STATISTICAL ANALYSIS PLAN

Version 3.0, dated 27 JUN 2023

A Phase 1/2 Open-label Study Investigating the Safety, Tolerability and Efficacy of ASP7517 in Subjects with Relapsed/Refractory Acute Myeloid Leukemia (AML) and Relapsed/Refractory Higher Risk Myelodysplastic Syndrome (MDS)

ISN/Protocol: 7517-CL-0101

IND number: 19575

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
AEsi	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APGD	Astellas Pharma Global Development
ATC	Anatomical Therapeutic Chemical
AST	Aspartate Aminotransferase
BM	Bone Marrow
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Intervals
CR	Complete Remission
CRc	Composite Complete Remission
CRh	Complete Remission with Partial Hematalogic Recovery
CRi	Complete Remission with Incomplete Hematalogic Recovery
CRp	Complete Remission with Incomplete Platelet Recovery
CRF	Case Report Form
CS	Classification Specification
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DEAS	DLT Evaluation Analysis Set
DESC	Dose Escalation and Safety Committee
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
EOT	End of Treatment
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IP	Investigational Product
irAE	Immune-Related Adverse Event
IRR	Infusion Related Reactions
IRT	Interactive Response Technology
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Protocol Deviation/Progressive Disease

Abbreviations	Description of abbreviations
PDAS	Pharmacodynamics Analysis Set
PKAS	Pharmacokinetic Analysis Set
PR	Partial Remission
PS	Performance Status
PT	Preferred Term
QT	Q-T interval from electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	Fridericia-corrected QT interval
RAS	Response Analysis Set
RBC	Red Blood Cell
RDI	Relative Dose Intensity
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Stable Disease
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TLF	Tables, Listings and Figures
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

List of Key Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
End of Study	This date reflects when a subject completes follow-up.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (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 final SAP will be approved prior to the primary database lock.

If there are any changes from the planned analyses in the final version of the SAP that impact the statistical analyses, then they will be documented in the Clinical Study Report (CSR).

2 TREATMENT PROTOCOL OBJECTIVES AND DESIGN

2.1 Study Objectives

Primary:

- To evaluate the safety and tolerability of ASP7517 in subjects with R/R AML or R/R high risk MDS
- To determine the RP2D and/or the MTD of ASP7517 (phase 1)
- To evaluate the clinical response of ASP7517

Secondary:

- To evaluate other measures of anticancer activity of ASP7517

Exploratory:

- To evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome
- To evaluate pharmacodynamic activities of ASP7517
- To evaluate pharmacokinetics of ASP7517, determined by the kinetics of the cells

2.2 Study Design

This study is a phase 1/2, open-label study of ASP7517 in subjects with R/R AML and R/R higher risk MDS.

A total of approximately 122 subjects are planned for enrollment in this study.

In phase 1 (Dose Escalation), approximately 18 subjects with either R/R AML or R/R higher risk MDS will be enrolled.

In phase 2 (Dose Expansion), approximately 104 subjects will be enrolled per dose level. Each dose level may enroll up to 52 subjects with R/R AML and up to 52 subjects with R/R higher risk MDS. Both groups of subjects will enroll in parallel and independently. In this phase, there will be a separate cohort in China to evaluate safety, tolerability, and efficacy of ASP7517 in Chinese subjects. Approximately 6 R/R AML or R/R higher risk MDS subjects will be enrolled in this separate cohort.

ASP7517 Dose/Dose Regimen and Administration Periods

The study consists of the following periods:

- Screening (up to 14 days)
- Treatment (two 28-day cycles during escalation phase; up to six 28-day cycles during
- expansion phase)
- End-of-Treatment (EoT) visit
- Post-Treatment
    - Observation Period 1 (12 weeks or until 1 post-treatment discontinuation criterion is met, whichever occurs first)
    - Observation Period 2 (assessment visit every month until 1 post-treatment discontinuation criterion is met)
- Survival and subsequent treatment follow-up every 3 months

During the treatment period, subjects will receive an intravenous infusion of ASP7517 (human embryonic kidney cell transfected with encoding target antigen WT1). In phase 1 (dose escalation), subjects will receive 1 dose per cycle for a total of 2 doses. Each cycle is defined as 28 days with a total of 2 treatment cycles.

In phase 2 (dose expansion), subjects who have not met any individual treatment discontinuation criteria and who are receiving clinical benefit (defined as achieving CRc or PR for AML and CR, BM CR, PR or HI for MDS, or other clinical benefits as determined by the investigator) will continue further treatment with ASP7517 after the first 2 cycles, as decided by the investigator. After completing 4 cycles of treatment, subjects who achieve CR will not continue with ASP7517; subjects who do not reach CR, but also do not experience disease progression, may receive an additional 2 doses for a total of 6 doses. Each cycle is defined as 28 days with a total of up to 6 treatment cycles.
An End-of-Treatment (EoT) visit will be conducted for all subjects within 7 days of the principal investigator decision to discontinue the subject from treatment or prior to the initiation of new anticancer therapy, whichever occurs first. If a subject is completing all visits in the last treatment cycle, the EoT visit will be within 7 days from the last planned visit.

After the EoT visit, Observation Period 1 will be 12 weeks or until 1 post-treatment discontinuation criterion is met, whichever comes first. Subjects who achieve composite complete remission (CRc) or PR for AML and CR, bone marrow (BM) CR or PR or HI for MDS or other clinical benefits, as determined by the investigator, will remain in the study in Observation Period 2 until 1 post-treatment discontinuation criterion is met. Safety and efficacy will be monitored during Observation Periods 1 and 2.

Upon treatment or post-treatment discontinuation criterion is met and subjects discontinue from the Treatment Period, Observation Period 1, or Observation Period 2, all subjects will be followed for survival and subsequent anti-cancer treatments and outcomes by telephone calls every 3 months.

This study consists of 2 parts: phase 1 dose escalation and phase 2 dose expansion.

Phase 1: Dose Escalation

The dose escalation portion will assess safety and tolerability of ASP7517. Subjects must be managed under hospitalization for at least 7 days during the first cycle of the dose escalation

phase. In addition, prior to hospital discharge, the investigator must ensure subject safety by performing medical tests and procedures listed on day 7 of cycle 1 and tests considered clinically necessary to evaluate the subject's general condition and AE resolution. The subjects will also be followed on an outpatient basis on planned visits during cycle 1 and 2 after hospital discharge during the DLT assessment period to closely monitor any AEs.

After dosing of ASP7517, subjects must be observed for safety for a minimum 4 hours. The safety observation will consist of hourly vital signs and AE observations. If new AEs are observed that are ≥ grade 3 during this time, subjects should continue to be observed at the investigator's discretion.

In phase 1 (dose escalation), the starting dose level is 1×10^6 cells/dose and the decision to dose escalate to the next dose levels (1×10^7 and 1×10^8 cells/dose) will be made based on the assessment of safety variables, including the occurrence of dose limiting toxicities (DLTs).

