarubicin for Phase 1 part: Calculated Dose in mg on CRF
  - Idarubicin for Phase 2 part: 12 mg/m^2 * BSA

  Average of BSA and Calculated Dose across the days when administered will be used in the calculation of planned dose intensity.

- Previous and concomitant medication

  The period of evaluation for previous medications is as follows:

  - 28 days before Day 1 of induction period – before Day 1 of induction period.

  Concomitant medication is defined as medication used between Day 1 of induction period and the last dose of treatment. For subjects who undergo HSCT without leaving the study and plan to resume ASP2215 treatment after HSCT, concomitant medication is defined as medication with at least one dose taken between Day1 of induction period and the start of the HSCT conditioning regimen, or between resumption of ASP2215 and the last dose of the study drug.

- Previous and concomitant transfusion

Previous transfusion is defined as transfusion received before Day 1 of induction period, i.e. transfusion completed before Day 1 of induction period.

Concomitant transfusion is defined as transfusion received between Day 1 of induction period and the last dose of treatment. For subjects who undergo HSCT without leaving the study and plan to resume ASP2215 treatment after HSCT, concomitant transfusion is defined as transfusion received between Day1 of induction period and the start of the HSCT conditioning regimen, or between resumption of ASP2215 and the last dose of the study drug.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

- For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, minimum, Q1, median, Q3 and maximum. When needed, the use of other percentiles (e.g.10% and 90%) will be mentioned in the relevant Section.
- For continuous PK parameters, the coefficient of variation will be calculated, and for C_{max} and AUCs, the geometric mean will also be calculated. GM will not be calculated if at least one value is the BLQ.
- t_{max} will be summarized using median and range.
- Frequencies and percentages will be displayed for categorical data.
- Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.
- All data processing, summarization, and analyses will be performed using SAS (ver. 9.4) or higher on Red Hat Enterprise Linux.
- Specifications for Table, Figures, and data listing formats can be found in the TLF specifications for this study.
- MedDRA (version 23.0) will be used as the coding dictionary for adverse event and medical history.
- WHODD(B2) (V2016Sep) for Phase 1 part and WHODD(B3) (V2018Mar) for Phase 2 part will be used as the coding dictionary for previous and concomitant medications.
- The assessments impacted by COVID-19 will be listed and sensitivity analyses to assess the impact of COVID-19 for some efficacy may be performed if needed.
- [Phase 1 part] All analysis will be presented by the dose-evaluation part, expansion part and overall, unless specifically stated otherwise.
- [Phase 1 part] The data of a subject who was allocated to ASP2215 40 mg per day will be used only for listings.

7.2 Study Population

7.2.1 Disposition of Subjects

[Phase 1 part]

The following subject data will be presented:

- Number and percentage of subjects with informed consent, discontinued before allocation to the treatment, allocated to the treatment (overall only).
- Number and percentage of subjects who were included/excluded in each analysis set.
- Number and percentage of subjects excluded from each analysis set by reason.
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation for subjects allocated to the treatment.
- Number and percentage of subjects completed and discontinued the post-study, by primary reason for post-study discontinuation for subjects allocated to the treatment.

[Phase 2 part]

- Number and percentage of subjects with informed consent, discontinued before pre-registration to the study, allocation to the treatment, discontinued before registration to the study and allocation to study drug.
- Number and percentage of subjects completed and discontinued the pre-registration period, by primary pre-registration status.
- Number and percentage of subjects completed and discontinued the registration period, by primary registration status.
- Number and percentage of subjects who were included/excluded in each analysis set.
- Number and percentage of subjects excluded from each analysis set by reason.
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation for subjects allocated to the treatment.
- Number and percentage of subjects completed and discontinued the follow-up, by primary reason for follow-up discontinuation for subjects allocated to the treatment.
- Number and percentage of subjects completed and discontinued the long-term follow-up, by primary reason for long-term follow-up discontinuation for subjects allocated to the treatment.

7.2.2 Protocol Deviations

[Phase 1 part]

Not applicable.

[Phase 2 part]

Protocol deviations as defined in the study protocol (Section 10.3 Major Protocol Deviations) will be assessed for all subjects who received treatment. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

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

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

[Phase 1 part]

Analysis set: SAF, FAS, DDAS, PKAS, PDAS

Demographic and other baseline characteristics will be summarized by descriptive statistics or categorical analysis.

