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

Version 7.5

Incorporating Nonsubstantial Amendment 5 [See Section 13]

19 Sep 2022

IND 19575

IND Grantor: CBER

Sponsor:

Astellas Pharma Global Development Inc.

1 Astellas Way
Northbrook, IL 60062, US

Protocol History:
Version 1.0 [19 Apr 2019]
Version 2.0 [09 May 2019] Incorporating Substantial Amendment 1
Version 3.0 [11 Jun 2019] Incorporating Substantial Amendment 2
Version 4.0 [CN] [12 Sep 2019] Incorporating Country-specific Substantial Amendment 3 for China
Version 5.0 [23 Apr 2020] Incorporating Substantial Amendment 4
Version 6.0 [CN] [13 May 2020] Incorporating Country-specific Substantial Amendment 5 for China
Version 7.0 [26 Apr 2021] Incorporating Substantial Amendment 6
Version 7.1 [19 May 2021] Incorporating Nonsubstantial Amendment 1
Version 7.2 [23 Jun 2021] Incorporating Nonsubstantial Amendment 2
Version 7.3 [CN] [05 Aug 2021] Incorporating Country-specific Nonsubstantial Amendment 3 for China
Version 7.4 [14 Oct 2021] Incorporating Nonsubstantial Amendment 4

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SIGNATURES

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

This study will be conducted in adherence to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable laws and regulatory requirements, as well as this protocol.

This study will be conducted in compliance with Japanese regenerative medicine GCP (for Japan only). As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement by signature or "printed name and seal."

2. SPONSOR'S SIGNATURES

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

3. INVESTIGATOR'S SIGNATURE

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

Version 7.5 Incorporating Nonsubstantial Amendment 5

19 Sep 2022

I have read all pages of this protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my personnel have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

Date (DD MMM YYYY)

Printed Name: _____

<Insert name and qualification of the investigator>

Address: _____

_____

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events or Defect of Investigational Product]	Please fax or email the serious adverse events/special situations worksheet to: **Astellas Pharma Global Development Inc.** **Pharmacovigilance** **North America fax number: +1-888-396-3750** **North America alternate fax number: +1-847-317-1241** **International fax number: +44-800-471-5263** **Email: safety-us@astellas.com** ***Specific to Japan:*** JUTOKUNA YUUGAIJISHOU OYOBIFUGUAI HOUKOKUSHO or JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the special situations worksheet to: **Astellas Pharma Inc. - Japan** **Pharmacovigilance** **Fax number: 03-3243-5747** **Email: rk-safety-jp@jp.astellas.com**
Medical Monitor/Study Physician	PPD Astellas Pharma Global Development Inc. PPD
Clinical Research Contact (Global)	PPD Astellas Pharma Global Development Inc. PPD
Clinical Research Contacts (Local Japan, as needed)	Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8411, Japan Telephone number: +81-3-3244-0635 Fax number: +81-3-3243-5737 Sponsor's personnel: PPD Contact numbers during nonbusiness hours and for emergency: Telephone number: PPD

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1 PROTOCOL SUMMARY

1.1 Synopsis

Date and Version of Protocol Synopsis:	19 Sep 2022, Version 7.5
Sponsor: Astellas Pharma Global Development Inc. (APGD)	**Protocol Number:** 7517-CL-0101
Compound Name: ASP7517 Injection	**Phase of Development:** Phase 1/2
Title of Study: 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)	
Planned Study Period: From approximately 3Q2019 to 4Q2024	

Study Objective(s) and Endpoint(s):

Objective(s)	Endpoint(s)
Primary	
● To evaluate the safety and tolerability of ASP7517 ● To determine the RP2D and/or the MTD of ASP7517 (phase 1) ● To evaluate the clinical response of ASP7517	● Safety and tolerability as noted by: DLTs, AEs, SAEs, laboratory test results (serum, chemistry, hematology, coagulation, and urinalysis, pregnancy test) ECGs, vital signs, physical exams and ECOG performance status scores ● CRc rate for subjects with R/R AML and (CR + BM CR+ PR) rate for R/R higher risk MDS (phase 2)
Secondary	
● To evaluate other measures of anticancer activity of ASP7517	● Duration of remission ● EFS ● OS ● CR, best response (CRc + PR) and CRh rates for subjects with R/R AML ● CR, HI and objective response (CR + BM CR + PR + HI) rates for subjects with R/R higher risk MDS
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, which is determined by the kinetics of the cells	● Exploratory biomarkers that may correlate with treatment outcome of ASP7517 ● Pharmacodynamic effects of ASP7517, such as changes in: o Cytokine expression and secretion (e.g., IFNg) o WT1-specific T lymphocytes (e.g., cytotoxic T lymphocytes) o Immune cell populations (NKT cells, NK cells, etc.) ● Cellular DNA load and kinetic parameter estimates for ASP7517

AE: adverse event; AML: acute myeloid leukemia; BM: bone marrow; CR: complete remission; CRc: composite complete remission; CRh: complete remission with partial hematologic recovery;

Footnotes continued on next page

DLT: dose limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; IFNg: interferon gamma; HI: hematologic improvement; MDS: myelodysplastic syndrome; MTD: maximum tolerated dose; NK: natural killer; NKT: natural killer T; OS: overall survival; PR: partial remission; R/R: relapsed/refractory; RP2D: recommended phase 2 dose; SAE: serious adverse event; WT1: Wilms' tumor 1 protein.

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

Approximately 30 centers in Japan, US and China

Phase 1 (Dose Escalation) will be conducted only in Japan

Study Population:

Phase 1 (Dose Escalation) and Phase 2 (Dose Expansion)

The study will be conducted in adult subjects with relapsed/refractory (R/R) acute myeloid leukemia (AML) or R/R higher risk myelodysplastic syndrome (MDS).

- A subject with R/R AML is defined as a subject who relapsed after or is refractory to induction and not a candidate for salvage therapy.
- A subject with R/R higher risk MDS is defined as a subject with Revised International Prognostic Scoring System (IPSS-R) for myelodysplasia of > 3.5 who relapsed after, or is refractory to, induction.

Number of Subjects to be Enrolled:

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

Phase 1 (Dose Escalation)

Approximately 18 subjects with either R/R AML or R/R higher risk MDS will be enrolled.

Phase 2 (Dose Expansion)

Approximately 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. Both groups of subjects will enroll in parallel and independently.

Study Design Overview:

This study is a phase 1/2, open-label study of ASP7517 (human embryonic kidney cell transfected with encoding target antigen Wilms' tumor protein 1 [WT1]) in subjects with R/R AML and R/R higher risk MDS. Subjects will receive an intravenous infusion of ASP7517. Subjects will receive 1 dose of ASP7517 per cycle for a total of up to 2 doses during the escalation phase and up to 6 doses during the expansion phase.

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. Subjects who achieve composite complete remission (CRc) or partial remission (PR) for AML and CR, bone marrow (BM) CR or PR or hematologic improvement (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.

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).

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.

Phase 1 Dose Escalation:

The dose escalation portion will assess safety and tolerability of ASP7517. Subjects will receive 2 single doses of ASP7517 via intravenous infusion. Dosing will occur on day 1 of each cycle, with a total of 2 cycles.

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 in the opinion of the investigator to evaluate the subject's general condition and adverse event (AE) resolution. The subject should also be followed on an outpatient basis on planned visits during cycles 1 and 2 after hospital discharge during the DLT assessment period to closely monitor any AEs. Subjects may be hospitalized days 1 to 7 during cycle 2 based on investigator opinion.

After dosing of ASP7517, subjects must be observed for safety for a minimum of 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.

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 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. Refer to [Section 9.2.6 DLT Evaluation Analysis Set] for definition of evaluable subjects. 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 dose of 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 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).

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.

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. Additional details regarding responsibilities, membership requirements and safety review time points are included in the DESC Charter. The DESC will also review the aggregate safety data from the phase 1 dose escalation and the phase 2 expansion cohorts.

While safety data from the DLT observation period in the escalation cohorts are the minimum safety data needed for the DESC meeting, all available safety findings will be considered by the DESC. The DESC will assess whether a longer DLT observation period is warranted based on emerging data. Additionally, only when determining the RP2D, the DESC may choose a more conservative dosing decision than the MTD selected by BOIN design, based on evaluation of the safety data and other available data.

The decision on the dose level for the next cohort will be based on the BOIN design. Also, MTD will be determined by BOIN from at least 6 subjects with the maximum of 8 subjects under the maximum of 2 cohorts. The dose for phase 2 expansion will not be higher than the MTD.

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 the DLT evaluation period.

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

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 below). Otherwise, the enrollment at that dose level will be closed.

When the total number of subjects reaches the maximum sample size of 52, it may be concluded that ASP7517 is efficacious if the number of responses is greater than or equal to 12 and 10 for

AML and MDS, respectively. The number of subjects in stage 1, stage 2 and stage 3 may be changed according to the optimized stopping boundaries.

Optimized Stopping Boundaries for AML	
Number of subjects treated	**Stop if number of responses ≤**
12	1
32	5

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

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.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

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

1. Institutional Review Board/Independent Ethics Committee-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization for US study sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing the informed consent form.
3. Subject diagnosed with R/R AML or R/R higher risk MDS is defined as:
    - R/R AML
        - Morphologically documented primary or secondary AML by the WHO criteria (2016),
          AND
        - Refractory to at least 2 cycles of induction chemotherapy/not a candidate for re-induction OR relapsed after achieving remission with a prior therapy,
          AND
        - Received all standard therapies including targeted therapies (unless the therapy is contraindicated or intolerable) which are known to provide clinical benefit in the opinion of the treating investigator,
          AND
        - Received salvage therapy OR is not a candidate for salvage therapy

- R/R Higher Risk MDS
  - Has MDS by the WHO criteria (2016),
    AND
  - Either relapsed after achieving remission or refractory to standard therapies, including ≥ 4 cycles of hypomethylating agents (unless the therapy is contraindicated or intolerable),
    AND
  - Is classified as higher risk MDS with a score of > 3.5 by Revised IPSS-R in MDS

4. Subject has an Eastern Cooperative Oncology Group performance status of ≤ 2.
5. Subject must meet the following criteria as indicated on the clinical laboratory tests during screening period:
   - Serum aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × upper limit of normal (ULN)
   - Serum total bilirubin ≤ 1.5 × ULN
   - Serum creatinine ≤ 1.5 × ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation.
   - Platelets ≥ 50,000/μL at cycle 1 day 1 (C1D1) in the dose escalation cohorts only
6. Subject has a life expectancy of ≥ 12 weeks at the time of screening in the opinion of the investigator.
7. Subjects with AML must have peripheral blood absolute blast count of < 20,000/μL at C1D1.
   Note: Blast count can be controlled by hydroxyurea during screening period.
8. Female subject is not pregnant [see Appendix 12.3 Contraception Requirements] and at least 1 of the following conditions apply:
   - Not a woman of childbearing potential (WOCBP) [see Appendix 12.3 Contraception Requirements]
   - WOCBP who agrees to follow the contraceptive guidance [see Appendix 12.3 Contraception Requirements] from the time of informed consent through at least 180 days after final study treatment administration.
9. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 180 days after the final study treatment administration.
10. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 180 days after final study treatment administration.
11. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception [see Appendix 12.3 Contraception Requirements] throughout the treatment period and for 180 days after final study treatment administration.
12. Male subject must not donate sperm during the treatment period and for 180 days after the final study treatment administration.
13. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 180 days after final study treatment administration.
14. Subject agrees not to participate in another interventional study while receiving study treatment in the present study.

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion Criteria:

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

1. Subject was diagnosed with acute promyelocytic leukemia.
2. Subject has breakpoint cluster region-Abelson-positive leukemia (BCR-ABL).
3. Subject has persistent non-hematological toxicities of ≥ grade 2 (National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 5.0), with symptoms and objective findings from prior AML or MDS treatment (including chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation or surgery).
4. Subject has received any of the following therapies:
   - Systemic immunomodulators or immunosuppressive drugs including steroids ≤ 28 days prior to C1D1 (steroids can be used if not intended for treatment of AML or MDS; steroids for AML/MDS related symptoms can be used at low doses [less than 10 mg/day dexamethasone])
   - Cytotoxic agents (except hydroxyurea given for controlling blast cells) ≤ 28 days prior to C1D1
   - Investigational products for the treatment of AML or MDS within 5 half-lives prior to screening visit
   - Hematopoietic stem cell transplant (HSCT)
   - Radiation therapy ≤ 28 days prior to C1D1
5. Subject has clinically active nervous system leukemia, per the investigator's judgment.
6. Subject has active or prior documented autoimmune or inflammatory disorders requiring systemic treatment.
7. Subject has ongoing, untreated malignancy with the exception of the following:
   - Subjects with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed.
   - Subjects with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
8. Subject with left ventricular ejection fraction of < 45% on echocardiogram or multigated acquisition scan (MUGA) performed within 28 days of screening.
9. Subject has laboratory abnormalities or clinical evidence of disseminated intravascular coagulation, or ongoing history of coagulation disorder manifested by bleeding or clotting.
10. Subject has an active uncontrolled infection.
11. Subject is known to have human immunodeficiency virus infection.
12. Subject has active hepatitis B or C or other active hepatic disorder.
13. Subject has any condition, which in the investigator's opinion, makes the subject unsuitable for study participation.
14. Subject has a known or suspected hypersensitivity to bovine-derived protein or has suspected hypersensitivity to any ingredients of ASP7517.
15. Subject is eligible for HSCT.

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Product(s):

ASP7517 injection 1×10^7 cells/mL, 2.5 mL/vial for intravenous infusion.

Dose(s):

Phase 1 (Dose Escalation)

Starting dose of ASP7517 is 1×10^6 cells/dose, with escalation doses of 1×10^7 and 1×10^8 cells/dose.

Subjects will receive 2 single doses of ASP7517 on C1D1 and cycle 2 day 1 (C2D1).

Phase 2 (Dose Expansion)

Subjects will receive 1 dose of ASP7517 on day 1 of each 28-day cycle at RP2D or MTD as established by phase 1 for up to 6 doses total during the expansion phase.

Mode(s) of Administration:

ASP7517 will be diluted with normal saline to 50 mL and administered by intravenous infusion at 4 to 6 mL/min infusion rate through a dedicated intravenous line, followed by flushing.

Dose Limiting Toxicity Criteria:

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 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 absolute neutrophil count < 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 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.

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.

Comparative Drug(s):

None

Concomitant Medication Restrictions or Requirements:

The following treatments are prohibited during the study:

- Interferon/polyethylene-interferon
- High-dose systemic corticosteroids with the exception for immune-related AEs
- Immunosuppressive agents
- Investigational agents other than ASP7517
- Any other treatments of AML or MDS (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during the study with ASP7517 with the following exceptions:
  - Hydroxyurea up to 5 g daily for up to 2 weeks to keep the absolute blast count < 20,000/μL
  - Subject undergoing HSCT will be discontinued from the study
  - Intrathecal chemotherapy used as prophylaxis

Duration of Treatment:

Treatment Period:

Phase 1 (Dose Escalation)

Subject will receive up to 2 single doses of ASP7517 via intravenous infusion on day 1 of each 28-day cycle.

Phase 2 (Dose Expansion):

Subject will receive up to 6 doses of ASP7517 via intravenous infusion on day 1 of each 28-day cycle.

Treatment Discontinuation Criteria

Subjects who meet any of the following criteria will be withdrawn from the study treatment:

- Subject declines further study participation (i.e., withdrawal of consent).
- Any clinical or unacceptable AE/SAE, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject.
- Subject is noncompliant with protocol based on the investigator or medical monitor assessment.
- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit and no DLT may be kept in the study after discussion with the medical monitor).
- Subject not achieving response (CRc or PR in AML or CR, BM CR or PR or HI in MDS) and the subject is no longer deriving clinical benefit, in the opinion of the investigator.
- Subject begins other anti-leukemic therapies or MDS therapies, including undergoing HSCT.
- Subject experiences disease relapse/progression.
- Investigator/subinvestigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death.
- Female subject becomes pregnant.
- Subject develops a grade 4 DLT during cycle 1.
- Delay of > 2 weeks of a subsequent scheduled dose of ASP7517 due to ASP7517-related toxicities.

Observation Period 1 and 2 Discontinuation Criteria

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject begins other anti-leukemic therapies or MDS therapies, including undergoing HSCT.
- Subject experiences disease relapse/progression.
- Subject is no longer deriving clinical benefit, in the opinion of the investigator.
- Female subject becomes pregnant.
- Death.

Formal Stopping Rules:

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 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 the Bayesian model 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.

Statistical Methods

Sample Size Justification:

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.

Efficacy:

For R/R AML: Response to treatment will be defined per modified Cheson criteria [Cheson et al, 2003].

For R/R higher risk MDS: Response to treatment will be defined per Cheson criteria [Cheson et al, 2006].

Response rates will be summarized using exact 90% confidence interval by dose level for phase 1 and by dose level and disease type for phase 2. Time to endpoints, including event free survival and overall survival, will be listed and summarized using Kaplan-Meier method.

Pharmacokinetics:

Summary statistics of pharmacokinetics may be tabulated. Exploratory analysis between pharmacokinetic parameter and clinical measures (e.g., efficacy or safety) may be performed.

Pharmacodynamics:

Descriptive statistics will be provided for pharmacodynamics parameters whenever applicable. Exploratory analysis of the relationship between pharmacodynamic measurements and pharmacokinetics, efficacy and safety profile in subjects may be performed.

Safety:

Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment received (safety analysis set).