Dose escalation will be guided according to the Bayesian optimal interval (BOIN) design [Liu et al., 2015] to determine the next dose level based on DLT occurrence. After the planned number of evaluable subjects have completed the DLT observation period for a given dose level, safety for that dose level will be assessed. Each dose level in the dose escalation phase will enroll a minimum of 3 and may enroll a maximum of 8 subjects with up to 4 evaluable subjects for the initial assessment of each dose level. Enrollment within each dose escalation cohort will be staggered such that there will be 28 calendar days between the treatment initiation of the first subject and the second subject, as well as 14 calendar days between the second subject and the third subject at the same dose level for all escalation cohorts. An interval of 28 calendar days will separate initiation of first dose of study treatment for the last subject in a dose cohort from the first subject in the subsequent dose cohort. The 28-day separation is equivalent to the 28-DLT evaluation period. If the decision is made to stay at the current dose level, then an additional 3 or 4 evaluable subjects may be enrolled to the current dose level.

Three to 18 subjects will be enrolled in the dose escalation phase. A minimum number of 6 subjects and a maximum number of 8 subjects must be enrolled at the dose level used to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D).

Safety data and other available clinical data will be reviewed on an ongoing basis to determine if the study will proceed to the next dose level/phase.

Subject Replacement during Dose Escalation:

Subjects may be replaced in the dose escalation cohort if:

- Subject is discovered to have enrolled without fully satisfying eligibility criteria.
- Subject received less than the planned dose in cycle 1 for reasons other than DLT.
- Subject has no DLT and withdraws from the study before the end of DLT evaluation period.

The decision regarding replacement of individual subjects will be made by the sponsor with discussions with the treating investigator.

Dose Escalation and Safety Committee

A Dose Escalation and Safety Committee (DESC) consisting of sponsor representatives and investigators will convene once a dose level cohort completes the DLT observation period and data are available for review. Refer to the DESC charter for additional details.

The DESC will also review the aggregate safety data from the phase 1 dose escalation and the phase 2 expansion cohorts.

Study enrollment and study treatment will be temporarily interrupted during dose escalation pending review of the following:

● Any death that is not related to disease progression occurring within 30 days of receiving investigational product.
● Occurrence of two grade ≥ 4 DLTs in 2 study subjects.
● Any grade 4 hypersensitivity reaction/anaphylaxis.

Additional information regarding DESC responsibilities, membership requirements and safety review time points are described the DESC Charter.

Phase 2: Dose Expansion

Phase 2 will assess the safety and efficacy of ASP7517. This phase of the study may open once the RP2D and/or MTD are determined from the dose escalation phase, OR all of the following conditions are met before the RP2D and/or MTD determination.

- At least 1 subject in the dose escalation cohort (phase 1) achieves CRc for AML subjects, or CR, BM CR, or PR for MDS subjects.
- The dose level to be expanded is deemed tolerable by the DESC.
- The dose that will be opened for expansion is determined to be equal or lower than possible MTD.

Phase 2 will include the following groups and may enroll in parallel and independently:

- Subjects with R/R AML.
- Subjects with R/R higher risk MDS.

The CRc rate for subjects with R/R AML and CR + BM CR + PR rate for R/R higher risk MDS are continuously monitored using the Bayesian optimal phase 2 (BOP2) design [Zhou et al, 2017]. The number of dose levels investigated during phase 2 will be based upon the data from phase 1. Initially, 12 subjects will be enrolled at each dose level for each disease type during stage 1 of BOP2. If the response rate does not meet the optimal stopping boundaries (see table below), then stage 2 will open, and an additional 20 subjects may be enrolled during this stage. Combining the data from stage 1 and stage 2, stage 3 may be opened for an additional 20 subjects for a total maximum sample size of 52 for each disease type, if the response rate does not meet the optimal stopping boundaries (see table in Section 6.8). Otherwise, the enrollment at that dose level will be closed.

In this phase, there will be a separate cohort in China to evaluate safety, tolerability, and efficacy of ASP7517 in Chinese subjects. Approximately 6 R/R AML or R/R higher risk MDS subjects will be enrolled in this separate cohort.

Stopping Rules based on Safety for Phase 2

The stopping rules described below will be applied to both AML and MDS disease types.

The safety in phase 2 will be continuously monitored using Bayesian logistic model based on safety events including:

- All DLT data obtained at the time of the analysis from both escalation and expansion cohorts.
- Drug related treatment emergent AEs leading to death.

Safety monitoring with these models will start when phase 2 is opened. Enrollment in phase 2 will be stopped based on the following 2 criteria:

- If the posterior mean of the safety event rate is higher than 30% as indicated by Bayesian logistic model across disease types at a given dose level, then enrollment will be stopped in phase 2 at that dose level and at higher dose levels for that therapy.
- Additionally, if the posterior mean of the safety event rate is higher than 30% as indicated by Bayesian logistic model in a specific disease type at a dose level, enrollment of that dose level and any higher dose-level will be stopped for that disease type.

For the cohort in China, dose evaluation and stopping rules will be based on the BOIN design with target DLT rate of 0.30 and optimal interval of (0.236, 0.359) as specified in phase 1 and detailed in Section 5.2.1.

2.3 Randomization (Subject Assignment)

This is an open-label study. Subject enrollment and dispensation of IP will be performed via the Interactive Response Technology (IRT) system. Priority for enrollment will be given to the phase 1 dose escalation portion before phase 2 dose expansion.

For phase 2 enrollment, if more than 1 dose level is open for enrollment within a selected disease type, the newly enrolled subjects with that disease type will be randomly allocated to 1 of the open dose levels. Randomization will be weighted toward newly opened dose levels, with the allocation ratio based on the number of open slots still available at each dose level. For example, if dose level ‘x’ enrolled 3 subjects and dose level ‘y’ is newly opened for expansion, the next subject would be randomly allocated to dose level ‘x’ or ‘y’ with the ratio of 9:12.

When escalation and expansion cohorts are both open for enrollment, enrollment into escalation cohorts takes priority such that subjects who are eligible for both will be preferentially enrolled in the escalation cohorts.

3 SAMPLE SIZE

Phase 1 (Dose Escalation)

The sample size for the dose escalation phase is not based on a statistical power calculation. The number of subjects enrolled will be dependent on the DLT incidence. The estimated number of subjects, a minimum of 6 evaluable and up to 18, should provide adequate information for the dose escalation and safety objectives of the study.

Phase 2 (Dose Expansion)

The sample size in phase 2 is up to 104 subjects per dose level. Each dose level may enroll up to 52 R/R AML subjects and up to 52 R/R higher risk MDS subjects. The response rate is monitored using the BOP2 design. For AML, with assumption of the efficacious CRc rate is 30% and the inefficacious CRc rate is 15%, the statistical power would be approximately 0.83 while controlling the type I error rate at 0.10. For MDS, with assumption of the efficacious CR + BM CR + PR rate is 25% and the inefficacious CR + BM CR + PR rate is 12%, the statistical power would be approximately 0.83, while controlling the type I error rate at 0.10.

China Cohort

The sample size for the China cohort is not based on a statistical power calculation. The planned number of approximately 6 subjects would provide adequate information for the objectives of the cohort.