The following demographic variables will be summarized and presented.

Table 1.1. Demographic Variables and Analysis Methods for all analysis sets

Item	Classification	Analysis Methods
Age (years)	Measurement value <65 years, >=65 years	Descriptive statistics Categorical analysis
Height [Screening](cm)	Measurement value	Descriptive statistics
Weight (kg)	Measurement value	Descriptive statistics
BMI (kg/m^2)	BMI (kg/m^2) = Weight (kg) / (Height (cm) / 100)^2	Descriptive statistics
BSA (m^2)	BSA (m^2) = Weight (kg) ^ 0.425 x Height (cm) ^ 0.725 x 0.007184	Descriptive statistics
Subject ECOG Status	0, 1, 2, 3, 4	Categorical analysis
Sex	Male, Female, Unknown	Categorical analysis
Race	White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other	Categorical analysis

BMI: Body Mass Index, BSA: Body Surface Area, ECOG: Eastern Cooperative Oncology Group

[Phase 2 part]

Analysis set: SAF, FAS, PKAS, MAS

Demographic and other baseline characteristics will be summarized by descriptive statistics or categorical analysis.

The following demographic variables will be summarized and presented.

Table 1.2. Demographic Variables and Analysis Methods for all analysis sets

Item	Classification	Analysis Methods
Age (years)	Measurement value <65 years, >=65 years	Descriptive statistics Categorical analysis
Height [Screening](cm)	Measurement value	Descriptive statistics
Weight [Screening] (kg)	Measurement value	Descriptive statistics
BMI (kg/m^2)	BMI (kg/m^2) = Weight (kg) / (Height (cm) / 100)^2	Descriptive statistics
BSA (m^2)	BSA (m^2) = Weight (kg) ^ 0.425 x Height (cm) ^ 0.725 x 0.007184	Descriptive statistics
Subject ECOG Status	0, 1, 2, 3, 4	Categorical analysis
Sex	Male, Female, Unknown	Categorical analysis
Race	White, Black or African American, American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Taiwanese, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan and Other Pacific Islander	Categorical analysis
Region	Japan, Korea, Taiwan	Categorical analysis

BMI: Body Mass Index, BSA: Body Surface Area, ECOG: Eastern Cooperative Oncology Group

Analysis set: SAF

Frequency tabulations for AML disease history including AML subtype as classified by WHO classification and FAB classification, risk status with specific cytogenetic patterns, antecedent hematological disorder (Phase 1 part only), central nervous system leukemia (Phase 1 part only), FLT3-ITD mutation status (Phase 1 part only), FLT3 point mutation status (Phase 1 part only) will be presented.

Medical history other than AML will be coded in MedDRA and summarized by SOC and PT as well as by PT alone. Baseline conditions are defined as those ongoing at the time of informed consent or arise following the time of informed consent and before the first dose of the treatment. For ongoing medical conditions, CTCAE grade will be provided in listing.

Result from MUGA scan or ECHO, if performed, will be provided in listing.

7.2.4 Previous and Concomitant Medications

Analysis set: SAF

Previous medications are coded with WHODD and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name.
As with previous medication, concomitant medication will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Concomitant medication will also be summarized by preferred WHO name, and presented in decreasing order of frequency based on the total number of subjects took each medication.

7.2.5 Previous and Concomitant Transfusions

Analysis set: SAF

Frequency tabulations of subjects received transfusions and blood product will be presented for previous transfusion and concomitant transfusion. Descriptive statistics will be presented for number of transfusion unit received per subject for each type of blood product.

7.2.6 Non-Medication Therapy

Analysis set: SAF

Frequency tabulations of subjects with non-medication therapy and reason for use will be presented. Number of non-medication therapy received per subject will be summarized using descriptive statistics.

7.3 Study Drugs

7.3.1 Exposure

Analysis set: SAF

The following information on ASP2215 exposure will be presented:

- Descriptive statistics for cumulative dose of the treatment subject was exposed to, number of dosing days, average of daily dose, dose intensity, and relative dose intensity; and
- Number and percent of subject with dose reduction and interruption.