Safety analyses will consist of data summaries of AEs, DLTs and other safety parameters. The number and percentage of subjects experiencing 1 or more AE(s) will be summarized by cohort and dose level. The relationship to IP and severity of AE will also be summarized. All summaries of AEs will include only treatment-emergent events unless otherwise stated. AEs will be coded to system organ class and preferred term using MedDRA terminology and will be graded by the investigator using the NCI-CTCAE severity grade (version 5.0).

Laboratory parameters will be summarized by cohort and dose level using descriptive statistics for shifts in change from baseline and will be presented in listings of clinically significant abnormalities. Vital signs and electrocardiogram parameters and their changes from baseline will be summarized by cohort and dose level using descriptive statistics.

Interim Analysis:

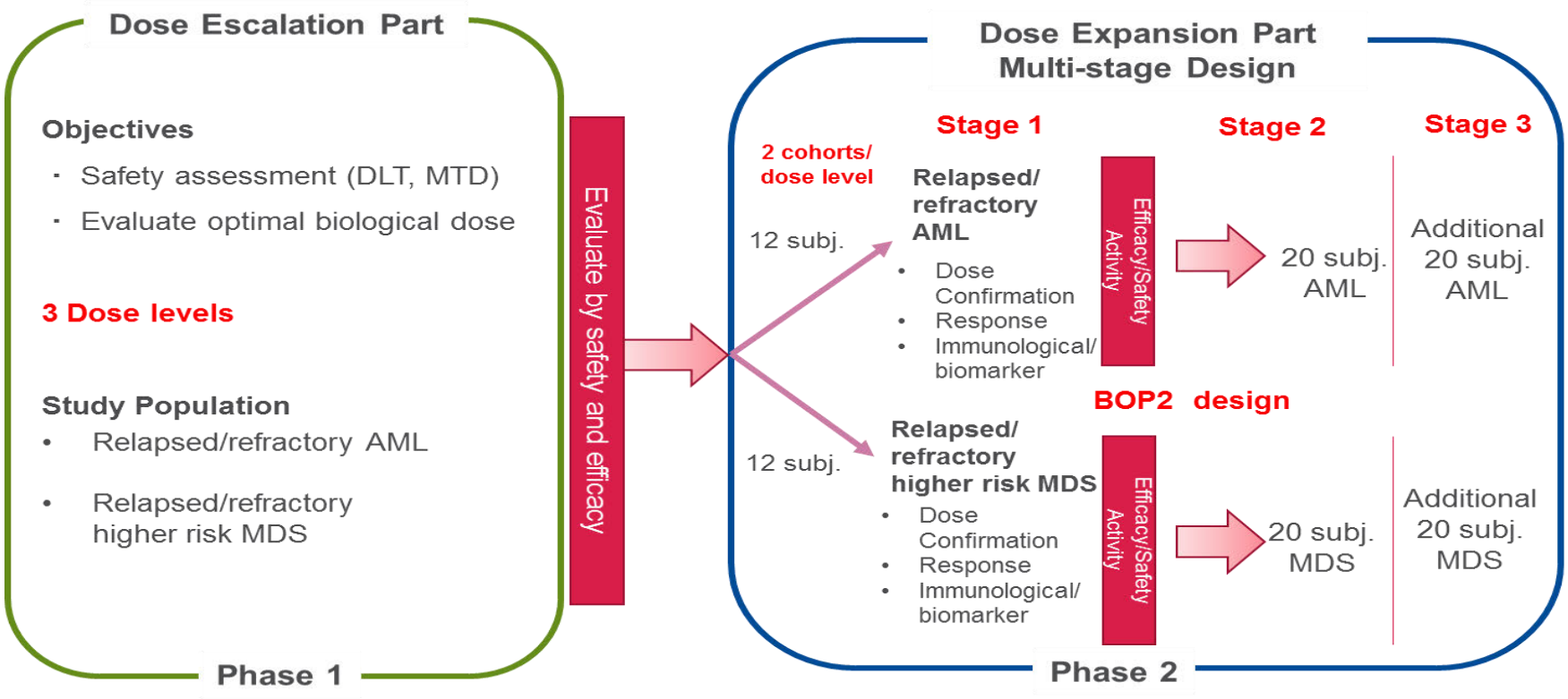
No interim analysis is planned.

Safety, pharmacokinetic and other clinical data will be reviewed on an ongoing basis to determine if the study will proceed 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.

1.2 Study Schema

Figure 1 Study Schema



Doses: 1×10^6, 1×10^7, 1×10^8 cells/dose

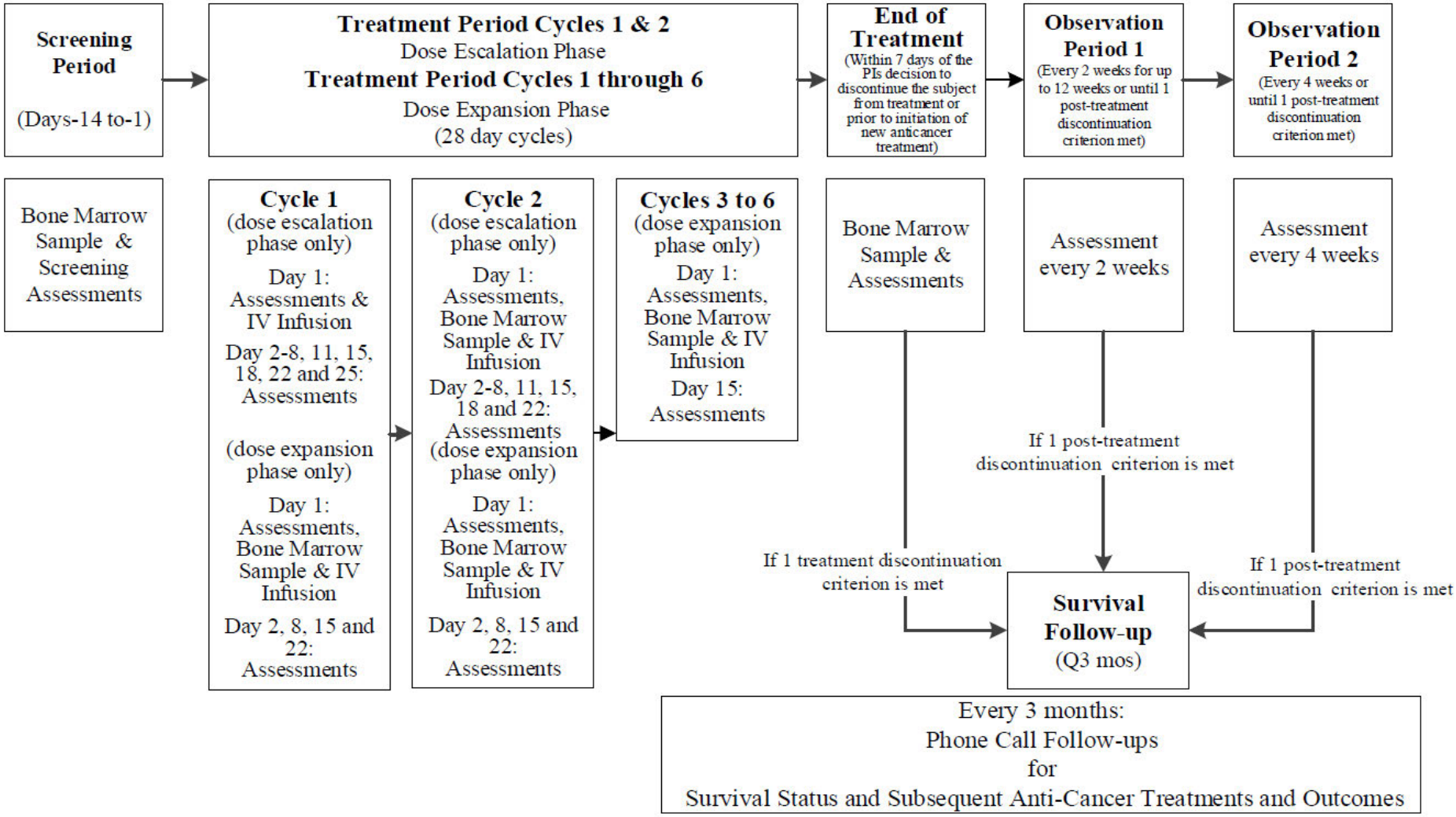
Dosing frequency:

Phase 1 (Dose Escalation): Subjects will receive 2 single doses of ASP7517 on day 1 of each 28 -day cycle.

Phase 2 (Dose Expansion): Subjects will receive 1 dose of ASP7517 on day 1 of each 28-day cycle at RP2D or MTD as established by phase 1 for up to 6 doses total during the expansion phase.

AML: acute myeloid leukemia; BOP2: Bayesian optimal phase 2; DLT: dose limiting toxicity; MDS: myelodysplastic syndrome; MTD: maximum tolerated dose; subj.: subjects.

Figure 2 Flow Chart



IV: intravenous; mos: months; PI: principal investigator; Q3: every 3.

1.3 Schedules of Assessments

Table 1 Schedule of Assessments – Phase 1 (Dose Escalation)

Assessments	Screening Period	Treatment Period																				End of Treatment[p]	Post-Treatment Period		Survival Follow-up Period[t]
		Cycle 1											Cycle 2										Obs Period 1	Obs Period 2	
Visit Days	-14 to -1	Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22	Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
		1	2	3	4	5	6	7																	
Window(days)			0	0	0	0	0	0	± 1	± 1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
Signed ICF	X																									
Medical and Disease History	X																									
Disease Assessment	X												X										X			
Physical Examination[c]	X	X[a]	X	X	X	X	X	X	X	X	X	X	X[a]	X	X	X	X	X	X	X	X	X	X[q]			
Vital Signs	X	X[b]	X		X				X	X	X	X	X[b]	X		X				X	X	X	X[q]			
ECOG Performance	X	X[a]	X		X				X	X	X	X	X[a]	X		X				X	X	X	X[q]			
Prior and Concomitant Medications	X[d]	X	X		X				X	X	X	X	X	X		X				X	X	X	X	Reference Table 3: Schedule of Post-Treatment Period Assessments		
Pregnancy Test for WOCBP	X[e]	X[a]											X[a]										X			
12-Lead ECG[f]	X[g]	X[b]											X[b]										X			
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[h]	X[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X[a]	X	X	X	X	X	X	X	X	X	X[q]			
Coagulation Profile (PT/INR, D-dimer, fibrinogen)[h]	X[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X[a]	X	X	X	X	X	X	X	X	X	X[q]			

Table continued on next page

Assessments	Screen-ing Period	Treatment Period																				End of Treatment[p]	Post-Treatment Period		Survival Follow-up Period[t]
		Cycle 1											Cycle 2										Obs Period 1	Obs Period 2	
Visit Days	-14 to -1	Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontin-uation criterion is met	Every 4 weeks or until 1 post-treatment discontin-uation criterion is met	Every 3 months
		1	2	3	4	5	6	7																	
Window(days)			0	0	0	0	0	0	± 1	± 1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
Chest X-ray (or CT of chest)	X[i]																									
MUGA or ECHO	X[j]																									
Bone Marrow Aspiration and/or Biopsy[k]	X[k]												X[a,k]										X[k]			
Blood Sample for Disease Assessment[l]	X												X										X			
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pharmacokinetic: Blood Sample for Cell Kinetics		See Table 5 for detailed sample time points																								
PGx		X[m]																								
Blood Sample for WT1 Expression		X[a]											X[a]										X[q]			
Blood Sample for Mutational Profiling		X[a]																					X[q]			
Blood Sample for Immune Response Biomarker (ELISpot)		X[a]							X		X		X[a]							X	X		X[q]			
Buccal Swab for HLA Typing		X[a]																								

Table continued on next page

Assessments	Screening Period	Treatment Period																				End of Treatment[p]	Post-Treatment Period		Survival Follow-up Period[t]
		Cycle 1											Cycle 2										Obs Period 1	Obs Period 2	
Visit Days	-14 to -1	Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
		1	2	3	4	5	6	7																	
Window(days)			0	0	0	0	0	0	± 1	± 1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
Blood Sample for Immune Response Biomarker (Tetramer)		X[a]									X		X[a]								X		X[q]	Reference Table 3: Schedule of Post-Treatment Period Assessments		
Blood Sample for Immune Cell Phenotyping		X[a]							X		X		X[a]							X	X		X[q]			
Blood Sample for Cytokines		X[a]	X		X				X		X		X[a]	X		X				X	X		X[q]			
Blood Sample for Anti-HLA Antibody		X[a]																			X		X			
IRT Transaction Required	X	X[n]											X										X			
ASP7517 Dosing at the Clinic		X[o]											X[o]													
Survival Follow-up[r]																										X

AE: adverse event; CT: computed tomography; C: cycle; D: day; C1D1: cycle 1 day 1; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EoT: end-of-treatment; HLA: human leukocyte antigen; ICF: informed consent form; INR: international normalization ratio; IRT: interactive response technology; MUGA: multigated acquisition scan; Obs: observation; PGx: pharmacogenomics; PT: prothrombin time; SAE: serious adverse event; WOCBP: women of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Obtained predose.

b. Obtained predose and postdose (including flushing) (vital signs: hourly [± 10 minute window] for up to 4 hours postdose; ECG: 1 to 2 hours postdose) on C1D1 and C2D1.

c. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

Footnotes continued on next page

d. Includes medications taken within 28 days prior to C1D1.
e. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.
f. The 12-lead ECGs will be recorded in triplicate (at least 2 minutes apart per time point) and transmitted electronically for central reading.
g. Laboratory samples will be analyzed by the institution's local laboratory. However, sample results must also be submitted for centralized data entry. Laboratory tests and/or ECG can be repeated during screening period.
h. Laboratory samples will be analyzed by the institution's local laboratory and results will be submitted for centralized data entry.
i. Chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of screening.
j. MUGA scans or ECHO (per standard of care) performed at screening or within 28 days prior to screening will be accepted.
k. Screening samples may be collected up to 28 days prior to C1D1. End of treatment bone marrow sample does not need to be repeated if collected within 2 weeks of the last disease assessment. Samples must be submitted to a central laboratory for analysis. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.
l. Samples must be submitted to a central laboratory for analysis.
m. Whole blood and buccal swab for optional PGx study may be collected at C1D1 prior to first investigational product administration.
n. Subject enrollment in the study will be conducted via IRT transaction.
o. 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.
p. The EoT visit will occur within 7 days of the principal investigator decision to discontinue the subject for treatment or prior to the initiation of new anticancer treatment, 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.
q. Assessment does not need to be repeated if collected at a regularly scheduled visit within 3 days of EoT visit.
r. Telephone contact for survival status and subsequent anti-cancer treatments and outcomes.

Table 2 Schedule of Assessments – Phase 2 (Dose Expansion)

Assessments	Screening Period	Treatment Period														End of Treatment[o]	Post-Treatment Period		Survival Follow-up Period
	Screening	Cycle 1					Cycle 2					Cycles 3 - 4[r]		Cycles 5 - 6[s]			Observation Period 1	Observation Period 2	Survival Follow-up
Visit Days	Days -14 to -1	D1	D2	D8	D15	D22	D1	D2	D8	D15	D22	D1	D15	D1	D15		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+ 7			± 3
Signed ICF	X																Reference Table 3: Schedule of Post-Treatment Period Assessments		
Medical and Disease History	X																		
Disease Assessment[t]	X						X					X		X		X			
Physical Examination[c]	X	X[a]	X	X	X	X	X[a]	X	X	X	X	X[a]	X	X[a]	X	X[p]			
Vital Signs	X	X[b]	X	X	X	X	X[b]	X	X	X	X	X[b]	X	X[b]	X	X[p]			
ECOG Performance	X	X[a]	X	X	X	X	X[a]	X	X	X	X	X[a]	X	X[a]	X	X[p]			
Prior and Concomitant Medications	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pregnancy Test for WOCBP	X[e]	X[a]					X[a]					X[a]		X[a]		X			
12-Lead ECG[f]	X[g]	X[b]					X[b]					X[b]		X[b]		X			
Clinical Laboratory Tests (chemistry, hematology, urinalysis)	X[g]	X[a]	X	X	X	X	X[a]	X	X	X	X	X[a]	X	X[a]	X	X[p]			
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	X[g]	X[a]	X	X	X	X	X[a]	X	X	X	X	X[a]	X	X[a]	X	X[p]			

Table continued on next page

Assessments	Screening Period	Treatment Period														End of Treatment[o]	Post-Treatment Period		Survival Follow-up Period
	Screening	Cycle 1					Cycle 2					Cycles 3 - 4[r]		Cycles 5 - 6[s]			Observation Period 1	Observation Period 2	Survival Follow-up
Visit Days	Days -14 to -1	D1	D2	D8	D15	D22	D1	D2	D8	D15	D22	D1	D15	D1	D15		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+ 7			± 3
Chest X-ray (or CT of chest)	X[h]																Reference Table 3: Schedule of Post-Treatment Period Assessments		
MUGA or ECHO	X[i]																		
Bone Marrow Aspiration and/or Biopsy[j]	X[j]						X[a,j]					X[a,j]		X[a,j]		X[j]			
Blood Sample for Disease Assessment[k]	X						X					X		X		X			
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pharmacokinetic: Blood Sample for Cell Kinetics		See Table 5 for detailed sample time points																	
PGx		X[l]															Reference Table 3: Schedule of Post-Treatment Period Assessments		
Blood Sample for WT1 Expression		X[a]					X[a]					X[a]		X[a]		X[p]			
Blood Sample for Mutational Profiling		X[a]														X[p]			
Blood Sample for Immune Response Biomarker (ELISpot)		X[a]		X	X		X[a]		X	X		X[a]	X	X[a]	X	X[p]			
Buccal Swab for HLA Typing		X[a]																	

Table continued on next page

Assessments	Screening Period	Treatment Period														End of Treatment[o]	Post-Treatment Period		Survival Follow-up Period
	Screening	Cycle 1					Cycle 2					Cycles 3 - 4[r]		Cycles 5 - 6[s]			Observation Period 1	Observation Period 2	Survival Follow-up
Visit Days	Days -14 to -1	D1	D2	D8	D15	D22	D1	D2	D8	D15	D22	D1	D15	D1	D15		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+ 7			± 3
Blood Sample for Immune Response Biomarker (Tetramer)		X[a]			X		X[a]			X		X[a]	X	X[a]	X	X[p]	Reference Table 3: Schedule of Post-Treatment Period Assessments		
Blood Sample for Immune Cell Phenotyping		X[a]		X	X		X[a]		X	X		X[a]	X	X[a]	X	X[p]			
Blood Sample for Cytokines		X[a]	X	X	X		X[a]	X	X	X		X[a]	X	X[a]	X	X[p]			
Blood Sample for Anti-HLA Antibody		X[a]					X[a]					X[a]		X[a]		X			
IRT Transaction Required	X	X[m]					X					X		X		X			
ASP7517 Dosing at the Clinic		X[n]					X[n]					X[n]		X[n]					
Survival Follow-up[q]																			X

AE: adverse event; CT: computed tomography; C: cycle; C1D1: cycle 1 day 1; CR: complete remission; D: day; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EoT: end-of-treatment; HLA: human leukocyte antigen; ICF: informed consent form; INR: international normalization ratio; IP: investigational product; IRT: interactive response technology; MUGA: multigated acquisition scan; PGx: pharmacogenomics; PT: prothrombin time; SAE: serious adverse event; WOCBP: women of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Obtained predose.

b. Obtained predose and postdose (vital signs: hourly [± 10 minute window] for up to 4 hours postdose; ECG: 1 to 2 hours postdose) on day 1 of each cycle.

c. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

d. Includes medications taken within 28 days prior to C1D1.