4 ANALYSIS SETS

In accordance with the International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses. Full Analysis Set (FAS) and Response Analysis Set (RAS) will be used for efficacy analysis. Safety Analysis Set (SAF) will be used for the analyses of safety variables. Pharmacokinetic Analysis Set (PKAS) will be used for pharmacokinetic analyses. The biomarker pharmacodynamics analysis set (PDAS) will be used for all analyses of pharmacodynamics data. Analysis sets are defined in the protocol section 9.2. All classification criteria for determining membership in FAS, RAS, SAF are programmable. The classification identify variables are defined in the datasets specification. The data from all patients who were enrolled in the study will be included in the data listings. All enrolled subjects are those who signed the informed consent form and were assigned a subject number.

For each dose level group, the number and percentage of subjects will be characterized for all treated subjects and by each analysis set.

4.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are enrolled and receive at least 1 dose of study treatment. This will be the primary analysis set for efficacy analyses.

4.2 Response Analysis Set

The response analysis set (RAS) will consist of all subjects who are enrolled and receive at least 1 dose of study treatment and have at least 1 post baseline primary efficacy measurement.

4.3 Safety Analysis Set

The safety analysis set (SAF) consists of all subjects who receive at least 1 dose of IP. The SAF will be used for all summaries of the safety data. The SAF will also be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

4.4 Pharmacokinetic Analysis Set

The Pharmacokinetics Analysis Set (PKAS) consists of the administered population for which pharmacokinetics data are available at least for 1 time point. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist.

The PKAS is used for all tables and graphical summaries of the PK data.

4.5 Pharmacodynamic Analysis Set *(Not Applicable for China)*

The pharmacodynamic analysis set (PDAS) will include the subjects from the administered population for whom sufficient pharmacodynamic measurements were collected.

The PDAS will be used for all analyses of pharmacodynamic data.

4.6 DLT Evaluation Analysis Set

The DLT Evaluation Analysis Set (DEAS) is defined as all subjects in SAF by excluding the subjects who meet any of the following criteria:

- Subject is discovered to have enrolled without fully satisfying eligibility criteria.
- Subject received less than the planned dose in cycle 1 for reasons other than DLT.
- Subject has no DLT and withdraws from the study before the end of DLT evaluation period.

The DEAS will be used for the analysis of DLT data.

5 ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint: Remission

For Phase 2, the primary efficacy endpoint will be CRc rate for subjects with R/R AML and (CR+ BM CR +PR) rate for subjects with R/R higher risk MDS.

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

- Complete Remission (CR): For subjects to be classified as being in CR at a post-baseline visit, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia free state and must have an absolute neutrophil count (ANC) $\geq 1 \times 10^9$ /L and platelet count $\geq 100 \times 10^9$ /L, and normal marrow differential with < 5% blasts, and they will be red blood cell (RBC) and platelet transfusion independent (defined as 1 weeks without RBC transfusion and 1 week without platelet transfusion). There must be no presence of Auer rods. There should be no evidence of extramedullary leukemia. The blast counts in peripheral blood must be ≤ 2%.
- Complete Remission with Incomplete Platelet Recovery (CRp): For subjects to be classified as being in CRp at a post-baseline visit, they must achieve CR except for incomplete platelet recovery ($< 100 \times 10^9$ /L).
- Complete Remission with Incomplete Hematological Recovery (CRi): For subjects to be classified as being in CRi at a post-baseline visit, they must fulfill all the criteria for CR except for incomplete hematological recovery with residual neutropenia ($ANC < 1 \times 10^9$ /L) with or without complete platelet recovery. RBC and platelet transfusion independence is not required.
- Composite Complete Remission (CRc): For subjects to be classified as being in CRc at a post-baseline visit, they must achieve CR, CRp or CRi at the visit.
- Complete Remission with Partial Hematologic Recovery (CRh): For subjects to be classified as CRh at a post-baseline visit, if they have marrow blasts< 5%, partial hematologic recovery ANC $\geq 0.5 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L, no evidence of extramedullary leukemia and cannot be classified as CR. The blast counts in peripheral blood must be ≤ 2%.
- Partial Remission (PR): For subjects to be classified as being in PR at a post-baseline visit, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25%. A value of less than or equal to 5% blasts is also considered a PR if Auer rods are present. 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 present, 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.

A complete response classification schema is presented in Table 1, below.

Table 1 Response Classification Schema for AML

Myeloblast in Bone Marrow Aspirate/Biopsy	Blast in Peripheral Blood	Extramedullary Leukemia	Auer Rod	RBC Transfusion	Platelet Transfusion	ANC	Platelet	Response
<5%	Missing or <=2%	Absent/Missing	Absent/Missing	No	No	$\geq 1 \times 10^9$/L	$\geq 100 \times 10^9$/L	CR
<5%	Missing or <=2%	Absent/Missing	Absent/Missing	No	No	$\geq 1 \times 10^9$/L	$< 100 \times 10^9$/L	CR_p
<5%	Missing or <=2%	Absent/Missing	-	-	-	$\geq 0.5 \times 10^9$/L	$\geq 50 \times 10^9$/L	CR_h
<5%	Missing or <=2%	Absent/Missing	Absent/Missing	-	-	-	-	CR_i
>=5% - <=25% and >=50% decrease from baseline	Missing or <=2%	Absent/Missing	-	-	-	-	-	PR
<5%	Missing or <=2%	Absent/Missing	Present	-	-	-	-	PR
Missing	Missing or <=2%	Absent/Missing	-	-	-	-	-	NE
Any case that cannot be categorized as CR, CR_p, CR_h, CR_i, PR, or NE								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 >2% 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.
- 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 response of CR, CRp, CRi or PR will be classified as responders. Subjects who do not achieve at least a best response of PR will be considered non-responders.

- MDS
  - Complete Remission (CR): For subjects to be classified as being in CR at a post-baseline visit, they must have all of the following maintained for a minimum of 4 weeks:
    - Bone marrow evaluation: ≤ 5% myeloblasts with normal maturation of all cell lines
    - Peripheral blood evaluation:
      - Hemoglobin ≥ 11 g/dL
      - Platelets ≥ 100×10^9 /L
      - Neutrophils ≥ 1.0×10^9/L
      - 0% blasts in blood
  - Partial Remission (PR): For subjects to be classified as being in PR at a post-baseline visit, they must have all CR criteria if abnormal before treatment except the following for a minimum of 4 weeks:
    - Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
    - Cellularity and morphology not relevant
  - Marrow CR: For subjects to be classified as being in marrow CR at a post-baseline visit, they must have all of the following for a minimum of 4 weeks:
    - Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment
      - Peripheral blood: if HI responses, they will be noted in addition to marrow CR
  - Hematologic Improvement (HI): For subjects to be classified as having hematologic improvement (HI) at a post-baseline visit, they must have 1 measurement of the following, maintained for at least 8 weeks without ongoing cytotoxic therapy:
    - HI – erythroid:

- Hemoglobin increase of ≥ 1.5 g/dL or
- For RBC transfusions performed for hemoglobin ≤ 9.0 g/dL: reduction in RBC units transfused in 8 weeks by ≥ 4 units compared to the number of units transfused in the 8 weeks prior to treatment

