CLINICAL STUDY PROTOCOL

A PHASE I STUDY OF DS-3201b IN SUBJECTS WITH ACUTE MYELOGENOUS LEUKEMIA (AML) or ACUTE LYMPHOCYTIC LEUKEMIA (ALL)

DS3201-A-U102

IND NUMBER: 132312/147600

VERSION 6.0, 29 JUN 2020

DAIICHI SANKYO, INC.
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INVESTIGATOR AGREEMENT

A Phase I Study of DS-3201b in Subjects with Acute Myelogenous Leukemia (AML) or Acute Lymphocytic Leukemia (ALL)

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo Inc. representative listed below.

PPD	PPD
Print Name	**Signature**
Senior Director, Global Oncology R&D	29-June-2020
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

IND Number:	132312/147600
Protocol Number:	DS3201-A-U102
Investigational Product:	DS-3201b
Active Ingredient(s)/INN:	(2R)-7-Chloro-2-[trans-4-(dimethylamino)cyclohexyl]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2,4-dimethyl-1,3-benzodioxole-5-carboxamide mono(4-methylbenzenesulfonate)
Study Title:	A Phase 1 Study of DS-3201b in Subjects with Acute Myelogenous Leukemia (AML) or Acute Lymphocytic Leukemia (ALL)
Study Phase:	Phase 1
Indication Studied:	DS-3201b will be evaluated in subjects with relapsed or refractory AML or ALL.
Study Objectives:	**Part 1 (Dose Escalation)** Primary Objectives: 1. To assess the safety and tolerability of DS-3201b in subjects with relapsed/refractory AML or ALL. 2. To determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE) of DS-3201b in subjects with relapsed/refractory AML or ALL. Secondary Objectives: 1. To assess the plasma pharmacokinetics (PK) after single and multiple doses of DS-3201b. Exploratory Objectives: 1. To assess the pharmacodynamics (PDy) of DS-3201b, such as trimethylation status of lysine 27 in histone H3 (H3K27) and quantitation of leukemic stem cells, in pre- and post-dose blood and/or bone marrow samples. 2. To evaluate response to DS-3201b per the revised International Working Group (IWG) response criteria (Cheson, 2003) in subjects with relapsed/refractory AML or National Comprehensive Cancer Network (NCCN)

	response criteria in subjects with relapsed/refractory ALL.
	Part 2 (Dose Expansion) Primary Objective: 1. To confirm the safety and tolerability of DS-3201b at the RDE in subjects with relapsed/refractory AML and ALL. Secondary Objectives: 1. To assess overall response rate (ORR) in subjects with relapsed/refractory AML and ALL using the revised IWG response criteria (Cheson, 2003) and NCCN response criteria, respectively, duration of response (DOR), and overall survival (OS). 2. To assess the PK after single and multiple doses of DS-3201b. Exploratory Objectives: 1. To evaluate the relationship between response rate in relapsed/refractory AML and ALL and cytogenetic and molecular-based biomarkers studied in pre-treatment bone marrow biopsies and/or blood samples. 2. To assess the PDy of DS-3201b. 3. To compare complete remission (CR) duration between that observed with DS-3201b treatment and that observed from the most recent therapeutic regimen.
Study Design	This will be a Phase 1, non-randomized, open-label study of DS-3201b in subjects with relapsed/refractory AML or ALL. Dose regimen DS-3201b will be administered orally once daily over a 28-day cycle (1 Cycle). In the first cohort, study treatment initiation will be staggered. A delay of at least 7 days will occur between the first subject dosed and the second and third subjects dosed. In subsequent cohorts, the study treatment can be started in the second and third subjects one day after first administration in the first subject. The starting dose will be 100 mg/day as a single dose. The dose will be administered without food (no food for at least 2 hours before and 1 hour after the dose). A missed dose of DS-3201b may be administered later that same day (until midnight). The dose will be assessed as a missed dose if not administered. No

replacement dose is administered if the subject vomits after taking DS-3201b.

Part 1 (Dose Escalation)

Dose escalation of DS-3201b to determine the MTD will be guided by a Bayesian logistic regression model (BLRM) (Neuenschwander et al., 2008), following the escalation with overdose control (EWOC) principle. The logistic regression model for the dose-limiting toxicity (DLT) rate will include 2 parameters: the intercept and the slope. After the first 3 subjects of each cohort complete the DLT evaluation during Cycle 1, the posterior distributions of the DLT rate will be derived for all provisional dose levels based on the BLRM using the DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level ([0%, 16%) as the DLT rate interval for under-dosing, [16%, 33%) as the target DLT rate interval, [33%, 60%) as the DLT rate interval for excessive toxicity, and [60%, 100%] as the DLT rate interval for unacceptable toxicity) will then be calculated and used for dose recommendation for the next cohort according to the EWOC principle.

The EWOC principle requires that the BLRM recommended dose for the next cohort of subjects is defined as the highest posterior probability of the DLT rate in the target DLT rate interval [16%, 33%) among all dose levels fulfilling the overdose control constraint there is less than 25% probability for the DLT rate >33% (probability for excessive or unacceptable toxicity). The dose increments will be as follows:

- The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure, but flexibility may be applied in selecting the dose to accommodate the available dosage form strengths.
- The dose level increment should be no more than 100% even if the model suggests a higher dose than 100% for the next cohort.
- In the event of a DLT, the next 2 subjects will receive DS-3201b treatment starting at least 1 week apart.

Cohorts of 3 to 6 subjects will be enrolled and assessed for DLT before escalation to a new higher dose. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 evaluable subjects experience DLT before the enrollment of the next subject after the BLRM dose recommendation. The dose for the next cohort will be chosen by the Sponsor and Principal Investigators based on the dose recommendation by the BLRM, clinical assessment of toxicity profiles and efficacy, and PK/PDy information observed thus far. Based on the safety results available so far from the Phase 1 study of DS-3201b currently ongoing in Japan (DS3201-A-J101), escalation from the starting dose of 100 mg to the second dose level will be by less than 100%. Enrollment of subjects to a new cohort requires completion of a DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed a DLT evaluation nor experienced a DLT will not be included in the BLRM update. In the event that subjects in the previous cohort experience a DLT after the enrollment of subjects to a new cohort has begun, dose level assignment of the next subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed doses.

- For a subject to be considered evaluable for dose escalation decisions, the subject must have received at least 75% of the doses (ie, 21 days) during the DLT evaluation period, or experienced a DLT in Cycle 1. The final MTD will be decided based on considerations of the respective MTD estimated by the BLRM, and on an overall assessment of safety data from subsequent cycles and of PK/PDy response collected at all different doses tested. For dose determination, the following stopping rules will be implemented for the Dose Escalation part: (a) at least 6 evaluable subjects at the MTD level with at least 21 evaluable subjects in total enrolled in the Dose Escalation part, or (b) at least 9 evaluable subjects have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level 1 is too toxic.

Cohorts may be expanded below the MTD dose level (at any time following conclusion of that cohort's safety window) or at the MTD in parallel with ongoing escalation up to a maximum of 20 subjects in each cohort for further elaboration of safety, PK, or PDy response parameters as deemed appropriate by Investigators and the Sponsor in order to define the RDE.

Part 2 (Dose Expansion)

Upon completion of Part 1 with the established MTD/RDE and drug administration schedule, the Dose Expansion part will begin with the intention of confirming the safety and tolerability of DS-3201b and evaluating preliminary efficacy of DS-3201b in 2 separate cohorts of subjects with relapsed or refractory AML and ALL.

Four subjects with AML and 4 subjects with ALL will initially be treated to further assess safety before enrolling the remaining subjects in the respective cohorts of AML and ALL. Following completion of Cycle 1 safety evaluations in all 4 subjects in the cohort, a safety analysis will be conducted to allow the re-evaluation of the appropriateness of the dosing level. If the incidence of DLTs has exceeded the EWOC principle guideline, no further treatment at the MTD/RDE level established in Part 1 will be done and dose de-escalation will be considered. Approximately 20 subjects each with AML and ALL will be enrolled in Part 2 to obtain a sufficient number of subjects treated at the RDE in these indications.

Pre-treatment bone marrow biopsies/aspirates will be required for participation in the study, and optional post-treatment bone marrow biopsies/aspirates may be collected within 30 days following the last dose of study drug treatment.

Dose-Limiting Toxicity Definition

Dose-limiting toxicity is defined as a clinically significant non-hematologic treatment-emergent adverse event (TEAE) or abnormal clinical laboratory value that are clearly not related to disease progression, intercurrent illness, and occurring during the first cycle (28 days) on study that meets any of the following criteria:

- National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (CTCAE), Version 4 Grade 3 aspartate aminotransferase (AST) (SGOT) or alanine aminotransferase (ALT) (SGPT) or bilirubin for ≥7 days.
- NCI-CTCAE Grade 4 AST (SGOT) or ALT (SGPT) of any duration.
- All Grade 4 non-hematologic toxicities of any duration.
- Any Grade 5 toxicity, unless proven to be clearly and incontrovertibly related to disease progression or intercurrent illness will constitute a DLT.

- All other clinically significant, non-hematological NCI-CTCAE Grade 3/4 adverse events (AEs).

  Exceptions are as follows:

  - Grade 3 or 4 nausea, vomiting, and diarrhea that do not require hospitalization or total parenteral nutrition (TPN) support and can be managed with supportive care to ≤Grade 2 within 48 hours.
  - Alopecia and study drug-related fever will not constitute DLT.
  - Grade 3 or 4 electrolyte abnormalities that are corrected to ≤Grade 2 within 24 hours.
  - Grade 3 or 4 differentiation syndrome which improves to ≤ Grade 1 within 7 days of the start date of ≥ Grade 3 differentiation syndrome and which is not associated with end-organ damage.

Myelosuppression and associated complications are expected events during leukemia therapy. Only prolonged myelosuppression, as defined by absolute neutrophil count (ANC) $<0.5 \times 10^9$/L, platelets $<20 \times 10^9$/L, and marrow cellularity <5% on Day 42 or later (6 weeks) from start of therapy without any evidence of leukemia, will be considered in defining the MTD and DLT. DLT evaluation of myelosuppression will be decided between the Investigators and Sponsor Medical Monitor during safety review meetings.

Subjects who are unable to complete at least 75% of the prescribed dose (ie, 21 days) of DS-3201b during the DLT evaluation period as a result of non-disease-related ≥Grade 2 AEs will be considered to have a DLT.

Disease Assessment

Bone marrow biopsies/aspirates and blood samples for disease assessment will be performed according to the study schedule at baseline and on Cycle 2/Day 1 while the subject remains on study. If aplasia is observed on Cycle 2/Day 1 with no evidence of leukemia and absolute neutrophil count (ANC) $<0.5 \times 10^9$/L and platelets $<20 \times 10^9$/L, study drug may be withheld and a confirmation bone marrow assessment performed in 2 weeks. For subjects who achieve CR, a follow-up bone marrow evaluation is only required as clinically indicated. All subjects with less than a CR must have a monthly bone marrow evaluation unless >5% blasts are present in the peripheral blood,

	in which case bone marrow sampling is only required as clinically indicated. Bone marrow re-biopsy at the End-of-study (EOS) treatment To search for possible mechanisms of acquired resistance to DS-3201b, an optional bone marrow re-biopsy may be performed within 30 days following the last dose of DS-3201b treatment for subjects who have achieved an initial CR/partial remission (PR) by standard response criteria, but later developed progressive disease while on therapy (both in Dose Escalation and Dose Expansion), preferably prior to initiating new therapy. Bone marrow biopsies and leukemic cell enrichment • Bone marrow biopsies/aspirates and blood samples: Bone marrow biopsies/aspirates or blood samples for disease status/response assessments, including flow cytometry and cytogenetics (per institutional guidelines and as clinically indicated), and exploratory resistance biomarker testing will be obtained as indicated in the study schedule. For Part 1 and Part 2, a bone marrow evaluation is required for all subjects at screening. • Leukemic cell enrichment: Blood samples and bone marrow biopsies/aspirates will be collected pre-treatment at baseline for all subjects and/or at the EOS for subjects who achieve a CR or PR but develop recurrence or progression. Specimens of blood and marrow may be enriched for leukemic cells for further analysis. Leukemic stem cell samples collected from pre- and post-dose bone marrow aspirates will be quantified by flow cytometry and/or mass cytometry and blood and/or bone marrow cells may be examined for H3K27 trimethylation (H3K27me3) status.
Study Duration:	The study duration is expected to last approximately 5 years from the time the first subject is enrolled in Part 1 of the study and including follow-up period (EOS follow-up and long-term follow-up). The number of treatment cycles is not fixed in this study. Subjects who continue to derive clinical benefit from treatment in the absence of withdrawal of subject consent, progression, or unacceptable toxicity may continue treatment cycles. Subjects in Part 1 and Part 2 who are still on study at least 6 months after enrollment of the last subject in the study

	may be eligible to continue receiving study drug in a separate extension phase of the protocol. Data collected from those subjects may be captured in a separate database.
Study Sites and Location:	Up to 10 sites in the United States are planned.
Planned Sample Size:	The Dose Escalation part of the study will enroll 3 to 6 subjects in each cohort, based on a BLRM under the EWOC principle. It is possible that a dose level may enroll more than one cohort based on the BLRM recommendation. The number of subjects enrolled depends on the observed DLTs, but it is expected that 21 or more subjects might be enrolled in the Dose Escalation part. For the Dose Expansion part, additional subjects will be enrolled at the RDE dose level as suggested based on data in the Dose Escalation part. Forty subjects, 20 subjects each with AML or ALL, will be enrolled at the RDE dose level, including those dosed at the same dose level in the Dose Escalation part, which is expected to number between 6 and 9 subjects. The size of 40 is deemed to be sufficient for the assessment of safety and tolerability, as well as the clinical antitumor activity. Assuming a true composite complete remission (CRc) rate of 20%, the probability of observing 3 or more CRc among the 20 subjects is 79.4%.

Subject Eligibility Criteria:	**Inclusion Criteria**
	
	1. Subjects with AML diagnosed according to WHO 2008 criteria and ALL that have failed any prior induction therapy regimen or have relapsed after prior therapy.
	   • Subjects with acute promyelocytic leukemia (APL) must be resistant and/or intolerant to both trans-retinoic acid (ATRA) and arsenic trioxide based-therapies to be considered for inclusion.
	2. Age ≥18 years old.
	3. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
	4. Has adequate renal function, defined as:
	   • Creatinine clearance ≥60 mL/min as calculated using the modified Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) formula OR serum creatinine ≤1.5 × upper limit of normal (ULN).

5. Has adequate hepatic function, defined as:
    - AST/ALT ≤3 × ULN (≤5.0 × ULN if due to leukemic involvement), and
    - Total bilirubin ≤2.0 × ULN (or ≤3.0 × ULN if deemed to be elevated due to Gilbert's disease or leukemia), and
    - International normalized ratio (INR), prothrombin time, and activated partial thromboplastin time (aPTT) ≤1.5 × ULN.
6. The interval from prior treatment with cytotoxic agents or noncytotoxic/hypomethylating/ investigational/biologic agents to time of initiation of DS-3201b administration will be at least 14 days after the final dose (except hydroxyurea, which is allowed until 48 hours prior to start of the study treatment).
7. Subject should be able to provide written informed consent, comply with protocol visits and procedures, be able to take oral medication, and not have any active infection or comorbidity that would interfere with therapy.
8. Women of childbearing potential and their partner must agree to use an adequate method of contraception during the study and until 3 months after the last treatment, and must not retrieve ova or donate from the time of screening and throughout the study treatment period and for ≥3 months after the final dose of study drug. Males and their partner must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment, and must not freeze or donate sperm starting at screening and throughout the study period and for ≥3 months after the final dose of study drug.
9. Is willing to provide bone marrow biopsies and comply with evaluations as requested by protocol.
10. Has a life expectancy of at least 3 months.

Exclusion Criteria

1. Presence of central nervous system (CNS) involvement of leukemia or a history of CNS leukemia.

2. Has a second concurrent active primary malignancy such as solid tumor or lymphoma under active treatment.
3. Refractory nausea and vomiting, malabsorption, biliary shunt, significant bowel resection, graft-versus-host disease (GVHD) significantly affecting gut motility or absorption, or any other condition that would preclude adequate absorption of DS-3201b in the opinion of the treating physician and/or Principal Investigator.
4. Has an uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals, known human immunodeficiency virus infection, or active hepatitis B or C infection tested at screening. Infections controlled on concurrent anti-microbial agents are acceptable and anti-microbial prophylaxis per institutional guidelines is acceptable.
5. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator or Sponsor.
6. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE, Version 4 ≤Grade 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator and Sponsor (eg, Grade 2 chemotherapy-induced neuropathy).
7. Receipt of hematopoietic cell transplantation (HCT) within 60 days of the first dose of DS-3201b.
8. Is receiving concomitant treatment with a strong inhibitor or inducer of cytochrome P450 (CYP)3A within 7 days of first receipt of DS-3201b.
9. Consumption of herbs/fruits that may have an influence on PK of DS-3201b, such as star fruit, Seville orange or Seville orange-containing foods and beverages, and grapefruit or grapefruit-containing food or beverages from 3 days prior to the first dose of DS-3201b up to the last dose of DS-3201b. St. John's wort (hypericin) will not be permitted from 14 days prior to the first dose of DS-3201b up to the last dose of DS-3201b.
10. Had major surgery within 4 weeks before study drug treatment.

	11. Prolongation of corrected QT interval by Fridericia's method (QTcF) at rest, where the mean QTcF interval is >450 milliseconds (ms) based on triplicate electrocardiograms (ECGs), additional risk factors for torsade des pointes (TdP; eg, active congestive heart failure or cardiomyopathy with New York Heart Association [NYHA] Grade 3/4 dyspnea or clinically significant rhythm abnormalities, hypokalemia, family history of Long QT Syndrome). 12. Pregnant or breastfeeding. 13. Substance abuse or medical, psychological, or social conditions that, in the opinion of the Investigator, may interfere with the subject's participation in the clinical study or evaluation of the clinical study results. 14. Prior treatment with enhancer of zeste homolog (EZH) inhibitor.
Dosage Form, Dose and Route of Administration:	DS-3201b is supplied as 25 mg and 100 mg capsules packaged in high-density polyethylene (HDPE) bottles. DS-3201b is administered orally at a starting dose of 100 mg once a day until disease progression.
Study Endpoints:	**Pharmacokinetic and Pharmacodynamic Parameters:** <u>Pharmacokinetic Parameters</u> Cycle 1/Days 1 and 2 (Part 1 and Part 2): • Maximum (peak) plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the plasma concentration-time curve up to the last quantifiable time (AUClast) • If appropriate: Area under the plasma concentration-time curve up to infinity (AUCinf), terminal elimination half-life (t1/2), apparent total body clearance following a single dose administration (Cycle 1/Day 1) (CL/F), apparent volume of distribution based on the terminal phase after a single dose administration (Vz/F) Cycle 1/Day 8 (Part 1 and Part 2): • Cmax, Tmax, AUClast, and comparison of Cmax and AUClast values between Day 8 and Day 1 (Cmax and AUClast ratio) (d8,d1) • If appropriate: Area under the plasma concentration-time curve during dosing interval (AUCtau), AUCinf,

t1/2, apparent total body clearance at steady state following multiple dose administration (Cycle 1/Day 8) (CLss/F), apparent volume of distribution at steady state after multiple-dose administration (Vss/F)

Cycle 1/Days 2, 8, 15, and 22 and Cycle 2/Day 1 (Part 1 and Part 2):

- Trough plasma concentration (Ctrough)

End-of-treatment (Part 1 and Part 2):

- Ctrough

Exploratory Biomarker Parameters

- Exploratory molecular testing in blood cells and/or bone marrow cells (at pre-dose and post-dose time points)
- Retrospective confirmatory analysis and correlation with pre-therapy cytogenetic and molecular subsets of AML or ALL to response

Pharmacodynamic Biomarker Parameters

- Quantitation of leukemic stem cells in pre- and post-dose bone marrow cells by flow cytometry and/or mass cytometry
- H3K27me3 status in leukemic stem cells in bone marrow and/or blood cells

Efficacy Parameters:

Primary efficacy variable is response to treatment, which will be defined per the revised IWG response criteria for AML (Cheson, 2003) or standard response criteria for ALL (NCCN 2016 ALL response criteria).