Footnotes continued on next page

e. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study treatment.

f. The 12-lead ECGs will be recorded in triplicate (at least 2 minutes apart per time point) and transmitted electronically for central reading.

g. Laboratory samples will be analyzed by the institution's local laboratory. However, sample results must also be submitted for centralized data entry. Laboratory tests and/or ECG can be repeated during screening period. Laboratory samples will be analyzed by the institution's local laboratory and results will be submitted for centralized data entry.

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

i. MUGA scans or ECHO (per standard of care) performed at screening or within 28 days prior to screening will be accepted.

j. Screening samples may be collected up to 28 days prior to C1D1. End of treatment bone marrow sample does not need to be repeated if collected within 2 weeks of the last disease assessment. Samples must be submitted to a central laboratory for analysis. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.

k. Samples must be submitted to a central laboratory for analysis. If a participant achieves CR at any point during the treatment period and ASP7517 is not continued, an EoT visit should be performed and the participant should proceed to observation period 1.

l. Whole blood and buccal swab for optional PGx study may be collected at C1D1 prior to first investigational product administration.

m. Subject enrollment in the study will be conducted via IRT transaction.

n. After dosing of ASP7517, subjects must be observed for safety for a minimum 4 hours. The safety observation will consist of 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.

o. The EoT visit will occur within 7 days of the principal investigator decision to discontinue the subject for treatment or prior to the initiation of a new anticancer treatment, 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.

p. Assessment does not need to be repeated if collected at a regularly scheduled visit within 3 days of EoT visit.

q. Telephone contact for survival status and subsequent anti-cancer treatments and outcomes.

r. After the first 2 cycles of treatment, subjects who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as achieve CRc or PR for AML and CR, BM CR or PR or HI for MDS or other clinical benefits, as determined by the investigator) will continue further treatment of ASP7517 as decided by the investigator.

s. After the first 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. If a participant experiences CR during cycle 5 or 6 (except if confirmed on day 1 of these cycles), the participant can complete the cycle and EoT will be performed as defined in footnote "o".

t. Extramedullary disease assessment is required at screening, day 1 of every cycle starting with cycle 2, EoT, and observation visits.

Table 3 Schedule of Post-Treatment Period Assessments for Dose Escalation and Dose Expansion

Assessments	Post-Treatment Period							
	Observation Period 1						Observation Period 2	
	12 weeks or until 1 post-treatment discontinuation criterion is met						Until 1 post-treatment discontinuation criterion is met	
Visit Week	**2**	**4**	**6**	**8**	**10**	**12**	**Monthly Safety Assessment Visit**	**Assessment Visit Every 3 months**
Window (days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Physical Examination[a]	X	X	X	X	X	X	X	X
Disease Assessment	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
ECOG Performance	X	X	X	X	X	X	X	X
Concomitant Medications[i]	X	X	X	X	X	X	X	X
12-Lead ECG[b]	X	X	X	X	X	X	X	X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[g]	X	X	X	X	X	X	X	X
Pregnancy Test for WOCBP	X	X	X	X	X	X	X	X
Bone Marrow Aspiration and/or Biopsy[c]						X[h]		X
Blood Sample for Disease Assessment[d]		X		X				X
AE/SAE Assessment[i]	X	X	X	X	X	X	X	X
Pharmacokinetic: Blood Sample for Cell Kinetics	See Table 5 for detailed sample time points							
Blood Sample for WT1 Expression		X		X		X[j]		X[f]
Blood Sample for Immune Response Biomarker (ELISpot)		X		X		X[j]		X[e]
Blood Sample for Immune Response Biomarker (Tetramer)		X		X		X[j]		X[f]
Blood Sample for Immune Cell Phenotyping		X		X		X[j]		X[e]
Blood Sample for Cytokines		X		X		X[j]		X[e]
Blood Sample for Anti-HLA Antibody						X[j]		X[f]

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; HLA: human leukocyte antigen; IP: investigational product; SAE: serious adverse event; WOCBP: women of childbearing potential; WT1: Wilms' tumor 1 protein.

Footnotes continued on next page

a. Height measurement performed only at screening.
b. The 12-lead ECGs will be recorded as a single assessment (in triplicate if deemed necessary, at least 2 minutes apart per time point) and read locally.
c. After the completion of Observation Period 1 (12 weeks), subjects remaining in the study will have bone marrow samples collected in Observation Period 2 every 3 months or if there is suspicion of relapse in the whole blood. Samples must be submitted to a central laboratory for analysis. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.
d. Samples must be submitted to a central laboratory for analysis.
e. Maximum of 1 sample collected during Observation Period 2.
f. Maximum of 5 samples collected during Observation Period 2.
g. Laboratory samples will be analyzed by the institution's local laboratory and results will be submitted for centralized data entry. Subjects who are transfusion dependent should be subjected to more frequent laboratory assessments to determine transfusion need based on the judgment of the investigator.
h. Subjects not proceeding to observation period 2 are required to provide a bone marrow sample at the last visit of observation period 1.
i. Concomitant medications and AEs are collected until post-treatment period and at least 30 days after last IP dose and prior to the start of new anticancer treatment. In addition, the following will be collected regardless of the start of new anticancer therapy: Any IP-related SAE that is ongoing will be followed until resolved, and any SAE that is deemed to be related to IP by the investigator.
j. Applicable only for subjects in dose expansion phase.

Table 4 Schedule of Replication Competent Lentivirus for Dose Escalation and Dose Expansion

Assessment	C1D1	3 Months After Treatment Initiation or End of Treatment, Whichever is First	6 Months After Treatment Initiation	12 Months After Treatment Initiation	18 Months After Treatment Initiation[c]
Window	0	± 1 day	± 1 month	± 1 month	**± 1 month**
Blood Sample for RCL[a]	X[b]	X	X	X	**X**

C1D1: cycle 1 day 1; RCL: replication competent lentivirus

a. If there are positive results, additional follow-up assessments may be required. Refer to Section 7.6.4 Sample for Replication Competent Lentivirus.

b. Obtained predose.

c. Only applicable to subjects in the expansion cohort.

Table 5 Pharmacokinetics Sample Collection Schedule-Dose Escalation Cohort and Dose Expansion Cohort

Cycle	Day	Time Point	Window	Dose Escalation	Dose Expansion
Cycle 1	1	Predose	- 60 min[a]	X	X
		End of ASP7517 Infusion	+ 10 min[b]	X	X
		30 minutes post ASP7517 Infusion	± 10 min		X
		1 hour post ASP7517 Infusion	± 10 min	X	X
		2 hours post ASP7517 Infusion	± 15 min		X
		5 hours post ASP7517 Infusion	± 15 min	X	X
	2	24 hours post ASP7517 Infusion	± 60 min	X	
	4	NA	-	X	
	8	NA	-	X	
	15	NA	-	X	
Cycle 2	1	Predose	- 60 min[a]	X	X
		End of ASP7517 Infusion	+ 10 min[b]	X	X
		30 minutes post ASP7517 Infusion	± 10 min		X
		1 hour post ASP7517 Infusion	± 10 min	X	X
		2 hours post ASP7517 Infusion	± 15 min		X
		5 hours post ASP7517 Infusion	± 15 min	X	X
	2	24 hours post ASP7517 Infusion	± 60 min	X	
	4	NA	-	X	
	8	NA	-	X	
	15	NA	-	X	
Cycle 4	1	Predose	- 60 min[a]		X
		End of ASP7517 Infusion	+ 10 min[b]		X
Cycle 6	1	Predose	- 60 min[a]		X
		End of ASP7517 Infusion	+ 10 min[b]		X
EoT	EoT	NA	± 1 day	X	X
Observation Period 1	4 weeks	NA	± 3 days	X	X

C: cycle; D: day; EoT: end of treatment; NA: not applicable.

a. Within 60 min prior to ASP7517 infusion.

b. Within 10 min after the end of ASP7517 infusion (including flushing).

2 INTRODUCTION

2.1 Background

Acute Myeloid Leukemia (AML) is the most common type of leukemia in adults. AML accounts for approximately 32% of acute leukemia diagnosed in adults [American Cancer Society, 2014]. The median age at diagnosis is 67 years of age, with 54% of patients diagnosed at 65 years or older [O'Donnell et al, 2012]. In Japan, it was estimated that 5600 patients were diagnosed with AML in 2017 [Kantar Health, 2017]. It is estimated that 19940 people will be diagnosed with AML, and 11180 will die from the disease in 2020 in the US [American Cancer Society, 2020]. While 60% to 80% of younger patients achieve a complete remission (CR) with standard therapy, only about 20% to 30% of the overall patient population has long-term disease-free survival. Outcomes are worse for patients aged 60 years or over, with CR rates in the range of 40% to 55% and poor long-term survival rates. Along with age, remission rates and overall survival (OS) depend on a number of other factors, including cytogenetics, previous bone marrow disorders (such as myelodysplastic syndromes [MDS]) and co-morbidities [Rowe & Tallman, 2010; Rowe et al, 2010; Breems et al, 2005; Karanes et al, 1999]. Although FDA approved targeted therapies for AML (both newly diagnosed and relapsed/refractory [R/R] patients) have become available, currently there is no effective cure for the disease.

Approximately 30% of adult AML patients are refractory to induction therapy. Furthermore, of those who achieve CR, approximately 75% will relapse. Several chemotherapy regimens have been used for patients with resistant or relapsed disease; however, the chemotherapy combinations are universally dose-intensive, with high risk of unacceptable toxicity in older patients. While these regimens may generate second remission rates of up to 50% in patients with a first remission of more than 1 year, toxicity is prohibitively high in most patients over 50 to 60 years [Rowe & Tallman, 2010; Rowe et al, 2010; Breems et al, 2005; Karanes et al, 1999]. Additionally, if the patient (including younger patients) relapses within 6 months of their initial CR, the chance of attaining a second remission is less than 20% with chemotherapy alone. Furthermore, survival after first relapse is approximately 10%, demonstrating the lack of an effective cure for patients in relapsed AML [Rowe & Tallman, 2010]. Patients who are in second relapse or refractory to first salvage have an extremely poor prognosis, with survival measured in weeks [Giles et al, 2005].

MDSs are a heterogeneous group of clonal stem cell disorders with an inherent tendency for leukemic transformation. In Japan, it was estimated that 8500 patients were diagnosed with MDS in 2017 [Kantar Health, 2018]. In the US, the incidence of MDS has been estimated between 5.3 and 13.1 cases per 100,000 population per year, rising with age to an estimated 75 to 162 cases per 100,000 population per year among patients ≥ 65 years of age [Cogle, 2015]. MDS is clinically characterized by peripheral blood cytopenias; as a result, the clinical course of MDS patients is often fraught with complications related to peripheral blood cytopenias along with an inherent risk for leukemic transformation, which is encountered in 30% of de novo MDS patients [Dotson & Lebowicz, 2018]. The outcome of MDS patients is extremely variable with median survival ranging from over 5 years to less than 9 months.

Therefore, over the years, several prognostic scoring systems have been developed to enable accurate risk-stratification of these patients [Greenberg et al, 2012; Greenberg et al, 1997; Malcovati et al, 2007; Kantarjian et al, 2008]. In addition, recent discovery of genes is being used to refine the current diagnostic and prognostic approach [Bejar et al, 2011; Bejar et al, 2012] and additionally serve as novel therapeutic targets for ongoing clinical trials in MDS. Currently approved drugs for the treatment of MDS are not curative and no standard of care is available for patients after failure to respond to hypomethylating agents [Uy et al, 2017]. Allogeneic stem cell transplant is the only curative therapy, but the morbidity and mortality associated with the latter precludes it from being a feasible option in the vast majority of MDS patients with a median age at diagnosis of 70 to 75 years [Sekeres & Culter, 2014].

The majority of patients with MDS and AML are not cured with available therapies, underscoring the urgent need for new therapeutic alternatives that will improve the clinical outcomes of these patients.

The Wilms' Tumor 1 (WT1) gene is located on the short arm of chromosome 11. WT1 suppresses transcription of hemopoietic related proteins including macrophage colony-stimulating factor, transforming growth factor-beta, and retinoic acid receptor-alpha [Rosenfeld et al, 2003]. This gene, originally defined as a tumor suppressor gene, is also a gene transcription factor overexpressed in leukemic cells, where it induces inhibition of apoptosis and differentiation [Polák et al, 2012]. The gene is essential in mesenchymal tissue maintenance through the Wnt4 pathway [Chau & Hastie, 2012] and it is expressed in a small percentage of bone marrow CD34+ cells [Fraizer et al, 1995]. It is upregulated in early myeloid progenitors and is down regulated at later stages of differentiation. Studies in mice have shown that WT1 overexpression is required for leukemogenesis [Hosen et al, 2007; Hohenstein & Hastie, 2006]. Most patients with AML (86% to 91%) [NCCN Guidelines, 2018] and MDS show overexpressed WT1 [Rautenberg et al, 2018; Miyagi et al, 1993; Miwa et al, 1992].

2.1.1 Nonclinical and Clinical Data

2.1.1.1 Pharmacology

ASP7517 is an artificial adjuvant vector cell (aAVC) vaccine that induces both natural killer (NK) cell dependent antitumor effects (innate immunity) and WT1-specific T cell dependent antitumor effects (adaptive immunity). In a B16-F10 mouse metastatic melanoma model, a single intravenous dose of the murine ASP7517-surrogate suppressed an increase of lung weights caused by lung metastasis. Under the condition of NK cell depletion in mice, the antitumor effect was canceled. These results provide a proof of mechanism that the ASP7517-surrogate exerts an antitumor effect through NK-cell derived innate immunity (Study 7517-PH-9007).

To assess adaptive immunity, a murine AML survival model was used, where mice were inoculated with murine C1498 AML cells. ASP7517-surrogate significantly prolonged survival time in mice inoculated with WT1 expressing C1498 cells, when compared with mice inoculated with C1498 cells not expressing WT1 (Study 7517-PH-9003).

In this same AML model, mice administered ASP7517-surrogate (5×10^2, 5×10^3 or 5×10^4 cells/mouse) showed a dose-related response to this therapeutic (Study 7517-PH-9012).

2.1.1.2 Nonclinical Pharmacokinetics

A biodistribution study for ASP7517 was performed by determining tissue distribution of the human genomic Alu sequence. After a single intravenous administration of ASP7517 to C57BL/6J mice at 1×10^8 cells/kg, ASP7517-derived human DNA in tissues was detected in the blood and in all tissues examined 1 hour after administration, and the levels of the ASP7517 DNA in the blood and lung were higher than in other tissues. ASP7517 DNA decreased rapidly and was below the limit of quantification in almost all tissues at 24 hours after administration. ASP7517 DNA was not detected in urine or feces. No remarkable sex differences were observed (Study 7517-ME-0001).

2.1.1.3 Nonclinical Toxicology

General toxicity of ASP7517 was evaluated in 2 Good Laboratory Practice toxicity studies in C57BL/6J mice (Studies 7517-TX-0002 and 7517-TX-0005).

The target organs of toxicity identified included the liver, spleen, kidney, pancreas, urinary bladder and epididymis. In addition, emboli were observed in the liver and spleen, and decreases in platelet counts were transiently noted on day 1 after the first or second dose. All of the observed toxicities listed above were reversible. No observed adverse effect level (NOAEL) was not determined.