▪ HI – platelets:
- For pre-treatment platelet count of >20 $\times 10^9$ /L platelet, absolute increase of ≥ 30 $\times 10^9$ /L
- For pre-treatment platelet count of < 20 $\times 10^9$ /L, platelet absolute increase of > 20 $\times 10^9$ /L and ≥ 100% increase from pre-treatment level

▪ HI – neutrophils:
- Neutrophil count increase of ≥ 100% from pre-treatment level and an absolute increase of > 0.5 $\times 10^9$ /L

o Relapse after CR or PR: For subjects to be classified as relapsing after CR or PR requires at least one of:
- Return to pre-treatment bone marrow blast percentage
- Decrement of ≥ 50% from maximum response levels in granulocytes or platelets
- Transfusion dependence or hemoglobin level ≥ 1.5 g/dL lower than prior to therapy

o Stable Disease (SD): For subjects to be classified as having Stable Disease (SD), they must fail to achieve at least PR but show no evidence of progression for >8 weeks

o Progressive Disease (PD): For subjects to be classified as having Progressive Disease (PD), they must show blast level increases depending on prior levels as follows:
- For patients with:
  - <5% blasts: ≥ 50% increase in blasts to > 5% blasts
  - 5%-10% blasts: ≥ 50% increase to > 10% blasts
  - 10%-20% blasts: ≥ 50% increase to > 20% blasts
  - 20%-30% blasts: ≥ 50% increase to > 30% blasts
- Or any of the following:
  - At least 50% decrement from maximum remission/response in granulocytes or platelets
  - Reduction in Hgb by ≥2 g/dL from maximum remission/response
  - Transfusion dependence: RBC or platelet transfusion after a previous CR, BM CR, PR, or HI response
  - A relapse from CR, BM CR, PR, or HI is also considered PD

5.1.2 Secondary Efficacy Endpoint: CR Rate

CR rate is defined as the number of subjects who achieve CR at any of the postbaseline visits divided by the number of subjects in the analysis population.

5.1.3 Secondary Efficacy Endpoint: CRh Rate

CRh rate is defined as the number of subjects who achieve CRh at any of the postbaseline visits divided by the number of subjects in the analysis population. CRh is applicable for AML subjects only.

5.1.4 Secondary Efficacy Endpoint: CR/CRh Rate

CR/CRh rate is defined as the number of subjects who achieve CR or CRh at any of the postbaseline visits divided by the number of subjects in the analysis population. CR/CRh is applicable for AML subjects only.

5.1.5 Secondary Efficacy Endpoint: Best Response Rate

Best Response Rate is defined as the number of subjects who achieve CRc or PR at any of the postbaseline visits divided by the number of subjects in the analysis population. Best response rate is applicable for AML subjects only.

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

5.1.6 Secondary Efficacy Endpoint: Objective Response Rate (ORR)

Objective Response Rate (ORR) is defined as the number of subjects who achieve CR, BM CR, or PR or HI at any of the postbaseline visits divided by the number of subjects in the analysis population. ORR is applicable for MDS subjects only.

5.1.7 Secondary Efficacy Endpoint: Overall Survival (OS)

OS is defined as the time from the date of first dose until the date of death from any cause (death date – first dose date + 1). For a subject who is not known to have died by the end of study follow-up, OS is censored at the date of last contact (date of last contact – first dose date + 1).

Table 2 OS Definition

Situation	Date of Event or Censor	Outcome
Death before or on analysis cutoff date	Date of death	Event
Death after analysis cutoff date	Analysis cutoff date	Censor
Last known alive is before or on cutoff date	Last known alive date	Censor
Last known alive is after cutoff date	Analysis cutoff date	Censor

OS = Date of Event or Censor – Date of first dose +1

5.1.8 Secondary Efficacy Endpoint: Event Free Survival (EFS)

EFS is defined as the time from the date of first dose until the date of documented relapse, treatment failure or death from any cause within 30 days after the last dose of IP (whichever occurs first earliest of [relapse date, treatment failure date, death date] – first dose date + 1).

Table 3 EFS Definition

Situation	Date of Event or Censor	Outcome
Death or relapse or premature discontinuation of the treatment, or initiation of other anti-leukemic treatment on or before analysis cutoff date	Date of relapse, death, premature discontinuation of treatment or initiation of other anti-leukemic treatment	Event
Death and relapse and premature discontinuation of the treatment and initiation of other anti-leukemic treatment after analysis cutoff date	Last disease assessment date	Censor
No EFS event	Last disease assessment date	Censor
No EFS event and no disease assessment	First dose date	Censor

5.1.9 Secondary Efficacy Endpoint: Duration of Response

Duration of response (DOR) for AML includes duration of CRc, duration of CR/CRh, duration of CRh, duration of CR, and duration of response (i.e., CRc + PR). DOR is defined as the time from the date of first response until the date of documented relapse.

Duration of response for MDS includes duration of CR and duration of response (i.e., CR + BM CR + PR). DOR is defined as the time from the date of first response date until the date of documented relapse.

5.1.10 Other Efficacy Endpoint: Progression Free Survival (PFS) (MDS Only)

PFS is defined as the time from the date of first dose to the date of documented disease progression or death (date of event or censor – first dose date + 1).

Table 4 PFS Definition

PFS		
Situation	**Date of Event or Censor**	**Outcome**
No evaluable post-baseline disease assessment, no death	Date of first dose	Censor
Subject did not receive new anti-cancer therapy:		
Disease progression documented	Date of disease progression	Event
No disease progression, but death recorded on eCRF	Date of death	Event
Neither disease progression nor death	Date of last disease assessment	Censor
Subject received new anti-cancer (ACT) therapy:		
Disease progression documented after new ACT	Date of last disease assessment before start of new anti-cancer therapy	Censor
Disease progression documented before new ACT	Date of disease progression	Event
No disease progression before new ACT but death recorded	Date of last disease assessment before start of new anti-cancer therapy	Censor
No disease progression nor death	Date of last disease assessment before start of new anti-cancer therapy	Censor

5.1.11 Other Efficacy Endpoint: Transfusion Status

Transfusion status (independent vs. dependent) at baseline period and post-baseline period are defined in the following for subjects who took at least one dose of study drug:

Baseline transfusion status:

- Baseline period is defined as the period from 28 days prior to first dose until 28 days after the first dose. For subjects who are on treatment <28 days, baseline period is from the 28 days prior to first dose until the end of treatment.
- Subjects are considered baseline transfusion independent if there is no RBC or platelet transfusions within the baseline period; otherwise, the subject is baseline transfusion dependent.

Post-baseline transfusion status:

- Post-baseline period is defined as the period from 29 days after first dose date until the end of Observation Period 2.

- For subjects who are on study >=84 days, subjects are considered post-baseline transfusion independent if there are 56 consecutive days without any RBC or platelet transfusion within post-baseline period.
- For subjects who are on study >28 days but <84 days, if there is no RBC or platelet transfusion within post-baseline period, post-baseline transfusion status is not evaluable.
- For subjects who are on study <=28 days, post-baseline transfusion status is not evaluable.
- Otherwise, the subject is considered post-baseline transfusion dependent.