The efficacy endpoints will be:

- CRc rate, including CR, complete remission with incomplete blood count recovery (CRi), and complete remission with incomplete platelet recovery (CRp)
- Morphologic leukemia-free state (MLFS)
- Partial remission (PR) rate
- Overall response rate (ORR) = CRc+PR
- DOR: Time from the first objective evidence of response to the first objective evidence of disease progression

	• OS: Time from the date of enrollment to the date of death from any cause • 30- and 60-day mortality rate **Safety Parameters:** Safety parameters will include AEs, DLTs, serious adverse events (SAEs), TEAEs, physical examination findings (including Eastern Cooperative Oncology Group – Performance Status [ECOG-PS]), vital sign measurements, standard clinical laboratory parameters, histamine level in plasma, and electrocardiogram (ECG) parameters. Adverse events will be graded according to the NCI-CTCAE, Version 4. In the Dose Escalation part, the incidence of DLTs will also be evaluated.
Statistical Analyses:	Demographic, safety, efficacy, and PK parameters as well as the free form of DS-3201b (DS-3201a) plasma concentrations will be summarized by dose level/study day/time points, as appropriate. Descriptive statistics on continuous variables will include means, medians, standard deviations, minimum, and maximum (as well as geometric means and geometric coefficient of variation for Cmax and area under the plasma concentration-time curve [AUC] PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. <u>Safety Analyses</u>: Frequency tables of subjects reporting TEAEs will be provided by the worst NCI-CTCAE grade, system organ class (SOC), preferred term, and by dose level. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as treatment-related TEAEs. The incidence of DLTs will be tabulated by dose level. Descriptive statistics by dose level will be provided on clinical laboratory parameters, histamine level in plasma, ECG parameters, and vital signs measurements, including the reported values and changes from baseline at each scheduled measurement. Frequency tables by dose level will be provided for physical examination and ECOG-PS, and other categorical assessments as appropriate. <u>Efficacy Analyses</u>: Response to treatment will be evaluated using the revised IWG response criteria for AML (Cheson, 2003) or the NCCN response criteria 2016 for ALL. The efficacy endpoints will be

CRc rate (including CR, CRi, and CRp), MLFS, PR rate, ORR, DOR, OS, and 30- and 60-day mortality rate.

For the binary efficacy endpoints, the point estimate and exact 95% confidence interval will be provided by dose level and overall. Time-to-event variables, such as DOR and OS, will be analyzed using the Kaplan-Meier method by dose level and overall.

The best overall response will be determined for each subject, in the order of CR, CRp or CRi, PR, and treatment failure (TF). For each category as well as response (CRc or PR), the point estimate and 95% confidence interval will be calculated for the proportion, by dose level, and overall.

OS is the time from the first dose of DS-3201b to death. The censoring rules will be specified in the statistical analysis plan (SAP).

Pharmacokinetic Analyses:

Plasma concentrations for DS-3201a will be listed, plotted, and summarized using descriptive statistics by dose level/study day at each nominal time point. Pharmacokinetic parameters will be listed and summarized using descriptive statistics by dose level/study day.

Biomarker Analyses:

Descriptive statistics will be used to summarize the reported values and changes from baseline of the biomarkers by dose level and by scheduled measurement. They include:

Exploratory Biomarkers

- molecular testing in blood cells and/or bone marrow cells
- cytogenetic and molecular subsets of AML and ALL

Pharmacodynamic Biomarkers

- leukemic stem cells in pre- and post-dose bone marrow cells
- H3K27me3 status in leukemic stem cells in bone marrow and/or blood cells

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DOCUMENT HISTORY

Version Number	Version Date
6.0	29 Jun 2020
5.0	24 Apr 2020
4.0	10 Aug 2017
3.0	01 Mar 2017
2.0	12 Dec 2016
1.0	31 Oct 2016

SUMMARY OF CHANGES

Amendment Rationale:

The main purpose of this amendment is to clarify that the exception for the dose-limiting toxicity of differentiation syndrome is for Grade 3 or 4 differentiation syndrome which improves to ≤ Grade 1 within 7 days of the start date of ≥ Grade 3 differentiation syndrome and which is not associated with end-organ damage.

Changes to the Protocol:

Please refer to the comparison document for protocol Version 6.0 (dated 29 Jun 2020) vs. protocol Version 5.0 (dated 24 Apr 2020) for actual changes in-text. The summary of changes below is a top-line summary of major changes in the DS3201-A-U102 study protocol (Version 6.0) by section.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES
All locations (Section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.
Minor edits, such as update to language that does not alter original meaning, update to version numbering, formatting, change in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or change in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
• Synopsis: Study Duration	Added "(EOS follow-up and long-term follow-up)" after follow-up period	To clarify that the follow-up period includes the EOS follow-up visit and long-term follow-up.
• Synopsis: Exclusion 11	Removed "or use of concomitant medications that prolong the QT/QTc interval"	Correction to match Section 4.1.2.
• Synopsis: Dose-limiting Toxicities • 3.1.7.2 Dose-limiting Toxicities • 3.1.8. Maximum Tolerated Dose and Recommended Dose for Expansion Definition	Exception of differentiation syndrome as a dose-limiting toxicity is defined as Grade 3 or 4 differentiation syndrome which improves to ≤ Grade 1 within 7 days of the start date of ≥ Grade 3 differentiation syndrome and which is not associated with end-organ damage.	To clarify the requirements associated with differentiation syndrome as an exception as a dose-limiting toxicity
• 3.1.8. Maximum Tolerated Dose and	Changed 5 to 4 subjects for safety assessment in the	Correction to match synopsis

Section # and Title	Description of Change	Brief Rationale
Recommended Dose for Expansion Definition	Dose Expansion cohort, third paragraph.	
• 6.4 Long-term Follow-up	Changed "30-day safety follow- up visit" to "EOS follow-up visit (30 [± 5] day safety, Section 6.3.1.11 and Section 6.3.2.12)"	Correction to match the rest of the document.
• 7 Efficacy Assessments	Added Cycle 1 Day 8 to the timing of efficacy assessments	Correction to match schedule of events.
• 15.2 Address List	Added "A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in the Study Site Manual." Deleted Subsections 15.2.1.1 through 15.2.1.3 with Sponsor specific information	Modified to provide guidance on location of all key study personnel information.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AAG	Alpha 1-acid glycoprotein;
AE	Adverse event
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASR	Age standardized rate
AST	Aspartate aminotransferase
ATL/L	Adult T-cell leukemia-lymphoma
AUC	Area under the plasma concentration-time curve
AUCinf	Area under the plasma concentration-time curve up to infinity
AUClast	Area under the plasma concentration-time curve up to the last quantifiable time
AUClast ratio	Comparison of AUClast values between Day 8 and Day 1
AUCtau	Area under the plasma concentration-time curve during dosing interval
BLRM	Bayesian logistic regression model
Cmax	Maximum plasma concentration
Cmax ratio	Comparison of Cmax values between Day 8 and Day 1
Ctrough	Trough plasma concentration
CFR	Code of Federal Regulations
CL/F	Apparent total body clearance
CLss/F	Apparent total body clearance at steady state
CNS	Central nervous system
CR	Complete remission
CRc	Composite complete remission
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CRF	Case report form
CRO	Contract research organization
CSPV	Clinical Safety and Pharmacovigilance

ABBREVIATION	DEFINITION
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRF	Dose range finding
DS-3201a	The free form of DS-3201b
DSI	Daiichi Sankyo, Inc.
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure in utero
EOS	End-of-study
EOT	End-of-treatment
EWOC	Escalation with overdose control
EZH	Enhancer of zeste homolog
FOB	Functional observational battery
F/U	Follow-up
GCP	Good Clinical Practice
GI_{50}	Concentrations causing 50% growth inhibition
GLP	Good Laboratory Practice
GVHD	Graft-versus-host disease
H3K27	Lysine 27 in histone H3
H3K27me3	H3K27 trimethylation
hERG	Human ether- à -go-go related gene
HNSTD	Highest non-severely toxic dose
HCT	Hematopoietic cell transplantation
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio

ABBREVIATION	DEFINITION
IRB	Institutional Review Board
IWG	International Working Group
MDRD	Modification of Diet in Renal Disease
MLFS	Morphologic leukemia-free state
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
ND	Not determined
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PEG	Polyethylene glycol
P-gp	P-glycoprotein
PJP	Pneumocystis jiroveci pneumonia
PRC2	Polycomb repressive complex 2
PD	Progressive disease
PDy	Pharmacodynamics
PEG	Polyethylene glycol
PK	Pharmacokinetics
PR	Partial remission
PRC2	Polycomb repressive complex 2
PT	Preferred term
QD	Once daily
QT_cB	Corrected QT interval using Bazett's formula
QT_cF	Corrected QT interval using Fridericia's formula
RBC	Red blood cell
RDE	Recommended dose for expansion
SAE	Serious adverse event
SAP	Statistical analysis plan
SAVER	Serious Adverse Event Report

ABBREVIATION	DEFINITION
SCID	Severe combined immune deficiency
SD	Stable disease
SID	Subject identification number
SOC	System organ class
STD_{10}	Severely toxic dose in 10% of animals
SUSAR	Suspected Unexpected Serious Adverse Event Reaction
t1/2	Terminal elimination half-life
TBD	To be determined
TdP	Torsade de pointes
TEAE	Treatment-emergent adverse event
TGIn	Tumor growth inhibition rate (net)
TF	Treatment failure
Tmax	Time to reach maximum plasma concentration
TPN	Total parenteral nutrition
TRR	Tumor regression rate
ULN	Upper limit of normal
Vz/F	Apparent volume of distribution based on the terminal phase
Vss/F	Apparent volume of distribution at steady state
WBC	White blood cell

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Data Summary

1.1.1. Investigational Product(s)

1.1.1.1. Name

DS-3201b

Chemical Name: (2R)-7-Chloro-2-[trans-4-(dimethylamino)cyclohexyl]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2,4-dimethyl-1,3-benzodioxole-5-carboxamide mono(4-methylbenzenesulfonate)

1.1.1.2. Description

DS-3201b is a dual inhibitor of enhancer of zeste homolog (EZH) 1 and EZH 2 being developed as an oral oncology agent. DS-3201a is the free form of DS-3201b.

1.1.1.3. Intended Use Under Investigation

DS-3201b will be evaluated in subjects with acute myelogenous leukemia (AML) or acute lymphocytic leukemia (ALL) that have failed any prior induction therapy regimen or have relapsed after prior therapy in Part 1 and in Part 2.

1.1.1.4. Pharmacological Target(s)

DS-3201b is a novel, specific, small molecule inhibitor of EZH1 and EZH2. EZH1 and EZH2 are methyltransferases, which specifically methylate H3K27. EZH1 and EZH2 exert methyltransferase activity by forming a multiprotein complex termed polycomb repressive complex 2 (PRC2). There are 2 kinds of PRC2 complexes, PRC2-EZH1 and PRC2-EZH2, whose catalytic subunits are EZH1 and EZH2, respectively.

EZH2 activity confers stemness and regulates differentiation during embryonic development. Given the roles of EZH2 and H3K27me3, plastic and dynamic features of cancer cells, especially cancer stem cells, may be closely associated with this epigenetic mechanism. EZH2 overexpression is implicated in tumorigenesis, and correlates with poor prognosis in several tumor types; a higher level of EZH2 expression is sometimes associated with aggressiveness of tumors. Since the PRC2-H3K27me3 regulatory mechanism dynamically changes gene expression in response to extracellular signals, it may confer plastic behavior on a certain population of cancer cells within tumors.

EZH2 was previously understood to be the sole histone methyltransferase which methylates H3K27 and mediates transcriptional silencing. However, it is now recognized that EZH1 also acts as an H3K27 methyltransferase in vivo and in vitro, and that the roles of EZH1 and EZH2 are complementary; for example, EZH1 mediates methylation on H3K27 and complements EZH2 in maintaining stem cell identity and executing pluripotency.

1.1.1.5. Nonclinical Studies

1.1.1.5.1. Pharmacology

Three in vitro studies provide evidence for the pharmacological activity/mechanism of action of DS-3201b. The inhibitory effects of DS-3201b on the methyltransferase activities of EZH1 and EZH2 were determined using a direct incubation method. For EZH2-inhibition, DS-3201b had similar activity (half maximal inhibitory concentration [IC_{50}] 6.0 nM) to comparator EZH2 inhibitors, and greater EZH1 inhibition activity (IC_{50} 10 nM) than the EZH2 inhibitors. The inhibitory effect of DS-3201b on tri-methylation of H3K27 in HCT116 human colon cancer cells was established. With an IC_{50} of 0.55 nM, DS-3201b was shown to have increased suppression activity on tri-methylation of H3K27 over comparator EZH2 inhibitors. The inhibitory effects of DS-3201b on tumor cell growth against human hematopoietic cancer cell lines KARPAS-422 (diffuse large B-cell lymphoma), MV-4-11 (acute myeloid leukemia), MM.1S (multiple myeloma), and TL-Om1 (adult T-cell leukemia) were studied. DS-3201b exhibited more potent growth inhibitory activity (concentrations causing 50% growth inhibition [GI_{50}] 1.43 nM to 18.4 nM) than comparator EZH2 inhibitors, against the all 4 cell lines, suggesting that DS-3201b has high potency as an antitumor drug to induce growth inhibition against a range of hematopoietic cancer cells.

The in vitro growth inhibition data are presented in Table 1.1. After 10 days of treatment, the GI_{50} against these 4 cell lines were 1.43 nM to 18.4 nM for DS-3201b, 35.6 nM to 185 nM for E7438, and 138 nM to 957 nM for GSK126.

Table 1.1: In Vitro Growth Inhibitory Effects of DS-3201b, E7438, and GSK126

Cell line	Cancer type	GI_{50}[a] value (nM), day 10		
		DS-3201b	E7438	GSK126
KARPAS-422	DLBCL[b]	12.6	119	221
MV-4-11	AML[c]	1.43	48.3	138
MM.1S	MM[d]	2.19	35.6	139
TL-Om1	ATL[e]	18.4	185	957

a: 50% growth inhibition concentration
b: diffuse large B-cell lymphoma
c: acute myeloid leukemia
d: multiple myeloma
e: adult T-cell leukemia

An in vivo study assessed the inhibitory effect of DS-3201b on growth of subcutaneously xenografted gain-of-function mutation EZH2 expressing human diffuse large B-cell lymphoma KARPAS-422 tumors in severe combined immune deficiency (SCID) mice. The mice were treated with DS-3201b or E7438 from Day 22 for 21 consecutive days. On Day 42, 100 mg/kg of DS-3201b once daily showed tumor growth inhibition rate (net) (TGIn) of >100% and tumor regression rate (TRR) of 19.2%, and 25 mg/kg of DS-3201b once daily produced notable, but less marked, effects. On Day 42, 50 mg/kg of DS-3201b twice daily showed TGIn of >100% and TRR of 51.7%, and 12.5 mg/kg of DS-3201b twice daily produced notable, but less marked, effects. On Day 42, the dose-dependent antitumor activity was confirmed by Spearman's rank coefficient ($P \leq 0.0001$). A comparator EZH2 inhibitor (E7438) demonstrated no significant

antitumor effect at either 200 mg/kg once daily or 100 mg/kg twice daily. It was concluded that DS-3201b demonstrated high potency as an antitumor drug, exerting significant antitumor activities against gain-of-function mutation EZH2-expressing human diffuse large B-cell lymphoma KARPAS-422 tumors in a dose-dependent manner after 21 consecutive days of administration with either once daily or twice daily dosing. The antitumor activities tended to increase or continued until 13 days after final administration.

1.1.1.5.2. Safety Pharmacology

In accordance with International Council for Harmonisation (ICH) S7A and ICH S7B, safety pharmacology assessments of major physiological systems including cardiovascular, respiratory, and central nervous system (CNS) have been investigated in standalone studies and in repeated-dose toxicity studies with DS-3201b.

In cardiovascular safety pharmacology studies, the potential of DS-3201b to affect the human ether-à-go-go related gene (hERG) was evaluated in human embryonic kidney cells stably expressing hERG channel. DS-3201b inhibited the hERG tail current with a 22.7% inhibition at the highest concentration of 100 μM. Therefore, the IC_{50} for DS-3201b was >100 μM.

In the 4-week repeated-dose toxicity study in dogs, QTc interval was increased at Week 4 only in females at ≥30 mg/kg/day. In order to confirm the no observed adverse effect level (NOAEL) in this study, a telemetered dog study was conducted. QT interval and QTc interval were significantly increased in females after 7 days of dosing at 60 mg/kg/day (up to 7.2% and 8.3%, respectively), but not at 15 mg/kg/day. Therefore, DS-3201b is thought to induce a mild effect on QTc prolongation, but a dose of 15 mg/kg/day is determined to be the NOAEL in the cardiovascular safety pharmacology.

In the 4-week repeated dose toxicity study in rats, daily doses of up to 600 mg/kg produced no adverse findings in functional observational battery (FOB) studies. There was a transient decrease in rearing activity in all groups receiving DS-3201b, but this finding was not considered adverse because it was not sustained as dosing continued. In whole body plethysmography, there were no adverse effects at any dose levels. Therefore, DS-3201b was considered to have no notable effects on central nervous or respiratory systems.

1.1.1.5.3. Pharmacokinetics and Drug Metabolism

Plasma protein binding of [^{14}C]DS-3201a at the respective 0.3 μg/mL, 3 μg/mL, and 30 μg/mL were 82.4%, 79.9%, and 70.4% in mouse; 62.5%, 59.1%, and 53.0% in rat; 84.4%, 82.2%, and 57.8% in dog; and 55.6%, 58.3%, and 54.3% in human. Plasma protein binding in human was observed to be concentration-dependent in rodent and dog plasma, but not in human plasma.

The in vitro incubations of [^{14}C]DS-3201a at 10 μM with recombinant human cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 enzymes suggested that [^{14}C]DS-3201a was metabolized extensively by CYP3A4 and CYP3A5, and to a lesser extent also by CYP2C8, under these experimental conditions.

The metabolism of [^{14}C]DS-3201a was investigated at 10 μM in male rat, male dog, and mixed gender human cryopreserved pooled hepatocytes for 240 min. Following incubation of [^{14}C]DS-3201a, moderate to low metabolism was observed in preclinical species where oxidation

and N-demethylation represented the main routes. Limited metabolism was observed in human with the major routes of metabolism being oxidation.

The direct and metabolism-dependent inhibition of human CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) by DS-3201a was assessed in vitro using pooled human liver microsomes incubated with probe substrates at concentrations approximating the corresponding Km values. DS-3201a inhibited CYP3A4 (Ki 56.4 μM) with midazolam as a probe substrate. DS-3201a did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or testosterone metabolism by CYP3A4. DS-3201a showed a tendency to be a metabolism-dependent inhibitor of CYP3A4 (IC50 7.8 fold change). However, determination of kinact/KI inactivation constants suggested that DS-3201a is not a potential CYP3A4 metabolism-dependent inhibitor, since the inactivation constants were not measurable. DS-3201a did not show metabolism-dependent inhibition of the other CYPs tested.

In rats and dogs, exposures from daily dose administration up to 4 weeks in duration generally demonstrated dose-proportionality across a range of doses from sub-efficacious to above the maximum tolerated dose (MTD). There was no consistent evidence of accumulation after repeated dosing and there were no differences in exposure between males and females. T1/2 was from 2.29 hours to 7.14 hours in rats and from 1.73 hours to 5.88 hours in dogs. Tmax on Day 28 ranged from 0.5 hours to 1.3 hours in dogs and from 1 hour to 24 hours in rats.

1.1.1.5.4. Toxicokinetics

A single-dose toxicokinetic (TK) study in rats comparing oral formulations of DS-3201b in either 80% v/v polyethylene glycol (PEG) 200 and 20% v/v water or propylene glycol demonstrated no relevant differences in exposure between the formulations.

1.1.1.5.5. Toxicology

The toxicity profile of DS-3201b was evaluated in dose range finding (DRF) and definitive repeated-dose studies in rats and dogs. In rat (10, 100, or 1000 mg/kg/day) and dog (30, 100, or 300 mg/kg/day) DRF studies, DS-3201b was given once daily by oral administration for 14 days to determine the MTD. In rat (60, 200, or 600 mg/kg/day) and dog (15, 30, or 60 mg/kg/day) definitive studies, DS-3201b was administered for 4 weeks, followed by a 4-week recovery period. Phototoxicity was also assessed in an in vitro study using 3T3 mouse fibroblast cells. All toxicology studies were conducted according to Good Laboratory Practice (GLP), except for the 14-day DRF studies in rats and dogs, which were conducted under non-GLP conditions.

In the rat and dog DRF studies, DS-3201b resulted in severe toxicity and/or death at 1000 mg/kg/day in rats and at ≥100 mg/kg/day in dogs. In the 4-week definitive studies, the rats given 600 mg/kg/day and dogs given 60 mg/kg/day died with similar findings to the DRF studies: lymphoreticular/hematopoietic toxicity, gastrointestinal toxicity, and renal toxicity. The doses of 200 mg/kg/day in rats and 30 mg/kg/day in dogs were determined to be generally tolerated, although a mild QTc prolongation was detected in the dog study. In the rat study, 1 death was observed in a TK animal at 200 mg/kg/day. Reductions in body weight gain and/or body weight loss were observed as well as alterations in clinical pathology parameters, which primarily included reductions in red blood cells (RBCs), white blood cells (WBCs), and platelets with changes in related parameters. There were also transient increases in serum histamine in dogs. Clinical signs suggestive of an allergic-related reaction were also noted in dogs. The

cause for the histamine release is unclear. Compounds such as polyamines and fluoroquinolones, which are known inducers of histamine release with high sensitivity in dogs, have not translated to high sensitivity in human clinical usage.