These preclinical studies have identified the liver as the dose limiting target organ of toxicity for ASP7517. Liver-related findings included increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), increased liver weight, white foci, emboli, mixed inflammatory cell infiltration and focal necrosis of hepatocytes at doses $\geq 1 \times 10^5$ cells/kg at 1 day after a single dose of ASP7517. These findings completely resolved by 28 days postdose. Administration of a second dose of ASP7517, 4 weeks after the first dose, resulted in liver findings similar to those seen after the first dose. Dose-related decreases in platelet counts were observed 1 day after administering ASP7517 at doses $\geq 1 \times 10^5$ cells/kg. Platelet counts showed signs of recovery by 7 days and fully recovered by day 28.

2.1.1.4 Clinical Studies

Aside from the ongoing trial, no clinical studies of ASP7517 have been conducted.

2.1.2 Summary of Key Safety Information for Investigational Product

2.1.2.1 Potential Risk

No studies with ASP7517 in humans have been conducted yet. The potential risks described below are based on ASP7517 nonclinical studies and clinical data from compounds with similar mechanism of action or composition. The management of toxicities should be based on institutional standard of care, published guidelines, as well as on investigator judgment, the protocol instructions regarding risk monitoring, and interruption or discontinuation of investigational product (IP) treatment.

Table 6 Potential Safety Concern of ASP7517

Key Safety Targets	Key Observations	Relevance to Human Usage
Liver	Increased liver weight, increased AST and ALT, emboli, hepatocyte focal necrosis, mixed inflammatory cell infiltration, microgranuloma, granulomatous inflammation (at $\geq 1 \times 10^5$ cells/kg); mononuclear cell aggregation, pigment laden macrophage infiltration (at $\geq 1 \times 10^7$ cells/kg)	Possible risk
Spleen	Increased spleen weight (at $\geq 1 \times 10^5$ cells/kg); extramedullary hematopoiesis (at $\geq 1 \times 10^6$ cells/kg)	Possible risk
Circulatory system	Emboli in the spleen and liver (at $\geq 1 \times 10^5$ cells/kg)	Possible risk
Kidney	Increased creatinine, tubular basophilia, mononuclear cell infiltration (at $\geq 1 \times 10^6$ cells/kg)	Possible risk
Hematology	Decreased platelet count 1 day after dose, increased platelet count 7 days after dose (at $\geq 1 \times 10^5$ cells/kg)	Possible risk
Pancreas	Focal necrosis (at 1×10^8 cells/kg)	Low potential risk
Urinary bladder	Mononuclear cell infiltration (at 1×10^8 cells/kg)	Low potential risk
Epididymis	Interstitial fibrosis and granuloma (at 1×10^8 cells/kg)	Low potential risk
Tumorigenicity	No colony formation in soft agar test No human cells (ASP7517) detected within 2-weeks in NOG mice after a dose of 1×10^8 cells/kg	Low potential risk
Embryo-fetal development	No embryo-fetal development studies have been performed to date	Unknown

ALT: alanine aminotransferase; AST: aspartate aminotransferase; NOG: NOD.Cg-Prkdcscid Il2rgtm1Sug/Jic.

2.1.2.1.1 Liver

Preclinical studies demonstrated that the liver could be the target organ of toxicity for ASP7517, which is related to the activation of an innate immune response by presenting α-GalCer linked to CD1d on the surface of ASP7517 to natural killer T (NKT) cells. The activation of NKT cells is thought to be responsible for the hepatic injury induced with ASP7517. The hepatic findings could be monitored (increased AST and ALT 1 day after administration) and were completely reversed by 28 days after ASP7517 administration. The adverse events (AEs) in mice included increased liver weight, AST and ALT elevation, emboli, hepatocyte focal necrosis, mixed inflammatory cell infiltration, microgranuloma, granulomatous inflammation, mononuclear cell aggregation and pigment laden macrophage infiltration. Close monitoring of liver function and toxicities is required during clinical studies.

2.1.2.1.2 Hematology

A dose-related decrease in platelet count was noted 1 day after the first dose. There was also a dose related decrease in platelet count following the second dose. Platelet counts were increased above baseline 7 days after the first and second dose and recovered to normal physiological ranges by day 28. The standard assessment of hematology is recommended in clinical studies.

2.1.2.1.3 Kidney

Increased serum creatinine was seen 1 day after the first dose. This finding was completely resolved 7 days after the first dose. In addition, histological assessment showed basophilic tubules and infiltration of mononuclear cells 7 days after the second dose. These histological findings were completely resolved 28 days after the second dose. The presence of basophilic tubules is interpreted as regeneration of renal tubules. The standard monitoring of kidney function parameters (creatinine, blood urea nitrogen) is recommended in clinical studies.

2.1.2.1.4 Spleen

Spleen weights were increased 1 day after the first and second dose and showed a trend toward recovery in 28 days. In addition, histological assessments showed apoptosis in lymphoid follicle of the spleen 1 day after the first or second dose. This finding was completely resolved by 7 days after ASP7517 administration. Also, emboli were observed in the spleen 1 day after administering the first and second dose of ASP7517 and resolved completely by 7 days after dosing.

In addition, lymphoid follicular hyperplasia was noted 7 days after the first or second dose that increased in incidence and severity with dose increase, whereas it had not been observed 1 day after the first and second doses. This finding was partially or completely resolved by 28 days post dosing. Standard hematology testing is recommended in clinical studies.

2.1.2.1.5 Other

AEs reported from solid tumor, early phase clinical trials using α-GalCer based immunotherapies include: fever, headache, fatigue, dizziness, chest pain, lymphopenia, hot flash, hyperkalemia, lactate dehydrogenase increase, creatinine increase, anemia, increased cancer pain and hyperbilirubinemia. In general, these therapies were shown to be safe and no severe adverse events (SAEs) are related to the treatment [Kunii et al, 2009; Motohashi et al, 2009; Uchida et al, 2008; Ishikawa et al, 2005].

The AEs reported in early phase WT1- peptide vaccine clinical studies in AML and MDS patients were mainly grade 1 or 2 events including fatigue, headache, pruritus, muscular weakness, bone pain, pain in extremity, flushing, dry skin, transient local erythema and induration, fever, transient erythema nodosum-like lesions and persistent cough. Also, grade 3 and 4 AEs reported as lymphocyte count decrease, neutrophil count decrease, white blood cell count decrease and platelet count decrease. Overall, the protocol treatments were well tolerated and associated only with transient local grade 1 or 2 toxicities [Maslak, 2018; Keilholz et al, 2009].

In addition, based on the above and the mechanism of action of ASP7517, immune-related adverse reactions (e.g., fever, headache, fatigue, hot flashes, diarrhea and muscular and joint pain) should be considered and managed as required per standard of care.

2.1.2.1.6 Infusion-related Reactions

In nonclinical studies with ASP7517, infusion-related reactions (IRRs)/cytokine-release syndrome (CRS) were not seen. However, there are potential toxicities with intravenous infusion immunotherapy and the exact mechanism causing standard infusion reactions is unclear, but most reactions appear to arise from cytokine release from immune-mediated mechanisms [Lee et al, 2014].

The symptoms and signs associated with a standard infusion reaction include fever, shaking chills, flushing and/or itching, changes in heart rate and blood pressure, shortness of breath or chest discomfort, pain in back or abdomen, nausea, vomiting and/or diarrhea and skin rash.

In addition to the signs and symptoms associated with a standard infusion reaction, CRS may result in neurologic signs and symptoms such as mental status changes, confusion and delirium. Renal and hepatic manifestations may include azotemia, elevated transaminases and hyperbilirubinemia, respectively. Coagulation parameters maybe also be affected and manifested by elevated D-dimer and hypofibrinogenemia, with or without bleeding. In addition, tumor lysis syndrome may also be associated with CRS [Lee et al, 2014]. Patients should be closely monitored for IRRs and CRS and appropriately managed per standard of care.

2.1.2.1.7 Allergic Reactions and Anaphylaxis

Based on the nonclinical data, no signs or symptoms of allergic reaction or anaphylaxis were seen following ASP7517 administration. The signs and symptoms of anaphylaxis overlap with those of standard infusion reactions. However, certain features are highly suggestive of anaphylaxis, such as urticaria, repetitive cough, wheeze, throat tightness and change in voice, angioedema (usually of face, eyelids or lip), hypotension, loss of consciousness, nausea, vomiting, abdominal cramping and diarrhea. Patients should be monitored closely for any signs or symptoms of allergic reaction or anaphylaxis and managed appropriately per standard of care.

2.1.2.1.8 Potential for Anti-HLA Antibodies

Anti-human leukocyte antigen (HLA) antibodies are formed following exposure to foreign HLA antigens, which may occur following the exposure to ASP7517. The presence of anti-HLA antibodies can result in engraftment failure in hematopoietic stem cell transplantation (HSCT). Patients will be monitored for the presence of Anti-HLA antibodies in clinical trials.

2.2 Study Rationale

Correlations between WT1 expression level and AML and MDS disease condition/ progression have been reported [Miyawaki et al, 2005; Tamaki et al, 1999]. In patients with MDS, expression of WT1 is associated with higher blast counts and an increased risk of progression to AML [Tamaki et al, 1999]. ASP7517 has effects against WT1 expressing

tumors by inducing both NK cell activity (innate immunity) and WT1-specific T cell dependent antitumor effects (adaptive immunity). Nonclinical studies were performed to demonstrate that both the innate and adaptive immune systems were activated by aAVC. In addition, nonclinical data suggest that ASP7517 is active in AML as described in [Section 2.1.1 Nonclinical and Clinical Data] and the Investigator's Brochure; therefore, ASP7517 is targeting WT1 for the treatment of AML/MDS and may result in clinical benefit.

2.3 Risk Benefit Assessment

Among AML patients, approximately 30% are refractory to induction therapy and of those who achieve CR, approximately 75% will relapse. Generally, there is no established standard of care for these patients and less than 20% will achieve CR with subsequent treatment. The response duration for patients who achieve CR with subsequent treatment is limited and most patients relapse. Patients who are in second relapse or refractory to first salvage have an extremely poor prognosis, with survival measured in weeks.

For MDS, the currently available treatments are not curative and no standard of care is available for patients after failure to respond to hypomethylating agents [Uy et al, 2017]. Patients with higher-risk disease have an expected median overall survival of less than 2 years. Patients who experience standard treatment failure have median survival of less than 6 months and limited treatment options with consideration given to clinical trials [Sekeres & Culter, 2014].

ASP7517 has effects against WT1 expressing tumors and showed no significant safety findings in the pre-clinical pharmacology studies. In the repeated dose toxicity studies with mice, all major findings were reversible and monitorable and will not interfere with human clinical studies recruiting AML and MDS patients, considering its potential benefit against the risk.

3 STUDY OBJECTIVE(S) AND ENDPOINT(S)

The study objectives and endpoints for this study are provided in Table 7.

Table 7 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
• To evaluate the safety and tolerability of ASP7517 • To determine the RP2D and/or the MTD of ASP7517 (phase 1) • To evaluate the clinical response of ASP7517	• Safety and tolerability as noted by: DLTs, AEs, SAEs, laboratory test results (serum, chemistry, hematology, coagulation, and urinalysis, pregnancy test) ECGs, vital signs, physical exams and ECOG performance status scores • CRc rate for subjects with R/R AML and (CR + BM CR + PR) rate for R/R higher risk MDS (phase 2)
Secondary	
• To evaluate other measures of anticancer activity of ASP7517	• Duration of remission • EFS • OS • CR, best response (CRc + PR) and CRh rates for subjects with R/R AML • CR, HI and objective response (CR + BM CR + PR + HI) rates for subjects with R/R higher risk MDS
Exploratory	
• To evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome	• Exploratory biomarkers that may correlate with treatment outcome of ASP7517
• To evaluate pharmacodynamic activities of ASP7517	• Pharmacodynamic effects of ASP7517, such as changes in: o Cytokine expression and secretion (e.g., IFNg) o WT1-specific T lymphocytes (e.g., cytotoxic T lymphocytes) o Immune cell populations (NKT cells, NK cells, etc.)
• To evaluate pharmacokinetics of ASP7517, which is determined by the kinetics of the cells	• Cellular DNA load and kinetic parameter estimates for ASP7517

AE: adverse event; AML: acute myeloid leukemia; BM: bone marrow; CR: complete remission; CRc: composite complete remission; CRh: complete remission with partial hematologic recovery; DLT: dose limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; IFNg: interferon gamma; HI: hematologic improvement; MDS: myelodysplastic syndrome; MTD: maximum tolerated dose; NK: natural killer; NKT: natural killer T; OS: overall survival; PR: partial remission; R/R: relapsed/refractory; RP2D: recommended phase 2 dose; SAE: serious adverse event; WT1: Wilms' tumor 1 protein.

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Study Design

This study is a phase 1/2, open-label study of ASP7517 (human embryonic kidney cell transfected with encoding target antigen WT1) 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 AML or 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.

4.1.1 Study 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)
- 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 of ASP7517 per cycle for a total of 2 doses.

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.

4.1.2 Phase 1 Dose Escalation

The dose escalation portion will assess safety and tolerability of ASP7517. In the dose escalation phase, 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 in the opinion of the investigator to evaluate the subject's general condition and AE resolution. The subject should 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. Subjects may be hospitalized days 1 to 7 during cycle 2 based on investigator opinion.

After dosing of ASP7517, subjects must be observed for safety for a minimum of 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 the DLT evaluation period.

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

4.1.3 Dose Limiting Toxicity Criteria

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 IP. Confirmation of DLTs will be made by the Dose Escalation and Safety Committee (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 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 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 doses 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:

Action	**Number of Subjects Treated at Current Dose Level**					
	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.

4.1.4 Dose Escalation and Safety Committee

A 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 [Section 10.4.1 Dose Escalation and Safety Committee] and 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 in [Section 10.4 Dose Escalation and Safety Committee] and further detailed in the DESC Charter.

4.1.5 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 the 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 below). Otherwise, the enrollment at that dose level will be closed.

When the total number of subjects reaches the maximum sample size of 52, it may be concluded that ASP7517 is efficacious if the number of responses is greater than or equal to 12 and 10 for AML and MDS, respectively. The number of subjects in stage 1, stage 2 and stage 3 may be changed according to the optimized stopping boundaries.

Optimized Stopping Boundaries for AML	
Number of subjects treated	**Stop if number of responses ≤**
12	1
32	5

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

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 monitored using a 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.

4.1.6 Dose Rationale

The starting dose for the first in human (FiH) study is anticipated to be safe with minimal pharmacological activity, as supported by the nonclinical studies. The starting dose of ASP7517 is set to 1×10^6 cells/dose by intravenous infusion.

Nonclinical pharmacology data suggest ASP7517-surrogate shows prolonged survival when administered intravenously to a C1498-WT1 inoculated mouse AML model (per 30 g mouse), and prolonged survival was confirmed at the lowest dose level (5×10^2 cells/mouse) in the study. The dose of 5×10^2 cells/mouse is calculated as 1.7×10^4 cells/kg (5×10^2 cells/30 g); therefore, the starting dose is estimated to be 1×10^6 cells/dose (1.7×10^4 cells/kg × 60 kg). The starting dose was also assessed according to the results of the nonclinical toxicology studies. Toxicities (e.g., liver findings, changes in platelet count) were observed after ASP7517 intravenous administration at the lowest dose used in nonclinical studies (1×10^5 cells/kg: equivalent to 6×10^6 cells/dose, administered per 60 kg human), and the NOAEL was not established in the studies. However, these adverse effects are considered to be immune-related reactions based on the mechanism of action of ASP7517, and it is expected that the toxicities are reversible and monitorable in the nonclinical studies. Consequently, it is considered possible to set the starting dose for the FiH study as 1×10^6 cells/dose, 6-fold lower than the lowest dose of nonclinical toxicology studies, with careful clinical monitoring.

The dosing regimen for the FiH study is a total of up to 2 doses in the escalation phase and up to 6 doses in the expansion phase, one dose in each 28-day cycle, which is supported by nonclinical pharmacology data. In mice immunized with specific antigen expressing aAVC at day 0 and day 28, NKT cells and T cells were stimulated after first and second administration. Also, long term antigen-specific antitumor immune memory was demonstrated in an EG7 inoculated mouse model after single administration.

4.2 End of Study Definition

The study start is defined as the date the first subject signs the informed consent form (ICF). End of the study is defined as the last visit or scheduled procedure shown in the Schedule of Assessments for the last subject in the study.

Study completion is defined as the conclusion of data collection for the defined study endpoints. The study may be closed within a participating country per local regulations once the study has been completed and if all subjects enrolled in the country are no longer receiving IP.

5 STUDY POPULATION

Subjects with R/R AML or R/R higher risk MDS will be included.

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

5.1 Inclusion Criteria

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

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization [HIPAA] for US study sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing the ICF.
3. Subject diagnosed with R/R AML or R/R higher risk MDS is defined as:
    - R/R AML
        - Morphologically documented primary or secondary AML by the WHO criteria (2016),
          AND
        - Refractory to at least 2 cycles of induction chemotherapy/not a candidate for re-induction OR relapsed after achieving remission with a prior therapy,
          AND
        - Received all standard therapies including targeted therapies (unless the therapy is contraindicated or intolerable) which are known to provide clinical benefit in the opinion of the investigator,
          AND
        - Received salvage therapy OR is not a candidate for salvage therapy
    - R/R Higher Risk MDS
        - Has MDS by the WHO criteria (2016),
          AND

  - Either relapsed after achieving remission or refractory to standard therapies, including ≥ 4 cycles of hypomethylating agents (unless the therapy is contraindicated or intolerable),
    AND
  - Is classified as higher risk MDS with a score of > 3.5 by Revised International Prognostic Scoring System (IPSS-R) in MDS

4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
5. Subject must meet the following criteria as indicated on the clinical laboratory tests during screening period:
   - Serum AST and ALT ≤ 2.5 × upper limit of normal (ULN)
   - Serum total bilirubin (TBL) ≤ 1.5 × ULN
   - Serum creatinine ≤ 1.5 × ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation
   - Platelets ≥ 50,000/μL at cycle 1 day 1 (C1D1) in the dose escalation cohort only
6. Subject has a life expectancy of ≥ 12 weeks at the time of screening in the opinion of the investigator.
7. Subjects with AML must have peripheral blood absolute blast count of < 20,000/μL at C1D1.