5.2 Safety Endpoints

Safety and tolerability (determine MTD) are the primary endpoints of the study. Safety endpoints are adverse events (AEs), laboratory measurements, vital signs, physical examination and ECOG performance status (PS). Safety will be assessed by evaluation of the following variables:

5.2.1 Safety Endpoint: Dose-Limiting Toxicity (DLT)

A DLT is defined as any of the following events that occur within 28 days starting with the first dose on C1D1 and that is considered to be related to investigation product (IP). Confirmation of DLTs will be made by the DESC. The severity of AEs will be assessed according to NCI-CTCAE, version 5.0.

DLT is defined as follows:

- Non-hematologic AEs that are ≥ grade 3.
- Confirmed Hy's law case.
- New onset of grade 4 thrombocytopenia (with minimum of 2 grade worsening from baseline) within 24 hours of dosing.
- Prolonged myelosuppression, defined as ANC < 500/μL for more than 28 days off therapy and in the absence of evidence of active leukemia or MDS in the marrow or blood, will be considered as a DLT.

The following AEs will not be considered as DLTs:

- Electrolyte abnormalities that are not associated with clinical sequelae or deemed not clinically significant and corrected with appropriate management or supplementation within 72 hours of the onset.
- Grade 3 infusion site reaction if successfully managed and resolved within 72 hours.
- Grade 3 febrile neutropenia with or without infection.
- Alopecia, anorexia or fatigue.
- Grade 3 nausea and/or vomiting if not requiring tube feeding or total parenteral nutrition, or diarrhea and/or constipation if not requiring or prolonging hospitalization that can be managed to grade ≤ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 7 days of onset.

- Grade 3 liver function test (LFT) elevations that resolve to ≤ grade 1 within 7 days; LFT elevations lasting > 7 days that are considered to be clinically significant and at least possibly related to ASP7517 will be considered to be a DLT.
- Immune-related AEs grade 3 that resolve to ≤ grade 1 within 7 days
- Grade 3 or higher hyperuricemia due to tumor lysis that resolves to ≤ grade 1 with medical interventions, including hospitalization with intravenous hydration and/or rasburicase.

Dose evaluation and dose escalation stopping rules based on the BOIN design with target DLT rate of 0.30 and optimal interval of (0.236, 0.359) are as follows:

	Number of Subjects Treated at Current Dose Level					
Action	**3**	**4**	**5**	**6**	**7**	**8**
Escalate dose if number of subjects with DLT ≤	0	0	1	1	1	1
Stay at current dose level if number of subjects with DLT =	1	1	-	2	2	2
De-escalate if number of subjects with DLT =	2	2	2 or 3	3	3 or 4	3 or 4
Stop if number of subjects with DLT ≥	3	3	4	4	5	5

DLT: dose limiting toxicity

Dose escalation within individual subjects will not be allowed.

5.2.2 Safety Endpoint: Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

Maximum Tolerated Dose

The MTD determination will be based on at least 6 evaluable subjects at that dose level based on the BOIN design. Based on the observed DLT(s) during the DLT observation period, the MTD is the highest dose for which the isotonic estimate of the DLT rate is closest to, but not over, the target DLT rate of 0.30. The dose level determined to be the MTD must have data from at least 6 subjects.

Recommended Phase 2 Dose

The sponsor, in conjunction with the DESC, will determine the RP2D of ASP7517 taking into consideration the safety and efficacy data, as well as other available data, such as pharmacokinetics and pharmacodynamics of ASP7517. The RP2D will not exceed the MTD. The dose level determined to be the RP2D must have data from at least 6 subjects.

5.2.3 Safety Endpoint: Adverse Events

AEs will be coded using MedDRA v26.0 and graded using NCI CTCAE 5.0. A treatment-emergent adverse event (TEAE) is defined as an AE observed after starting administration of the IP and 30 days after the final administration of IP. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as "yes" by the investigator or with missing assessment of the causal relationship. The number and percentage of subjects with TEAEs, IP-related TEAEs, serious TEAEs, IP-related serious TEASs, TEAEs leading to withdrawal of treatment and drug related TEAEs leading to withdrawal of treatment will be summarized by SOC, preferred term and treatment group. The number and percentage of TEAEs by severity will also be summarized. The worst severity will be summarized if the same AE is recorded more than once for a subject. AE data will be listed.

If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the preinvestigational period and during the investigational period, 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 study drug will also be counted as TEAE.

Immune-related AE (irAE) and infusion related reactions (IRR) will be considered as Adverse Events of Special Interest (AEsi). The list of events classified as AEsi may change during the study due to ongoing pharmacovigilance.

5.2.4 Safety Endpoint: Laboratory Assessments

- Clinical laboratory variables for hematology, chemistry including liver function test, coagulation, urinalysis, and bone marrow will be collected during the conduct of the study as listed in Table 5 below.

Additional laboratory tests should be performed according to institutional standard of care.

Table 5 Laboratory Assessments

Clinical Laboratory Tests

Panel/Assessments	Parameters to be Analyzed	NCI-CTCAE Grading (Hyper/Hypo)
Hematology	Blast count and cell count	N/A
	Hematocrit (Hct)	N/A
	Hemoglobin (Hgb)	Both
	Mean corpuscular volume (MCV)	N/A
	Mean corpuscular hemoglobin (MCH)	N/A
	Mean corpuscular hemoglobin concentration (MCHC)	N/A
	Platelet count	Hypo
	Red blood cell count (RBC)	N/A
	White blood cell count (WBC)	Both
	White blood cell count differential:	
	Neutrophils	Hypo
	Eosinophils	N/A
	Basophils	N/A
	Lymphocytes	Both
	Monocytes	N/A
Table continued on next page		

Panel/Assessments	**Parameters to be Analyzed**	**NCI-CTCAE Grading (Hyper/Hypo)**
Chemistry	Sodium (Na) Potassium (K) Chloride (Cl) Bicarbonate (HCO3) Blood urea nitrogen (BUN) Creatinine (Cr) Glucose (Gl) Calcium (Ca) Phosphate (Pi) Magnesium (Mg) Albumin (Alb) Total protein (T Prot) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatine phosphokinase (CK) Liver function tests including: Bilirubin total (TBL) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST)	Both Both N/A Hypo N/A Hyper Both Both Hypo Both Hypo N/A Hyper Hyper Hyper Hyper Hyper Hyper
Urinalysis	Color Appearance Specific gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen	
Urine/Serum Pregnancy Test **	hCG	
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	Activated partial thromboplastin time (aPTT) International normalized ratio (INR) Prothrombin time (sec) (PT) Fibrinogen D-Dimer	Hyper Hyper N/A

Table continued on next page

Panel/Assessments	Parameters to be Analyzed	NCI-CTCAE Grading (Hyper/Hypo)
Bone Marrow***	Blast count and cell counts * Flow cytometry for blasts	
Blood Sample for Disease Assessment***	Blast count and cell counts	

eCRF: electronic case report form; hCG: human chorionic gonadotrophin.

* In addition to the central read of these values, local results will also be collected and entered into the eCRF.

** Local results will be collected and entered into the eCRF.

*** Samples must be submitted to a central laboratory for analysis. Refer to the laboratory manual for additional information.