DS-3201b-related histopathological findings were noted in similar tissues in both rats and dogs. These changes primarily included bone marrow hypocellularity, atrophy and depletion of lymphoreticular tissues, and glandular mucosal degeneration of the gastrointestinal tract that was associated with mononuclear cell inflammation. Tubular degeneration of the kidney was also noted in both species. In the rat DRF study, there was vacuolation and/or infiltration of foam cells in many organs suggestive of a drug-induced phospholipidosis (PLD). All findings in surviving animals in both the rat and dog 4-week GLP studies reversed after a 4-week recovery period. Based on these findings, the severely toxic dose in 10% of animals (STD_{10}) in rats was 200 mg/kg/day and the highest non-severely toxic dose (HNSTD) in dogs was 30 mg/kg/day.

In the 13-week GLP toxicity study in rats, DS-3201b was given to rats (15/sex/group plus 3/sex/group for TK analysis) at doses of 0 (vehicle), 20, 60, and 200 mg/kg/day once daily for 13 weeks by oral administration. Five rats/sex/group remained on a 4-week recovery period to assess reversibility of DS-3201b effects. The histopathological examination of the recovery groups is ongoing. Preliminary results from the ongoing 3-month toxicity study in rats showed the potential risk of developing lymphoid malignancies during long-term administration of DS-3201b. However, no similar findings were noted in other animal 3-month toxicity studies of DS-3201b. Additionally, there have been no reports related to this new toxicity finding in subjects currently enrolled in any of the ongoing trials. Careful monitoring is mandated to maintain an acceptable benefit-risk balance as observed in the current and future study subjects.

Preliminary results from an ongoing 3-month toxicology study in dogs suggested a potential for scrotal swelling in males administered DS-3201b. Although the scrotal lesions appear to be a new finding, this is not expected to significantly impact the on-going clinical studies since these effects can be monitored and are reversible with discontinuation of dosing. The significance of this finding is unknown at this time, but the Sponsor will continue to monitor similar events during the course of the ongoing study.

1.1.1.5.5.1. Phototoxicity

An in vitro assessment of neutral red uptake in mouse fibroblasts predicted a lack of phototoxic potential of DS-3201b.

1.1.1.5.6. Human Starting Dose

The proposed DS-3201b starting dose is 100 mg administered orally once a day, which was established based on the dog (most sensitive species) repeated-dose toxicity studies. The HNSTD in dog was 30 mg/kg (600 mg/m^2; human equivalent dose 16.7 mg/kg or approximately 1000 mg in a subject weighing 60 kg). Applying the safety factor of 10, a starting dose of 60 mg/m^2 (100 mg in a subject weighing 60 kg) was selected as the starting dose for this study. The starting dose of 100 mg by applying a safety factor of 10 is based on the preliminary observation of platelet count decrease in 5 out of 7 lymphoma patients (two Grade 3, one Grade 2, and two Grade 1) at a starting dose of 150 mg once daily (QD) in the DS3201-A-J101 Phase 1 study in Japan, although no dose-limiting toxicities (DLTs) were observed at this dose (see Section 1.1.1.6). Since the starting dose of 150 mg, as well as a dose of 300 mg that

exceeded MTD in the DS3201-A-J101 study, showed almost the same level of inhibition of H3K27 methylation in the circulating granulocytes measured as a surrogate pharmacodynamic (PDy) effect of the treatment, a lower starting dose of 100 mg in the DS3201-A-U102 study is expected to be safe and pharmacologically effective. This is further supported by the preliminary pharmacokinetic (PK) data from the DS3201-A-J101 study in which the starting dose of 150 mg achieved plasma concentrations (mean Cmax 4446 nM; plasma protein unbound fraction 1854 nM) about 2 orders of magnitude higher than the concentrations needed for inhibition of H3K27 methylation (IC50) and growth inhibition (GI50) in the in vitro preclinical pharmacology studies (see Section 1.1.1.5.1).

1.1.1.6. Clinical Experience

As of 18 Jan 2020, 7 clinical studies have been conducted (2 completed and 5 ongoing) in patients as well as in healthy subjects. A total of 173 subjects have received DS-3201b: 61 subjects with non-Hodgkin's lymphoma (NHL), 22 subjects with AML/ALL, and 90 healthy subjects. Please refer to the DS-3201b Investigator's Brochure for additional information.[1]

1.2. Background

Relapsed/Refractory AML

Acute myelogenous leukemia (AML) is a malignancy of immature granulocytes or monocytes. The malignancy is characterized by accumulation of leukemic blasts and blockade of normal bone marrow production resulting in thrombocytopenia, anemia, and neutropenia. There are approximately 19,950 new cases of AML per year in the United States, with an estimated 10,430 deaths occurring in the same time period.[2]

GLOBOCAN estimates the worldwide total leukemia incidence of AML for 2012 to be 351,965, with an age standardized rate (ASR) per 100,000 of 4.7, a 5-year prevalence of 1.5%. Mortality was 265,461 worldwide with ASR 3.4 per 100,000.[3] Almost all newly diagnosed cases, as well as deaths, will be in adults.[4] Standard treatment for AML includes systemic combination chemotherapy to control bone marrow and systemic disease. Treatment is generally divided into an induction phase, to attain remission, and a consolidation/maintenance phase. Standard treatment regimens for AML consist of 1 to 2 cycles of induction therapy of 7 days of cytarabine and 3 days of daunorubicin (or idarubicin) followed by 2 to 4 cycles of consolidation therapy with cytarabine. In patients >65 years, the daunorubicin dose may be reduced to 45 mg/m^2. Very frail patients are treated with low-dose cytarabine, 5-azacitidine (decitabine) or hydroxyurea cytoreduction, and basic supportive care only. Allogeneic stem cell transplantation consolidation is considered for patients with available donor and appropriate performance status.

Traditional induction chemotherapy can produce complete remissions in most (50% to 75%) subjects with AML.[5,6] Unfortunately, between 60% and 80% of subjects with AML (especially those with adverse cytogenetic features, adverse molecular mutations, or antecedent hematological disorder) will be refractory or relapse after initial response to induction therapy. As a result, only 20% to 30% will achieve long-term, disease-free survival. For subjects with AML refractory to initial therapy or who relapse after a brief remission (<12 months), outcomes are more dismal. Ravandi[7] reported median OS of 3.8 months for subjects with AML who are refractory to induction therapy. Similarly, subjects with relapsed AML have a poor outcome

with response rates ranging from 10% to 30% and overall survival less than 6 months with salvage therapy.[8,9]

These results emphasize the need to explore alternate salvage regimens for subjects with relapsed/refractory AML. The development of novel and effective anti-AML agents is crucial to improving the outcome of AML.

1.3. Study Rationale

Current treatment options for relapsed or refractory AML and ALL reflect an unmet medical need and additional options for treatment are needed. Preclinical data reviewed above strongly suggest antileukemic activity with DS-3201b in AML. The current study focuses on evaluating DS-3201b as monotherapy. The primary goal of this clinical trial is to assess the safety profile of DS-3201b as monotherapy and to establish the recommended dose for expansion (RDE) and preliminary clinical efficacy in subjects with confirmed relapsed or refractory AML or ALL. The results from this study will form the basis for decisions for future studies and combination approaches.

1.4. Risks and Benefits for Study Subjects

1.4.1. Benefit/Risk Assessment

At this point in the development of DS-3201b, the assessment of benefit/risk is based on both clinical and nonclinical data.

DS-3201b showed high potency as an inhibitor of the methyltransferase activities of EZH1 and EZH2 both in vitro, and high efficacy in an in vivo mouse tumor model. Safety pharmacology studies showed a low possibility for unexpected pharmacology-related AEs with DS-3201b. Completed studies showed no effects upon the CNS or respiratory systems of rats. In terms of cardiovascular effects, a potential for prolongation of QT/QTc interval was observed both in the 4-week repeated-dose toxicity study in dogs (where QTc interval was extended in females) and in the dog telemetry study (where QT and QTc were increased). There were no effects on cardiac pathology in either the rat or dog in the 4-week repeated-dose toxicity studies.

After 4 weeks of dosing of DS-3201b in definitive toxicity studies, the STD_{10} in rats was 200 mg/kg/day, and the HNSTD in dogs was 30 mg/kg/day.

Cumulatively within the DS3201-A-U102 Phase 1 study, there have been 9 deaths with 3 subjects experiencing events, including sepsis, acute respiratory failure (2 events), intracranial hemorrhage and acute kidney injury. The remaining 6 subjects had disease progression. All events were assessed to be not related to DS-3201b by the Investigators. There were 3 DLTs of which 1 event of hypocellular bone marrow at the dose of 700 mg/day was assessed related by Investigator. Other events assessed not related included decreased appetite and nasal congestion. Differentiation syndrome was reported from 1 patient with AML. This subject achieved complete remission with incomplete platelet recovery (CRp) after the first episode of differentiation syndrome.

In relation to safety data derived from animal studies, no cardiotoxicity, hepatotoxicity, hypersensitivity, or phototoxicity was observed in the initial Phase 1 clinical study. On the basis

of the nonclinical and clinical data available to date, the potential benefits of DS-3201b exceed the risks with careful dosing and monitoring in clinical studies.

1.4.2. Potential Risks Associated with DS-3201b

Based on the ongoing clinical studies, serious adverse reactions (SAR) of pneumocystis jiroveci pneumonia (PJP) in the system organ class (SOC) of infections and infestations has been reported in subjects with lymphoma. Otherwise, no additional risks have emerged in the ongoing clinical studies that may have an impact on the subject safety.

The following list of important potential risks was included in the latest development safety update report by the Sponsor:

- Increased QTc interval
- Increased histamine levels
- Differentiation syndrome
- Hyperplastic lymphocytic reaction and/or developing lymphoid malignancy

In subjects with acute leukemia, treatment with DS-3201b may result in differentiation syndrome, which can be life-threatening or fatal if not treated. In other compounds known to cause differentiation syndrome in AML, symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusion, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, tumor lysis syndrome, noninfectious leukocytosis, and hepatic, renal, or multi-organ dysfunction.[10,11,12] If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with hemodynamic monitoring until symptom resolution. For severe signs and/or symptoms, the dose of DS-3201b should be interrupted until signs and symptoms are no longer severe.

In this Phase 1 study of DS-3201b, subjects should be monitored with due care throughout the study and prompt action taken in case any of these AEs occur. It is suggested that the concomitant use of DS-3201b with CYP3A inhibitors or inducers may affect the metabolism of DS-3201b (Section 1.4.3). Therefore, concomitant use of moderate or strong CYP3A inducers should be avoided unless medically needed, in which case dose interruption of DS-3201b is not needed (Section 5.2.1). Moderate or strong CYP3A inhibitors and P-glycoprotein (P-gp) inhibitors can be used after the first dose of the study drug. However, dose reduction of DS-3201b is required when strong CYP3A inhibitors and P-gp inhibitors are used (Section 3.2.3).

In view of the results of 4-week repeated-dose toxicity studies in rats and dogs, potential target organs of DS-3201b were suggested to be the kidney (tubular degeneration), gastrointestinal tract (increased inflammatory infiltrate and mucosal degeneration), lymphoid organs (eg, decrease in WBC count, thymic atrophy, hypocellularity of bone marrow), and hematopoietic system (eg, changes in RBC parameters, platelets, and reticulocytes). There were effects on the clotting system in rats, whereas there was evidence of increased histamine levels with associated clinical signs in dogs. In terms of the cardiovascular effects, an increase in QTc interval was observed in 4-week repeated-dose toxicity and safety pharmacology studies in dogs.

In the 13-week GLP toxicity study in rats, malignant lymphoma was observed in the thymus and had metastasized to multiple organs. Increased cellularity, suggestive of a hyperplastic condition, was also observed. The new findings from the GLP toxicity study suggest a potential risk of the development of lymphoid malignancies in humans. No similar findings were noted in the 3-month toxicity study of DS 3201b in dogs. T-cell lymphomas have been observed in animals treated with DS-3201b (an EZH1/2-inhibitor) in repeat dose toxicology studies. This has also been observed in tazemetostat (an EZH2-inhibitor).

Secondary malignancies, including malignant lymphoma, have not been reported from DS-3201b studies. However, the treatment of patients with tazemetostat has been seen to increase the risk of developing a secondary T-cell malignancy, where a pediatric patient treated with tazemetostat developed a secondary T-cell lymphoblastic lymphoma after approximately 15 months of therapy. The dose or duration of therapy at which EZH2 inhibition and/or EZH1/2 inhibition do not increase the risk of a secondary lymphoid malignancy is unknown.

Preliminary results from an ongoing 3-month toxicology study in dogs suggested a potential for scrotal swelling in males administered DS-3201b. Although the scrotal lesions appear to be a new finding, this is not expected to significantly impact the ongoing clinical studies since these effects can be monitored, and are reversible with discontinuation of dosing. The significance of this finding is unknown at this time, but the Sponsor will continue to monitor similar events during the course of the ongoing study.

Additionally, a Phase 1 study DS3201-A-J101 (ClinicalTrials.gov Identifier: NCT02732275) in subjects with NHL including ATL/L is currently ongoing in Japan. As of the data cut-off date of 11 July 2017, a total of 15 subjects have been enrolled. Five subjects discontinued due to disease progression and 4 subjects withdrew from the study. One subject discontinued the study due to Grade 3 pneumocystis pneumonia requiring hospitalization, defined as an SAE. Overall 3 subjects had 4 TEAEs that met the definition for a DLT.

Detailed information on the potential risks and safety profile of DS-3201b can be found in the Investigator's Brochure.[1]

1.4.3. Potential Risk of Drug-Drug Interaction

In vitro, DS-3201a was metabolized extensively by CYP3A4 (approximately 66%) and CYP3A5 (approximately 30%), and to a lesser extent also by CYP2C8 (approximately 16%). The results of the in vitro study showed that DS-3201a is a substrate for P-gp. Drugs that are moderate-to-strong inducers of CYP3A4 may alter the PK of DS-3201a.

Study DS-3201-A-J104 demonstrated that the co-administration of itraconazole, a dual P-gp and strong CYP3A inhibitor, resulted in an approximately 4-fold increase in the AUCs and an approximately 3-fold increase in Cmax of DS-3201a. The co-administration of DS-3201b and the moderate CYP3A inhibitor fluconazole resulted in a 1.6-fold increase in the Cmax and AUCs of DS-3201a.

Additionally, the results of the DS3201-A-J104 study investigating drug interactions with CYP3A inhibitors and physiologically-based pharmacokinetic (PBPK) modeling analyses predicted that the combination of a single dose of DS-3201b and a strong CYP3A and P-gp inhibitor would increase the AUC of DS-3201a by approximately 4-fold, and a strong CYP3A inhibitor (no P-gp inhibitory effect) or a P-gp inhibitor (no CYP3A inhibitory effect) would

increase the AUC of DS-3201a by approximately 2-fold, respectively. If strong CYP3A inhibitors and/or P-gp inhibitors are co-administered, the dose adjustment guidance provided in Table 3.1 must be followed. The increase in AUC of DS-3201a was less significant when DS-3201b was concomitantly administered with a moderate CYP3A4 inhibitor. Therefore, no dose reduction of DS-3201b is required when it is concomitantly administered with a moderate CYP3A inhibitor.

DS-3201a inhibited CYP3A4 (tested with midazolam, IC_{50} 55.2 μM) but did not directly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or testosterone metabolism by CYP3A4. The potential DS-3201a inhibition on CYP3A4 (midazolam) was confirmed by subsequent determination of a K_i of 56.4 μM. DS-3201a showed a tendency to be a metabolism-dependent inhibitor of CYP3A4, with an IC_{50} fold change of 7.8-fold. Determination of k_{inact}/K_I inactivation constants suggested that DS-3201a is not a potential CYP3A4 metabolism-dependent inhibitor, since the inactivation constants were not measurable. DS-3201a did not show metabolism-dependent inhibition of any other CYPs tested.

1.4.4. Potential Benefit Associated with DS-3201b

Current treatment options for relapsed or refractory AML and ALL reflect an unmet medical need and additional options for treatment are needed. Preclinical data strongly suggest antileukemic activity with DS-3201b in AML. The current study focuses on evaluating DS-3201b as monotherapy. The primary goal of this clinical trial is to assess the safety profile of DS-3201b as monotherapy and to establish the RDE and preliminary clinical efficacy in subjects with confirmed relapsed or refractory AML or ALL.

The results from this study will form the basis for decisions for future studies and combination approaches.

1.5. Population, Route, Dosage, Dosage Regimen, Treatment Period

DS-3201b is supplied as 25 mg and 100 mg capsules packaged in high-density polyethylene (HDPE) bottles. DS-3201b will be administered orally at a starting dose of 100 mg once a day until disease progression.

See Section 3.1 for a detailed description of the study drug administration schedule, treatment cycle duration, and follow-up after discontinuation.

1.5.1. Part 1 (Dose Escalation)

Part 1 of this study will enroll adult subjects with relapsed or refractory AML or ALL. See Section 4.1.1 and Section 4.1.2 for a detailed description of all inclusion and exclusion criteria, respectively.

1.5.2. Part 2 (Dose Expansion)

Part 2 of this study will enroll adult subjects with relapsed or refractory AML and ALL. Subjects in the Dose Escalation and Dose Expansion parts of the study will have common inclusion and exclusion criteria.

1.6. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), US Food and Drug Administration GCP Regulations: Code of Federal Regulations (CFR) Title 21, Parts 11, 50, 54, 56, and 312, as appropriate, and other applicable local regulations.

1.6.1. Subject Confidentiality

The Investigators and the Sponsor, Daiichi Sankyo, Inc. (DSI), will preserve the confidentiality of all subjects taking part in the study in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the electronic case report forms (eCRFs) or other documents submitted to DSI and/or its contract research organization (CRO) designee ("Agent" or CRO), subjects should be identified by a unique subject identifier as designated by DSI. Documents that are not for submission to DSI and/or CRO (eg, signed informed consent forms [ICFs]) should be kept in strict confidence by the Investigator.

In compliance with applicable local guidelines and ICH GCP guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

1.6.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

If the subject or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) and assent forms for pediatric subjects (if applicable) are provided in the DSI ICF template for the Investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Clinical Study Manager.

Exploratory biomarkers will be analyzed with the intent of identifying subjects who will most likely derive clinical benefit from treatment with DS-3201b. The following candidate exploratory biomarkers are currently envisaged (other exploratory biomarkers in addition to or in place of these may be considered as suggested by emerging information): molecular testing in blood cells and/or bone marrow cells and cytogenetic and molecular subsets of AML and ALL. These exploratory biomarkers will be assessed in blood samples, bone marrow samples (archived or recent biopsies/aspirates), and/or other collected samples, using assays that have been established or are being established. Further exploratory studies may be performed on tissue, soluble, or genomic biomarkers based on emerging scientific knowledge to better understand the target disease, the effects of study treatment, and potential mediators of primary and acquired resistance to therapy.

1.6.3. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the statistical analysis plan (SAP).

The Investigator must submit and, where necessary, obtain approval from the IRB and/or DSI for all subsequent protocol amendments and changes to the informed consent document or changes to the investigational site, facilities or personnel. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from DSI and/or CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will ensure approval from the appropriate regulatory authorities is obtained prior to study initiation and that relevant regulatory authorities receive appropriate notification of, or if necessary, approve, substantive changes to the initial protocol.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

2.1.1.1. Part 1 (Dose Escalation)

The primary objectives of Part 1 are as follows:

1. To assess the safety and tolerability of DS-3201b in subjects with relapsed/refractory AML or ALL.
2. To determine the MTD and RDE of DS-3201b in subjects with relapsed/refractory AML or ALL.

2.1.1.2. Part 2 (Dose Expansion)

The primary objective of Part 2 is as follows:

1. To confirm the safety and tolerability of DS-3201b at the RDE in subjects with relapsed/refractory AML and ALL.

2.1.2. Secondary Objectives

2.1.2.1. Part 1 (Dose Escalation)

The secondary objective of Part 1 is as follows:

1. To assess the plasma PK after single and multiple doses of DS-3201b.

2.1.2.2. Part 2 (Dose Expansion)

The secondary objectives of Part 2 are as follows:

1. To assess overall response rate (ORR) in subjects with relapsed/refractory AML and ALL using the revised International Working Group (IWG) response criteria[13] and NCCN response criteria, respectively, duration of response (DOR), and OS.
2. To assess the PK after single and multiple doses of DS-3201b.