   Note: Blast count can be controlled by hydroxyurea during screening period.
8. Female subject is not pregnant [see Appendix 12.3 Contraception Requirements] and at least 1 of the following conditions apply:
   - Not a woman of childbearing potential (WOCBP) [see Appendix 12.3 Contraception Requirements]
   - WOCBP who agrees to follow the contraceptive guidance [see Appendix 12.3 Contraception Requirements] from the time of informed consent through at least 180 days after final study treatment administration
9. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 180 days after the final study treatment administration.
10. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 180 days after final study treatment administration.
11. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception [see Appendix 12.3 Contraception Requirements] throughout the treatment period and for 180 days after final study treatment administration.
12. Male subject must not donate sperm during the treatment period and for 180 days after the final study treatment administration.

13. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 180 days after final study treatment administration.
14. Subject agrees not to participate in another interventional study while receiving study treatment in the present study.

Waivers to the inclusion criteria will **NOT** be allowed.

5.2 Exclusion Criteria

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

1. Subject was diagnosed with acute promyelocytic leukemia.
2. Subject has breakpoint cluster region-Abelson-positive leukemia (BCR-ABL).
3. Subject has persistent non-hematological toxicities of ≥ grade 2 (National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 5.0), with symptoms and objective findings from prior AML or MDS treatment (including chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation or surgery).
4. Subject has received any of the following therapies:
    - Systemic immunomodulators or immunosuppressive drugs including steroids ≤ 28 days prior to C1D1 (steroids can be used if not intended for treatment of AML or MDS; steroids for AML/MDS related symptoms can be used at low doses [less than 10 mg/day dexamethasone])
    - Cytotoxic agents (except hydroxyurea given for controlling blast cells) ≤ 28 days prior to C1D1
    - IPs for the treatment of AML or MDS within 5 half-lives prior to screening visit
    - HSCT
    - Radiation therapy ≤ 28 days prior to C1D1
5. Subject has clinically active nervous system leukemia, per the investigator's judgment.
6. Subject has active or prior documented autoimmune or inflammatory disorders requiring systemic treatment.
7. Subject has ongoing, untreated malignancy with the exception of the following:
    - Subjects with treated non-melanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed.
    - Subjects with organ-confined prostate cancer with no evidence of recurrent or progressive disease are eligible if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.
8. Subject with left ventricular ejection fraction of < 45% on echocardiogram (ECHO) or multigated acquisition scan (MUGA) performed within 28 days of screening.

9. Subject has laboratory abnormalities or clinical evidence of disseminated intravascular coagulation, or ongoing history of coagulation disorder manifested by bleeding or clotting.
10. Subject has an active uncontrolled infection.
11. Subject is known to have human immunodeficiency virus infection.
12. Subject has active hepatitis B or C or other active hepatic disorder.
13. Subject has any condition, which in the investigator's opinion, makes the subject unsuitable for study participation.
14. Subject has a known or suspected hypersensitivity to bovine-derived protein or has suspected hypersensitivity to any ingredients of ASP7517.
15. Subject is eligible for HSCT.

Waivers to the exclusion criteria will **NOT** be allowed.

5.3 Restrictions During The Study

Not applicable.

5.4 Screen Failures

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

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic case report form (eCRF).

5.4.1 Rescreening

Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, electrocardiogram [ECG], etc.) may be repeated once within the 14-day screening period without the need to register the subject as a screen failure. If more than 14 days elapse from the date of signing the ICF, the subject must be documented as a screen failure. In order to rescreen, a new ICF must be signed and the subject must be entered into screening with a new subject identification number. Rescreening is only allowed once for an individual subject. The bone marrow sample and ECHO/MUGA screening assessments completed within 28 days prior to first dose do not need to be repeated.

6 INVESTIGATIONAL PRODUCT

6.1 Investigational Product Administered

Table 8 Investigational Product

Name	**ASP7517**
Dosage Formulation	Suspension for injection
Physical Description	Opalescent and white to slightly yellowish-white suspension
Unit Dose Strength	1×10^7 cells/mL
Packaging and Labeling	Clear single use vial
Route of Administration	Intravenous infusion
Administration Instruction	Fifty (50) mL of diluted IP will be administered by intravenous infusion at 4 to 6 mL/min infusion rate through a dedicated intravenous line, followed by flushing
IMP or Non-IMP	IMP
Storage	-150°C or below
Sourcing	Provided centrally by sponsor

IMP: Investigational Medicinal Product.

Refer to the pharmacy manual for detailed information regarding preparation, handling and storage of the IP.

6.1.1 Administration

ASP7517 will be infused in 50 mL of normal saline solution at 1×10^6, 1×10^7, or 1×10^8 total cells/dose. It will be administered by intravenous infusion with an infusion rate between 4 to 6 mL/min through a dedicated intravenous line, followed by flushing.

Refer to the pharmacy manual for detailed information regarding administration of the IP.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All IP used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at Astellas Pharma Global Development Inc. (APGD) or sponsor's designee in accordance with APGD or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations. The intravenous infusion will be prepared onsite by a pharmacist or qualified person using aseptic technique as specified in the pharmacy manual.

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

Refer to the pharmacy manual for detailed information regarding packaging and labeling of the IP.

6.2.2 Handling, Storage and Accountability

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

Refer to the pharmacy manual for detailed information regarding IP handling, storage and accountability of the IP.

6.3 Randomization and Blinding

This is an open-label study. Subject enrollment and dispensation of IP will be performed via the interactive response technology (IRT) system. Specific IRT procedures will be described in the respective study manual.

6.3.1 Assignment and Allocation

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 towards 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.

6.4 Investigational Product Compliance

Dosing will take place in the clinical unit. The administration of IP will be supervised to ensure treatment compliance. The exact day and time of IP administration will be documented.

6.5 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

The following treatments are prohibited during the study:

- Interferon/polyethylene-interferon
- High-dose systemic corticosteroids with the exception for immune-related AEs
- Immunosuppressive agents
- Investigational agents other than ASP7517
- Any other treatments of AML or MDS (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during the study with ASP7517 with the following exceptions:
    - Hydroxyurea up to 5 g daily for up to 2 weeks to keep the absolute blast count < 20,000/µL
    - Subject undergoing HSCT will be discontinued from the study
    - Intrathecal chemotherapy used as prophylaxis

Refer to [Appendix 12.6 List of Excluded Concomitant Medications] for a detailed list of drug classes and/or specific medications that are prohibited during participation in the study.

6.6 Dose Modification

Dose modifications are not allowed. Any subjects who do not receive a subsequent dose within the scheduled time window in the Schedule of Assessments [Table 1 and Table 2] can only resume treatment after discussion with the medical monitor. Any subject experiencing a grade 3 AE related to IP after receiving a dose of ASP7517 may receive the subsequent scheduled dose of ASP7517 only after the observed grade 3 AE has resolved to grade 1; the subsequent dose of ASP7517 may be reduced to a dose level deemed safe by the DESC. Further treatment reduction/withdrawal can be implemented after discussion with the medical monitor, including for any clinically significant AEs affecting vital organs (e.g., cardiac events).

6.7 Criteria for Continuation of Treatment

ASP7517 will not be made available after conclusion of the study to subjects who are still receiving and benefitting from study treatment in countries where the product does not have marketing approval and is not commercially available. ASP7517 is given as a maximum of 6 doses (up to 2 doses in the escalation phase; up to 6 doses in the expansion phase).

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Efficacy Assessments

7.1.1 Response Criteria Definitions

7.1.1.1 Acute Myeloid Leukemia Response Criteria

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

- 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 week 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 either 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 or equal than 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.

- Relapse

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

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

7.1.1.2 Myelodysplastic Syndrome Response Criteria

Response to treatment will be defined according to the modified International Working Group response criteria [Cheson et al, 2006] as outlined below.

- 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)

  Requires 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

- Relapse after CR or PR

  Requires at least 1 of the following:
  - 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

7.1.1.3 Hematology Laboratory Assessments

Primary endpoints of hematology clinical laboratory tests will be performed at every visit. Refer to [Section 9.4.1 Analysis of Primary Endpoint] for definitions of CRc for subjects with R/R AML and CR + BM CR + PR for R/R higher risk MDS.

Secondary endpoints of hematology clinical laboratory tests will be performed at every visit. Refer to [Section 9.4.1 Analysis of Primary Endpoint] for definitions of duration of remission, event-free survival (EFS), OS, CR, BM CR, best response, CRh, HI, and objective response.

7.1.2 Bone Marrow Aspirations and/or Biopsies

Study procedures and their timing are summarized in the Schedules of Assessments [Table 1 and Table 2]. After the completion of Observation Period 1 (8 weeks), subjects remaining in the study, because they achieved remission (CRc or PR for AML subjects and CR, BM CR, PR, or HI for MDS subjects) or have clinical benefit as determined by investigator, will have bone marrow samples collected in Observation Period 2 every 3 months or if there is suspicion of relapse in the whole blood. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required. Samples must be submitted to a central laboratory for analysis. Please refer to the laboratory manual for additional information.

7.2 Safety Assessments

Study procedures and their timing are summarized in the Schedules of Assessments [Table 1 and Table 2]. Protocol waivers or exemptions are not allowed.

Procedures conducted as part of a subject's routine clinical management (i.e., standard of care) obtained before signing the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the timeframe, as defined in the Schedules of Assessments [Table 1 and Table 2].

7.2.1 Adverse Events

See [Section 7.3 Adverse Events and Other Safety Aspects] and [Section 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting] for information regarding AE collection and data handling.

7.2.2 Laboratory Assessments

- See [Appendix 12.7 Laboratory Assessments] for the list of clinical laboratory tests to be performed and refer to the Schedules of Assessments [Table 1 and Table 2] for timing and frequency.
- Laboratory samples will be analyzed by the institution's local laboratory. However, ONLY local sample results must be submitted for centralized data entry. Refer to the laboratory manual for additional information.
- Additional laboratory tests should be performed according to institutional standard of care.
- Local testing of bone marrow aspirate and/or biopsy will be reported in the eCRF; however, samples must also be submitted to a central laboratory for analysis. Refer to the laboratory manual for additional information.
- The investigator or subinvestigator must review the laboratory report and document this review.
- Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or subinvestigator who is a qualified physician.

7.2.3 Vital Signs

Blood pressure, radial pulse rate and body temperature will be measured as specified in the Schedules of Assessments [Table 1 to Table 2]. Blood pressure should be measured prior to other clinical assessments. Whenever possible, the blood pressure determinations should be undertaken at approximately the same time of day for each study visit.

A calibrated blood pressure measuring device should be used for all blood pressure measurements.

Prior to measuring blood pressure, the study subject should be seated in a quiet room for at least 5 minutes, with his/her back supported and feet comfortably resting on the floor.

7.2.4 Physical Examination

The investigator or designee (a physician or licensed practitioner) will perform standard, full physical examinations as specified in the Schedules of Assessments [Table 1 and Table 2]. Height and body weight will be measured at the screening visit, and the body weight measurement will be repeated on day 1 of each cycle.

7.2.5 Electrocardiogram

A standard 12-lead ECG will be performed at the screening visit for purposes of assessing subject eligibility. ECG can be repeated during the screening period. ECG assessments will be performed and assessed locally at predose and postdose (1 to 2 hours) day 1 of each cycle, at EoT visit, and during observation periods 1 and 2. The 12-lead ECGs will be recorded in triplicate (at least 2 minutes apart per time point) and transmitted electronically for central read during the Screening and Treatment Periods, and as a single assessment (in triplicate, if deemed necessary, at least 2 minutes apart per time point) and read locally during the Observation Periods 1 and 2.

ECGs will be recorded after the subject has been in a resting, supine position for at least 5 minutes. Further details of the procedure will be separately specified in the procedural manual.

7.2.6 Imaging

Chest X-ray or computed tomography (CT) scan is to be performed at screening. A chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of screening.

7.2.7 Eastern Cooperative Oncology Group

The ECOG Scale [Oken et al, 1982] will be used to assess performance status [Table 9] at time points outlined in the Schedules of Assessments [Table 1 and Table 2].

Table 9 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG: Eastern Cooperative Oncology Group

7.2.8 Multigated Acquisition Scan or Echocardiogram

A MUGA or ECHO (as per standard of care) is to be performed at screening or within 28 days prior to screening.

7.2.9 Disease Assessment

Disease assessments as per standard of care and including extramedullary leukemia assessment will be performed as specified in the Schedule of Assessments [Table 1 and Table 2]. The extramedullary leukemia assessment results must be entered into the eCRF. Blood samples must be submitted to a central laboratory for analysis. Please refer to the laboratory manual for additional information.

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Appendix 12.4 AEs: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an AE or SAE. Collection, reporting and follow-up of Special Situations and defect in IP follow the procedures for AE and SAE.

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

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, the sponsor collects AEs even if the subject has not received IP. AE collection will begin from time of informed consent and continue through post-treatment period and at least 30 days after last IP dose and prior to the start of new anticancer treatment. In addition, the following will be collected regardless of the start of new anticancer therapy:

- Any IP-related SAE that is ongoing will be followed until resolved
- Any SAE that is deemed to be related to IP by the investigator

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The methods of recording, evaluating and assessing seriousness, causality and severity of AEs and SAEs are described in [Appendix 12.4 AEs: Definitions and Procedures for Recording, Evaluating, Follow-up or Reporting]. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

An AE with a change in severity is recorded as a new AE.

7.3.3 Follow-up of Adverse Events

If after the protocol-defined AE collection period [see Section 7.3.1 Time Period for Collecting AE and SAE Information], an AE progresses to an SAE, or the investigator learns of any (S)AE (SAE or AE) including death, where he/she considers there is reasonable possibility it is related to the IP or study participation, the investigator must promptly notify

the sponsor. Such events should be collected and followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

7.3.4 Reporting of Serious Adverse Events

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

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

Procedures for reporting SAEs to the sponsor are described in [Section 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product].

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

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

- Disease progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data as outlined in [Section 7.1 Efficacy Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the IP and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of IP must be reported as an SAE, even if attributed to disease progression.
- Pre-planned and elective hospital/clinical procedures/interventions or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the study. For example, admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the preexisting condition such as transfusion for preexisting anemia, leukopenia or thrombocytopenia will not be reported as an SAE. These procedures are collected per the eCRF's completion guidelines.

7.3.6 Special Situations

Certain special situations observed in association with the IP, such as incorrect administration (e.g., wrong dose of IP or background therapy) are collected in the eCRF, as protocol deviation per [Section 10.3 Major Protocol Deviations] or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in the eCRF. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Section 12.4.5 Reporting

Procedures for SAEs or Defect of Investigational Product] and the details of the associated special situation are to be included in the clinical description on the SAE worksheet.

The special situations are:

- Pregnancy
- Medication error, overdose and use outside protocol
- Misuse/abuse
- Occupational exposure
- (Suspicion of) Transmission of infectious agent related to microbiological contamination at the site
- Suspected drug-drug interaction

Instructions and procedures for reporting special situations are provided in [Appendix 12.4.6 Reporting Procedures for Special Situations].

7.3.7 Defects of Investigational Product

Defect is defined as the product defect, which may cause generally poor conditions where the cells cause adverse reactions that affect the human body. When a defect in IP occurs, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness). Instructions and procedures for the expedited reporting of defects are provided in [Appendix 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product].

7.3.8 Supply of New Information Affecting the Conduct of the Study

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

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

Specific to Japan:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the sponsor should inform all investigators involved in the study, head of the study site and appropriate regulatory authorities of such information. The head of the study site who receives such information will decide whether the study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [Appendix 12.1.5.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information].

2. In addition, when the head of the study site receives the revisions of the investigator's brochure, protocol, written information, information on the matters covering the quality of the test product, efficacy and safety, information necessary for conducting the study properly or documents to be examined by the IRB, these documents should be sent to the IRB.
3. When the sponsor receives a safety issue from any source either Japan or worldwide that requires an urgent safety measure (USM) to be implemented, then the sponsor will report that safety information to all study sites in Japan and rest of world (within 24 hours of awareness).

7.3.9 Urgent Safety Measures

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

7.3.10 Reporting Urgent Safety Measures

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

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the subjects. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant CA and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

7.4 Pharmacokinetics

Whole blood will be collected to monitor pharmacokinetics of ASP7517 cells via determination of genomic DNA in the cell by a quantitative polymerase chain reaction method. Sampling time points are as shown in the Pharmacokinetics Sample Collection Schedule-Dose Escalation Cohort and Dose Expansion Cohort [Table 5].

Refer to the laboratory manual for detailed information regarding sampling, processing, shipping and storage instructions.

7.5 Pharmacodynamics | Biomarkers

Samples for exploratory pharmacodynamics and biomarker analyses will be collected according to the Schedules of Assessments [Table 1 and Table 2].

The samples described in [Sections 7.5.1 Blood Samples and 7.5.2 Bone Marrow Aspirate Samples for Biomarker Analysis] may be analyzed for other biomarkers including DNA, RNA and protein, to investigate possible associations with mechanisms of resistance or sensitivity to study treatment, dynamic changes associated with study treatment (in terms of dose, safety, tolerability and efficacy, etc.) and method development or validation of diagnostic assays related to ASP7517.