Duration of exposure will be summarized in two ways:

- Descriptive statistics will be presented.
- Exposure time will be categorized according to the following categories (study drug only):
    - less than 14 days
    - at least 14 days, less than 42 days
    - at least 42 days, less than 84 days
    - at least 84 days, less than 168 days
    - 168 days or more
    - Unknown.

Number and percentage of subjects in each of these categories will be summarized.

Listing of subjects with dose reduction and interruption will also be provided.

7.4 Analysis of Efficacy

[Phase 1 part]

The efficacy analysis will be performed on the FAS.

For response variables, best response after each treatment therapy period will be summarized. The number and percentage of subjects in each category will be presented together with two-sided exact 95% CIs based on binomial distribution. Swimmer's plot will be presented for response variables.
For time-to-event variables efficacy analysis will be summarized using descriptive statistics. The survival curve and the median will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% CIs.
[Phase 2 part]
The efficacy analysis will be performed on the FAS and TTE-FAS. The interpretation of statistical results will be based on the FAS. The TTE-FAS will be used to analyze OS and EFS. Analysis of MRD and MR will be performed using MAS.

Primary efficacy variable

For primary efficacy variable, CR rate after induction therapy period, the two-sided 90% exact CI by Clopper-Pearson method will be calculated. The lower limit will be used to compare with the benchmark of CR rate of 55%. The number and percentage of subjects in each category and swimmer's plot will also be presented. As a supportive analysis, CR rate after induction therapy period reported by Day 60 and CR rate after induction therapy period not being dependent on RBC and platelet transfusion (No Transfusion of RBC and Platelet within 1 week prior to disease assessment) will also be calculated.

Other efficacy variables

For other efficacy variables, analysis method will be described as follows:

Categorical variables:

The number and percentage of subjects in each category will be presented together with two-sided exact 95% CIs based on binomial distribution. Swimmer's plot will be presented for response variables.

For response assessment variables, best response rate after each treatment therapy will be summarized. The number and percentage of subjects in each category will be presented together with two-sided exact 95% CIs based on binomial distribution. For subjects who undergo HSCT, any response assessment data after HSCT will not be used (i.e. for those subjects, only response assessment data before HSCT will be used).
As a sensitivity analysis, response assessment will be defined similarly as the above analysis, however, all response assessment data will be used even if there were subjects who undergo HSCT (i.e. response assessment data after HSCT will also be used).

Time-to-event variables:

For time-to-event variables efficacy analysis will be summarized using descriptive statistics. The survival curve and the median will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% CIs. Kaplan-Meier plot will be presented.

7.5 Analysis of Safety

Some analyses that do not depend on the measurement time point such as the summary of TEAEs will be performed for not only Phase 1 part and Phase 2 part separately but also Phase 1/Phase 2 part totally. The details are described in the following Sections.

7.5.1 DLT (Phase 1 part only)

Analysis set: DDAS

The following data will be summarized for the DDAS.

- For DLT incidence, the number and percentage of subjects will be summarized.
- The posterior mean of the DLT rate will be estimated from the Bayesian-CRM using the following statistical models.

The dose-response relationship against DLT occurrence assumes power model, as shown below.

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

Power model:

$$\Pr(Y_{ik} = 1 | dose = d_k) = \pi(x_k, \alpha) = x_k^{\exp(\alpha)}$$

where α is the model parameter, x_k is the skeleton of DLT incidence probability in the dose for number k used in the statistical model, d_k is the administered dose level of number k, Y_{ik} is the presence/absence of DLT in subject i and dose level of number k (1 is present) 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 ESS, 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.

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

7.5.2 Adverse Events (AEs)

[Phase 1 part, Phase 2 part, Phase 1/Phase 2 part]

Analysis set: SAF

AEs will be coded using MedDRA and graded using NCI-CTCAE (V4.0). All AE recorded on treatment including within 30 days after the last administration will be summarized.

TEAEs will be graded using National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE).