2.1.3. Exploratory Objectives

2.1.3.1. Part 1 (Dose Escalation)

The exploratory objectives of Part 1 are as follows:

1. To assess the PDy of DS-3201b, such as trimethylation status of H3K27 and quantitation of leukemic stem cells, in pre- and post-dose blood and/or bone marrow samples.
2. To evaluate response to DS-3201b per revised IWG response criteria[13] in subjects with relapsed/refractory AML or NCCN response criteria in subjects with relapsed/refractory ALL.

2.1.3.2. Part 2 (Dose Expansion)

The exploratory objectives of Part 2 are as follows:

1. To evaluate the relationship between response rate in relapsed/refractory AML and ALL and cytogenetic and molecular-based biomarkers studied in pre-treatment bone marrow biopsies and/or blood samples.
2. To assess the PDy of DS-3201b.
3. To compare CR duration between that observed with DS-3201b treatment and that observed from the most recent therapeutic regimen.

2.2. Study Hypothesis

DS-3201b will be well-tolerated and will exhibit acceptable PK/PDy response properties in subjects with relapsed or refractory AML or ALL. DS-3201b will manifest activity as evidenced by objective response in subjects with relapsed or refractory AML or ALL, using the appropriate response criteria according to the revised IWG guidelines (for AML) or NCCN guidelines (for ALL).

3. STUDY DESIGN

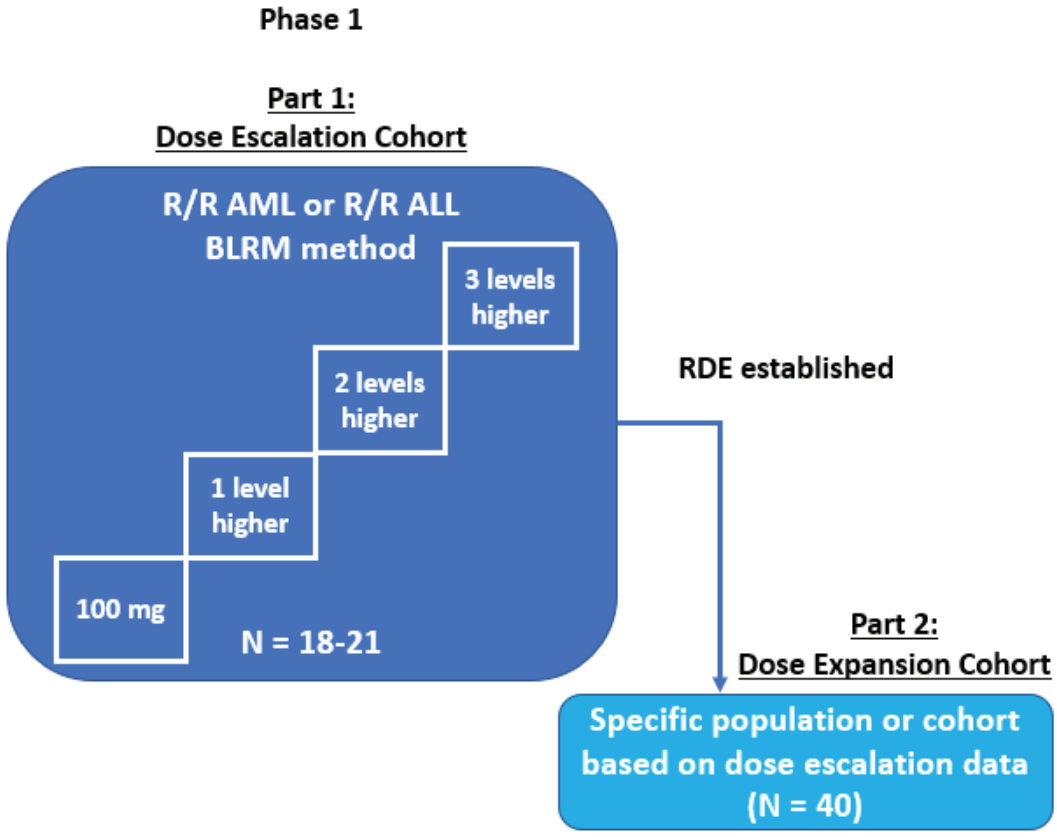
3.1. Overall Plan

3.1.1. Study Type

This will be a Phase 1, non-randomized, open-label study of DS-3201b in subjects with relapsed/refractory AML or ALL. This 2-part study will include both a Dose Escalation portion to assess the safety and tolerability of DS-3201b, identify a RDE, assess its PK/PDy properties, and evaluate the response to DS-3201b by revised IWG or NCCN response criteria for AML and ALL, respectively, and a Dose Expansion portion to confirm the safety and tolerability of DS-3201b at the RDE, assess the ORR, DOR, and OS, evaluate the relationship between response rate and selected cytogenetic and molecular biomarkers studied in pre-treatment bone marrow biopsies and/or blood samples, assess the PK and PDy of DS-3201b, and compare CR duration between that observed with DS-3201b treatment and that observed from the most recent therapeutic regimen.

Up to 10 sites in the United States are planned for the study. A schematic diagram of the study is provided in Figure 3.1.

Figure 3.1: Study Flow Chart



Note: In Dose Escalation, cohorts may be expanded below the MTD dose level (at any time following conclusion of that cohort's safety window) or at the MTD in parallel with ongoing escalation up to a maximum of 20 subjects in each cohort for further elaboration of safety, PK, or PDy response parameters as deemed appropriate by Investigators and Sponsor in order to define the RDE.

3.1.2. Treatment Groups

In this Phase 1, non-randomized, open-label study, each subject will be administered DS-3201b orally once daily over a 28-day cycle (1 cycle). In the first cohort, study treatment initiation will be staggered. A delay of at least 7 days will occur between the first subject dosed and the second and third subjects dosed. In subsequent cohorts, the study treatment can be started in the second and third subjects 1 day after first administration in the first subject.

The starting dose will be 100 mg/day as a single dose. The dose will be administered without food (no food for at least 2 hours before and 1 hour after the dose). A missed dose of DS-3201b may be administered later that same day (until midnight). The dose will be assessed as a missed dose if not administered. No replacement dose is administered if the subject vomits after taking DS-3201b.

After discontinuation of the study treatment, subjects will be contacted for an End-of-study (EOS) Follow-up visit 30 (± 5) days after the last dose of study drug, followed by a Long-term Follow-up (LTFU) period with follow-up contact every 3 months via telephone until death, loss to follow-up, or termination of study by the Sponsor (see Section 6.4).

3.1.2.1. Part 1 (Dose Escalation)

Dose escalation of DS-3201b to determine the MTD will be guided by a Bayesian logistic regression model (BLRM),[14] following the escalation with overdose control (EWOC) principle. The logistic regression model for the DLT rate will include 2 parameters: the intercept and the slope. After the first 3 subjects of each cohort complete the DLT evaluation during Cycle 1 (see Section 3.1.7.2), the posterior distributions of the DLT rate will be derived for all provisional dose levels based on the BLRM using the DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level ([0%, 16%) as the DLT rate interval for under-dosing, [16%, 33%) as the target DLT rate interval, [33%, 60%) as the DLT rate interval for excessive toxicity, and [60%, 100%] as the DLT rate interval for unacceptable toxicity) will then be calculated and used for dose recommendation for the next cohort according to the EWOC principle.

The EWOC principle requires that the BLRM recommended dose for the next cohort of subjects is defined as the highest posterior probability of the DLT rate in the target DLT rate interval [16%, 33%) among all dose levels fulfilling the overdose control constraint: there is less than a 25% probability for the DLT rate >33% (probability for excessive or unacceptable toxicity). The dose increment will be as follows:

- The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure, but flexibility may be applied in selecting the dose to accommodate the available dosage form strengths.
- The dose level increment should be no more than 100% even if the model suggests a higher dose than 100% for the next cohort.

Cohorts of 3 to 6 subjects will be enrolled and assessed for DLT before escalation to a new higher dose. In the event of a DLT, the next 2 subjects will receive DS-3201b treatment starting

at least 1 week apart. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 evaluable subjects experience DLT before the enrollment of the next subject after the BLRM dose recommendation. The dose for the next cohort will be chosen by the Sponsor and Principal Investigators based on the dose recommendation by the BLRM, clinical assessment of toxicity profiles and efficacy, and PK/PDy information observed thus far.

Based on the safety results available so far from the Phase 1 study of DS-3201 currently ongoing in Japan (DS3201-A-J101), escalation from the starting dose of 100 mg to the second dose level will be by less than 100%.

Enrollment of subjects to a new cohort requires completion of a DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed a DLT evaluation nor experienced a DLT will not be included in the BLRM update. In the event that subjects in the previous cohort experience a DLT after the enrollment of subjects to a new cohort has begun, dose level assignment of the next subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed doses.

For a subject to be considered evaluable for dose escalation decisions, the subject must have received at least 75% of the doses (ie, 21 days) during the DLT evaluation period or experienced a DLT in Cycle 1. The final MTD will be decided based on considerations of the respective MTD estimated by the BLRM, and on an overall assessment of safety data from subsequent cycles and of PK/PDy response collected at all different doses tested. For dose determination, the following stopping rules will be implemented for the Dose Escalation part: (a) at least 6 evaluable subjects at the MTD level with at least 21 evaluable subjects in total enrolled in the Dose Escalation part, (b) at least 9 evaluable subjects have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level 1 is too toxic.

Cohorts may be expanded below the MTD dose level (at any time following conclusion of that cohort's safety window) or at the MTD in parallel with ongoing escalation up to a maximum of 20 subjects in each cohort for further elaboration of safety, PK, or PDy response parameters as deemed appropriate by Investigators and Sponsor in order to define the RDE. Further details can be found in the Cohort Management Plan.

Dose escalation using alternative drug administration schedule

Based on safety, PK data, and PDy data collected during Dose Escalation using the QD × 28/28 days schedule of DS-3201b, alternative, less frequent drug administration schedules for dose escalation may be considered following review by the Principal Investigators and Sponsor. Modeling and simulation will be performed to evaluate DS-3201 exposure relationship to PDy and toxicity. If the results indicate that using an alternative dosing schedule may provide less toxicity (eg, myelosuppression) while offering pharmacodynamic benefits based on available biomarkers or a better PK profile, dose escalation using this recommended alternative dosing schedule will be performed in lieu of, or in parallel with, the QD × 28/28 days schedule. For example:

If the recommended dosing schedule is less frequent than QD × 28/28 days (eg, QD × 14/28 days, or QD × 7/28), the starting daily dose of the new schedule will be same as the

highest daily dose tested for the QD × 28/28 day schedule that showed DLT in less than one-third of evaluable subjects.

Dose escalation/de-escalation in the alternative schedule will follow the BLRM method as described in Section 11.11 in order to determine an MTD for the alternate dose schedule. When both the original QD × 28/28 days and alternative dosing schedules are explored in parallel, limiting a site to only 1 active regimen may be done at the discretion of the Sponsor. The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the BLRM, and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. Upon determining the final MTD of the original QD × 28/28 days and/or alternative dosing schedules, 1 dosing regimen will be selected for further evaluation in Part 2 (Dose Expansion). This regimen given at the final MTD determined in Part 1 is referred to as the "recommended dose for the expansion phase".

3.1.2.2. Part 2 (Dose Expansion)

Upon completion of Part 1 with the established MTD, RDE, and drug administration schedule, the Dose Expansion part will begin with the intention of confirming the safety and tolerability of DS-3201b and evaluating preliminary efficacy of DS-3201b in 2 separate cohorts of subjects with relapsed or refractory AML and ALL.

Four subjects with AML and 4 subjects with ALL will initially be treated to further assess safety before enrolling the remaining subjects in the respective cohorts of AML and ALL. Following completion of the Cycle 1 safety evaluation in all 4 subjects in the cohort, a safety analysis will be conducted to allow the reevaluation of the appropriateness of the dosing level. If the incidence of DLT has exceeded the EWOC principle guideline, no further treatment at the MTD and RDE level established in Part 1 will be done and dose de-escalation will be considered. Approximately 20 subjects each with AML and ALL will be enrolled in Part 2 to obtain a sufficient number of subjects treated at the RDE in these indications.

Pre-treatment bone marrow biopsies/aspirates will be required for participation in the study and optional post-treatment bone marrow biopsies/aspirates may be collected within 30 days following the last dose of study drug treatment.

3.1.2.3. Intrasubject Dose Escalation

No intrasubject dose escalation will be permitted.

3.1.3. Study Endpoints

The endpoints for the study include the following:

- **Pharmacokinetic Parameters**

  Cycle 1/Days 1 and 2 (Part 1 and Part 2):

  – Maximum (peak) plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the plasma concentration-time curve up to the last quantifiable time (AUClast)

  – If appropriate: Area under the plasma concentration-time curve up to infinity (AUCinf), terminal elimination half-life (t1/2), apparent total body clearance

following a single dose administration (Cycle 1/Day 1) (CL/F), apparent volume of distribution based on the terminal phase (Vz/F)

Cycle 1/Day 8 (Part 1 and Part 2):

- Cmax, Tmax, AUClast, and comparison of Cmax and AUClast values between Day 8 and Day 1 (Cmax and AUClast ratio) (d8,d1)
- If appropriate: Area under the plasma concentration-time curve during dosing interval (AUCtau), AUCinf, t1/2, apparent total body clearance at steady state following multiple dose administration (Cycle 1/Day 8) (CLss/F), apparent volume of distribution at steady state after multiple-dose administration (Vss/F)

Cycle 1/Days 2, 8, 15, and 22 and Cycle 2/Day 1 (Part 1 and Part 2):

- Trough plasma concentration (Ctrough)

End-of-treatment (EOT) (Part 1 and Part 2):

- Ctrough

- **Exploratory Biomarker Parameters**
  - Exploratory molecular testing in blood cells and/or bone marrow cells (at pre-dose and post-dose time points)
  - Retrospective confirmatory analysis and correlation with pre-therapy cytogenetic and molecular subsets of AML or ALL to response
- **Pharmacodynamic Parameters**
  - Quantitation of leukemic stem cells in pre- and post-dose bone marrow cells by flow cytometry and/or mass cytometry
  - H3K27me3 status in leukemic stem cells in bone marrow and/or blood cells
- **Efficacy Parameters**

  Primary efficacy variable is response to treatment, which will be defined per the revised IWG response criteria[13] for AML or standard response criteria for ALL as defined in Appendix Section 17.3 (NCCN 2016 ALL response criteria).[15]

  The efficacy endpoints will be:

  - Composite complete remission (CRc) rate, including complete remission (CR), complete remission with incomplete blood count recovery (CRi), and CRp
  - Morphologic leukemia-free state (MLFS)
  - Partial remission (PR) rate
  - Overall response rate (ORR) = CRc+PR
  - Duration of response (DOR): Time from the first objective evidence of response to the first objective evidence of disease progression
  - Overall survival (OS): Time from the date of enrollment to the date of death from any cause
  - 30- and 60-day mortality rate

Best Response Measurement

Best response is defined to be the best-measured response (PR, MLFS, CRp or CRi, CR for AML, or CRi or CR for ALL). Best response will be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

3.1.4. Disease Assessment

Bone marrow biopsies/aspirates and blood samples for disease assessment will be performed according to the study schedule at baseline and on Cycle 2/Day 1 while the subject remains on study. If aplasia is observed on Cycle 2/Day 1 with no evidence of leukemia and absolute neutrophil count (ANC) $<0.5 \times 10^9$/L and platelets $<20 \times 10^9$/L, study drug may be withheld and a confirmation bone marrow assessment performed in 2 weeks. For subjects who achieve CR, a follow-up bone marrow evaluation is only required as clinically indicated. All subjects with less than CR must have a monthly bone marrow evaluation unless >5% blasts are present in the peripheral blood, in which case bone marrow sampling is only required as clinically indicated. Additionally, based on the Investigator's clinical judgment, the frequency of bone marrow biopsies/aspirates can be reduced to once every 3 cycles after Cycle 3/Day1 until Cycle 12/Day1 (eg, Day 1 of Cycles 6, 9, and 12). After Cycle 12/Day1, the frequency of bone marrow biopsies/aspirates can be reduced up to once every 6 cycles (eg, Day 1 of Cycles 18, 24, etc).

Bone marrow re-biopsy at the End-of-study (EOS) treatment

To search for possible mechanisms of acquired resistance to DS-3201b, an optional bone marrow re-biopsy may be performed within 30 days following the last dose of DS-3201b treatment for subjects who have achieved an initial CR/PR by standard response criteria but later developed progressive disease while on therapy (both in Dose Escalation and Dose Expansion), preferably prior to initiating new therapy.

Bone marrow biopsies and leukemic cell enrichment

- Bone marrow biopsies/aspirates and blood samples:

  Bone marrow biopsies/aspirates or blood samples for disease status/response assessments, including flow cytometry and cytogenetics (per institutional guidelines and as clinically indicated), and exploratory resistance biomarker testing will be obtained as indicated in the study schedule.

  For Part 1 and Part 2, a bone marrow evaluation is required for all subjects at screening.

- Leukemic cell enrichment:

  Blood samples and bone marrow biopsies/aspirates will be collected pre-treatment at baseline for all subjects and/or at the EOS for subjects who achieve a CR or PR but develop recurrence or progression. Specimens of blood and marrow may be enriched for leukemic cells for further analysis.

  Leukemic stem cell samples collected from pre- and post-dose bone marrow aspirates will be quantified by flow cytometry and/or mass cytometry and blood and/or bone marrow cells may be examined for H3K27me3 status.

3.1.5. Duration of the Study

The study duration is expected to last approximately 5 years from the time the first subject is enrolled in Part 1 of the study and including the LTFU Period.

3.1.6. Duration of Subject Participation

The number of treatment cycles is not fixed in this study. Subjects who continue to derive clinical benefit from treatment in the absence of withdrawal of subject consent, progression, or unacceptable toxicity may continue treatment cycles. Subjects in Part 1 and Part 2 who are still on study at least 6 months after enrollment of the last subject in the study may be eligible to continue receiving study drug in a separate extension phase of the protocol (see Section 17.9). Data collected from those subjects may be captured in a separate database.

3.1.7. Stopping Rules

The Sponsor has the right to terminate the study at any time and study termination may also be requested by (a) competent authority(ies). Additional consideration includes any frequency in TEAEs that may reflect subject deterioration or further compromise including fatal outcome or which may be related to the overall efficacy of study therapy. Please also see the DLT definition (Section 3.1.7.2) and the stopping rules during dose expansion (Section 3.1.8).

3.1.7.1. Stopping Rule for Maximum Tolerated Dose Determination

The final MTD will be decided based on considerations of the MTD estimated by the BLRM, and on an overall assessment of safety data from subsequent cycles and of PK/PDy response collected at all different doses tested. For dose determination, the following stopping rules will be implemented for the Dose Escalation part: (a) at least 6 evaluable subjects at the MTD level with at least 21 evaluable subjects in total enrolled in the Dose Escalation part, (b) at least 9 evaluable subjects have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level 1 is too toxic.

3.1.7.2. Dose-limiting Toxicities

Dose-limiting toxicity is defined as a clinically significant non-hematologic TEAE or abnormal clinical laboratory value that is clearly not related to disease progression, intercurrent illness, and occurring during the first cycle (28 days) on study that meets any of the following criteria:

- National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (CTCAE), Version 4 Grade 3 aspartate aminotransferase (AST) (SGOT), alanine aminotransferase (ALT) (SGPT), or bilirubin for ≥7 days.
- NCI-CTCAE Grade 4 AST (SGOT) or ALT (SGPT) of any duration.
- All Grade 4 non-hematologic toxicities of any duration.
- Any Grade 5 toxicity, unless proven to be clearly and incontrovertibly related to disease progression or intercurrent illness will constitute a DLT.
- All other clinically significant, non-hematological NCI-CTCAE Grade 3/4 AEs.

Exceptions are as follows:

- Grade 3 or 4 nausea, vomiting, and diarrhea that do not require hospitalization or total parenteral nutrition (TPN) support and can be managed with supportive care to ≤Grade 2 within 48 hours.
- Alopecia and study drug-related fever will not constitute DLT.
- Grade 3 or 4 electrolyte abnormalities that are corrected to ≤Grade 2 within 24 hours.
- Grade 3 or 4 differentiation syndrome which improves to ≤ Grade 1 within 7 days of the start date of ≥ Grade 3 differentiation syndrome and which is not associated with end-organ damage.

Myelosuppression and associated complications are expected events during leukemia therapy. Only prolonged myelosuppression, as defined by absolute neutrophil count (ANC) $<0.5 \times 10^9$/L, platelets $<20 \times 10^9$/L, and marrow cellularity <5% on Day 42 or later (6 weeks) from start of therapy without any evidence of leukemia will be considered in defining the MTD and DLT. DLT evaluation of myelosuppression will be decided between the Investigators and Sponsor Medical Monitor during safety review meetings.