The samples may be stored at the study sponsor's facility or a contract laboratory facility for up to 15 years after study database closure, at which time the samples will be destroyed.

The procedures for the collection, handling and shipping of laboratory samples will be specified in a laboratory manual.

7.5.1 Blood Samples

Blood samples will be collected from all subjects and used for the analysis of pharmacodynamics changes related to treatment effect and potential biomarkers of response or resistance related to treatment effect as described in [Section 9.4.3.1 Analysis of Biomarkers]. Examples of these biomarkers include, but are not limited to, cytokine expression and secretion (e.g., IFNγ), WT1-specific T lymphocytes (e.g., cytotoxic T lymphocytes), immune cell populations (e.g., NKT cells, NK cells, etc.), expression levels of WT1 and mutations in AML/MDS related genes that may modify treatment effect.

7.5.2 Bone Marrow Aspirate Samples

Bone marrow aspirate samples will be collected at the time points indicated in the Schedule of Assessments [Table 1 and Table 2] (as clinically indicated). Bone marrow aspirate samples will be used for biomarker analyses as described in [Section 9.4.3.1 Analysis of Biomarkers]. Examples of biomarkers include, but are not limited to, expression of WT1 and other genes and proteins that may be related to treatment response or treatment effect.

7.6 Other Assessments

7.6.1 Sample for the Analysis of Genes Related to Pharmacogenomics

Buccal swabs for biomarker analysis will be used to genotype the human leukocyte antigen (HLA) gene complex. Knowledge of the specific HLA gene complex in each subject may help understand/explain observed differences in efficacy or treatment effect. For detailed sample collection, sample labeling and sample shipment procedures refer to the laboratory manual. All samples will be transferred to the analytical laboratory; pharmacogenomic (PGx) samples will be kept for up to 15 years, or as specified in the ICF.

7.6.2 Sample for Optional Banked Pharmacogenomic Sample Analysis

PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety. An optional 4 to 6 mL whole blood and buccal swab sample for possible banked PGx analysis will be collected as indicated in the Schedule of Assessments [Table 1 and Table 2]. Samples will be shipped to a sponsor-designated banking clinical research organization (CRO).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.8 Pharmacogenomic Analysis with Banked Sample] for further details on the banking procedures.

7.6.3 Sample for Anti-HLA Antibody

Blood samples will be collected from all subjects and used for the analysis of anti-HLA antibody production. Sampling time points are as shown in the Schedule of Assessments [Table 1 and Table 2]. Sample processing, storage and shipment instructions will be provided in the laboratory manual.

7.6.4 Sample for Replication Competent Lentivirus

Blood samples will be collected from all subjects and used to monitor the absence of replication competent lentivirus (RCL). Sampling time points are as shown in the Schedule of Assessments [Table 4]. If there is a positive result during the first year of assessments, additional follow-up assessments may be required on an annual basis. Sample processing, storage and shipment instructions will be provided in the laboratory manual.

7.7 Total Amount of Blood

The total amount of blood for each subject will vary depending on the course of their disease, duration on treatment and local laboratory requirements. At any time during the study, if any laboratory abnormality is found for a subject, additional blood may be drawn for safety monitoring or local standard of care.

The maximum amount of blood planned to be collected within 24 hours is approximately 71 mL on C1D1.

8 DISCONTINUATION

8.1 Discontinuation of Individual Subject(s)

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

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

8.1.1 Discontinuation Criteria from Treatment for Individual Subject(s)

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

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

- Subject declines further study participation (i.e., withdrawal of consent).

- Any clinical or unacceptable AE/SAE, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject.
- Subject is noncompliant with protocol based on the investigator or medical monitor assessment.
- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit and no DLT may be kept in the study after discussion with the medical monitor).
- Subject not achieving remission (CRc or PR in AML or CR, BM CR or PR or HI in MDS) and the subject is no longer deriving clinical benefit, in the opinion of the investigator.
- Subject begins other anti-leukemic therapies or MDS therapies, including undergoing HSCT.
- Subject experiences disease relapse/progression.
- Investigator/subinvestigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Female subject becomes pregnant.
- Death.
- Subject develops a grade 4 DLT during cycle 1.
- Delay of > 2 weeks of a subsequent scheduled dose of ASP7517 due to ASP7517-related toxicities.

8.1.2 Discontinuation Criteria Post-Treatment for Individual Subject(s)

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

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

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject begins other anti-leukemic therapies or MDS therapies, including undergoing HSCT.
- Subject experiences disease relapse/progression.
- Subject is no longer deriving clinical benefit, in the opinion of the investigator.
- Female subject becomes pregnant.
- Death.

8.2 Discontinuation of Individual Subject(s) from Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in [Section 4.1 Study Design] and the Schedule of Assessments [Table 1, Table 2, Table 3 and Table 4]. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

All subjects who discontinue study treatment are to be followed for survival every 3 months after their final visit until death or the final analysis, whichever occurs first per [Section 4.1 Study Design] and the Schedule of Assessments [Table 1, Table 2, Table 3 and Table 4].

8.2.1 Lost to Follow-up

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

8.3 Discontinuation of the Study Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor and the head of the study site.

8.4 Discontinuation of the Study

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

9 STATISTICAL METHODOLOGY

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

In general, all data will be summarized by dose level and overall with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by categories will be based on the number of subjects with no missing data (i.e., will add up to 100%). Kaplan-Meier estimates will be provided for time-to-event endpoints. Separate data displays will be produced for each phase of the study. For phase 1 dose escalation, all data will be summarized by dose level and overall, unless otherwise specified. For phase 2 dose expansion, all data will be summarized by disease group, dose level and overall, unless otherwise specified.

Baseline will be defined as the last nonmissing observation on or prior to first administration of IP, unless otherwise specified.

9.1 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.

9.2 Analysis Sets

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

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

9.2.1 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.

9.2.2 Response Analysis Set

The response analysis set 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. This will be used as a sensitivity analysis set for response related endpoints.

9.2.3 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.

9.2.4 Pharmacokinetic Analysis Set

The pharmacokinetic 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.

9.2.5 Pharmacodynamic Analysis Set

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.

9.2.6 DLT Evaluation Analysis Set

The DLT Evaluation Analysis Set (DEAS) is defined as all subjects in SAF by excluding 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 the DLT evaluation period

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

9.3 Demographics and Baseline Characteristics

9.3.1 Demographics

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

9.3.2 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all enrolled subjects by dose level group and overall. Similar tables for screening disposition, observation period disposition and follow-up disposition will also be presented for all treated subjects by dose level and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

9.3.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

All previous and concomitant treatment will be listed. The frequency of previous and concomitant medications (prescription, over-the-counter, and nutritional supplements) will be summarized by dose level and overall.

9.3.4 Medical History

Medical history for each subject will be listed.

9.3.5 Investigational Product Exposure

The number and percentage of subjects exposed to IP will be summarized by dose level and cycle.

All IP exposure data will be listed.

9.4 Analysis of Efficacy

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

9.4.1 Analysis of Primary Endpoint

9.4.1.1 Primary Analysis

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 modified Cheson criteria [Cheson et al, 2003].

CR + BM CR + PR rate is defined for MDS subjects as the number of subjects who achieve the best response of CR + BM CR + PR divided by the number of subjects in the analysis population. Response to treatment will be defined per Cheson criteria [Cheson et al, 2006].

Response rates will be calculated and its 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.

9.4.1.2 Sensitivity Analysis

Sensitivity analysis will be defined in the SAP.

9.4.1.3 Phase 2 Expansion

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 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 below). Otherwise, the enrollment at that dose level will be closed.

When the total number of subjects reaches the maximum sample size of 52, it may be concluded that ASP7517 is efficacious if the number of responses is greater than or equal to 12 and 10 for AML and MDS, respectively. The number of subjects in stage 1, stage 2 and stage 3 may be changed according to the optimized stopping boundaries.

Optimized Stopping Boundaries for AML	
Number of subjects treated	**Stop if number of responses ≤**
12	1
32	5

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

9.4.2 Analysis of Secondary Endpoints

- 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.
- 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.
- 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.
- 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) 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 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, HI, SD and PD) post-baseline. Subjects who achieve the best responses of 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.
- 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.

CR, CRh, CR/CRh, best response and ORRs will be calculated and its 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.

- 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).
- 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).
- Duration of remission for AML includes duration of CRc, duration of CR/CRh, duration of CRh, duration of CR, and duration of response (i.e., CRc + PR).
- Duration of remission for MDS includes duration of CR and duration of response (i.e., CR + BM CR + PR).

The distribution of OS, EFS and duration of remission will be estimated for each dose level using Kaplan-Meier methodology.

9.4.3 Analysis of Exploratory Endpoints

9.4.3.1 Analysis of Biomarkers

Associations between biomarkers [Section 7.5 Pharmacodynamics | Biomarkers] and clinical results (efficacy, safety or pharmacodynamics) may be performed on subjects who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest.

Biomarkers may be summarized graphically or descriptively as they relate to clinical measures, as applicable. Summary statistics may be tabulated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches, may be conducted. All analyses described in this section are based on the availability of the data.

9.4.3.2 Analysis of Pharmacodynamic Activities

Descriptive statistics will be provided for pharmacodynamics parameters whenever applicable. Exploratory analysis of the relationship between pharmacodynamic measurements and pharmacokinetics, efficacy and safety profile in subjects may be performed.

9.4.3.3 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. Time-course of cellular DNA load will be plotted as appropriate.

Subjects with sufficient cellular DNA samples will have kinetic parameter estimates for ASP7517 including calculation of AUC, C_{max}, C_{trough} and t_{max} using standard noncompartmental analysis. Exploratory analysis between pharmacokinetic parameter and clinical measures (e.g., efficacy or safety) may be performed.

9.5 Analysis of Safety

Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment received (SAF).

9.5.1 Adverse Events

AEs will be coded using MedDRA v21.1 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.

The number and percentage of subjects with TEAEs, drug-related TEAEs, serious TEAEs, drug-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.

9.5.2 Laboratory Assessments

For quantitative clinical laboratory measurements (hematology and biochemistry), descriptive statistics will be used to summarize results and change from baseline by dose level and time point.

Shifts from baseline to the worst grade based on NCI CTCAE 5.0 during the treatment period in clinical laboratory tests will be tabulated.

Laboratory data will be listed.

9.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF by dose level and time point.

Vital signs data will be listed.

9.5.4 Physical Examination

Physical examination will be listed.

9.5.5 12-lead Electrocardiogram

For all analyses, replicates at each time point will be averaged for each 12-lead ECG parameter. Baseline will be defined as the average of the triplicate readings at screening.

Descriptive statistics will be used to summarize the 12-lead ECG parameter results and changes from baseline by dose level and time point.

A shift analysis table showing shifts from baseline in overall ECG (normal and abnormal) will be provided.

The 12-lead ECG data (individual replicates and the averages) will be listed.

9.5.6 Eastern Cooperative Oncology Group Performance Status

Summary statistics (number and percent of subjects) for each category of the ECOG performance status at each assessment will be provided. The change from baseline to final visit or early termination will also be summarized. Negative change scores indicate an improvement. Positive scores indicate a decline in performance.

9.5.7 Dose Limiting Toxicities

A DLT event, as defined in [Section 4.1.3 Dose Limiting Toxicity Criteria], will be summarized by dose level using DEAS. Details of DLTs will be presented in listings and subject narratives.

DLT review for dose escalation decisions and declaration of DLT and MTD will be performed for each dose level throughout the trial. Dose escalation decisions will be guided by BOIN as described in [Section 4.1.3 Dose Limiting Toxicity Criteria].

9.5.8 Liver Safety Assessment

The liver safety assessments will be summarized by the categories below based on the measurements from alkaline phosphatase (ALP), ALT, TBL, AST and their combination. The subject's highest post-baseline value will be used.

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- ALT or AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- ALP > 1.5 × ULN
- TBL > 2 × ULN
- (ALT or AST > 3 × ULN) and TBL > 2 × ULN
- (ALT or AST > 3 × ULN) and ALP < 2 × ULN and TBL > 2 × ULN

The last 2 criteria where 2 or more parameters are evaluated will be with the measurements on the same day.

9.6 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 10.3 Major Protocol Deviations] will be summarized for all treated subjects by dose level and overall, as well as by study site.

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

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

9.7 Interim Analysis (and Early Discontinuation of the 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 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.

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.

9.8 Additional Conventions

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

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

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

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medications if they are missing on day of first IP administration. The imputed dates will be used to assess if the AEs or concomitant medications are treatment emergent or concomitant, respectively. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

10 OPERATIONAL CONSIDERATIONS

10.1 Data Collection

The investigator or site designee will enter data collected using an electronic data capture system. In the interest of collecting data in the most efficient manner, the investigator or designee should record data (including clinical laboratory values, if applicable) in the eCRF within 5 days after the subject’s visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with the source. These documents should be appropriately maintained by the study site.

The monitor should verify the data in the eCRFs with the source and confirm that there are no inconsistencies among them.

Clinical laboratory tests are performed and analyzed by the institution’s local laboratory. The local laboratory results must be submitted for centralized data entry (centralized laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study). The centralized laboratory data vendor will provide the sponsor or designee with a complete and clean copy of the data.

10.2 Demographics and Baseline Characteristics

10.2.1 Demographics

Demographics and other baseline characteristics will be summarized by treatment group. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints and frequency and percentage for categorical endpoints.

10.2.2 Medical History

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

10.3 Major Protocol Deviations

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

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and well-being of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to subjects.

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

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

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

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

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

PD3 - Received wrong treatment or incorrect dose

PD4 - Received excluded concomitant treatment

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

10.4 STUDY ORGANIZATION

10.4.1 Dose Escalation and Safety Committee

A 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. Additional details regarding responsibilities, membership requirements and safety review time points are included in the DESC Charter. The DESC will also review the aggregate safety data from the phase 1 dose escalation and the phase 2 expansion cohorts.

While safety data from the DLT observation period in the escalation cohorts are the minimum safety data needed for the DESC meeting, all available safety findings will be considered by the DESC. The DESC will assess whether a longer DLT observation period is warranted, based on emerging data. Additionally, only when determining RP2D, the DESC may choose a more conservative dosing decision than the MTD selected by BOIN design, based on evaluation of the safety data and other available data.

The decision on the dose level for the next cohort will be based on the BOIN design. Also, MTD will be determined by BOIN from at least 6 subjects with the maximum of 8 subjects under the maximum of 2 cohorts. The dose for phase 2 expansion will not be higher than the MTD.

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12 APPENDICES

12.1 Ethical, Regulatory and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

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

12.1.2 Institutional Review Board/Independent Ethics Committee/Competent Authorities

There will be a subsequent conclusion of contracts with the study sites after the approval.

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

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

The investigator will be responsible for the following:

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

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments and/or revisions: substantial amendments/revisions and/or nonsubstantial amendments/revisions. Depending on the nature of the amendment and/or revisions, either IRB/IEC or CA approval or notification may be required. The changes will become effective only after the approval of the sponsor, investigator, IRB/IEC and appropriate regulatory authorities.

Amendments to this protocol and/or revisions must be signed by the sponsor and investigator. Written verification of IRB/IEC approval will be obtained before any amendment and/or revision is implemented. Modifications to the protocol that are administrative in nature do not

require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

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

12.1.4 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.1.5 Informed Consent of Subjects

12.1.5.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed, signed or place a personal seal, and dated by the subject, the person who administered the ICF and any other signatories according to local requirements. A voluntary ICF for PGx samples will be reviewed, signed or place a personal seal, and dated by the subject, the person who administered the ICF and any other signatories according to local requirements. A copy of the signed or sealed ICF(s) will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that the ICF was signed prior to any study-related procedures and that the subject received a signed copy of the ICF.

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

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

1. The investigator or his/her representative will immediately inform the subject verbally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participating in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update the subject's ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF even if relevant information was provided verbally. The investigator or his/her representative

who obtained the written informed consent and the subject should sign and date the ICF or place a personal seal. A copy of the signed or sealed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the reconsent process.

12.1.6 Source Documents

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

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

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

12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data case report forms and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US study sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the study site/investigator if the NDA/MAA/J-NDA is approved or if the IND/investigational medicinal product dossier/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

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

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

1. Source documents (clinical data, documents and records for preparing the eCRF) hospital records, medical records, test records, memoranda, checklists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the sponsor, records of clinical coordinators, and records related to the study selected from those verified in other departments or hospitals.
2. Study contracts, written ICFs, written information and other documents or their copies prepared by the study personnel. A letter of request for study (including a request for continuation/amendment), letter of request for review, notice of study contract, study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), curriculum vitae of investigators, list of subinvestigators, list of signatures and print of seals (copy) and eCRF (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a study whose period exceeds 1 year or the adequacy of continuously conducting the study from which information on adverse drug reactions is obtained, and other documents obtained. A finalized protocol (including revisions), finalized investigator's brochure (including revisions), operational procedures for the investigator, materials and information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation) and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for IP and other duties related to the study. Procedure for controlling the IP, drug inventory and accountability record, vouchers for the receipt and return of the IP, and the prescriptions for concomitant medications

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

12.1.8 Subject Confidentiality and Privacy

For clinical research performed at a facility that is not a covered entity under HIPAA, language consistent with the principles of HIPAA should be included in the ICF to describe the provisions in place to protect subject privacy and to seek consent for use of private information obtained during the study.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the study without justifiable reasons.