- Vital signs (systolic and diastolic blood pressures (mmHg), pulse (beats/minute) and body temperature)
- Weight and height
- Eastern Cooperative Oncology Group performance status (ECOG PS)
    - The ECOG Scale [Oken et al., 1982] will be used to assess performance status at time points outlined in the Schedules of Assessments
- 12-lead electrocardiogram (ECG)
    - 12-lead ECGs will be recorded in triplicate (at least 2 minutes apart per time point) at the scheduled time points. ECGs will be recorded after the subject has been in a resting, supine position for at least 5 minutes. ECGs will be read at the site for clinical decision making and transmitted to a central reviewer. Data from the central reviewer will be used in summary presentations.

6 STATISTICAL METHODOLOGY

6.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g., 10%, 25%, 75% and 90%) will be reported in the relevant section. In addition, for plasma concentrations and continuous PK parameters, the coefficient of variation and the geometric mean will also be calculated. 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%.

Summaries based on FAS and RAS (e.g. disposition, baseline and efficacy data) will be presented by planned treatment, unless specifically stated otherwise. Safety analysis and other summaries based on SAF, PKAS or PDAS will be presented by actual dose level received. Pharmacokinetic summaries based on PKAS and pharmacodynamic summaries based on PDAS will be presented by actual dose level received. Data for the China cohort will be summarized separately, by dose level.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher on Unix. Specifications for table, figure, and data listing formats can be found in the TLF specifications for this study.

Baseline is defined as the last available measurement prior to the first dose of IP. Unless otherwise specified, all summaries will be presented overall, by dose level and by phase.

6.2 Study Population

6.2.1 Disposition of Subjects

The following subject data will be presented:

- Number and percentage of subjects with informed consent, discontinued before allocation to treatment/randomization, allocated to treatment/randomized (overall only)
- Number and percentage of subjects allocated to treatment/randomized in each analysis set, by phase, disease type, dose level and overall
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation for allocated/randomized subjects, by phase, disease type, and dose level
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation for allocated/randomized subjects and by phase, disease type, and dose level
- Number and percentage of subjects completed and discontinued the post-study period, by primary reason for post-study period discontinuation for allocated/randomized subjects and by phase, disease type, and dose level
- Number and percentage of subjects excluded from RAS by reason for exclusion, by phase, disease type, and dose level for FAS

All disposition details and dates of first and last evaluations for each subject will be listed.

6.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 10.3 Major Protocol Deviations) will be assessed for all subjects allocated to treatment/randomized. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group and overall as well as 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,

PD5- Informed Consent Form (ICF) not updated for safety information or other pertinent information that might impact subject participation per local regulations or Ethics Committee (EC)requirements.

PD6- Serious Adverse Events (SAEs) not reported within the expected turn-around time per protocol reporting requirements.

PD7 -Missed safety or efficacy assessments related to primary or key secondary endpoints.

6.2.3 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized by dose level and overall for all treated subjects.

Number and percentage of subjects randomized in each country and site will be presented by treatment group and overall for the SAF.

Descriptive statistics for age, weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (defined in Section 6.6), race, region, baseline ECOG, and cytogenetic risk status will be presented. This will be done for SAF and RAS and by dose level, phase, and overall and by disease type.

Frequency tabulations will be presented for AML/MDS disease history including AML or MDS subtype by World Health Organization (WHO) classification and French-American-British (FAB) classification, risk status, antecedent hematological disorder, central nervous system leukemia, and rapidly progressing disease.

Medical history other than AML/MDS and conditions existing at baseline will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by treatment group and overall for the SAF. 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 study drug. For ongoing medical conditions, Common Terminology Criteria for Adverse Events (CTCAE) grade will be provided in listing.

Results from echocardiogram and MUGA scan, if performed, will be provided in listing.

6.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the SAF.

As with previous medication, concomitant medication will be summarized for each treatment group by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. 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.

6.2.5 Previous and Concomitant Transfusions

All transfusions received by subjects within 28 days prior to Day 1 of Cycle 1 through end of treatment will be recorded on the eCRF. Data will include the date, blood product, start and stop date, indication, and the number of units given.

Frequency tabulations of subjects received transfusions and blood product will be presented for previous transfusion and concomitant transfusion by cohort and dose level for SAF. Descriptive statistics will be presented for number of transfusion unit received per subject.

6.2.6 Prior Chemotherapy for Primary Disease

Frequency tabulations of subjects with prior AML/MDS chemotherapy, regimen, type of treatment, best response to prior AML/MDS therapy, lines of therapy received and subjects with prior Tyrosine Kinase Inhibitor (TKI) therapy will be presented by cohort and dose level for SAF. Descriptive statistics will be presented for duration of response to prior AML/MDS therapy.

6.2.7 Non-Medication Therapy

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

6.3 Study Drug

6.3.1 Exposure

The following information on drug exposure will be presented with descriptive statistics (n, mean, standard deviation, median, minimum, maximum) for the SAF:

- Duration of exposure (days)
  - Duration of exposure to a study drug will be calculated in days, using the following formula:
  - (Last date of exposure – date of first dose) + 1; where last date of exposure = initial infusion date of the last cycle + 27, death date if death occurs within last cycle, start date of new anticancer therapy, or treatment discontinuation date.
    - When the start or stop date is missing, then the exposure will be treated as missing.
- Cumulative actual dose (# of cells)
  - Total amount of IP administered to the patient from first dose date to last dose date
- Number of cycles initiated
  - Total number of cycles with non-zero dosing in the cycle
- Actual dose intensity
  - Defined as the cumulative actual dose divided by number of cycles
- Relative dose intensity (RDI; %)
  - Actual Dose Intensity
    ---------- x 100
    Planned Dose Intensity

Number and percentage of subjects with infusions not administered, delays, interruptions, or premature discontinuations at any cycle will be presented for the SAF. The reasons for infusions not administered, delays, interruptions, and premature discontinuations at any cycle will be listed.

6.4 Analysis of Efficacy

Efficacy analyses will be conducted on the FAS and RAS. The interpretation of results from statistical tests will be based on the FAS. The RAS will be used to assess the robustness of the results from the statistical tests based on the FAS. All randomized subjects will be analyzed according to the treatment to which they are randomized/assigned. Efficacy data from the China cohort will be analyzed separately.

Derived response based on central assessment supplemented by local assessment: response will be derived based on the definitions in Section 7.1.1 using centrally evaluated myeloblast counts from bone marrow aspirate or biopsy assessments whichever is present (if both are present, both must qualify for the criteria) and centrally evaluated hematology results including ANC, platelet count and blast count in peripheral blood. If neither central bone marrow aspirate nor biopsy is available at baseline assessment, then myeloblast counts from locally evaluated bone marrow aspirate/biopsy assessments (if both are present, both must qualify for the criteria) will be used for all timepoints of assessment. Missing hematology results will not be imputed.

Derived response will be considered as primary and investigator reported response will be considered as supportive.

6.4.1 Analysis of Primary Efficacy Endpoints

For Phase 2, the primary efficacy endpoint will be CRc rate for subjects with R/R AML and (CR+ BM CR +PR) rate for subjects with R/R higher risk MDS.