An overview table will include the following details:

- Number and percentage of subjects with TEAEs
- Number and percentage of subjects with ASP2215-related TEAEs
- Number and percentage of subjects with regimen-related TEAEs
- Number and percentage of subjects with serious TEAEs
- Number and percentage of subjects with ASP2215-related serious TEAEs
- Number and percentage of subjects with regimen-related serious TEAEs
- Number and percentage of subjects with TEAEs leading to dose reduction of ASP2215
- Number and percentage of subjects with ASP2215-related TEAEs leading to dose reduction of ASP2215

- Number and percentage of subjects with regimen-related TEAEs leading to dose reduction of ASP2215
- Number and percentage of subjects with TEAEs leading to dose interruption of ASP2215
- Number and percentage of subjects with ASP2215-related TEAEs leading to dose interruption of ASP2215
- Number and percentage of subjects with regimen-related TEAEs leading to dose interruption of ASP2215
- Number and percentage of subjects with TEAEs leading to withdrawal of treatment
- Number and percentage of subjects with ASP2215-related TEAEs leading to withdrawal of treatment
- Number and percentage of subjects with regimen-related TEAEs leading to withdrawal of treatment
- Number and percentage of subjects with TEAEs leading to death
- Number and percentage of subjects with ASP2215-related TEAEs leading to death
- Number and percentage of subjects with regimen-related TEAEs leading to death
- Number and percentage of subjects with grade 3 or higher TEAEs
- Number and percentage of subjects with ASP2215-related grade 3 or higher TEAEs
- Number and percentage of subjects with regimen-related grade 3 or higher TEAEs
- Number and percentage of subjects with deaths
- Number of TEAEs
- Number of ASP2215-related TEAEs
- Number of regimen-related TEAEs
- Number of serious TEAEs
- Number of ASP2215-related serious TEAEs
- Number of regimen-related serious TEAEs
- Number of TEAEs leading to dose reduction of ASP2215
- Number of ASP2215-related TEAEs leading to dose reduction of ASP2215
- Number of regimen-related TEAEs leading to dose reduction of ASP2215
- Number of TEAEs leading to dose interruption of ASP2215
- Number of ASP2215-related TEAEs leading to dose interruption of ASP2215
- Number of regimen-related TEAEs leading to dose interruption of ASP2215
- Number of TEAEs leading to withdrawal of treatment
- Number of ASP2215-related TEAEs leading to withdrawal of treatment
- Number of regimen-related TEAEs leading to withdrawal of treatment
- Number of TEAEs leading to death
- Number of ASP2215-related TEAEs leading to death
- Number of regimen-related TEAEs leading to death
- Number of grade 3 or higher TEAEs
- Number of ASP2215-related grade 3 or higher TEAEs
- Number of regimen-related grade 3 or higher TEAEs

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized. Summaries will be provided for:

- TEAEs
- ASP2215-related TEAEs
- Regimen-related TEAEs
- Serious TEAEs
- ASP2215-related serious TEAEs
- Regimen-related serious TEAEs
- TEAEs leading to dose reduction of ASP2215
- ASP2215-related TEAEs leading to dose reduction of ASP2215
- Regimen-related TEAEs leading to dose reduction of ASP2215
- TEAEs leading to dose interruption of ASP2215
- ASP2215-related TEAEs leading to dose interruption of ASP2215
- Regimen-related TEAEs leading to dose interruption of ASP2215
- TEAEs leading to withdrawal of treatment
- ASP2215-related TEAEs leading to withdrawal of treatment
- Regimen-related TEAEs leading to withdrawal of treatment
- TEAEs leading to death
- ASP2215-related TEAEs leading to death
- Regimen-related TEAEs leading to death
- Grade 3 or higher TEAEs
- ASP2215-related grade 3 or higher TEAEs
- Regimen-related grade 3 or higher TEAEs
- Common (>=10%) TEAEs excluding serious adverse events

AE summary tables will include subject counts as opposed to AE counts. If a subject experiences more than one episode of a particular AE, that subject will be counted only once for that event. If a subject has more than one AE that code to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a body system, the subject will be counted only once in that body system.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by NCI-CTCAE severity grade and by relationship to ASP2215 and regimen. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity grade or relationship, then the subject will be counted only once with the worst severity grade and highest degree of relationship, however, if any of the severity grade or relationship values are missing then the subject will be counted only once with missing severity grade or relationship.

AESI are defined in the Safety Review Plan for ASP2215 as specified in (Appendix 2).