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

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

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

12.1.9 Arrangement for Use of Information and Publication of the Study

Information concerning the test product, patent applications, processes, unpublished scientific data, the investigator’s brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the study agreement.

12.1.10 Insurance of Subjects and Others *(Specific to Japan)*

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

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

12.1.11 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final CSR that forms part of a marketing authorization application, be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator(s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for the coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database hard-lock.

12.2 Procedure for Study Quality Control

12.2.1 Study Monitoring

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

12.2.2 Direct Access to Source Data/Documents

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

12.2.3 Data Management

Data management will be coordinated by the designee of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by data management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and the WHO Drug Dictionary, respectively. Data management is accountable for eCOA.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

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

- QTLs will be predefined in the applicable plan(s) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

12.3 Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the Schedules of Assessments [Table 1 and Table 2]. Pregnancy test results must confirm that the subject is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

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

Females in the following categories are not considered WOCBP:

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

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

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than 1 follicle-stimulating hormone (FSH) measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

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

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 6 months after the final IP administration.[a]

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

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
- Other combined (estrogen- and progesterone-containing) methods
    - Vaginal ring
    - Injectable
    - Implantable
    - Intrauterine hormone-releasing system or intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner

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

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

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

(Specific to Japan)

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral
- Other Hormonal methods of contraception containing progesterone
    - Intrauterine hormone-releasing system(IUS)
- Other methods of contraception
    - Intrauterine device(IUD)
    - Bilateral tubal occlusion
- Vasectomized partner

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

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

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

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

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

Male subjects with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 6 months after final drug administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator
- Use a condom
- Female partners of male subjects who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception

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

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

12.4.1 Definition of Adverse Events

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

12.4.1.1 Abnormal Laboratory Findings

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

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

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

12.4.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Appendix 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product].

12.4.2 Definition of Serious Adverse Events

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

- Results in death
- Is life-threatening (An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death; it does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.3 Criteria for Causal Relationship to Investigational Product

A medically qualified investigator is obligated to assess the relationship between IP and each occurrence of each (S)AE. This investigator will use medical judgment as well as the reference safety information [Section 2.1.2 Summary of Key Safety Information for Investigational Product] to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

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

Following a review of the relevant data, the causal relationship between the IP and each (S)AE will be assessed by answering “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the IP?”

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

- Has the subject been administered IP?
- Plausibility (i.e., could the event been caused by the suspect drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- De-challenge/dose reduction/rechallenge:
    - De-challenge: Did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?
    - Dose reduction: Did the (S)AE resolve or improve after reducing the dose of the suspect drug?
    - Rechallenge: Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?

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

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

12.4.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI-CTCAE guidelines (version 5.0). The items that are not stipulated in the NCI-CTCAE guidelines (version 5.0) will be assessed according to the criteria below and entered into the eCRF:

Table 10 Grading Scale Defining the Severity of an Adverse Event

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

ADL: activities of daily living; AE: adverse event.

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

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

12.4.5 Reporting Procedures for Serious Adverse Events or Defect of Investigational Product

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

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

For contact details, see Contact Details of Sponsor's Key Personnel. Fax or email the SAE/special situations worksheet to:

Astellas Pharma Global Development Inc.
Pharmacovigilance
North America fax number: +1-888-396-3750
North America alternate fax number: +1-847-317-1241
Email: safety-us@astellas.com

Specific to Japan:

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

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

Fax or email JUTOKUNA YUUGAIJISHOU OYOBIFUGUAI HOUKOKUSHO or JUTOKUNA YUUGAIJISHOU HOUKOKUSHO and special situations worksheet to:

Astellas Pharma Inc. – Japan
Pharmacovigilance
Fax number: 03-3243-5747
Email: rk-safety-jp@jp.astellas.com

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

Follow-up information for the event should be sent promptly (as soon as available, but no longer than within 7 days of the initial notification or for Japan sites, within 2 days for the initial notification).

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

The following minimum information is **required**:

- International study number/study number
- Subject number, sex and age
- Date of report
- Description of the SAE (event and seriousness criteria) and defect (if applicable)
- Causal relationship to the IP (including reason)
- Drug provided (if any)

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

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

The heads of the study sites/investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

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

12.4.6 Reporting Procedures for Special Situations

12.4.6.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 180 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in [Appendix 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product] using the SAE worksheet as a special situation and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 180 days from the discontinuation of dosing and report the information to sponsor according to the timelines in [Appendix 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product] using the SAE worksheet as a special situation.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in this information.

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

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

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

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination or other means as appropriate. (S)AEs experienced by the newborn/infant should be reported via the pregnancy reporting form. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date.

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

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

No information on overdose of ASP7517 is available. As ASP7517 is administered intravenously, the pharmacy manual will provide detailed instructions for preparation to ensure that the correct dose is dispensed. In the event of an overdose, subjects should be managed by symptomatic and supportive care and observed in a controlled medical setting. In the event of suspected ASP7517 medication error, the subject should receive supportive care and monitoring. The medical monitor/expert should be contacted as applicable.

12.4.6.3 Misuse/Abuse

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

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

If misuse or abuse of the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product] together with details of the misuse or abuse of the IP.

12.4.6.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the subject) to the IP occurs, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the special situation are to be reported on the special situations worksheet.

12.4.6.5 (Suspicion of)Transmission of Infectious Agent

If transmission of an infectious agent related to the microbiological contamination at the site is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness) and any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product] together with the details of the suspected transmission of infectious agent.

12.4.6.6 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for SAEs or Defect of Investigational Product] together with details of the suspected drug-drug interaction.

12.5 Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of drug-induced liver injury during the course of the study. It should be noted that this section does not specify the End of Study analyses of liver enzymes. The end of study liver enzymes analyses will be described in the SAP. Any subject enrolled in a study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALP, ALT, AST and TBL). Testing should be repeated within 72 hours of notification of the test results. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN is as shown below.

Table 11 Moderate and Severe Liver Abnormalities

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

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal
†Samples taken simultaneously or within maximum 24 hours.

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or international normalized ratio (INR) > 1.5 (if INR testing is applicable/evaluated)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

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

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and clinical laboratory tests. The study site personnel are to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal LFTs should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the IP has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to IP are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases are to be recorded as "AEs" within the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects, and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications are to be entered in the eCRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents)
    - Ultrasound or other imaging to assess biliary tract disease
    - Other clinical laboratory tests, including INR and direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or INR > 1.5) (if INR testing is applicable/evaluated)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

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

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

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

The 2 "requirements" for Hy's Law are:

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

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

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

References

Temple R. Hy's Law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15(4):241-3.

12.6 List of Excluded Concomitant Medications

12.6.1 Concomitant Medications

The following list describes concomitant medications that are prohibited. This list should not be considered all inclusive. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the medical monitor is strongly encouraged.

Drug Type	Generic Drug Name
Corticosteroids*	Dexamethasone Prednisone (Deltasone, Orasone, Predone, RAYOS, Sterapred, etc.)
Interferon/polyethylene-interferon	
Immunosuppressive Agents	Abatacept (Orencia, etc.) Adalimumab (Humira, etc.) Anajunra (Kineret, etc.) Azathioprine (Azasan, Imuran, etc.) Budesonide (Entocort EC, etc.) Certolizumab (Cimzia, etc.) Cyclosporine (Neoral, Sandimmune, SangCya, etc.) Etanercept (Enbrel, etc) Everolimus (Afinitor, Zortress, etc.) Golimumab (Simponi, etc.) Infliximab (Remicade, etc.) Ixekizumab (Taltz, etc.) Leflunomide (Arava, etc.) Mycophenolate (CellCept, Myfortic, etc.) Natalizumab (Tysabri, etc.) Prednisolone (Millipred, etc.) Rituximab (Rituxan, etc.) Secukinumab (Cosentyx, etc.) Sirolimus (Rapamune, etc.) Tocilizumab (Actemra, etc.) Tofacitinib (Xeljanz, etc.) Ustekinumab (Stelara, etc.) Vedolizumab (Entyvio, etc.)

*The use of high dose system corticosteroids are prohibited, with the exception of immune-related AEs (steroids can be used if not intended for treatment of AML or MDS; steroids for AML/MDS related symptoms can be used at low doses [less than 10 mg/day dexamethasone]).

12.6.2 Other Investigational Agents

Treatment with investigational agents other than ASP7517 is prohibited. If there are concerns or questions about concomitant use of these drugs, discussion with the co-chairs and protocol officer is strongly encouraged.

12.6.3 Other Treatments for Acute Myeloid Leukemia and/or Myelodysplastic Syndrome

Any other treatments of AML or MDS (including, but not limited to, chemotherapy, radiotherapy, surgery, immunotherapy and cellular therapy) are prohibited, with the following exceptions:

- Hydroxyurea up to 5 g daily for up to 2 weeks to keep the absolute blast count < 20,000/μL.
- Subject undergoing HSCT will be discontinued from the study.
- Intrathecal chemotherapy used as prophylaxis.

If there are concerns or questions about concomitant use of these drugs, discussion with the medical monitor is strongly encouraged.

12.7 Laboratory Assessments

Laboratory tests will be performed and analyzed by the institution's local laboratory according to the Schedules of Assessments [Table 1 and Table 2] and results submitted for centralized data entry.

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

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/or delegated subinvestigator who is a qualified physician.

Table 12 Clinical Laboratory Tests

Panel/Assessments	Parameters to be Analyzed
Hematology	Blast count and cell count Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Platelet count Red blood cell count (RBC) White blood cell count (WBC) White blood cell count differential
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)
Table continued on next page	

Panel/Assessments	Parameters to be Analyzed
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
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.

12.8 Pharmacogenomic Analysis With Banked Sample

INTRODUCTION

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

OBJECTIVES

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

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

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in the PGx substudy. Subjects must provide written consent prior to providing any blood samples that may be used at a later time for PGx analysis.

SAMPLE COLLECTION AND STORAGE

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

PGx ANALYSIS

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

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hard-lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely unless otherwise specified by local regulation.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the study, if applicable. The results of the PGx analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.9 Clinical Study Continuity

INTRODUCTION

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

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study subjects and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedules of Assessments [Table 1, Table 2, Table 3 and Table 4] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

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

INFORMED CONSENT

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

SUBJECT PROCEDURES ASSESSMENT

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

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

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

Adherence to the original protocol as reflected in the Schedules of Assessments [Table 1, Table 2, Table 3 and Table 4] is expected, where plausible, in the case of a crisis. The alternate measures as noted in Table 13, Table 14, Table 15 and Table 16 below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate measures. This is to allow for continuity of receiving Investigational Medicinal Product (IMP) and maintaining critical safety and efficacy assessments for subjects participating in the study at a time of crisis.

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

Table 13 Alternate Schedule of Assessments in Response to a Crisis – Phase 1 (Dose Escalation)

Assessments	Alternate Approach(es)	Treatment Period																					End of Treatment[k]	Post-Treatment Period		Survival Follow-up Period[s]
		Cycle 1											Cycle 2											Obs Period 1	Obs Period 2	
Visit Days		Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
		1	2	3	4	5	6	7																		
Window(days)			0	0	0	0	0	0	±1	±1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
Physical Examination[c]	For Cycle 1, there are 7 days of hospitalization and each cycle day 1 are IP administration days. Other visits can be obtained at local facility and results submitted to PI.																									
Disease Assessment	Except for IP administration days, assessment can be performed locally and results submitted to PI												X										X			
Vital Signs	Except for IP administration days and hospitalization on C1D1 to C1D7, exams can be performed at a local facility and results submitted to PI.	X[b]	X		X				X	X	X	X	X[b]	X		X				X	X	X	X[l]	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
ECOG Performance	Except for IP administration days and hospitalization on C1D1 to C1D7, can be completed by remote/ telemedicine visit.	X[a]	X		X				X	X	X	X	X[a]	X		X				X	X	X	X[l]			

Table continued on next page

Assessments	Alternate Approach(es)	Treatment Period																					End of Treatment[k]	Post-Treatment Period		Survival Follow-up Period[s]
		Cycle 1											Cycle 2											Obs Period 1	Obs Period 2	
Visit Days		Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
		1	2	3	4	5	6	7																		
Window(days)			0	0	0	0	0	0	±1	±1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
Prior and Concomitant Medications	Remote/Virtual/Telemedicine Visits allowed for nondosing visits. Please refer to protocol schedule of assessments. Every Visit.																									
Pregnancy Test for WOCBP	Test must be completed prior to dosing, however EoT test may be performed at local clinic and result submitted to PI.	X[a]											X[a]										X	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
12-Lead ECG[d]	Except for IP administration days triplicate may be performed as possible at a local clinic and results submitted to PI. If cannot be performed, Astellas medical monitor to assess for study continuation.	X[b]											X[b]										X			
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[e]	Except for IP administration days and hospitalization on C1D1 to C1D7, collection of samples at local facility acceptable if results can be made available to investigative site.																									

Table continued on next page

Assessments	Alternate Approach(es)	Treatment Period																					End of Treatment[k]	Post-Treatment Period		Survival Follow-up Period[s]
		Cycle 1											Cycle 2											Obs Period 1	Obs Period 2	
Visit Days		Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
		1	2	3	4	5	6	7	8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22				
Window(days)			0	0	0	0	0	0	±1	±1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
Coagulation Profile (PT/INR, D-dimer, fibrinogen)[e]	Except for IP administration days and hospitalization on C1D1 to C1D7, collection of samples at local facility acceptable if results can be made available to investigative site.	X[a]	X	X	X	X	X	X	X	X	X	X	X[a]	X	X	X	X	X	X	X	X	X	X[l]	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Bone Marrow Aspiration and/or Biopsy[f]	May be obtained at a delayed time point when subject can visit the site and local BM collection is option to collect this data.												X[a,f]										X[f]			
Blood Sample for Disease Assessment[g]	May be obtained at a local clinical and results submitted to Investigator												X										X			
AE/SAE Assessment	Completion by phone contact allowed for non-dosing visits with further assessment at local clinic if needed. Every Visit.																									
Pharmacokinetic: Blood Sample for Cell Kinetics	None	See Table 5 for detailed sample time points																								

Table continued on next page

Assessments	Alternate Approach(es)	Treatment Period																					End of Treatment[k]	Post-Treatment Period		Survival Follow-up Period[s]
		Cycle 1											Cycle 2											Obs Period 1	Obs Period 2	
Visit Days		Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
		1	2	3	4	5	6	7	8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22				
Window(days)			0	0	0	0	0	0	±1	±1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
PGx	None	X[h]																						Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Blood Sample for WT1 Expression	None	X[a]											X[a]										X[l]			
Blood Sample for Mutational Profiling	None	X[a]																					X[l]			
Blood Sample for Immune Response Biomarker (ELISpot)	None	X[a]							X		X		X[a]							X	X		X[l]			
Buccal Swab for HLA Typing	None	X[a]																								
Blood Sample for Immune Response Biomarker (Tetramer)	None	X[a]									X		X[a]								X		X[l]	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Blood Sample for Immune Cell Phenotyping	None	X[a]							X		X		X[a]							X	X		X[l]			
Blood Sample for Cytokines	None	X[a]	X		X				X		X		X[a]	X		X				X	X		X[l]			
Blood Sample for Anti-HLA Antibody	None	X[a]																			X		X			
IRT Transaction Required	None	X[i]											X										X			

Table continued on next page

Assessments	Alternate Approach(es)	Treatment Period																					End of Treatment[k]	Post-Treatment Period		Survival Follow-up Period[s]
		Cycle 1											Cycle 2											Obs Period 1	Obs Period 2	
Visit Days		Hospitalization Days 1 to 7 during phase 1							8	11	15	18 22 25	1	2	3	4	5	6	7	8	15	22		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
		1	2	3	4	5	6	7																		
Window(days)			0	0	0	0	0	0	±1	±1	± 1	± 1	+ 3	0	0	0	0	0	0	± 1	± 1	± 1	+ 7			± 3
ASP7517 Dosing at the Clinic	None	X[j]											X[j]											Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Survival Follow-up[m]	Can be completed by phone contact per protocol design																									X

AE: adverse event; CT: computed tomography; C: cycle; D: day; C1D1: cycle 1 day 1; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EoT: end-of-treatment; HLA: human leukocyte antigen; ICF: informed consent form; INR: international normalization ratio; IP: investigational product; IRT: interactive response technology; MUGA: multigated acquisition scan; Obs: observation; PGx: pharmacogenomics; PI: principal investigator; PT: prothrombin time; SAE: serious adverse event; WOCBP: women of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Obtained predose.

b. Obtained predose and postdose (including flushing) (vital signs: hourly [± 10 minute window] for up to 4 hours postdose; ECG: 1 to 2 hours postdose) on C1D1 and C2D1.

c. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

d. The 12-lead ECGs will be recorded in triplicate (at least 2 minutes apart per time point) and transmitted electronically for central reading.

e. Laboratory samples will be analyzed by the institution's local laboratory and results will be submitted for centralized data entry.

f. Screening samples may be collected up to 28 days prior to C1D1. End of treatment bone marrow sample does not need to be repeated if collected within 2 weeks of the last disease assessment. Samples must be submitted to a central laboratory for analysis. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.

g. Samples must be submitted to a central laboratory for analysis.

h. Whole blood and buccal swab for optional PGx study may be collected at C1D1 prior to first investigational product administration.

Footnotes continued on next page

i. Subject enrollment in the study will be conducted via IRT transaction.

j. 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.

k. The EoT visit will occur within 7 days of the principal investigator decision to discontinue the subject for treatment or prior to the initiation of new anticancer treatment, 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.

l. Assessment does not need to be repeated if collected at a regularly scheduled visit within 3 days of EoT visit.

m. Telephone contact for survival status and subsequent anti-cancer treatments and outcomes.