- AML
  - CRc rate is defined for AML subjects as the number of subjects who achieve the best response of CRc (CR, CRp or CRi) divided by the number of subjects in the analysis population.
  - Response to treatment will be defined per Cheson et al., 2003
  - Response rates will be calculated and their 2-sided 90% confidence intervals will be constructed by Clopper-Pearson method by dose level for phase 1 and by dose level and disease type for phase 2.
- MDS
  - CR + BM CR + PR rate is defined for MDS subjects as the number of subjects who achieve the best response of CR or BM CR plus the number of subjects who achieve the best response of PR divided by the number of subjects in the analysis population.
  - Response to treatment will be defined per Cheson et al., 2006
  - Response rates will be calculated and their 90% confidence interval will be constructed by Clopper-Pearson method by dose level for phase 1 and by dose level and disease type for phase 2.

6.4.2 Analysis of Secondary Efficacy Endpoints

6.4.2.1 Best Response

The best response rate will be estimated and its 90% confidence interval (CI) will be constructed by dose level and disease type using the Clopper-Pearson method using the RAS.

6.4.2.2 Objective Response Rate (ORR)

Objective Response Rate (ORR) is defined for MDS subjects as the number of subjects who achieve CR, BM CR, PR or HI at any of the postbaseline visits divided by the number of subjects in the analysis population. ORR is applicable for MDS subjects only.

The ORR will be estimated and its 90% confidence interval (CI) will be constructed by Clopper-Pearson method by dose level using the RAS.

6.4.2.3 Overall Survival (OS)

The date of last contact is the latest date the subject is known to be alive.

Subjects will be followed from first dose date until death or last contact.

For a subject who is not known to have died by the end of study follow-up, OS is censored at the date of last contact (date of last contact – first dose date + 1). OS will be presented in listing only.

6.4.2.4 Event Free Survival (EFS)

For a subject with none of these events as relapse, treatment failure or death, EFS is censored at the date of last relapse-free disease assessment (last relapse-free disease assessment date – first dose date +1). Subject without post-treatment disease assessment will be censored at randomization date.

Treatment failure includes those subjects who discontinued the treatment due to “progressive disease” or “lack of efficacy” without a previous response of CR, CRp, CRi or PR.

EFS will be presented in listing only.

6.4.2.5 Duration of Response

Duration of Response will be presented in listing only.

6.4.2.6 Progression Free Survival (MDS only)

PFS will be presented in listing only.

6.4.3 Analysis of Exploratory Endpoints

6.4.3.1 Biomarkers / Pharmacodynamics *(Not Applicable for China)*

WT1 RNA expression will be summarized by change from baseline at each time point. Selected immune cell phenotypes will be summarized by change from baseline at each time point by percentage. Gene mutations, immune cell phenotypes, anti-HLA antibodies and replication competent lentivirus (RCL) will be assessed and reported in listings.

6.5 Analysis of Safety

All analysis of safety will be presented overall and by dose level for SAF, unless specified otherwise. Safety data for the China cohort will be summarized separately.

6.5.1 Adverse Events

For the purpose of safety assessments in this study, events recorded during the pre-investigational period will be classified as Baseline Signs and Symptoms. All adverse events (AE) recorded on treatment including within 30 days from the last study treatment will be summarized.

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by SOC and PT. AEs will be graded using National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE).

An overview table will include the following details by phase, disease type, and dose level:

- Number and percentage of subjects with TEAEs
- Number and percentage of subjects with IP related TEAEs
- Number and percentage of subjects with TEAE leading to death
- Number and percentage of subjects with IP-related TEAE leading to death
- Number and percentage of subjects with serious TEAEs and Astellas upgraded serious TEAE
- Number and percentage of subjects with serious IP related TEAEs and Astellas upgraded serious IP related TEAE
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study IP
- Number and percentage of subjects with IP related TEAEs leading to permanent discontinuation of study IP

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

- TEAEs
- IP related TEAEs
- serious TEAEs and Astellas upgraded serious TEAE
- IP related serious TEAEs and IP related Astellas upgraded serious TEAE
- TEAEs leading to permanent discontinuation of study IP
- IP related TEAEs leading to permanent discontinuation of study IP
- TEAEs leading to dose interruption
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any dose level
- Frequency reported TEAEs that equal to or exceed a threshold of 5% in any dose level

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized by phase and dose level.

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 study drug. 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. The number and percentage of subjects with CTCAE grade 3 or higher TEAE and number and percentage of subjects with CTCAE grade 3 or higher IP related TEAE will be summarized by phase and dose level.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by dose level for safety analysis set.

All AEs, deaths, SAEs, withdrawals due to adverse events, and AEs for subjects will be displayed in listings.

The list of adverse events to be summarized may change during the course of the study due to ongoing pharmacovigilance.

6.5.2 Adverse Events of Special Interest (AEsi)

The number and percentage of subjects with Adverse Events of Special Interest (AEsi) such as IRR and irAE, and as classified by SOC and PT, will be summarized overall and by dose level.

An IRR overview table will include the following details by phase and dose level:

- Number and percentage of subjects with IRR TEAEs
- Number and percentage of subjects with IRR IP related TEAEs
- Number and percentage of subjects with serious IRR TEAE
- Number and percentage of subjects with IP-related IRR TEAE
- Number and percentage of subjects with IRR TEAE leading to death
- Number and percentage of subjects with IP related IRR TEAE leading to death
- Number and percentage of subjects with IRR TEAEs leading to permanent discontinuation of study IP
- Number and percentage of subjects with IP related IRR TEAEs leading to permanent discontinuation of study IP
- Number and percentage of subjects who died

An irAE overview table will include the following details by phase and dose level:

- Number and percentage of subjects with irAE TEAEs
- Number and percentage of subjects with irAE IP related TEAEs
- Number and percentage of subjects with serious irAE TEAE
- Number and percentage of subjects with IP-related irAE TEAE
- Number and percentage of subjects with irAE TEAE leading to death
- Number and percentage of subjects with IP related irAE TEAE leading to death
- Number and percentage of subjects with irAE TEAEs leading to permanent discontinuation of study IP
- Number and percentage of subjects with IP related irAE TEAEs leading to permanent discontinuation of study IP
- Number and percentage of subjects who died

6.5.3 Clinical Laboratory Evaluation

The baseline visit is the last available measurement prior to the first dose of IP.

Quantitative clinical laboratory variables, i.e., hematology and biochemistry will be summarized using mean, standard deviation, minimum, maximum and median by phase and dose level at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Laboratory results will also be graded using NCI-CTCAE, where possible. Following the Table 5 in Section 5.2.4, 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 on hematology and chemistry will be summarized by number and percentage of subjects for each visit. Shift tables of NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented.

Laboratory results based on central assessment will be used for summaries as described above. Laboratory results based on local assessment and bone marrow results will be listed only.

6.5.3.1 Liver Safety Assessment

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

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

(*) Combination of values measured within same sample; ULN: Upper Limit of Normal

The number and percentage of subjects with potentially clinically significant values in liver enzymes and total bilirubin during the investigational period will be presented overall and by dose level.

6.5.4 Vital Signs

The baseline value is the last available measurement prior to the first dose of IP.

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse, body temperature and weight) will be summarized using mean, standard deviation, minimum, maximum and median by phase, dose level, and visit. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by visit.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest post-baseline value for each subject.