Subjects who are unable to complete at least 75% of the prescribed dose (ie, 21 days) of DS-3201b during the DLT evaluation period as a result of non-disease-related ≥Grade 2 AEs will be considered to have a DLT.

3.1.8. Maximum Tolerated Dose and Recommended Dose for Expansion Definition

Once the stopping criteria are met, the MTD estimated by BLRM + EWOC is the dose with the highest posterior probability of the DLT rate in the target DLT rate interval of [16%, 33%] among all doses fulfilling the following 2 constraints:

- The overdose control constraint: There is less than a 25% probability for the DLT rate >33% (probability for excessive or unacceptable toxicity) (Section 3.1.2.1);
- The mean of the posterior distribution of DLT target rate at this dose is ≤25%.

Since an alternative drug administration schedule may be explored in lieu of or in parallel with the original QD × 28/28 days schedule, separate MTDs may be identified for each regimen. The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy response information collected at all different doses tested. Upon determining the final MTD of the original QD × 28/28 days and/or alternative dosing schedules, 1 dosing regimen will be selected for further evaluation in Part 2 (Dose Expansion). This regimen given at the final MTD determined in Part 1 is referred to as the "Tentative Recommended Dose for Expansion".

In the Dose Expansion cohort, the safety will be assessed continuously after 4 subjects are enrolled in each cohort of AML and ALL. The study will be stopped if the cumulative incidence of clinically relevant ≥Grade 3 toxicities exceed 30%. The exceptions are:

- Grade 3 and higher nausea, vomiting, or diarrhea that do not require hospitalization or TPN support and can be managed with supportive care to ≤Grade 2 within 48 hours.

- Alopecia and study drug-related fever.
- Grade 3 or 4 electrolyte abnormalities that are corrected to ≤Grade 2 within 24 hours.
- Grade 3 or 4 differentiation syndrome which improves to ≤ Grade 1 within 7 days of the start date of ≥ Grade 3 differentiation syndrome and which is not associated with end-organ damage.

Evaluation of myelosuppression will be decided between the Investigators and Sponsor Medical Monitor during safety review meetings.

In the Dose Expansion cohort, the efficacy will be assessed continuously after 10 subjects are enrolled. The study will be stopped if the cumulative ORR will be less than 10%.

3.1.9. Management of Subjects with Adverse Events

Treatment-related toxicities meeting the DLT definition (see Section 3.1.7.2 for DLT definitions) occurring during the study will result in interruption and/or discontinuation of therapy. For subjects deriving clinical benefit from treatment, an option to resume the therapy at 1 dose level below that at which the toxicity occurred may be considered after the toxicity returns to NCI-CTCAE ≤Grade 1 or to baseline values. However, subjects requiring more than 4 weeks to recover from acute toxicities will be withdrawn from treatment. If a subject experiences NCI-CTCAE Grade 3 or 4 toxicity or an SAE that is unequivocally attributable to the underlying malignancy, DS-3201b treatment may be postponed until the toxicity has resolved to NCI-CTCAE ≤Grade 1, or returns to baseline values.

3.1.10. Guidelines for Dose Delays

Dosing of DS-3201b should be interrupted if the following AEs develop at any time during treatment:

- NCI-CTCAE ≥Grade 2 non-hematological, non-disease-related toxicities, except alopecia and >Grade 2 fatigue lasting <48 hours.
- For other NCI-CTCAE ≥Grade 2 laboratory abnormalities that are not DLTs, treatment continuation with DS-3201b will be at the discretion of the Investigator.
- Bone marrow aplasia, as per institutional guidelines, and peripheral ANC $<0.5 \times 10^9$/L and platelets $<20 \times 10^9$/L, with no residual leukemia.

Commencing rules for DS-3201b administration after dose interruption due to hematological AEs are:

- ANC $\geq 0.5 \times 10^9$/L.
- Platelet count $\geq 20 \times 10^9$/L.
- All other NCI-CTCAE ≥Grade 2 non-hematological toxicities (excluding alopecia) must have resolved to ≤Grade 1 or baseline values.

These parameters are only guidelines and are not intended to supersede the clinical judgment of the treating physician. All adjustments should be made in consultation with the Sponsor Medical Monitor. In the event of a dose delay occurring prior to completion of the PK/PDy sampling in

the study, Investigators should contact DSI for guidance regarding rescheduling these procedures.

In the event of a dose delay due to noncompliance, the study site should notify DSI at the earliest possible time. Subjects missing more than 25% of scheduled doses in Cycle 1 for non-toxicity-related reasons will not be evaluable for DLT and may be removed from the study.

3.2. Selection of Doses

3.2.1. Experimental Treatments

In this Phase 1, non-randomized, open-label study, each subject will be administered DS-3201b orally once daily over a 28-day cycle (1 Cycle). In the first cohort, study treatment initiation will be staggered. A delay of at least 7 days will occur between the first subject dosed and the second and third subjects dosed. In subsequent cohorts, the study treatment can be started in the second and third subjects 1 day after first administration in the first subject.

The starting dose will be 100 mg once a day. The dose will be administered without food (no food for at least 2 hours before and 1 hour after the dose). A missed dose of DS-3201b may be administered later that same day (until midnight). The dose will be assessed as a missed dose if not administered. No replacement dose is administered if the subject vomits after taking DS-3201b.

3.2.1.1. Part 1 (Dose Escalation)

The study will enroll subjects into cohorts with dose escalation determined by BLRM with the EWOC principle as outlined in Section 3.1.2.1. The starting dose will be 100 mg/day (see Section 3.1.2.1 for justification of the starting dose). In the event of a DLT, the next 2 subjects will receive DS-3201b treatment starting at least 1 week apart.

3.2.1.2. Part 2 (Dose Expansion)

Upon completion of Part 1 (Dose Escalation) and determination of the MTD/RDE, Part 2 (Dose Expansion) will immediately begin. Subjects will receive DS-3201b at the MTD/RDE defined in Section 3.1.2.1.

3.2.2. Control Treatments

Not applicable.

3.2.3. DS-3201b Dose Reduction Guidelines

The dose of DS-3201b will be reduced when concomitant strong CYP3A and/or P-gp inhibitors are co-administered (Table 3.1). When the strong CYP3A and/or P-gp inhibitors are discontinued, the subject will remain on the reduced dose for 3 days after the last dose of the inhibitor(s). After 3 days, the DS-3201b dose may be returned to the dose level that the subject was given before taking the inhibitor(s).

During this period of co-administration of moderate or strong CYP3A and/or P-gp inhibitors with DS-3201b, additional blood samples for PK analyses (total and unbound concentrations) should be collected (see Section 8 for additional details).

A list of CYP3Ainhibitors/inducers and P-gp inhibitors is presented in Section 17.5.

Table 3.1: Criteria for Dose Reduction When Using Strong CYP3A Inhibitors and/or P-gp Inhibitors

Drugs to be Co-administered with Care	Dose Adjustment Guideline	Examples of the dose reduction		
		When the Dose of the Study Drug is 500 mg Once Daily	When the Dose of the Study Drug is 250 mg Once Daily[a]	When the Dose of the Study Drug is 150 mg or 100 mg Once Daily[a]
Strong CYP3A inhibitors	Reduce DS-3201b dose to 50%	Reduce the dose of the study drug to 250 mg once daily	Reduce the dose of the study drug to 100 mg once daily	Reduce the dose of the study drug to 50 mg once daily
P-gp inhibitors	Reduce DS-3201b dose to 50%	Reduce the dose of the study drug to 250 mg once daily	Reduce the dose of the study drug to 100 mg once daily	Reduce the dose of the study drug to 50 mg once daily
Drugs having a strong CYP3A inhibitory effect and a P-gp inhibitory effect	Reduce DS-3201b dose to 25%	Reduce the dose of the study drug to 100 mg once daily	Reduce the dose of the study drug to 50 mg once daily	Interrupt the study drug

CYP3A = cytochrome P450 3A; P-gp = P-glycoprotein

[a] When the dose of study drug is 250 mg, 150 mg or 100 mg once daily, the Investigator should consult the Sponsor Medical Monitor before further reduction of the dose due to concomitant use of strong CYP3A or/and P-gp inhibitors

4. STUDY POPULATION

The study population will comprise subjects aged 18 years and older with relapsed or refractory AML or ALL (Part 1 and Part 2). Specific inclusion and exclusion criteria are available in Section 4.1.1 and Section 4.1.2.

4.1. Enrollment

Subjects must sign and date the informed consent form (ICF) provided by the study sites before any study-specific qualification procedures are conducted.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex), date, and outcome of screening process (eg, enroll in the study, reason for ineligibility, refused to participate).

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects who have been allocated to study numbers upon enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

Each subject or legally acceptable representative will be provided with information about the study, will have all questions answered to their satisfaction, and will sign and date an ICF. This will be completed before any study-specific procedures are performed. Additional information about informed consent procedures is provided in Section 1.6.2.

A subject is considered enrolled in the study upon the Investigator or designee obtaining written informed consent from the subject or the subject's legally acceptable representative (Section 1.6.2) and upon determination that all inclusion and exclusion criteria have been satisfied. After assigning a subject identification number (SID) to each subject at the timing of screening, Investigators will assess the eligibility of a subject based on the inclusion and exclusion criteria after obtaining written informed consent from the subject. After assessment by Investigators, the inclusion criteria/exclusion criteria form will be completed for registration. The Sponsor will perform registration after verifying that the subject meets the inclusion/exclusion criteria provided by the Investigator. Directly after registration, the Sponsor will forward the results of registration to the Investigator. At this time, the subject will be assigned to study drug treatment.

Data for all study visits will be recorded on the eCRF for subjects who receive study drug treatment. Only minimal data per the eCRF guidelines will be recorded on the eCRF for subjects who fail inclusion/exclusion criteria and/or do not receive study drug. Further data, such as AEs, will not be collected from subjects once they are considered screen failures or have decided to withdraw prior to receiving study drug.

4.1.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Subjects with AML diagnosed according to WHO 2008 criteria and ALL that have failed any prior induction therapy regimen or have relapsed after prior therapy.

- Subjects with acute promyelocytic leukemia (APL) must be resistant and/or intolerant to both trans-retinoic acid (ATRA) and arsenic trioxide based-therapies to be considered for inclusion.

2. Age ≥18 years old.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
4. Has adequate renal function, defined as:
   - Creatinine clearance ≥60 mL/min as calculated using the modified Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) formula (see Section 17.4) OR serum creatinine ≤1.5 × upper limit of normal (ULN).
5. Has adequate hepatic function, defined as:
   - AST/ALT ≤3 × ULN (≤5.0 × ULN if due to leukemic involvement), and
   - Total bilirubin ≤2.0 × ULN (or ≤3.0 × ULN if deemed to be elevated due to Gilbert's disease or leukemia), and
   - International normalized ratio (INR), prothrombin time, and activated partial thromboplastin time (aPTT) ≤1.5 × ULN.
6. The interval from prior treatment with cytotoxic agents or noncytotoxic/ hypomethylating/investigational/biologic agents to time of initiation of DS-3201b administration will be at least 14 days after the final dose (except hydroxyurea, which is allowed until 48 hours prior to start of the study treatment).
7. Subject should be able to provide written informed consent, comply with protocol visits and procedures, be able to take oral medication, and not have any active infection or comorbidity that would interfere with therapy.
8. Women of childbearing potential and their partner must agree to use an adequate method of contraception during the study and until 3 months after the last treatment, and must not retrieve ova or donate from the time of screening and throughout the study treatment period and for ≥3 months after the final dose of study drug. Males and their partner must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment, and must not freeze or donate sperm starting at screening and throughout the study period and for ≥3 months after the final dose of study drug (see Section 17.7).
9. Is willing to provide bone marrow biopsies and comply with evaluations as requested by protocol.
10. Has a life expectancy of at least 3 months.

4.1.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Presence of CNS involvement of leukemia or a history of CNS leukemia.
2. Has a second concurrent active primary malignancy such as solid tumor or lymphoma under active treatment.

3. Refractory nausea and vomiting, malabsorption, biliary shunt, significant bowel resection, graft-versus-host disease (GVHD) significantly affecting gut motility or absorption, or any other condition that would preclude adequate absorption of DS-3201b in the opinion of the treating physician and/or Principal Investigator.
4. Has an uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals, known human immunodeficiency virus infection, or active hepatitis B or C infection tested at screening. Infections controlled on concurrent anti-microbial agents are acceptable, and anti-microbial prophylaxis per institutional guidelines is acceptable.
5. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator or Sponsor.
6. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE, Version 4 ≤Grade 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator and Sponsor (eg, Grade 2 chemotherapy-induced neuropathy).
7. Receipt of hematopoietic cell transplantation (HCT) within 60 days of the first dose of DS-3201b.
8. Is receiving concomitant treatment with a strong inhibitor or inducer of CYP3A within 7 days of first receipt of DS-3201b (Refer to Section 17.5.).
9. Consumption of herbs/fruits that may have an influence on PK of DS-3201b, such as star fruit, Seville orange or Seville orange-containing foods and beverages, and grapefruit or grapefruit-containing food or beverages from 3 days prior to the first dose of DS-3201b up to the last dose of DS-3201b. St. John's wort (hypericin) will not be permitted from 14 days prior to the first dose of DS-3201b up to the last dose of DS-3201b.
10. Had major surgery within 4 weeks before study drug treatment.
11. Prolongation of corrected QT interval by Fridericia's method (QTcF) at rest, where the mean QTcF interval is >450 milliseconds (ms) based on triplicate electrocardiograms (ECGs), or additional risk factors for torsade de pointes (TdP; eg, active congestive heart failure or cardiomyopathy with New York Heart Association [NYHA] Grade 3/4 dyspnea or clinically significant rhythm abnormalities, hypokalemia, family history of Long QT Syndrome).
12. Pregnant or breastfeeding.
13. Substance abuse or medical, psychological, or social conditions that, in the opinion of the Investigator, may interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
14. Prior treatment with EZH inhibitors.

4.2. Removal of Subjects from Therapy

A subject may withdraw from receiving study drug treatment (but remain available for follow-up) or withdraw completely from all study participation at any time. For subjects with AML, therapy will be discontinued if there is a lack of leukemic response (ie, CR, CRi, CRp, or PR) after 3 cycles of therapy, unless the Investigator has determined that the subject is deriving

clinically benefit from treatment. For subjects with ALL, therapy will be discontinued if there is progressive disease per NCCN. Subjects with persistent bone marrow aplasia lasting more than 4 weeks, as per institutional guidelines, in the absence of malignant cell infiltration >4 weeks and peripheral ANC $<0.5 \times 10^9$/L and platelets $<20 \times 10^9$/L, will also be discontinued from therapy.

4.2.1. Reasons for Discontinuing Study Drug

Any subject who discontinues from the study drug for any reason will have their study drug discontinuation recorded.

Subjects may discontinue the study drug after signing informed consent for the following reasons:

- AE
- Lost to follow-up
- Death
- Protocol violation
- Withdrawal of consent by subject
- Withdrawal by subject (to discontinue study drug)
  - NOTE: This indicates that the subject discontinues study drug but continues on follow-up.
- Start of new therapy
- Study terminated by Sponsor
- Failure to achieve response
- Progressive disease
- Persistent bone marrow aplasia
- Other (eg, discretion of the Investigator or clinical progression)

If a subject discontinues study drug, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If the subject discontinues study drug due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized. Progressive disease (including relapse) or clinical progression is considered a sufficient reason to discontinue the study drug; however, after consultation with the Sponsor Medical Monitor, the Investigator may continue the study drug until the Investigator has alternative leukemia therapies and considers the study drug to be no longer beneficial to the subject. The Investigator may also continue the study drug when progressive disease is considered as a clinical sign of differentiation syndrome after consultation with the Sponsor Medical Monitor. The decision to discontinue a subject from study drug remains the responsibility of the Investigator.

4.2.1.1. Procedures for Discontinuation from Study Drug

Subjects who discontinue study drug should be instructed to contact the Investigator or study site staff before or at the time study drug is discontinued.

If a subject is discontinued from the study drug:

- The reason(s) for discontinuation and the last dose date should be documented in the subject's medical record and eCRF.
  - If study drug discontinuation is due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized or until the subject is available for follow-up.
- An EOT evaluation should be performed as described in the Schedule of Events (Section 17.8).
- A safety follow-up evaluation should be performed approximately 30 days after the last dose of study drug as described in the Schedule of Events.
- If subject has not discontinued for progressive disease (PD) or clinical progression, continue response assessments until progression or start of new therapy, if applicable, and survival as described in the Schedule of Events.
- Long-term follow-up evaluations will be performed to assess survival as described in the Schedule of Events.

The Investigator will complete and report the observations as thoroughly as possible up to the date of discontinuation, including the date of last dose. All procedures and tumor assessments specified for the EOT visit will be conducted.

4.2.2. Subject Withdrawal/Discontinuation from the Study

Subjects may discontinue from the study for any of the following reasons:

- Death
- Withdrawal by subject (from the study)
  - NOTE: This indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for survival
- Lost to follow-up
- Study termination by Sponsor
- Other (the reason should be specified on the eCRF)

Only subjects who refuse all of the following methods of follow-up will be considered to have withdrawn consent from study participation (ie, from the interventional portion and follow-up):

- Attendance at study visits per protocol
- Study personnel contacting the subject by telephone
- Study personnel contacting an alternative person

- Study personnel accessing and reviewing the subject's medical information from alternative sources

If the subject refuses all of the above methods of follow-up, the Investigator should personally speak to the subject to ensure that the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the Investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

4.2.2.1. Procedures for Withdrawal from Study Participation

Protocol-specified withdrawal procedures will involve an EOT visit (if possible) within 30 days and an EOS Follow-up visit (if possible) 30 (± 5) days after last dose of study drug. Protocol-specified withdrawal procedures are the same as those to be performed at the EOT visit (Section 6.3.1.10 and Section 6.3.2.11).

4.2.3. Subject Replacement

During Part 1 of the study, any subject who discontinues study participation before completing the first cycle of treatment and is not evaluable for DLT may be replaced. See Section 3.1.7.2 for definitions of DLTs.

4.2.4. Subject Re-screening Procedures

The study will allow re-screening for any subject who failed to meet eligibility criteria upon initial screening. The Principal Investigator will consult with the Sponsor before making the re-screen decision. For both Parts 1 and 2, the SID must remain the same at the time of re-screening. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for re-screening subjects.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

DS-3201b is supplied as 25 mg and 100 mg capsules packaged in high-density polyethylene (HDPE) bottles. DS-3201b is administered orally at a starting dose of 100 mg once a day until disease progression.

5.1.1. Method of Assigning Subjects to Treatments and Blinding

5.1.1.1. Randomization

Not applicable because this is a non-randomized study.

5.1.1.2. Blinding

The study is open-label and no blinding will be performed.

5.1.2. Method of Assessing Treatment Compliance

The following measures will be employed to ensure treatment compliance during dosing at the study site:

- DS-3201b only administered to subjects participating in the study and complying with the instructions from the clinical study personnel.
- Doses on the visit days of Cycle 1 should be administered to subjects under the supervision of clinical study personnel at the site. A mouth and hand check of all subjects should be completed to ensure that all capsules have been swallowed.
- DS-3201b may be dispensed in amounts exceeding the minimum amount required for the period of time until the next visit. Subjects will be instructed to return all unused DS-3201b at the next visit. Alternatively, to ensure compliance, the site personnel may choose to dispense only an adequate amount of study drug bottles required until the next scheduled visit. Compliance with the study drug regimen will be determined by counting unused capsules and needs to be ≥75% in the DLT evaluation period.
- DS-3201b administration that occurs at clinic visits will be supervised by a member of the site staff.

5.1.3. Labeling and Packaging

DS-3201b will be packaged in HDPE bottles labeled with the investigational product name and number, batch number, storage information, warning language (eg, “Caution: New Drug-Limited by Federal Law to Investigational Use”), and Sponsor name.

The study site will dispense take-home medication and will instruct subjects on its use.

5.1.4. Preparation

Procedures for proper handling and disposal of anticancer drugs should be followed in accordance with the standard operating procedures (SOPs) of the study site.

5.1.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions listed below:

- DS-3201b capsules should be stored at up to 25°C (77°F) (excursions permitted up to 30°C [86°F]) in HDPE bottles.

If storage conditions are not maintained per specified requirements, the site must not dispense the affected supplies (affected supplies should be placed in quarantine) and must contact Sponsor Quality Assurance personnel or designee to determine if the affected supplies can be used.

5.1.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be processed as instructed on the form. The original will be retained at the site. In addition, the Investigator or designee shall contact DSI as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the investigational product. The record must be kept current and should contain: the dates and quantities of drug received, subject (identification number and/or initials or supply number as applicable) for whom the investigational product was dispensed, the date and quantity of investigational product dispensed and remaining, if from individual subject drug units, as well as the initials of the dispenser.