The number and percentage of subjects with TEAE of special safety interest, as classified by AESI category and PT will be summarized for the followings:

- TEAEs with special safety interest
- Grade 3 or higher TEAEs with special safety interest

- ASP2215-related Grade 3 or higher TEAEs with special safety interest
- Regimen-related Grade 3 or higher TEAEs with special safety interest

All AEs, deaths, SAEs and withdrawals due to AEs will be displayed in listings.

7.5.3 Clinical Laboratory Evaluation

Analysis set: SAF

All clinical laboratory evaluations including hematology and bone marrow, biochemistry, coagulation and urinalysis will be performed locally (for Phase 2 par, both centrally and locally).

The baseline visit is the last measurement taken prior to initial treatment.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, coagulation and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median by measurement time point. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as L, N, or H by measurement time point according to supplied reference ranges. SI unit will be used for display. Summary shifts in each laboratory test result will be presented by measurement time point.

The number and percentage of subjects below and above reference range will be summarized by measurement time point.

Frequency tabulations of qualitative clinical laboratory variable (urinalysis) will be presented by measurement time point.

For hematology and biochemistry two types of shift tables will be presented:

- Shift tables of reference range changes from baseline to each treatment visit (low, normal, high), and
- Summary shifts of reference range changes from baseline to each treatment visit (shift from normal or high to low, shift from normal or low to high, categorized increase [shift from low to normal or from normal to high], categorized no change [value stays in the same reference range], categorized decrease [shift from high to normal or from normal to low]).

Laboratory results will also be graded using NCI-CTCAE, where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same subject can be counted for both values if the subject has different laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of subjects by measurement time point. Shift tables of NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented.
Bone marrow results will be listed only.

7.5.3.1 Liver function tests

The following potentially clinically significant criteria in liver function tests for ALP, ALT, AST and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 8xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 8xULN
	> 10xULN
	> 20xULN
ALT or AST	> 3xULN
	> 5xULN
	> 8xULN
	> 10xULN
	> 20xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN
ALT and/or AST AND Alkaline Phosphatase AND Total Bilirubin(*)	ALT and/or AST > 3xULN AND Alkaline Phosphatase < 2xULN AND Total Bilirubin > 2xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzymes and total bilirubin during the investigational period will be presented for Phase 1 part, Phase 2 part and Phase 1/Phase 2 part totally.

7.5.4 Vital Signs

Analysis set: SAF

The baseline visit is the last measurement taken prior to initial treatment.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse and body temperature) will be summarized using mean, standard deviation, minimum, maximum and median by measurement time point. Additionally, a within-subject change will be calculated per

measurement time point as the post-baseline measurement minus the baseline measurement and summarized by measurement time point.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest value obtained during treatment for each subject for Phase 1 part, Phase 2 part and Phase 1/Phase 2 part totally.

The following potentially clinically significant criteria are defined for each parameter:

Vital Sign Variable	Criteria
SBP	≥180 mmHg AND ≥20 mmHg change from baseline
DBP	≥105 mmHg AND ≥15 mmHg change from baseline
Pulse	≥120 bpm AND ≥15 bpm change from baseline

DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure

7.5.5 Electrocardiograms (ECGs)

Analysis set: SAF

The 12-lead ECG will be measured at the scheduled time points. 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.

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each measurement time point, including changes from baseline.

Number and percentage of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the overall interpretation of 12 lead ECG will be tabulated by measurement time point. A shift analysis table showing shift in overall ECG interpretation from baseline to each time point will be provided. The worst of the three overall ECG interpretations will be used as the time-specific overall ECG interpretation for a subject.

The QT interval corrected for heart rate by Fridericia's formula, QTcF, is defined as: $QTc\ (F) = QT/(RR)^{0.33}$.

The QTcF interval variables will be summarized by the frequencies of subjects with following categories for each measurement time point.

	QTc Interval Criteria Value (msec)
Normal	≤ 450
Borderline	> 450 to ≤ 480
Prolonged	> 480 to ≤ 500
Clinically significant	> 500

QTc: Corrected Q-T Interval

The change from baseline of QTcF interval variables will be summarized by the frequencies of subjects with following categories for each measurement time point.

Variable	Change from Baseline
QTc Interval (msec)	<0 ≥ 0 to ≤ 30 > 30 to ≤ 60 > 60

QTc: Corrected Q-T Interval

7.5.6 ECOG Performance Status

Analysis set: SAF

Number and percentage of subjects for each category of the ECOG performance status at each assessment time will be provided. Negative change scores indicate an improvement and positive scores indicate a decline in performance.