Table 14 Alternate Schedule of Assessments in Response to a Crisis – Phase 2 (Dose Expansion)

Assessments	Alternative Approach(es)	Treatment Period														EoT[j]	Post-Treatment Period		Survival Follow-up Period
		Cycle 1					Cycle 2					Cycles 3 – 4[m]		Cycles 5 – 6[n]			Obs Period 1	Obs Period 2	Survival Follow-up
Visit Days		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15**		**Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 4 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 3 months**
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+7			± 3
Physical Examination[c]	Cycle day 1 are IP administration days and must be performed in office. Other visits can be obtained at local facility and results submitted to PI.																		
Disease Assessment[o]	Except for IP administration days, assessment can be performed locally and results submitted to PI						X					X		X		X	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Vital Signs	Except for IP administration days, exams can be performed at a local facility and results submitted to PI	X[b]	X	X	X	X	X[b]	X	X	X	X	X[b]	X	X[b]	X	X[k]			

Table continued on next page

Assessments	Alternative Approach(es)	Treatment Period														EoT[j]	Post-Treatment Period		Survival Follow-up Period
		Cycle 1					Cycle 2					Cycles 3 – 4[m]		Cycles 5 – 6[n]			Obs Period 1	Obs Period 2	Survival Follow-up
Visit Days		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15**		**Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 4 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 3 months**
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+7			± 3
ECOG Performance	Except for IP administration days, can be completed by remote/ telemedicine visit	X[a]	X	X	X	X	X[a]	X	X	X	X	X	X	X	X	X[k]	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Pregnancy Test for WOCBP	Test must be completed prior to dosing, however EoT test may be performed at local clinic and result submitted to PI	X[a]					X[a]					X[a]		X[a]		X			
Prior and Concomitant Medications	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.																		

Table continued on next page

Assessments	Alternative Approach(es)	Treatment Period														EoT[j]	Post-Treatment Period		Survival Follow-up Period
		Cycle 1					Cycle 2					Cycles 3 – 4[m]		Cycles 5 – 6[n]			Obs Period 1	Obs Period 2	Survival Follow-up
Visit Days		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15**		**Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 4 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 3 months**
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+7			± 3
12-Lead ECG[d]	Except for IP administration days triplicate may be performed as possible at a local clinic and results submitted to PI. If cannot be performed, Astellas Medical Monitor to assess for study continuation.	X[b]					X[b]					X[b]		X[b]		X	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Clinical Laboratory Tests (chemistry, hematology, urinalysis)	Except for IP administration days, collection of samples at local facility acceptable if results can be made available to investigative site.																		

Table continued on next page

Assessments	Alternative Approach(es)	Treatment Period														EoT[j]	Post-Treatment Period		Survival Follow-up Period
		Cycle 1					Cycle 2					Cycles 3 – 4[m]		Cycles 5 – 6[n]			Obs Period 1	Obs Period 2	Survival Follow-up
Visit Days		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15**		**Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 4 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 3 months**
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+7			± 3
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	Except for IP administration days, collection of samples at local facility acceptable if results can be made available to investigative site	X[a]	X	X	X	X	X[a]	X	X	X	X	X[a]	X	X[a]	X	X[k]	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Bone Marrow Aspiration and/or Biopsy[e]	May be obtained at a delayed time point when subject can visit the site and local BM collection is option to collect this data						X[a,e]					X[a,e]		X[a,e]		X[e]			
Blood Sample for Disease Assessment[r]	Except for IP administration days, may be obtained locally and results submitted to PI						X					X		X		X			

Table continued on next page

Assessments	Alternative Approach(es)	Treatment Period														EoT[j]	Post-Treatment Period		Survival Follow-up Period
		Cycle 1					Cycle 2					Cycles 3 – 4[m]		Cycles 5 – 6[n]			Obs Period 1	Obs Period 2	Survival Follow-up
Visit Days		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15**		**Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 4 weeks or until 1 post-treatment discontinuation criterion is met**	**Every 3 months**
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+7			± 3
AE/SAE Assessment	Completion by phone contact allowed for non-dosing visits with further assessment at local clinic if needed.																		
Pharmacokinetic: Blood Sample for Cell Kinetics	None	See Table 5 for detailed sample time points																	
PGx	None	X[g]															Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Blood Sample for WT1 Expression	None	X[a]					X[a]					X[a]		X[a]		X[k]			
Blood Sample for Mutational Profiling	None	X[a]														X[k]			
Blood Sample for Immune Response Biomarker (ELISpot)	None	X[a]		X	X		X[a]		X	X		X[a]	X	X[a]	X	X[k]			
Buccal Swab for HLA Typing	None	X[a]																	
Blood Sample for Immune Response Biomarker (Tetramer)	None	X[a]			X		X[a]			X		X[a]	X	X[a]	X	X[k]			

Table continued on next page

Assessments	Alternative Approach(es)	Treatment Period														EoT[j]	Post-Treatment Period		Survival Follow-up Period
		Cycle 1					Cycle 2					Cycles 3 – 4[m]		Cycles 5 – 6[n]			Obs Period 1	Obs Period 2	Survival Follow-up
Visit Days		D1	D2	D8	D15	D22	D1	D2	D8	D15	D22	D1	D15	D1	D15		Every 2 weeks for up to 12 weeks or until 1 post-treatment discontinuation criterion is met	Every 4 weeks or until 1 post-treatment discontinuation criterion is met	Every 3 months
Window(days)			0	± 1	± 1	± 1	+ 3	0	± 1	± 1	± 1	+ 3	± 1	+ 3	± 1	+7			± 3
Blood Sample for Immune Cell Phenotyping	None	X[a]		X	X		X[a]		X	X		X[a]	X	X[a]	X	X[k]	Reference Table 15: Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis		
Blood Sample for Cytokines	None	X[a]	X	X	X		X[a]	X	X	X		X[a]	X	X[a]	X	X[k]			
Blood Sample for Anti-HLA Antibody	None	X[a]					X[a]					X[a]		X[a]		X			
IRT Transaction Required	None	X[h]					X					X		X		X			
ASP7517 Dosing at the Clinic	None	X[i]					X[i]					X[i]		X[i]					
Survival Follow-up[l]	None																		X

AE: adverse event; CT: computed tomography; C: cycle; C1D1: cycle 1 day 1; CR: complete remission; D: day; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EoT: end-of-treatment; HLA: human leukocyte antigen; ICF: informed consent form; INR: international normalization ratio; IP: investigational product; IRT: interactive response technology; MUGA: multigated acquisition scan; PGx: pharmacogenomics; PI: principal investigator; PT: prothrombin time; SAE: serious adverse event; WOCBP: women of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Obtained predose.

b. Obtained predose and postdose (vital signs: hourly [± 10 minute window] for up to 4 hours postdose; ECG: 1 to 2 hours postdose) on day 1 of each cycle.

c. Height measurement performed only at screening. Weight measurement should be performed at screening and day 1 of each cycle.

d. The 12-lead ECGs will be recorded in triplicate (at least 2 minutes apart per time point) and transmitted electronically for central reading.

e. Screening samples may be collected up to 28 days prior to C1D1. End of treatment bone marrow sample does not need to be repeated if collected within 2 weeks of the last disease assessment. Samples must be submitted to a central laboratory for analysis. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.

Footnotes continued on next page

f. Samples must be submitted to a central laboratory for analysis. If a participant achieves CR at any point during the treatment period and ASP7517 is not continued, an EoT visit should be performed and the participant should proceed to observation period 1.

g. Whole blood and buccal swab for optional PGx study may be collected at C1D1 prior to first investigational product administration.

h. Subject enrollment in the study will be conducted via IRT transaction.

i. After dosing of ASP7517, subjects must be observed for safety for a minimum 4 hours. The safety observation will consist of 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.

j. The EoT visit will occur within 7 days of the principal investigator decision to discontinue the subject for treatment or prior to the initiation of new anticancer treatment, 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.

k. Assessment does not need to be repeated if collected at a regularly scheduled visit within 3 days of EoT visit.

l. Telephone contact for survival status and subsequent anti-cancer treatments and outcomes.

m. After the first 2 cycles of treatment, subjects who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as achieve CRc or PR for AML and CR, BM CR or PR or HI for MDS or other clinical benefits, as determined by the investigator) will continue further treatment of ASP7517 as decided by the investigator.

n. After the first 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. If a participant experiences CR during cycle 5 or 6 (except if confirmed on day 1 of these cycles), the participant can complete the cycle and EoT will be performed as defined in footnote "j".

o. Extramedullary disease assessment is required at screening, day 1 of every cycle starting with cycle 2, EoT, and observation visits.

Table 15 Alternative Schedule of Post-Treatment Period Assessments in Response to a Crisis for Dose Escalation and Dose Expansion

Assessments	Alternate Approach(es)	Post-Treatment Period							
		Observation Period 1						Observation Period 2	
		12 weeks or until 1 post-treatment discontinuation criterion is met						Until 1 post-treatment discontinuation criterion is met	
Visit Week		**2**	**4**	**6**	**8**	**10**	**12**	**Monthly Safety Assessment Visit**	**Assessment Visit Every 3 months**
Window (days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Physical Examination[a]	Can be obtained at local facility and results submitted to PI	X	X	X	X	X	X	X	X
Disease Assessment	Except for IP administration days, assessment can be performed locally and results submitted to PI	X	X	X	X	X	X	X	X
Vital Signs	Exams can be performed at a local clinic per SOC and results submitted to PI for evaluation	X	X	X	X	X	X	X	X
ECOG Performance	Can be completed by phone contact	X	X	X	X	X	X	X	X
Concomitant Medications[i]	Can be completed by phone contact	X	X	X	X	X	X	X	X
12-Lead ECG[b]	Except for IP administration days, assessment may be performed, as possible, at a local clinic and results submitted to PI. If cannot be performed, Astellas medical monitor to assess for study continuation.	X	X	X	X	X	X	X	X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[g]	Collection of samples at local facility acceptable if results can be made available to investigative site	X	X	X	X	X	X	X	X

Table continued on next page

Assessments	Alternate Approach(es)	Post-Treatment Period							
		Observation Period 1						Observation Period 2	
		12 weeks or until 1 post-treatment discontinuation criterion is met						Until 1 post-treatment discontinuation criterion is met	
Visit Week		**2**	**4**	**6**	**8**	**10**	**12**	**Monthly Safety Assessment Visit**	**Assessment Visit Every 3 months**
Window (days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Pregnancy Test for WOCBP	Test may be performed at local clinical and result submitted to PI	X	X	X	X	X	X	X	X
Bone Marrow Aspiration and/or Biopsy[c]	Except for IP administration days, may be obtained locally and results submitted to PI						X[h]		X
Blood Sample for Disease Assessment[d]	Except for IP administration days, may be obtained locally and results submitted to PI		X		X				X
AE/SAE Assessment	Completed by phone contact allowed with further assessment at local clinic if needed	X	X	X	X	X	X	X	X
Pharmacokinetic: Blood Sample for Cell Kinetics	None	See Table 5 for detailed sample time points							
Blood Sample for WT1 Expression	None		X		X		X[j]		X[f]
Blood Sample for Immune Response Biomarker (ELISpot)	None		X		X		X[j]		X[e]
Blood Sample for Immune Response Biomarker (Tetramer)	None		X		X		X[j]		X[f]
Blood Sample for Immune Cell Phenotyping	None		X		X		X[j]		X[e]
Blood Sample for Cytokines	None		X		X		X[j]		X[e]

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; HLA: human leukocyte antigen; PI: principal investigator; SAE: serious adverse event; WOCBP: women of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Height measurement performed only at screening.

b. The 12-lead ECGs will be recorded as a single assessment (in triplicate if deemed necessary, at least 2 minutes apart per time point) and read locally.

Footnotes continued on next page

c. After the completion of Observation Period 1 (12 weeks), subjects remaining in the study will have bone marrow samples collected in Observation Period 2 every 3 months or if there is suspicion of relapse in the whole blood. Samples must be submitted to a central laboratory for analysis. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional ethylenediaminetetraacetic acid tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.
d. Samples must be submitted to a central laboratory for analysis.
e. Maximum of 1 sample collected during Observation Period 2.
f. Maximum of 5 samples collected during Observation Period 2.
g. Laboratory samples will be analyzed by the institution's local laboratory and results will be submitted for centralized data entry. Subjects who are transfusion dependent should be subjected to more frequent laboratory assessments to determine transfusion need based on the judgment of the investigator.
h. Subjects not proceeding to observation period 2 are required to provide a bone marrow sample at the last visit of observation period 1.
i. Concomitant medications and AEs are collected until post-treatment period and at least 30 days after last IP dose and prior to the start of new anticancer treatment. In addition, the following will be collected regardless of the start of new anticancer therapy: Any IP-related SAE that is ongoing will be followed until resolved, and any SAE that is deemed to be related to IP by the investigator.
j. Applicable only for subjects in dose expansion phase.

Table 16 Alternative Schedule of Assessments of Replication Competent Lentivirus for Dose Escalation and Dose Expansion in Response to a Crisis

Assessment	Alternate Approach(es)	C1D1	3 Months After Treatment Initiation or End of Treatment, Whichever is First	6 Months After Treatment Initiation	12 Months After Treatment Initiation	18 Months After Treatment Initiation[c]
Window		0	± 1 day	± 1 month	+1 month	±1 month
Blood Sample for RCL[a]	None: to collect at the first time subject is able to come to the clinic	X[b]	X	X	X	X

C1D1: cycle 1 day 1; RCL: replication competent lentivirus

a. If there are positive results, additional follow-up assessments may be required. Refer to [Section 7.6.4 Sample for Replication Competent Lentivirus].

b. Obtained predose.

c. Only applicable to subjects in the expansion cohort.

INVESTIGATIONAL PRODUCT SUPPLY

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

- Increase stock of IP on site to reduce number of shipments required, if site space will allow.

DATA COLLECTION REQUIREMENTS

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

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

12.10 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviations	Description of Abbreviations
aAVC	artificial adjuvant vector cell
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APGD	Astellas Pharma Global Development Inc.
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR-ABL	breakpoint cluster region-Abelson-positive leukemia
BM	bone marrow
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal phase 2
C1D1	cycle 1 day 1
C2D1	cycle 2 day 1
CA	competent authorities
C_{max}	maximum concentration
CR	complete remission
CRc	composite complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematological recovery
CRp	complete remission with incomplete platelet recovery
CRO	contract research organization
CRS	cytokine-release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
C_{trough}	trough concentration; the lowest concentration reached by a drug before the next dose is administered
CV	coefficient of variation
DESC	dose escalation and safety committee
DLT	dose limiting toxicity
DPD	Data Protection Directive
ECG	electrocardiogram

Abbreviations	Description of Abbreviations
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
EFS	event-free survival
EoT	end-of-treatment
FAS	full analysis set
FiH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HI	hematologic improvement
HIPAA	Health Insurance Portability and Accountability Act
HLA	human leukocyte antigen
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IRR	Infusion-related reactions
IRT	interactive response technology
ISN	international study number
iv	intravenous
LA-CRF	liver abnormality case report form
LFT	liver function test
MDS	myelodysplastic syndrome
mRNA	messenger RNA
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI-CTCAE	National Cancer Institute’s common terminology criteria for adverse events
NE	not evaluable
NK	natural killer

Abbreviations	Description of Abbreviations
NKT	natural killer T
NR	no response
ORR	objective response rate
OS	overall survival
PGx	pharmacogenomics
PKAS	pharmacokinetic analysis set
PR	partial remission
QA	quality assurance
QC	quality control
QTcF	QT corrected by Fridericia's Correction formula
R/R	relapsed/refractory
RBC	red blood cell
RCL	replication competent lentivirus
RP2D	recommended phase 2 dose
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TBL	total bilirubin
t_{max}	time of maximum concentration
ULN	upper limit of normal
USM	urgent safety measure
WOCBP	woman of childbearing potential
WT1	Wilms’ tumor 1protein

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of subjects as they enter a study before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a study. Note: Once a subject has received the investigational product or placebo, the protocol applies to the subject.
Intervention	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a subject, and continues until the last assessment after completing administration of the test product or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. Note: Unequal randomization is used to allocate subjects into groups at a differential rate; for example, 3 subjects may be assigned to a treatment group for every one assigned to the control group.
Screening	A process of active consideration of potential subjects for enrollment in a study.
Screen failure	Potential subject who signed the informed consent form, but did not meet 1 or more criteria required for participation in the study and was not enrolled.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 5

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol 7517-CL-0101 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)

Amendment 5 Nonsubstantial 19 Sep 2022

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to update the protocol to adjust study timelines, provide clarification and correct errors.

Summary of Changes

Table 1 Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
Clinical Research Contacts, 14	Contact details for the clinical research contacts are updated.	Contact details of sponsor personnel are updated based on changes to study personnel.
1.1	The approximate study end date is adjusted from 4Q2022 to 4Q2024.	To update timelines for this study.
1.3 (Table 1)	Cycle 2 blood sample for Anti-HLA Antibody moved from day 1 to day 15.	Updated to correct an error.
1.3 (Table 5)	Several PK time point sampling windows changed from 15 to 10 minutes.	To obtain accurate PK samples as defined in Table 5.
12.2.2.4	Replace QTL text in Quality Assurance section with bullet point from current template.	To reflect the current protocol template version. QTL definitions and details will be managed in a separate plan.

14 SPONSOR SIGNATURES

Astellas Signatories

(Electronic signatures are attached at the end of the document.)

PPD Medical Science

PPD Data Science