At the end of the study, or as directed, all DS-3201b capsules and containers, including unused, partially used, or empty containers will be returned to a designee as instructed by DSI. Investigational product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of investigational product must be documented and the documentation included in the shipment. At the end of the study, a final investigational product reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by DSI/delegate and DSI/delegate has received copies of the site's drug handling and disposition SOPs.

All investigational product inventory forms must be made available for inspection by a DSI-authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

5.1.7. Retention Samples

Not applicable.

5.2. Concomitant Medications

Medications including any over-the-counter supplements and herbals administered within 2 weeks of screening will be recorded. All concomitant medications will be recorded on the eCRF.

5.2.1. Prohibited Concomitant Medications/Activities

The following medications and products will be prohibited:

- Administration of other antineoplastic agents during the study is prohibited.
  - Concomitant use of hydroxyurea is permitted in Cycle 1 up to a maximum of 8 days and up to a maximum dose of 5 g/day. If there is a clinical need to administer hydroxyurea for longer than 8 days or beyond Cycle 1, it should be discussed with the Sponsor. However, hydroxyurea is not allowed on Days -2 to 8 of Cycle 1, when blood and/or bone marrow samples will be collected for characterization of PK parameters from single and multiple doses of DS-3201b and initial PDy assessments.
- Prior to enrollment, strong CYP3A inhibitors, and moderate or strong CYP3A inducers are prohibited within 7 days of first dose of DS-3201b.
  - Consumption of herbs/fruits that may have an influence on PK of DS-3201b, such as star fruit, Seville orange or Seville orange-containing foods and beverages, and grapefruit or grapefruit-containing food or beverages, are prohibited from 3 days prior to the first dose of DS-3201b up to the last dose of DS-3201b.
  - St. John's wort (hypericin) is not be permitted from 14 days prior to the first dose of DS-3201b up to the last dose of DS-3201b
- During study participation, strong CYP3A inhibitors and/or P-gp inhibitors, if required for prophylactic administration for the treatment of symptoms such as infection, are permitted with a dose reduction of DS-3201b (see Section 3.2.3).
- During study participation, moderate and strong CYP3A inducers are prohibited, as drugs having moderate or strong CYP3A inducing properties may decrease plasma DS-3201a concentrations and it is therefore necessary to avoid concomitant use of these drugs with DS-3201b.
  - However, if medically essential to use as supportive care, concomitant use of moderate and strong CYP3A inducers is permissible after the first dose of the study drug. In this case, dose interruption of DS-3201b is not needed.
- A list of CYP3A inhibitors/inducers and P-gp inhibitors is provided in Section 17.5.
- Potentially QT/QTc prolonging drugs. Use of concomitant medications that prolong the QT/QTc interval is permissible only when medically needed. A list of concomitant therapies that are prohibited during the study as they may induce QT changes are provided in Section 17.6.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 17.8.

6.1. Screening

6.1.1. Part 1 (Dose Escalation), Screening (Pre-cycle)

The screening (Pre-cycle) period occurs within 14 days prior to starting study therapy.

The following procedures will be performed during the Part 1 screening period:

- Obtain written (ie, signed and dated) informed consent.
- Assign a SID number.
- Record demographic, medical history information including DOR post the most recent prior therapy, and prior medication history information for cancer.
- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record prior and concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
- Complete the Inclusion/Exclusion Criteria Form for subject registration.
  - The Sponsor will perform registration after verifying that the subject meets the inclusion/exclusion criteria (Section 4.1) provided by the Investigator. If the Sponsor has any questions regarding the information sent by the Investigator, he or she will immediately contact the Investigator to check the details. Directly after registration, the Sponsor will forward the results of registration to the Investigator.
  - The Investigator must not prescribe or administer the study drug until the subject has completed registration. If the Sponsor disqualifies a subject from participation in the clinical study, the Investigator will be notified. The Investigator will then explain this outcome to the relevant subject.

6.2. Randomization

Not applicable because this is a non-randomized, open-label study.

6.3. Treatment Period

6.3.1. Treatment Period, Part 1 (Dose Escalation)

Unless otherwise stated, an activity occurs before study drug administration.

6.3.1.1. Part 1 (Dose Escalation), Cycle 1/Day 1

The following procedures will be completed pre-dose during the Part 1, Cycle 1/Day 1 visit. If the screening visit for Part 1 is completed within 24 hours of Cycle 1/Day 1, the assessments do not need to be repeated.

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a blood sample for biomarkers.
- Obtain a blood sample for histamine measurement.
- Obtain serum for alpha 1-acid glycoprotein (AAG) measurements.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Administer DS-3201b per protocol (at the site).

The following procedures will be completed post-dose during the Part 1, Cycle 1/Day 1 visit:

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at 1 hour post-dose.
- Perform a 12-lead ECG in triplicate at 1, 2, 4, and 8 hours post-dose (5 minutes apart).
  - Note: If the ECG at 8 hours post-dose is not possible, then ECG may be performed at 6 hours (± 10 minutes) post-dose.

- Obtain blood samples for DS-3201a PK measurement and for protein binding determination at the following time points: 0.5, 1, 2, 4, 6, and 8 hours post-dose.
- Obtain a blood sample for histamine measurement at 1, 2, and 6 hours post-dose.

6.3.1.2. Part 1 (Dose Escalation), Cycle 1/Day 2

The following procedures will be performed pre-dose during the Part 1, Cycle 1/Day 2 visit.

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a blood sample for histamine measurement.
- Obtain a blood sample for biomarkers.
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense a pill diary with dose administration instructions to assess treatment compliance.

6.3.1.3. Part 1 (Dose Escalation), Cycle 1/Day 8

The following procedures will be performed pre-dose during the Part 1, Cycle 1/Day 8 visit (± 2 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a blood sample for histamine measurement.
- Obtain a blood sample for biomarkers.
- Obtain serum for AAG measurements.

- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home), if needed.
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

The following procedures will be completed post-dose during the Part 1, Cycle 1/Day 8 visit:

- Perform a 12-lead ECG in triplicate at 1, 2, 4, and 8 hours post-dose (5 minutes apart).
  - Note: If the ECG at 8 hours post-dose is not possible, then ECG may be performed at 6 hours (± 10 minutes) post-dose.
- Obtain blood samples for DS-3201a PK measurements and for protein binding determination at the following time points: 0.5, 1, 2, 4, 6, and 8 hours post-dose.

6.3.1.4. Part 1 (Dose Escalation), Cycle 1/Day 15

The following procedures will be completed pre-dose during the Part 1, Cycle 1/Day 15 visit (± 2 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for histamine measurement.
- Obtain a blood sample for biomarkers.
- Obtain a blood sample for protein binding determination.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.

- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home), if needed.
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.1.5. Part 1 (Dose Escalation), Cycle 1/Day 22

The following procedures will be completed pre-dose during the Part 1, Cycle 1/Day 22 visit (± 2 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for biomarkers.
- Obtain a blood sample for protein binding determination
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home), if needed.
- Review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.1.6. Part 1 (Dose Escalation), Cycle 2/Day 1

The following procedures will be performed pre-dose during the Part 1, Cycle 2/Day 1 visit (± 4 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.

- Obtain a blood sample for biomarkers.
- Obtain a blood sample for protein binding determination
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.1.7. Part 1 (Dose Escalation), Cycle 2/Day 15

The following procedures will be performed pre-dose at the Part 1, Cycle 2/Day 15 visit (± 4 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a urine sample for urinalysis (Section 9.7).
- Record concomitant medications.
- Assess subjects for AEs.
- Perform a bone marrow assessment if Cycle 2/Day 1 bone marrow revealed aplasia.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.1.8. Part 1 (Dose Escalation), Cycle 3/Day 1

The following procedures will be performed pre-dose at the Part 1, Cycle 3/Day 1 visit (± 4 days):

- Perform a complete physical examination and record weight.

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.1.9. Part 1 (Dose Escalation), Cycle 4 and All Subsequent Cycles/Day 1

The following procedures will be performed pre-dose at the Part 1, Cycle 4/Day 1 visit and all additional cycle Day 1 visits (± 4 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
  - Based on the Investigator's clinical judgment, the frequency of bone marrow biopsies/aspirates can be reduced to once every 3 cycles after Cycle 3/Day1 until Cycle 12/Day1 (eg, Day 1 of Cycles 6, 9, and 12).
    - After Cycle 12/Day1, the frequency of bone marrow biopsies/aspirates can be reduced up to once every 6 cycles (eg, Day 1 of Cycles 18, 24, etc).
- Administer DS-3201b per protocol (at the site).

- Dispense DS-3201b per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.1.10. Part 1 (Dose Escalation), End-of-treatment (Post-cycle)

This EOT visit should occur at the earliest day possible within 30 days after the last administration of DS-3201b, but before beginning any other form of anticancer therapy.

The following assessments will be performed at this visit:

- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a blood sample for biomarkers.
- Obtain a blood sample for protein binding determination
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.
- Record reason for treatment discontinuation.
- Bone marrow re-biopsy (optional) for subjects who achieved an initial CR/PR to DS-3201b but later developed progressive disease while on therapy (Section 6.3.1.12).

6.3.1.11. Part 1 (Dose Escalation) End-of-study Follow-up

The EOS Follow-up should occur 30 (± 5) days after the last administration of DS-3201b. Follow-up information will be collected via a phone call or site visit. If the subject begins another form of anticancer therapy before the end of the 30 (± 5)-day period, every effort will be made to complete all the EOS assessments prior to commencing the new therapy. The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal clinical laboratory values

at the EOT assessment, these events will be followed-up until resolution or until they become clinically not relevant.

The following information will be collected at this follow-up:

- Assessment of AEs.
- Current medications.
- Subject survival status.
- Collection of any empty bottle(s) along with any unused medication.

If the EOS Follow-up is not performed (ie, due to death, lost to follow-up, etc.), record the reason.

6.3.1.12. Part 1 (Dose Escalation) Bone Marrow Re-biopsy

To search for possible mechanisms of acquired resistance to DS-3201b, an optional bone marrow re-biopsy may be performed in subjects who have achieved an initial CR/PR to DS-3201b by revised IWG response criteria for AML or NCCN response criteria for ALL but later develop progressive disease while on therapy. Bone marrow re-biopsy would be performed within 30 days following the last dose of DS-3201b treatment, preferably prior to initiating new therapy.

6.3.2. Treatment Period, Part 2 (Dose Expansion)

Unless otherwise stated, an activity occurs before study drug administration.

6.3.2.1. Part 2 (Dose Expansion), Screening (Pre-cycle)

The screening (Pre-cycle) period is within 14 days before starting study therapy.

The following assessments will be performed during the Part 2 screening period:

- Obtain written (ie, signed and dated) informed consent.
- Record demographic, medical history information including DOR post the most recent prior therapy, and prior medication history information for cancer.
- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record prior and concomitant medications.

- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and biomarker tests.
- Complete the Inclusion/Exclusion Criteria Form for subject registration.
  - The Sponsor will perform registration after verifying that the subject meets the inclusion/exclusion criteria provided by the Investigator. If the Sponsor has any questions regarding the information sent by the Investigator, he or she will immediately contact the Investigator to check the details. Directly after registration, the Sponsor will forward the results of registration to the Investigator.
  - The Investigator must not prescribe or administer the study drug until the subject has completed registration. If the Sponsor disqualifies a subject from participation in the clinical study, the Investigator will be notified. The Investigator will then explain this outcome to the relevant subject.

6.3.2.2. Part 2 (Dose Expansion), Cycle 1/Day 1

The following will be completed pre-dose during the Part 2, Cycle 1/Day 1 visit. If the screening visit for Part 2 is completed within 24 hours of Cycle 1/Day 1, the assessments do not need to be repeated.

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for biomarkers.
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a blood sample for histamine measurement.
- Obtain serum for AAG measurements.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Administer DS-3201b per protocol (at the site).

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 1 visit:

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at 1 hour post-dose.

- Perform a 12-lead ECG in triplicate at 1, 2, 4, and 8 hours post-dose (5 minutes apart).
  - Note: If the ECG at 8 hours post-dose is not possible, then ECG may be performed at 6 hours (± 10 minutes) post-dose.
- Obtain blood samples for DS-3201a PK measurements and for protein binding determination at the following time points: 0.5, 1, 2, 4, 6, and 8 hours post-dose.
- Obtain a blood sample for histamine measurement at 1, 2, and 6 hours post-dose.

6.3.2.3. Part 2 (Dose Expansion), Cycle 1/Day 2

The following procedures will be performed pre-dose during the Part 2, Cycle 1/Day 2 visit:

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a blood sample for histamine measurement.
- Obtain a blood sample for biomarkers.
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense a pill diary with dose administration instructions to assess treatment compliance.

6.3.2.4. Part 2 (Dose Expansion), Cycle 1/Day 8

The following procedures will be performed pre-dose during the Part 2, Cycle 1/Day 8 visit (± 2 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.

- Obtain a blood sample for histamine measurement.
- Obtain a blood sample for biomarkers.
- Obtain serum for AAG measurements.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home), if needed.
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 8 visit:

- Perform a 12-lead ECG in triplicate at 1, 2, 4, and 8 hours post-dose (5 minutes apart).
  - Note: If the ECG at 8 hours post-dose is not possible, then ECG may be performed at 6 hours (± 10 minutes) post-dose.
- Obtain blood samples for DS-3201a PK measurement and for protein binding determination at the following time points: 0.5, 1, 2, 4, 6, and 8 hours post-dose.

6.3.2.5. Part 2 (Dose Expansion), Cycle 1/Day 15

The following procedures will be performed pre-dose during the Part 2, Cycle 1/Day 15 visit (± 2 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a blood sample for histamine measurement.
- Obtain a blood sample for biomarkers.
- Obtain a urine sample for urinalysis (Section 9.7).

- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home), if needed.
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.2.6. Part 2 (Dose Expansion), Cycle 1/Day 22

The following procedures will be performed pre-dose during the Part 2, Cycle 1/Day 22 visit (± 2 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a blood sample for biomarkers.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home), if needed.
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.2.7. Part 2 (Dose Expansion), Cycle 2/Day 1

The following procedures will be performed pre-dose during the Part 2, Cycle 2/Day 1 visit (± 4 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a blood sample for biomarkers.
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.2.8. Part 2 (Dose Expansion), Cycle 2/Day 15

The following procedures will be performed pre-dose during the Part 2, Cycle 2/Day 15 visit (± 4 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a urine sample for urinalysis (Section 9.7).
- Record concomitant medications.
- Assess subjects for AEs.
- Perform a bone marrow assessment if Cycle 2/Day 1 bone marrow revealed aplasia.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home), if needed.
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.2.9. Part 2 (Dose Expansion), Cycle 3/Day 1

The following procedures will be performed at the Part 2, Cycle 3/Day 1 visit (± 4 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.2.10. Part 2 (Dose Expansion), Cycle 4 and All Subsequent Cycles/Day 1

The following procedures will be performed pre-dose at the Part 2, Cycle 4/Day 1 visit and all additional cycle Day 1 visits (± 4 days):

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Record concomitant medications.
- Assess subjects for AEs.
- Obtain bone marrow biopsies/aspirates for marrow assessment and/or biomarker tests.
  - Based on the Investigator's clinical judgment, the frequency of bone marrow biopsies/aspirates can be reduced to once every 3 cycles after Cycle 3/Day1 until Cycle 12/Day1 (eg, Day 1 of Cycles 6, 9, and 12).

  - After Cycle 12/Day1, the frequency of bone marrow biopsies/aspirates can be reduced up to once every 6 cycles (eg, Day 1 of Cycles 18, 24, etc).

- Administer DS-3201b per protocol (at the site).
- Dispense DS-3201b per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.

6.3.2.11. Part 2 (Dose Expansion), End-of-treatment (Post-cycle)

This EOT visit should occur at the earliest day possible within 30 days after the last administration of DS-3201b, but before beginning any other form of anticancer therapy.

The following assessments will be performed at this visit:

- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG-PS Scale (Section 17.1).
- Obtain blood samples for clinical laboratories (Section 9.7).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a blood sample for biomarkers.
- Obtain a blood sample for DS-3201a PK measurement.
- Obtain a blood sample for protein binding determination.
- Obtain a urine sample for urinalysis (Section 9.7).
- Perform a 12-lead ECG in triplicate (5 minutes apart).
- Record concomitant medications.
- Assess subjects for AEs.
- Review pill diary to assess treatment compliance.
- Review of returned study medication and assessment of compliance.
- Record reason for treatment discontinuation.
- Bone marrow re-biopsy (optional) for subjects who achieved an initial CR/PR to DS-3201b but later developed progressive disease while on therapy (Section 6.3.1.12).

6.3.2.12. Part 2 (Dose Expansion) End-of-study Follow-up

The EOS Follow-up should occur 30 (± 5) days after the last administration of DS-3201b. Follow-up information will be collected via a phone call or site visit. If the subject begins

another form of anticancer therapy before the end of the 30 (± 5)-day period, every effort will be made to complete all the EOS assessments prior to commencing the new therapy. The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal clinical laboratory values at the EOT assessment, these events will be followed-up until resolution or until they become clinically not relevant.

The following information will be collected at this follow-up:

- Assessment of AEs
- Current medications
- Subject survival status
- Collection of any empty bottle(s) along with any unused medication

If the EOS Follow-up is not performed (ie, due to death, lost to follow-up, etc.), record the reason.

6.3.2.13. Part 2 (Dose Expansion) Bone Marrow Re-biopsy

Please see Section 6.3.1.12 for details regarding performing bone marrow re-biopsy in Part 2.

6.4. Long-term Follow-up

After completion of the EOS follow-up visit (30 [± 5] day safety, Section 6.3.1.11 and Section 6.3.2.12), subjects will then enter the LTFU Period, during which they will be followed every 3 months for collection of information on subsequent AML/ALL treatment (including stem cell transplants), HCT and HCT-relevant information (if performed), response to treatment, and survival, including the cause and date of death. LTFU will continue until death, loss to follow-up, or until the Sponsor terminates the study. These visits will be conducted via telephone.

If direct contacts are not possible or if LTFU is not performed due to withdrawal of consent, subject refusal to participate in LTFU, or loss to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws and document as best possible the specific reason for inability to collect LTFU data.

6.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by DSI and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB.

A deviation to any protocol procedure, or waiver to any stated criteria, will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. DSI must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or investigational treatment, and had at least one administration of investigational product, data should be collected for safety purposes.

The Investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

7. EFFICACY ASSESSMENTS

Efficacy assessments will be based on bone marrow assessments to be performed at Screening, Cycle 1 Day 8, and every cycle of treatment (ie, at start of Cycles 2, 3, 4, etc.) while the subject remains on study drug. The clinical activity of DS-3201b will be assessed using the revised IWG response criteria for AML or the NCCN Guidelines (Version 3.2013) for ALL (Section 17.3).

The efficacy endpoints will be:

- CRc rate (CR, CRi, and CRp)
- CR
- CRi or CRp
- MLFS
- PR rate
- ORR = CRc+PR
- DOR: Time from the first objective evidence of response to the first objective evidence of disease progression
- OS: Time from the date of enrollment to the date of death from any cause
- 30- and 60-day mortality rate

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Blood samples for DS-3201a PK analyses (eg, total and unbound concentrations) will be obtained at the time points specified in the Schedule of Events (Section 17.8) for subjects in the Dose Escalation and Dose Expansion parts of the study.

Additionally, blood samples may be obtained at any time during the study if deemed clinically necessary or when moderate or strong CYP3A and/or P-gp inhibitors are co-administered with DS-3201b. In the event of co-administration of moderate or strong CYP3A and/or P-gp inhibitors, blood samples for PK analyses (total and unbound concentrations) should be collected at the following timepoints relative to DS-3201b dosing:

- Pre-dose, 4 hours, and 8 hours post-dose of DS-3201b on the first day of CYP3A and/or P-gp inhibitor dosing
- Pre-dose, 4 hours, and 8 hours post-dose of DS-3201b within 28 days after last day of CYP3A and/or P-gp inhibitors dosing

At each time point, blood samples will be collected for analysis of total and unbound concentrations of DS-3201a.

Instructions for the handling of blood samples and shipping of plasma samples for DS-3201a PK analyses are included in a separate document (eg, laboratory manual). The actual time of study drug administration and the exact time of blood sampling for DS-3201a PK analysis must be recorded on the eCRF.

The DS-3201a PK samples will be shipped to a central laboratory for forwarding to a Sponsor -designated bioanalytical laboratory. Plasma concentrations of DS-3201a will be measured using a validated assay at the bioanalytical laboratory. Plasma metabolites of DS-3201a may also be measured based on the assay availability.