ECOG scores will also be summarized using shift table from baseline to post-baseline score by visit.

7.6 Analysis of PK

The pharmacokinetic analysis will be performed on the PKAS. For plasma concentrations of ASP2215 and Cytarabine, descriptive statistics will be calculated by time and treatment period.

The PK parameters will be calculated using WinNonlin software (Pharsight Corp, Mountain View, California, US) version 8.0. Non-compartmental methods will be used to derive the values of the PK parameters.

7.6.1 Pharmacokinetic ASP2215 Parameters

The following PK parameters will be estimated in both induction and consolidation period, using plasma concentrations of ASP2215 and actual elapsed times from dosing, provided enough data are available for accurate estimations. Exclusion of PK parameter estimates from the descriptive statistics will be considered by the pharmacokineticist on a case-by-case basis.

[Phase 1 part]

Single dose period: AUC_{24}, AUC_{last}, C_{max}, and t_{max}

[Phase 2 part]

Not applicable.

7.6.2 Change from the Protocol

Note that ASP2215 has a longer half-life (> 24 hours) than the dosing interval thus the following parameters will not be evaluated due to lack of accuracy under the planned PK sampling scheme:

AUC_{inf}, CL/F, Lambda z, $t_{1/2}$ and V_z/F

7.7 Analysis of PD

Not applicable for this study except for a subject who was allocated to 40 mg per day. The total concentrations of FLT3 and AXL of the subject will be used only for listings.

7.7.1 Change from the Protocol

Inhibition of FLT3 phosphorylation and inhibition of AXL phosphorylation have not been measured.

7.8 Subgroups of Interest

[Phase 1 part]

For analysis of response variable, subgroup analysis will be conducted using the FAS. Subgroup is defined on the basis of the categorized variables listed below:

Grouping variable	Subgroups
FLT3-ITD Mutation Status	Positive
	Negative
FLT3-TKD Mutation Status	Positive
	Negative
FLT3 Mutation Status	Positive
	Negative

[Phase 2 part]

For primary efficacy analysis and OS analysis, subgroup analysis will be conducted using the TTE-FAS. Subgroups are defined on the basis of the categorized variables listed below:

Grouping variable	Subgroups
Age group	< 65 Years
	>=65 Years
Sex	Female
	Male
Region	Japan
	Korea
	Taiwan
FLT3 Mutation Type	FLT3-ITD Mutation Status is positive
	FLT3-TKD Mutation Status is positive
	FLT3-ITD Mutation Status and FLT3-TKD Mutation Status are positive

7.9 Other Analyses

7.9.1 FLT3 Mutation Test

[Phase 1 part]

Analysis set: SAF, FAS

The presence/absence of FLT3-ITD mutation status, FLT3-TKD mutation status, FLT3 mutation status and FLT3-ITD mutation status/FLT3-TKD mutation status will be summarized by frequency at each visit.

[Phase 2 part]

Analysis set: SAF, FAS

FLT3 mutation type 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. The presence of FLT3-ITD mutation status, FLT3-TKD mutation status and both of them will be summarized by frequency.

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

Not applicable.

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

7.11.1 Missing Data

The detail of missing efficacy variable is in Section 6.1.

Missing or partial start and stop dates of adverse events and concomitant medication will be imputed using the following algorithm:

- Imputation rules for partial or missing stop dates:
  - If the month and year are present, then impute as the last day of that month.
  - If only the year is present, impute as December 31 of that year.
  - If the stop date is entirely missing, assume the event or medication is ongoing.
- Imputation rules for partial or missing start dates:

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute as the date of first dose; 2 = Impute as the first of the month; 3 = Impute as January 1 of the year; 4 = Impute as January 1 of the stop year

The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 LLOQ

- LLOQ for ASP2215

The LLOQ of the plasma sample which was measured by inVentiv is 10 ng/mL when using 0.050 mL of plasma.

As for the plasma sample of P06101 which was measured by ARIA, the LLOQ of the plasma sample is 0.5 ng/mL when using 0.050 mL of plasma.