The following criteria are defined as clinically significant 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 Rate	≥120 bpm AND ≥15 bpm change from baseline

Vital signs data will be displayed in listings.

6.5.5 Electrocardiograms (ECGs)

The three values of each ECG parameter within a time point from the central reviewer will be averaged to determine time-specific parameter for a subject, and used in summaries.

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each cohort and dose level at each treatment visit and time point, including changes from baseline.

Number and percentage of subjects with normal and abnormal results as assessed by central review for the overall interpretation will be tabulated by cohort and dose level at each treatment visit and 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: $QTc\ (F) = QT/(RR)^{0.33}$, where RR interval is inversely proportional to heart rate (approximately RR = 60/heart rate).

The QTcF interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

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

The QTcF interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

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

Number and percent of subjects with 12 lead ECG abnormalities as well as number and percent of subjects whose 12 lead ECG reading changed from normal at baseline to abnormal will be tabulated by phase and dose level at each treatment visit and time point.

6.5.6 Pregnancies

A detailed listing of all pregnancies will be provided.

6.5.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

Number and percent of subjects for each category of the ECOG performance status at each assessment time will be provided. The change from baseline to EOT score will also be summarized. Negative change scores indicate an improvement. Positive change scores indicate a decline in performance.

ECOG will also be summarized using shift table from baseline to post-baseline score for each dose level by visit.

6.6 Analysis of Pharmacokinetics

Cellular DNA load and kinetic parameters will be summarized by using descriptive statistics including n, mean, standard deviation, minimum, median, maximum, coefficient of variation (CV), geometric mean, and geometric CV. Spaghetti and mean time-course of cellular DNA load will be constructed. Pharmacokinetic data from the China cohort will be analyzed separately.

6.6.1 Estimation of Pharmacokinetic Parameters

Subjects with sufficient cellular DNA samples will have kinetic parameter estimates for ASP7517 including calculation of AUC, C_{max}, and t_{max}. estimated by the pharmacokineticist using a non-compartmental analysis method in reference to Manual for Non-Compartmental Analysis of Pharmacokinetic Data from Studies using PhoenixTM® WinNonlin® (Certara, Saint Louis, Missouri, US) software version 6.4 or higher.

Exploratory analysis between pharmacokinetic parameters and clinical measures (e.g., efficacy or safety) may be performed.

Kinetic parameters will be plotted against dose to make an assessment of their relationship.

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

No interim analysis is planned. Safety, pharmacokinetic and other clinical data will be reviewed on an ongoing basis to determine if the study will proceed on to the next dose level/phase. For phase 2, according to the BOP2 design, the futility analysis for efficacy will be performed at the end of stage 1 and stage 2. Twelve subjects will be enrolled at each dose level for each disease type during stage 1 of BOP2. If the response rate does not meet the optimal stopping boundaries, then stage 2 will open and an additional 20 subjects may be enrolled during this stage. Combining the data from stage 1 and stage 2, stage 3 may be opened for an additional 20 subjects for a total maximum sample size of 52 for each disease type, if the response rate does not meet the optimal stopping boundaries after stage 2.

Optimized Stopping Boundaries for AML	
Number of subjects treated	**Stop if number of responses ≤**
12	1
32	6

AML: acute myeloid leukemia

Optimized Stopping Boundaries for MDS	
Number of subjects treated	**Stop if number of responses ≤**
12	0
32	4

MDS: myelodysplastic syndrome

The safety in phase 2 will be monitored using Bayesian logistic model based on all DLT data obtained at the time of the analysis for both escalation and expansion cohorts and drug related TEAEs leading to death. Safety monitoring with these models will start when phase 2 is opened. Enrollment in phase 2 may be held based on the following 2 criteria: 1. If the posterior mean of the DLT rate is higher than 30% as indicated by Bayesian logistic model across disease types at a given dose level, then enrollment will be stopped in phase 2 at that dose level and at higher dose levels for that therapy. 2. Additionally, if the posterior mean of the DLT rate is higher than 30% as indicated by Bayesian logistic model in a specific disease type at a dose level, enrollment of that dose level and any higher dose-level will be stopped for that disease type.

6.8 Additional Conventions

6.8.1 Analysis Windows

No visit window will be used; nominal visit date will be considered date of visit.

6.8.2 Imputation Rules for Incomplete Dates

Missing or partial start and stop dates of adverse events and concomitant medication will be imputed according to Astellas standards 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	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		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

6.8.3 Outliers

All values will be included in the analyses.

7 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	06-SEP-2019	N/A	
2.0	18-FEB-2020	Language was added to pages 9, 11, 12, 13, 14, 27, 31, 33, 34, and 39 to specify the analytic treatment of data arising from the cohort in China.	To incorporate provisions for China-specific protocol amendment.
2.1	18-MAY-2020	• Language was added to pages 8, 9, and 40 to specify the analytic treatment of data arising from the cohort in China. • Language was added to pages 5, 9, 10, 11, 12, 13, 15, 18, 20, 22, 24, 33, and 34 to incorporate operational changes in the study related to regulatory feedback	To incorporate provisions for China-specific protocol amendment in Protocol v6.0.
3.0	27-JUN-2023	• Contents were updated on section 5.1.1 on Primary Efficacy Endpoint. • Section 5.1.9 was added to Secondary Efficacy Endpoint. • Section 5.1.10 Removed some efficacy endpoints that will not be presented in the final TLF delivery. • Section 5.1.11 Removed Transfusion conversion rate and transfusion maintenance rate, which will not be presented in the final TLF delivery. • Section 5.2.3 Updated MedDRA to v26.0. Removed Time to first onset of irAE. • Statistical methodology Section 6.1 Removed Kaplan-Meier survival curve as it will not be reported in the final TLF delivery.	For clarification, specifically for PD and Transfusion dependence.

Version	Date	Changes	Comment/rationale for change
3.0	27-JUN-2023	• Section 6.2.2 Added PD5, PD6, and PD7 based on newly released Deviation Management and Escalation Plan (DvMEP) v2.0. • Section 6.2.3 - 6.2.7 Removed contents which will not be presented in the final TLF delivery. • Section 6.3.1 Updated contents for clarification. • Section 6.4. Updated derived response to "If neither central bone marrow aspirate nor biopsy is available at baseline assessment, then myeloblast counts from locally evaluated bone marrow aspirate/biopsy assessments (if both are present, both must qualify for the criteria) will be used for all timepoints of assessment. Missing hematology results will not be imputed". • Section 6.4.2.3 -6.4.2.5 Updated such that OS, EFS and DOR will be presented only in listings. • Removed Time to Response as this will not be presented in final TLF. • Section 6.4.3.1 Removed some biomarkers from the final TLF. • Section 6.5.2 Removed time to onset of AEsi and added ORR tables. • Section 6.5.3 Removed some contents which will not be presented in final TLF. • Removed Subgroups of Interest (original Section 6.7).	For clarification, specifically for PD and Transfusion dependence.

8 REFERENCES

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9 APPENDICES

9.1 Appendix 1: Key Contributors and Approvers

List of Key Contributors and Approvers

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