8.1. Pharmacokinetic Variables

Plasma concentrations (total and unbound) of DS-3201a will be used to determine the following PK parameters using standard non-compartmental method. Plasma concentration-versus-time data will be summarized using summary statistics by dose/study day/time.

Cycle 1/Days 1 and 2 (Part 1 and Part 2):

- Cmax, Tmax, AUClast
- If appropriate: AUCinf, t1/2, CL/F, Vz/F

Cycle 1/Day 8 (Part 1 and Part 2):

- Cmax, Tmax, AUClast, Cmax and AUClast ratio (d8,d1)
- If appropriate: AUCtau, AUCinf, t1/2, CLss/F, Vss/F

Cycle 1/Days 2, 8, 15, and 22 and Cycle 2/Day 1 (Part 1 and Part 2):

- Ctrough

End-of-treatment (Part 1 and Part 2):

- Ctrough

8.2. Pharmacodynamic/Exploratory Biomarker Variables

8.2.1. Pharmacodynamic Biomarker Variables

- Quantitation of leukemic stem cells in pre- and post-dose bone marrow cells by flow cytometry and/or mass cytometry
- H3K27me3 status in leukemic stem cells in bone marrow and/or blood cells

8.2.2. Exploratory Biomarker Analysis

- Exploratory molecular testing in blood cells and/or bone marrow cells (at pre-dose and post-dose time points)
- Retrospective confirmatory analysis and correlation with pre-therapy cytogenetic and molecular subsets of AML or ALL to response

Optional bone marrow re-biopsy will be performed within 30 days of the last dose of DS-3201b in subjects who have achieved an initial CR/PR to DS-3201b but later developed progressive disease while on therapy.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

All clinical AEs occurring after the subject signs the ICF and up to 30 (± 5) days after the last dose of study drug during either Part 1 or Part 2, whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including clinical laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 9.5 SAE Reporting Procedure for Investigators. Always report diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and, consequently, should not be reported as an AE or SAE. However, when a subject dies from disease progression with no other immediate causes, “disease progression” should be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. All clinical laboratory values must be appraised by the Investigator as to clinical significance. All post-baseline abnormal clinical laboratory values considered clinically significant by the Investigator must be recorded as an AE on the eCRF, and if serious, reported as an SAE following the procedures in Section 9.5.

Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs including significant abnormal clinical laboratory values at the EOT assessment, these events will be followed-up until resolution or until they become clinically not relevant.

9.2. Safety Endpoints

Safety endpoints will include incidence of AEs, SAEs, TEAEs, DLTs, physical examination findings (including ECOG-PS), vital sign measurements, standard clinical laboratory parameters, histamine level in plasma, and ECG parameters.

9.3. Adverse Events of Special Interest

Differentiation syndrome is an adverse event of special interest (AESI) for DS3201-A-U102 and as of 18 Jan 2020, it has been reported in 1 subject with AML.

When subjects with acute leukemia are treated with DS-3201b, vigilance should be exercised in while monitoring them for development of possible differentiation syndrome. It is important to both promptly recognize the signs and symptoms of differentiation syndrome and implement prompt management.

9.4. Definitions

9.4.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product 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 clinical laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal clinical laboratory findings that should be considered AEs.

9.4.2. Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias, or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatment requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Adverse Event Severity

All AEs will be graded (1 to 5; see below) according to the NCI-CTCAE, Version 4:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is a universal and global regulatory definition based on subject/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria. For example, an event of headache may be classified moderate by an Investigator, but upon presentation to a medical facility, subject is admitted overnight for observation upgrading this report to serious based upon international regulatory definition.

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an AE and DS-3201b on the basis of his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- 2 = Not Related:

- The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding the Study Drug

- 1 = None: No change in study drug dosage was made.
- 2 = Discontinued Permanently: The study drug was permanently stopped.
- 3 = Reduced: The dosage of study drug was reduced.
- 4 = Interrupted: The study drug was temporarily stopped.
- 5 = Increased: The dosage of study drug was increased.

9.4.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Identify sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- 4 = Fatal
- 5 = Unknown

9.4.7. Other Action Taken for Event

- 1 = None
  - No treatment was required.
- 2 = Medication required
  - Prescription and/or over-the-counter medication was required to treat the AE.
- 3 = Hospitalization or prolongation of hospitalization required
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- 4 = Other

9.5. Serious Adverse Event Reporting Procedure for Investigators

9.5.1. Initial Reports

Within 24 hours of receipt of an SAE report:

- Complete a Daiichi Sankyo Serious Adverse Event Report (SAVER) form, sign it, and fax it to the CRO using the designated fax transmittal form. The CRO will review and forward the SAVER form to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV).
- Call the CRO SAE hotline for any questions regarding SAE reporting.
- Place the initial version of SAVER in the subject's file.

9.5.2. Follow-up Reports

This is NEW information received on a previously reported SAE that is clinically significant.

Within 24 hours of the receipt of new information for a clinically significant reported SAE:

- Complete a Daiichi Sankyo SAVER form with the new information. Please complete Sections 1 through 3 even if they contain no new information. For Sections 4 through 10, provide only the new information. Sign and fax the form to the CRO using the fax transmittal form.
- For SAEs that resulted in death, provide the autopsy report via e-mail, fax, or express mail.
- The CRO will review and forward the follow-up SAVER form and supporting documents to Daiichi Sankyo CSPV PPD .
- Place the follow-up version of the SAVER form and all supporting documentation in the subject's file.

9.5.3. Notifying Regulatory Authorities, Investigators, and IRBs

Daiichi Sankyo and/or CRO will inform Investigators and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in other study centers or other Daiichi Sankyo studies of the investigational product, as appropriate per local reporting requirements.

In the United States, it is the Investigator's responsibility to inform the IRB upon receipt of the Sponsor's notification of SUSARs that occurred with the investigational product.

9.6. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving study drug or up to 30 (± 2) days after the last administration of study drug. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU

Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs as outlined in Section 9.5.

The potential for DS-3201b to affect fertility and embryo-fetal development has not been tested. Women of childbearing potential should be informed of the potential risk, have periodic pregnancy tests, and use highly effective methods of birth control during treatment and for an additional 90 days after the end of treatment. Women should not breastfeed during the study and for an additional 90 days after the end of treatment.

The potential of DS-3201b to be transferred by semen and its effect on sperm is unknown. Male subjects with partners of childbearing potential should inform their partners of their participation in the clinical study and use highly effective methods of birth control during treatment and for an additional 90 days after the end of treatment.

Additional information can be found in the Investigator's Brochure.[1]

9.7. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

- Hematology variables include red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count with 5-part differential, including ANC and reticulocyte count, and peripheral blood blasts.
- Serum chemistry variables include sodium, potassium, bicarbonate, chloride, magnesium, calcium, phosphorus, albumin, glucose, serum creatinine, uric acid, total protein, blood urea nitrogen, AST, ALT, alkaline phosphatase, lactose dehydrogenase, total and direct bilirubin, and lipid profile (triglycerides and cholesterol).
- Urinalysis variables include protein, glucose, and blood, microscopy assessments, and specific gravity.
- Coagulation: INR, prothrombin time, and aPTT.
- Serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test (see Schedule of Events in Section 17.8).

All clinical laboratory values must be appraised by the Investigator as to clinical significance. All abnormal clinical laboratory values considered clinically significant by the Investigator must be recorded on the AE page of the eCRF. Abnormal clinical laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.8. Vital Signs

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.

9.9. Electrocardiograms

Standard supine 12-lead ECGs will be performed by qualified technicians in triplicate (5 minutes apart) as noted in the Schedule of Events. Electrocardiograms will be reviewed at the site for treatment of any urgent issues. The clinical significance of any ECG change must be assessed by the Investigator in the context of the subject's medical history, physical examination, and concomitant medications. The Investigator or delegated physician will review, sign, and date all ECGs.

Whenever there are time matched ECGs and PK sampling, ECGs should be done first. PK samples should be collected within 15 minutes of ECG collection.

9.10. Physical Findings

Physical examinations will evaluate the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological. Weight and height will be recorded in kilograms and centimeters, respectively.

9.11. Other Safety Assessments

Not applicable.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Enrolled Analysis Set

The Enrolled Analysis Set will include all subjects who signed an ICF and were enrolled in either the Dose Escalation part or Dose Expansion part of the study.

11.1.2. Safety Analysis Set

The Safety Analysis Set will include all subjects enrolled who received any amount of DS-3201b. Subjects will be summarized according to dose of DS-3201b received.

Four groups of subjects will be identified within the Safety Analysis Set: (1) subjects in the Dose Escalation part, (2) subjects in the Dose Expansion part, (3) subjects treated at the dose level of RDE, and (4) all subjects in the study.

11.1.3. Full Analysis Set

The Full Analysis Set will include all subjects enrolled in the Dose Escalation part or the Dose Expansion part who received any amount of DS-3201b and who had at least 1 post-baseline bone marrow assessment.

11.1.4. Dose-Limiting Toxicity Evaluable Set

The DLT-evaluable Set will include all subjects enrolled in the Dose Escalation part who had a DLT within the first cycle (28 days) on study, or without DLT but received at least 75% of scheduled DS-3201b doses during the DLT evaluation period.

11.1.5. Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects in the Enrolled Analysis Set who received at least 1 dose of DS-3201b and had sufficient plasma concentration data to characterize DS-3201a PK.

11.1.6. Pharmacodynamic Biomarker Analysis Set

The PDy Biomarker Analysis Set will include all subjects in the Enrolled Analysis Set who received any amount of DS-3201b and who had the mandatory baseline assessment and, where applicable, at least 1 post-baseline assessment for biomarkers.

11.2. General Statistical Considerations

The primary analysis is to assess the safety and tolerability of DS-3201b in subjects with relapsed or refractory AML or ALL and to determine the RDE or establish the safety and tolerability of DS-3201b at the RDE.

The primary analysis will occur after all subjects in Part 2 have either discontinued the study or have completed at least 6 months of treatment. After the primary analysis, the main study will be closed. Subjects in Part 1 and Part 2 who are still on study at least 6 months after enrollment

of the last subject in the study may be eligible to continue receiving study drug in a separate extension phase of the protocol (see Section 17.9). Data collected from those subjects may be captured in a separate database.

Descriptive statistics will be provided for selected demographic, safety, efficacy, and PK parameters as well as plasma DS-3201a concentrations, and will be summarized by dose level/study day/time points, as appropriate. Descriptive statistics on continuous variables will include means, medians, standard deviations, minimum, and maximum (as well as geometric means and geometric coefficient of variation for Cmax and AUC PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

The last non-missing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

Safety analyses will be performed based on the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set and biomarker analyses will be based on the PDy Biomarker Analysis Set. Efficacy endpoints will be analyzed based on the Full Analysis Set. Data from the Dose Escalation part will be summarized by dose level and overall.

A detailed SAP describing the methodology to be used in the final analysis will be prepared and finalized before database lock. Statistical methods described within this document may be changed based on advances in research.

11.3. Study Population Data

Disposition and reasons for ending the treatment and discontinuing from the study will be summarized and listed for subjects in the Enrolled Analysis Set.

Demographic and baseline characteristics such as age, sex, race, baseline ECOG-PS, organ dysfunction, histology, cancer stage, cytogenetics, de novo versus therapy-related status, molecular mutations (if available), prior stem cell transplant status, best response to prior chemotherapy, lines of prior regimens, and prior treatment regimens will be summarized for the Enrolled Analysis Set, Full Analysis Set, and Safety Analysis Set. If 2 analysis sets within a part of the study are identical to each other, the table will be presented only once.

Study drug exposure, treatment duration, and compliance with study therapy will be summarized using descriptive statistics for the Safety Analysis Set.

11.4. Efficacy Analyses

Response to treatment will be evaluated using the revised IWG response criteria for AML or the NCCN response criteria 2016 for ALL, respectively (Section 17.3). The efficacy endpoints will

be CRc rate (including CR, CRi, and CRp), MLFS, PR rate, ORR, DOR, OS, and 30- and 60-day mortality rate for AML and ALL, respectively.

For the binary efficacy endpoints, the point estimate and exact 95% confidence interval will be provided. Time-to-event variables, such as DOR and OS, will be analyzed using the Kaplan-Meier method by dose level and overall.

The best overall response will be determined for each subject, in the order of CR, CRp or CRi, PR, and treatment failure (TF). For each category as well as response (CRc or PR), the point estimate and 95% confidence interval will be calculated for the proportion.

OS is the time from the first dose of DS-3201b to the death. The censoring rules will be specified in the SAP.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

11.5.1. Pharmacokinetic Analyses

Plasma concentrations for DS-3201a will be listed, plotted, and summarized using descriptive statistics by dose level/study day at each time point. Pharmacokinetic parameters will be listed and summarized using descriptive statistics by dose level/study day.

A concentration-QTc analysis will be done using pooled data from all subjects.

11.5.2. Pharmacodynamic/Biomarker/Exploratory Analyses

Descriptive statistics will be used to summarize the reported values and changes from baseline of the biomarkers by dose level and by scheduled measurement. They include:

Exploratory Biomarkers

- Molecular testing in blood cells and/or bone marrow cells
- Cytogenetic and molecular subsets of AML and ALL

Pharmacodynamic Biomarkers

- Leukemic stem cells in pre- and post-dose bone marrow cells
- H3K27me3 status in leukemic stem cells in bone marrow and/or blood cells

11.6. Safety Analyses

Safety parameters will include AEs, SAEs, TEAEs, DLTs, physical examination findings (including ECOG-PS), vital sign measurements, standard clinical laboratory parameters, histamine level in plasma, and ECG parameters.

Frequency tables of subjects reporting TEAEs will be provided by the worst NCI-CTCAE grade, SOC, preferred term (PT), and by dose level. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as treatment-related TEAEs. The incidence of DLTs will be tabulated by dose level. Descriptive statistics by dose level will be provided on clinical laboratory parameters, histamine level in plasma, ECG parameters, and vital sign measurements, including the reported values and changes from baseline at each scheduled

measurement. Frequency tables by dose level will be provided for physical examination and ECOG-PS, and other categorical assessments as appropriate.

Adverse events will be graded according to the NCI-CTCAE. In the Dose Escalation part, the incidence of DLTs will also be evaluated.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the Dose Escalation part, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable Set will be listed and summarized for each dose of DS-3201b.

11.6.1. Adverse Event Analyses

A TEAE is defined as an AE that emerges during the treatment period, having been absent at pre-treatment; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-treatment state, when the AE is continuous.

The number and percentage of subjects reporting TEAEs will be tabulated by the worst NCI-CTCAE grade, SOC, PT, and by dose level.

Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to DS-3201b.

A by-subject AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, PT, SOC, NCI-CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from DS-3201b, will be listed.

11.6.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for selected clinical laboratory test results (ie, hematology [including coagulation] and blood chemistry) and changes from baseline by scheduled time of evaluation including the EOT visit, maximum post-treatment value, and minimum post-treatment value.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE, Version 4, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

11.6.3. Vital Signs Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation, including the EOT visit, and the maximum and minimum post-baseline values.

11.6.4. Electrocardiogram Analyses

Electrocardiogram parameters (PR, RR, QRS, QT intervals, and corrected QT interval using Bazett's [QT_cB], and Fridericia's [QT_cF] formulas) will be summarized using descriptive

statistics for actual values and for changes from baseline by scheduled time of evaluation, including the EOT visit and the maximum post-baseline value. The corrected QT intervals using Bazett's and Fridericia's formula will be calculated as follows:

$QT_cB = QT/(RR)^{1/2}$ and $QT_cF = QT/(RR)^{1/3}$

The number and percentage of subjects with maximum absolute QT, QT_cF, and QT_cB intervals meeting pre-defined categories (>450 ms, >480 ms, and >500 ms) over all post-treatment evaluations, as well as in QT, QT_cF, and QT_cB maximum changes from baseline (>30 ms and >60 ms) over all post-treatment evaluations will be tabulated. A listing of ECG data will be provided.

11.6.5. Physical Finding Analyses

Physical examination findings will be listed for the Safety Analysis Set.

11.6.6. Other Safety Analyses

11.6.6.1. Histamine

Descriptive statistics by dose level will be provided for histamine level in plasma including the reported values and changes from baseline at each scheduled measurement.

11.6.6.2. Eastern Cooperative Oncology Group – Performance Status

The ECOG-PS at baseline (pre-dose) will be listed for the safety analysis sets. A shift table, presenting the 2-way frequency tabulation for baseline and EOT visit, will be provided for ECOG-PS.

11.7. Other Analyses

Not applicable.

11.8. Interim Analyses

No formal interim analysis is planned, except for the assessment of the MTD after each escalation cohort in the Dose Escalation part. Before dose escalation, the available safety data, including DLT information and other study data, will be reviewed in this open-label study.

11.9. Data and Safety Monitoring Board

Not applicable.

11.10. Sample Size Determination

The Dose Escalation part of the study will enroll 3 to 6 subjects in each cohort, based on a BLRM under the EWOC principle. It is possible that a dose level may enroll more than one cohort based on the BLRM recommendation. The number of subjects enrolled depends on the observed DLTs, but it is expected that 21 or more subjects might be enrolled in the Dose Escalation part.

For the Dose Expansion part, additional subjects will be enrolled at the RDE dose level as suggested based on data in the Dose Escalation part. Approximately 20 subjects each with AML and ALL will be enrolled at the RDE dose level, including those dosed at the same dose level in the Dose Escalation part, which is expected to number between 6 and 9. The size of 40 is deemed to be sufficient for the assessment of safety and tolerability, as well as the clinical antitumor activity. Assuming a true CRc rate of 20%, the probability of observing 3 or more CRc among the 20 subjects is 79.4% for AML and ALL, respectively.

11.11. Specification of Modified Continual Reassessment Method with Escalation with Overdose Control

11.11.1. Bayesian Logistic Regression Model for Bayesian Logistic Regression Model

The dose-toxicity relationship for BLRM with the EWOC principle will be described by a 2-parameter BLRM:

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*), \qquad \alpha>0, \beta>0$$

where $\text{logit}(\pi(d)) = \ln(\pi(d)/(1-\pi(d)))$, $\pi(d)$ is the probability of a DLT or the DLT rate at dose d. Doses are rescaled as d/d* with the reference dose d* = 700 mg. As a consequence, α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

11.11.2. Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally-informative bivariate normal prior[14] for the model parameters (log(α),log(β)) is obtained as follows:

- The best guess of MTD is projected to be around 700 mg in humans. The median prior probabilities of DLT are set to be approximately 8% and 24% at 100 mg (projected starting dose for dose escalation using BLRM) and the projected MTD of 700 mg, respectively.
- For the remaining doses, the prior medians of probability of DLT are assumed linear in log-dose on the logit-scale.
- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals (obtained from minimally informative beta distributions[14]), the optimal parameters of the bivariate normal distribution can be obtained as follows:

Parameters	Means	Standard deviations	Correlation
log(α), log(β)	(-1.005, -0.093)	(1.289, 1.098)	-0.182

11.11.3. Escalation with Overdose Control Principle

Dose recommendation for the next cohort will be based on summaries of the posterior probability of the DLT rate for possible doses: 100 mg, 150 mg, 250 mg, 350 mg, 500 mg, and 700 mg, and if MTD has not been reached, 1000 mg. The above dose levels are only a guideline, and the exact dose level for the next dose escalation cohort will be determined after reviewing the available safety and study data from all enrolled subjects. After the first 3 subjects of each cohort complete the DLT evaluation during Cycle 1, the posterior distributions of the DLT rate will be derived for all provisional dose levels based on the BLRM using the DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level ([0%, 16%) as the DLT rate interval for under-dosing, [16%, 33%) as the target DLT rate interval, [33%, 60%) as the DLT rate interval for excessive toxicity, and [60%, 100%] as the DLT rate interval for unacceptable toxicity) will then be calculated and used for dose recommendation for the next cohort according to the EWOC principle. It is therefore conceivable that the posterior probability of DLT rate for dose recommendation may be generated using alternative provisional doses as long as the predicted exposure increments are between 30% and 100% (Section 3.1.2.1).

The EWOC principle requires that the BLRM recommended dose for the next cohort of subjects is defined as the highest posterior probability of the DLT rate in the target DLT rate interval [16%, 33%) among all doses fulfilling the overdose control constraint: there is less than a 25% probability for the DLT rate >33% (probability for excessive or unacceptable toxicity).

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The DSI and CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study sites facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

Electronic case report form (eCRF) completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. Electronic CRFs will be completed, reviewed and signed off or e-signed by the Investigator as described in the Data Management Plan and in the monitoring plan for clinical research associates. Instructions for completion of the eCRFs will be provided. Corrections to electronic forms will be automatically documented by using the software's "audit trail".

The eCRF should be kept current to enable the study monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed-off by the Investigator via the electronic data capture (EDC) system's electronic signature. This signature will indicate that the Investigator inspected or reviewed the data in the eCRF, the data queries, and the site notifications and agrees with the eCRF content.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.3. Data Management

This is an open-label study. Each subject will be identified in the database by a unique SID as defined by DSI.