- LLOQ for Cytarabine

The LLOQ is 0.5 ng/mL when using 0.050 mL of plasma.

7.11.4 BLQ data

Plasma concentrations below the LLOQ will be presented as "<LLOQ" in listings while treated as zero in the analyses.

7.11.5 Visit Windows

[Phase 1 part]

Visit windows are allowed for certain visits per the schedule of assessments. Subject data will not be excluded from analyses due to the subject's failure to comply with the visit schedule. In the case of multiple observations at a specific visit, the observation which is closest to the target date will be used. If the observations have the same distance to the target visit, the latest one will be used. The baseline visit is the last measurement taken prior to initial treatment.

- Visit Windows 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	
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.

- Visit Windows 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	

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.

- Visit Windows 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	
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.

ECG: Electrocardiogram

- Visit Windows 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.

- Visit Windows 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%).

ECHO: Echocardiogram; MUGA: Multiple Gate Acquisition; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction

- Visit Windows 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).	

Chest X-ray or chest CT at screening is not necessary if either was performed within 7 days before study enrollment even before obtaining consent. During any treatment period, chest X-ray or chest CT will be performed whenever it is determined to be clinically necessary based on the subject's clinical conditions.

- Visit Windows 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
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.

- Visit Windows for Pregnancy Test (for WOCBP)

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	
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.

- Visit Windows for Bone Marrow Tests (Bone Marrow Aspiration or Biopsy)

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
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.

During the maintenance period, the bone marrow test will be performed whenever it is determined to be clinically necessary.

- Visit Windows for Plasma PK Assessment for 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	

Consolidation 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 ASP2215
Cycle 1 Day 1 1 hour post-dose	Day 1	Scheduled date, scheduled time ± 10 minutes	
Cycle 1 Day 1 2 hours post-dose	Day 1	Scheduled date, scheduled time ± 10 minutes	
Cycle 1 Day 1 4 hours post-dose	Day 1	Scheduled date, scheduled time ± 20 minutes	
Cycle 1 Day 1 6 hours post-dose	Day 1	Scheduled date, scheduled time ± 20 minutes	
Cycle 1 Day 1 10 hours post-dose	Day 1	Scheduled date, scheduled time ± 20 minutes	
Cycle 1 Day 1 24 hours post-dose	Day 2	Scheduled date, scheduled time ± 60 minutes and prior to Day 2 dosing	Blood sampling for ASP2215 and cytarabine
Cycle 1 Day 6 pre-dose	Day 6	Scheduled date, within 30 minutes before dosing	
Cycle 1 Day 15	Day 15	Scheduled date − 1 day	Blood sampling for ASP2215. If performed on Day 14 within the allowed visit window [−1] for Day 15, blood sampling will be performed at pre-dose.
End of treatment (for any period)	Date of judgment of discontinuation	Scheduled date + 7 days	Blood sampling for ASP2215 is strongly recommended if possible

Both in the induction and consolidation periods, blood sampling for PK analysis is performed only during Cycle 1.

- Visit Windows for FLT3 Mutation 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: 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]

All analyses except for the analysis based on central laboratory data will be based on CRF visit except for the baseline. The baseline visit is the last measurement taken prior to initial treatment.

For the analysis based on central laboratory data, visit windows are allowed for certain visits per the schedule of assessments. Subject data will not be excluded from analyses due to the subject's failure to comply with the visit schedule. The visit windows for assessments are described in the following table.

CRF visit	Visit Window
Induction Day 8	Scheduled day
Induction Day 15	D15 ± 2
Induction Day 21	D21 ± 2
Induction Day 28	D28 + 7
Induction Day 42	D42 + 7
Induction Day 56	D56 + 7
Consolidation Day 8	Scheduled day
Consolidation Day 15	D15 ± 2
Consolidation Day 21	D21 + 7
Maintenance Cycle 2 Day 1	(Maintenance Cycle 1 Day 1+28) ± 7
Maintenance Cycle 5 Day 1	(Maintenance Cycle 1 Day 1+112) ± 7
Maintenance Cycle 8 Day 1	(Maintenance Cycle 1 Day 1+196) ± 7
Maintenance Cycle 11 Day 1	(Maintenance Cycle 1 Day 1+280) ± 7
Maintenance Cycle 14 Day 1	(Maintenance Cycle 1 Day 1+364) ± 7
Maintenance Cycle 17 Day 1	(Maintenance Cycle 1 Day 1+448) ± 7
Maintenance Cycle 20 Day 1	(Maintenance Cycle 1 Day 1+532) ± 7
Maintenance Cycle 23 Day 1	(Maintenance Cycle 1 Day 1+616) ± 7
Maintenance Cycle 26 Day 1	(Maintenance Cycle 1 Day 1+700) ± 7

In the case of multiple observations at a specific visit, the observation which is closest to the target date will be used. If the observations have the same distance to the target visit, the latest one will be used. The baseline visit is the last measurement taken prior to initial treatment. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	16-NOV-2021	NA	Document finalized

9 REFERENCES

Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Reporting Standards for Therapeutic Trials in Acute Myeloid, L. (2003). Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol, 21*(24), 4642-4649. doi: 10.1200/JCO.2003.04.036.

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ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

10 APPENDICES

10.1 Appendix 1: Signature

Author and Approver Signatories

(E-signatures are attached at end of document)

PPD, Data Science Department, Astellas Pharma Inc. was the study statistician for this study and the primary author of this Statistical Analysis Plan

PPD was the Statistical Lead for this study and the biostatistics peer reviewer of this Statistical Analysis Plan

This Statistical Analysis Plan was approved by:
PPD

10.2 Appendix 2: Search Strategy for Adverse Events of Interest

Risk	**Search Strategy: MedDRA Version 23.0**
Anaphylactic reaction	Anaphylactic reaction (SMQ Broad)
Cardiac failure	Cardiac failure (SMQ Narrow)
Creatine phosphokinase increased	Rhabdomyolysis/ myopathy (SMQ Narrow)
	Blood creatine phosphokinase abnormal (PT=10005468 and Grade >=3)
	Blood creatine phosphokinase increased (PT=10005470 and Grade>=3)
	Blood creatine phosphokinase MM increased (PT=10005477 and Grade>=3)
	PT: Myalgia
	PT: Myositis
	PT: Muscular weakness
Diarrhea	Noninfectious diarrhoea (SMQ Broad)

Differentiation Syndrome [a]	PT: Acute interstitial pneumonitis, Acute kidney injury, Acute lung injury, Acute pulmonary oedema, Acute respiratory distress syndrome, Acute respiratory failure, Anuria, Atypical pneumonia, Blood creatinine increased, Blood pressure systolic decreased, Body temperature increased, Capillary leak syndrome, Cardiopulmonary failure, Cardiorenal syndrome, Cardiorespiratory distress, Cough, Differentiation syndrome, Dyspnoea, Febrile neutropenia, Fluid overload, Fluid retention, Generalised oedema, Hepatorenal failure, Hydraemia, Hypervolaemia, Hypotension, Lower respiratory tract infection, Lower respiratory tract inflammation, Lung infection, Lung infiltration, Multiple organ dysfunction syndrome, Noncardiogenic pulmonary oedema, Oedema, Oedema peripheral, Pericardial effusion, Pleural effusion, Pneumonia, Pneumonitis, Prerenal failure, Pulmonary congestion, Pulmonary oedema, Pulmonary toxicity, Pyrexia, Renal failure, Renal impairment, Renal injury, Respiratory arrest, Respiratory distress, Respiratory failure, Weight increased PTs
Gastrointestinal obstruction	Gastrointestinal obstruction (SMQ Narrow)
Gastrointestinal perforation	Gastrointestinal perforation (SMQ Narrow)
Liver transaminase increased	Liver related investigations, signs, and symptoms (SMQ Narrow)
Pancreatitis	Acute pancreatitis (SMQ Broad)
Pericarditis/Pericardial effusion	HLT Noninfectious pericarditis
	PT Pericardial effusion
PRES	Noninfectious encephalopathy/delirium (SMQ Narrow)
QT Prolongation	Torsade de pointes/QT prolongation (SMQ Narrow)
Teratogenicity and Embryo- Fetal Deaths	SMQ Broad-All Pregnancy

HLT: high level term; PRES: posterior reversible encephalopathy syndrome; PT: preferred term; SMQ: standard MedDRA queries

a: Only adverse events occur within the first 90 days