To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data according to specifications given to the CRO. Data will be vetted both electronically and manually. For eCRFs, the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application (Medidata RAVE). During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, eCRFs queries will be raised and resolved within the EDC application.

Data received from external sources such as central labs will be reconciled to the clinical database.

Serious adverse events in the clinical database will be reconciled with the safety database. All prior cancer therapy and prior/concomitant medications entered into the database will be coded by using the latest version of World Health Organization Drug Dictionary. All AEs will be coded by using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

12.4. Study Documentation and Storage

The Investigator will maintain a signature list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the signature list.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, date, and outcome of screening process.

Investigators will be expected to maintain an enrollment log of all subjects enrolled in the study indicating their assigned study number.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from DSI and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed eCRFs, informed consents, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB and DSI.
- Records related to the investigational product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, and distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records DSI must be notified in writing and be given the opportunity to further store such records.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with DSI. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until 1 year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that DSI has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of DSI Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

All information regarding DS-3201b supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of DS-3201b and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, public databases (eg, ClinicalTrials.gov, EU Clinical Trial Register), or consultants as required.

Upon completion of the clinical study and evaluation of results by the Sponsor, the hospital or institution and/or Investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprised of Sponsor employees and study Investigators will be formed to oversee the publication of the study results that will reflect the experience of all participating study sites. Subsequently, individual Investigators may publish results from the study in compliance with their agreements with the Sponsor.

A prepublication manuscript or abstract is to be provided to the Sponsor a minimum of 30 days prior to the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by the Sponsor of the notification, the Sponsor shall inform the sites whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from the Sponsor's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at the Sponsor's request.

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by DSI or the CRO. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days. The Sponsor will assure the timely submission of amendments to regulatory authorities in accordance with the governing regulations.

15.2. Address List

A list of key study personnel (including personnel at the sponsor, CRO, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in the Study Site Manual.

15.2.1. Sponsor

Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920-2311
Phone: PPD
Fax: PPD

15.2.2. Drug Safety

15.2.2.1. DSI Clinical Safety and Pharmacovigilance

PPD

15.2.3. Biological Specimens

Refer to the Study Laboratory Manual

15.2.4. Bioanalytical Laboratory

Refer to the Study Laboratory Manual

16. REFERENCES

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17. APPENDICES

17.1. Eastern Cooperative Oncology Group Performance Status Scale

GRADE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, 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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.[16]

17.2. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When 2 different criteria grades might be applicable for rating a particular toxicity, or similar toxicities, the more severe grade should be used.
3. Any toxicity resulting in death is defined as Grade 5.
4. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
5. For links to the NCI-CTCAE, Version 4, please refer to PPD

17.3. Response Criteria

17.3.1. International Working Group Response Criteria for AML

Category	Neutrophils (cells/μL)	Platelets (plt/μL)	Bone Marrow Blasts (%)	Other Requirements
CR Complete remission	> 1000	≥ 100,000	< 5	No leukemic blasts in peripheral blood Transfusion independence, except for infection, bleeding, or medical/surgical conditions predisposing to bleeding No extramedullary disease
CRp CR with incomplete platelet recovery	> 1000	≥ 30,000 to < 100,000	< 5	Meets criteria for CR except for platelet count
CRi CR with incomplete blood count recovery	≤ 1000	≥ 100,000	< 5	Meets criteria for CR except for neutrophils
		OR		
	> 1000	< 30,000	< 5	Meets criteria for CRp except for platelets
PR Partial remission	> 1000	≥ 100,000	Decrease of ≥ 50% to a value between 5% and 25%	Blasts < 5% if Auer-rod positive
TF Treatment failure	Persistent acute myeloid leukemia in blood or bone marrow, or therapy fails to achieve a remission of any category, or death prior to response assessment			

Source: Cheson BD, et al[13]

17.3.2. National Comprehensive Cancer Network Response Criteria for ALL

Category	Response Criteria for Blood and Bone Marrow
Complete remission (CR)	No circulating blasts or extramedullary disease No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement Trilineage hematopoiesis (TLH) and <5% blasts Absolute neutrophil count (ANC) >1000/microL Platelets >100,000/microL No recurrence for 4 weeks
CR with incomplete blood count recovery (CRi)	Recovery of platelets but <100,000 or ANC is <1000/microL
Overall response rate (ORR)	CR + CRi
Refractory disease	Failure to achieve CR
Progressive disease (PD)	Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
Relapsed disease	Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site or after a CR

17.4. Modification of Diet in Renal Disease

MDRD Formula[17]:

$$GFR\ (mL/min/1.73\ m^2) = 186.3 \times (Scr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

Cockcroft-Gault equation[18]:

([{140 – age in years} × {actual weight in kg}] divided by [{72 × serum creatinine in mg/dL} multiply by 0.85 if female]), OR creatinine ≤1.5 × ULN

17.5. YP3A Inducers and CYP3A/P-gp Inhibitors

Prior to enrollment, strong CYP3A inhibitors, and moderate or strong CYP3A inducers are prohibited within 7 days of first dose of DS-3201b.

- Consumption of herbs/fruits that may have an influence on PK of DS-3201b, such as star fruit, Seville orange or Seville orange-containing foods and beverages, and grapefruit or grapefruit-containing food or beverages, are prohibited from 3 days prior to the first dose of DS-3201b up to the last dose of DS-3201b.
- St. John's wort (hypericin) is not be permitted from 14 days prior to the first dose of DS-3201b up to the last dose of DS-3201b

During study participation, strong CYP3A inhibitors and/or P-gp inhibitors, if required for prophylactic administration for the treatment of symptoms such as infection, are permitted with a dose reduction of DS-3201b.

During study participation, moderate and strong CYP3A inducers are prohibited, as drugs having moderate or strong CYP3A inducing properties may decrease plasma DS-3201a concentrations and it is therefore necessary to avoid concomitant use of these drugs with DS-3201b. However, if medically essential to use as supportive care, concomitant use of moderate and strong CYP3A inducers is permissible after the first dose of the study drug. In this case, dose interruption of DS-3201b is not needed.

Please refer to the following links as well as to Table 17.1:

PPD

Table 17.1: List of CYP3A Inhibitors/Inducers and P-gp Inhibitors

Please note that the following list of CYP3A inhibitor/inducers and P-gp inhibitors is not all-inclusive:

CYP3A/P-gp Inhibitors	CYP3A Inducers
Drugs having a strong CYP3A inhibitory effect and a P-gp inhibitory effect clarithromycin itraconazole lopinavir and ritonavir ritonavir saquinavir and ritonavir telaprevir tipranavir and ritonavir Strong CYP3A inhibitors boceprevir cobicistat danoprevir and ritonavir elvitegravir and ritonavir grapefruit juice idelalisib indinavir and ritonavir ketoconazole mibefradil nefazodone nelfinavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole telithromycin troleandomycin voriconazole Moderate CYP3A inhibitors aprepitant ciprofloxacin conivaptan crizotinib cyclosporine diltiazem	Strong CYP3A inducers apalutamide avasimibe carbamazepine enzalutamide mitotane phenytoin rifampicin rifapentine St. John's wort Moderate CYP3A inducers bosentan efavirenz etravirine phenobarbital primidone rifabutin Weak CYP3A inducers armodafinil modafinil rufinamide

CYP3A/P-gp Inhibitors	CYP3A Inducers
dronedarone erythromycin fluconazole fluvoxamine imatinib isavuconazole tofisopam verapamil <u>Weak CYP3A inhibitors</u> chlorzoxazone cilostazol cimetidine clotrimazole fosaprepitant istradefylline ivacaftor lomitapide ranitidine ranolazine ticagrelor <u>P-gp inhibitors (no strong CYP3A inhibition)</u> amiodarone carvedilol dronedarone lapatinib propafenone quinidine ranolazine verapamil External medicine is excluded	

CYP3A = Cytochrome P450 3A; P-gp = P-glycoprotein

17.6. Potential QT/QTc Prolonging Drugs

Concomitant drugs to be avoided during treatment with DS3201b.

The following list describes medications which prolong QTc interval.

This list should not be considered all-inclusive. Consult individual drug labels for specific information on a drug's propensity to prolong QTc interval.

Potential QT/QTc Prolonging Drugs	Generic Drug Name
Macrolide antibiotics	azithromycin erythromycin clarithromycin roxithromycin
Fluoroquinolone antibacterials	moxifloxacin ciprofloxacin gatifloxacin grepafloxacin levofloxacin sparfloxacin
Azole antifungals	fluconazole
Antimalarials	chloroquine halofantrine quinidine
Antiprotozoals	pentamidine
Antiemetics, gastrokinetics	droperidol ondansetron cisapride domperidone
Antipsychotics, antidepressants and other CNS agents	chlorpromazine cocaine citalopram donepezil escitalopram haloperidol ibogaine levomepromazine levomethadyl acetate levosulpiride methadone mesoridazine primozide

Potential QT/QTc Prolonging Drugs	Generic Drug Name
	propofol sevofluran sulpiride sultopride thioridazine
Antiplatelet agents	anagrelide cilostazol
Antihistamines	astemizole terfenadine
Antiarrhythmics, antihypertensives, antihyperlipidemics	amiodarone bepridil disopyramide dofetilide dronedarone flecainide ibutilide papaverine HCl probucol procainamide sotalol terilpressin terodiline

CCI

17.7. Highly Effective Methods of Birth Control[19]

Female subjects of reproductive/childbearing potential with a male sexual partner must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 3 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective birth control include:

a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal delivery).
b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable delivery).
c. Intrauterine device (IUD).
d. Intrauterine hormone-releasing system (IUS).
e. Bilateral tubal occlusion.
f. Vasectomized partner.
g. Complete sexual abstinence.

Non-childbearing potential is defined as pre-menopausal with documented tubal ligation or hysterectomy; OR postmenopausal with documented ≥12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] >40 mIU/mL and estradiol <40 pg/mL [<140 pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods outlined above for women of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

Female subjects must not retrieve ova or donate from the time of screening and throughout the study treatment period, and for ≥3 months after the final dose of study drug.

A male subject with a sexual partner who is a woman of childbearing potential must be willing and able to use a highly effective contraceptive method for the entire study treatment period and for ≥3 months after the final dose of study drug. Acceptable forms of contraception include condoms and highly effective contraception used by the usual female partner (see above for forms of highly effective contraception). Male subjects must not freeze or donate sperm starting at screening and throughout the study period, and ≥3 months after the final dose of study drug.

17.8. Schedule of Events

Table 17.2: Schedule of Events Part 1 (Dose Escalation)

Cycle (1 cycle = 28 days) (a)	Pre-Cycle	1														2		3	4 and beyond	Post-Cycle		LTFU
Visit Number	1	2						3	4						5	6	7	8	9	10 and beyond	TBD		TBD
Visit Description	Screening	Exam and 1st Dose						Exam	Exam						Exam	Exam	Exam	Exam	Exam	Exam	EOT (b)	EOS F/U*	LTFU (q)
Cycle Day(s)	-14 to -1	1						2	8						15	22	1	15	1	1	ND	ND	ND
Visit Window (days)									± 2						± 2	± 2	± 4	± 4	± 4	± 4			
Time post-dose (hours)		Pre-dose	0.5	1	2	4	6	8	Pre-dose	0.5	1	2	4	6	8								
Informed consent	X																						
SID number assigned	X																						
Demographics	X																						
Medical history	X																						
Inclusion/exclusion criteria	X																						
Pregnancy test (c)	X																		X		X		
Adverse events	X	X							X	X							X	X	X	X	X	X	X	X	
Prior/concomitant medications	X	X							X	X							X	X	X	X	X	X	X	X	
ECOG-PS	X	X								X							X	X	X	X	X	X	X		
Height	X																						X		
Physical examination, including weight	X	X								X							X	X	X	X	X	X	X		
Vital signs	X	X		X					X	X							X	X	X	X	X	X	X		
Clinical laboratory (d)	X	X							X	X							X	X	X	X	X	X	X		
Urinalysis (e)	X	X								X							X	X	X	X	X		X		
Triplicate ECG (12-lead) (f)	X	X		X	X	X	X (g)	X	X	X		X	X	X	X (g)	X	X	X	X		X	X	X		
Bone marrow assessment (h)	X									X									X	X (i)	X	X (p)			
Biomarker blood sample (j)		X							X	X							X	X	X				X		
DS-3201b administration (k)		X							X	X							X	X	X	X	X	X			
Blood sample for DS-3201a PK (l) (m)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
Blood collection for histamine (n)		X		X	X		X		X	X							X								
Blood collection for protein binding determination (l) (m)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
Serum collection for AAG		X								X															

Cycle (1 cycle = 28 days) (a)	Pre-Cycle	1														2		3	4 and beyond	Post-Cycle		LTFU
Visit Number	1	2							3	4						5	6	7	8	9	10 and beyond	TBD		TBD
Visit Description	Screening	Exam and 1st Dose							Exam	Exam						Exam	Exam	Exam	Exam	Exam	Exam	EOT (b)	EOS F/U*	LTFU (q)
Cycle Day(s)	-14 to -1	1							2	8						15	22	1	15	1	1	ND	ND	ND
Visit Window (days)										± 2						± 2	± 2	± 4	± 4	± 4	± 4			
Time post-dose (hours)		Pre-dose	0.5	1	2	4	6	8		Pre-dose	0.5	1	2	4	6	8								
Dispense DS-3201b									X	X							X	X	X	X	X	X			
Pill diaries dispensed/reviewed									X	X							X	X	X	X	X	X	X		
Medication compliance reviewed										X							X	X	X	X	X	X	X		
Optional marrow re-biopsy (o)																							X		
Reason for treatment discontinuation recorded																							X		
Survival status assessed																								X	X
Unused meds & bottles collected																								X	
Subsequent AML/ALL treatments																									X (r)

a: Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.

b: End-of-treatment visit will occur within 30 days after the last administration of DS-3201b. If the subject begins another form of anticancer therapy before the end of the 30 day period, every effort will be made to complete all the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution or confirmed stability of the abnormality.

c: Pregnancy test will be performed in female subjects of childbearing potential at screening, Cycle 3/Day 1, and EOT visit.

d: Clinical laboratory samples for Day 1 pre-dose (complete blood count with differential and absolute neutrophil counts, reticulocyte counts and peripheral blood blasts, serum chemistry, urinalysis, and coagulation profile) can be collected within 72 hours before the first dose. Creatinine clearance will be calculated at screening.

e: Urinalysis will be performed for the indicated visits up to Cycle 3/Day 1 and at EOT visit.

f: Electrocardiograms will be performed pre-dose at Cycle 1/Days 1, 2, 8, 15, and 22, Cycle 2/Day 1, Cycle 3/Day 1, Cycle 4 and beyond/Day 1, and EOT, and additionally at 1, 2, 4, and 8 hours post-dose on Cycle 1/Days 1 and 8. Procedure window is ± 1 hour. Electrocardiograms will be performed in triplicate (5 minutes apart). Whenever there are time matched ECGs and PK sampling, ECGs should be done first. PK samples should be collected within 15 minutes of ECG collection.

g: If the ECG at 8 hours post-dose is not possible, then ECG may be performed at 6 hours (± 10 minutes) post-dose.

h: All unscheduled bone marrow assessments of disease burden performed on non-visit days must be reported as unscheduled visits and samples for flow cytometry and/or mass cytometry, cytogenetics, and other biomarkers should be obtained.

i: Perform a bone marrow assessment if Cycle 2/Day 1 bone marrow revealed aplasia.

j: Blood samples drawn pre-dose at Cycle 1/Days 1, 2, 8, 15, and 22, Cycle 2/Day 1, and EOT visit for exploratory biomarker analysis.

k: DS-3201b is administered per protocol at the clinical site at the indicated time. Subjects should avoid food for 2 hours before and 1 hour after drug administration.

l: Blood samples for DS-3201a PK measurements and protein binding will be collected pre-dose at the indicated visits (Cycle 1/Days 1, 2, 8, 15, and 22, and Cycle 2/Day 1), at the indicated time points on Cycle 1/Days 1 and 8, and at EOT. Subjects will be instructed not to take their dose until after sample has been collected on clinic days. Additional samples will be collected at the indicated time points. The window for sample collection will be ± 15% of the specified time. Based on the PK profile established from the initial subjects treated in the study, sample collection time points may be modified upon notification by the Sponsor. Blood samples should be collected within 15 minutes of ECG collection on days with time matched ECGs and blood sampling.

m: If moderate or strong CYP3A and/or P-gp inhibitors are co-administered with DS-3201b, blood samples for DS-3201a PK measurements and protein binding should be collected on the first day of moderate or strong CYP3A and/or P-gp inhibitor dosing at pre-dose, 4 hours, and 8 hours post-dose of DS-3201b; and within 28 days after last day of moderate or strong CYP3A and/or P-gp inhibitor dosing at pre-dose, 4 hours, and 8 hours post-dose of DS-3201b.

n: Blood for histamine measurement will be obtained at the indicated time points (pre-dose and at 1, 2, and 6 hours post-dose on Cycle 1/Day 1 and pre-dose on Cycle 1/Days, 2, 8, and 15).

o: A bone marrow re-biopsy may be performed within 30 days of the last dose of DS-3201b in subjects who have achieved an initial complete remission/partial remission to DS-3201b by revised IWG response criteria or NCCN response criteria but later developed progressive disease while on therapy.

p: Based on the Investigator's clinical judgment, the frequency of bone marrow biopsies/aspirates can be reduced to once every 3 cycles after Cycle 3/Day1 until Cycle 12/Day1 (eg, Day 1 of Cycles 6, 9, and 12). After Cycle 12/Day1, the frequency of bone marrow biopsies/aspirates can be reduced up to once every 6 cycles (eg, Day 1 of Cycles 18, 24, etc).

q: LTFU will occur every 3 months after EOS Follow-up via telephone until death, loss to follow-up, or termination of study by the Sponsor.

r: Information on AML/ALL treatment (including stem cell transplants), HCT and HCT-relevant information (if performed), and response to treatment should be collected.

* Note: The EOS Follow-up will occur 30 (± 5) days after the last administration of DS-3201b. Follow-up information will be collected via a phone call or site visit. If the subject begins another form of anticancer therapy before the end of the 30 (± 5)-day period, every effort will be made to complete all of the following EOS assessments prior to commencing the new therapy: assessment of AEs, current medications, subject survival status, and collection of any empty bottle(s) along with any unused medication.

AAG = alpha 1-acid glycoprotein; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia ; CYP = cytochrome P450; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG-PS= Eastern Cooperative Oncology Group – Performance Status; EOS = End-of-study; EOT = End-of-treatment; F/U = follow-up; IWG = International Working Group; LTFU = Long-term Follow-up, NCCN = National Comprehensive Cancer Network; ND = not determined; P-gp = P-glycoprotein; PK = pharmacokinetics; SID = subject identification; TBD = to be determined.

Table 17.3: Schedule of Events Part 2 (Dose Expansion)

Cycle (1 cycle = 28 days) (a)	Pre-Cycle	1														2		3	4 and beyond	Post-Cycle		LTFU
Visit Number	1	2						3	4						5	6	7	8	9	10 and beyond	TBD		TBD
Visit Description	Screening	Exam and 1st Dose						Exam	Exam						Exam	Exam	Exam	Exam	Exam	Exam	EOT (b)	EOS F/U *	LTFU (q)
Cycle Day(s)	-14 to -1	1						2	8						15	22	1	15	1	1	ND	ND	ND
Visit Window (days)									± 2						± 2	± 2	± 4	± 4	± 4	± 4			
Time post-dose (hours)		Pre-dose	0.5	1	2	4	6	8	Pre-dose	0.5	1	2	4	6	8								
Informed consent	X																						
SID number assigned	X																						
Demographics	X																						
Medical history	X																						
Inclusion/exclusion criteria	X																						
Pregnancy test (c)	X																		X		X		
Adverse events	X	X							X	X						X	X	X	X	X	X	X	X	
Prior/concomitant medications	X	X							X	X						X	X	X	X	X	X	X	X	
ECOG-PS	X	X								X						X	X	X	X	X	X	X		
Height	X																					X		
Physical examination, including weight	X	X								X						X	X	X	X	X	X	X		
Vital signs	X	X		X					X	X						X	X	X	X	X	X	X		
Clinical laboratory (d)	X	X							X	X						X	X	X	X	X	X	X		
Urinalysis (e)	X	X								X						X	X	X	X	X		X		
Triplicate ECG (12-lead) (f)	X	X		X	X	X	X (g)	X	X	X		X	X	X	X (g)	X	X	X	X	X		X		
Bone marrow assessment (h)	X									X								X	X (i)	X	X (p)			
Biomarker blood sample (j)		X							X	X						X	X	X				X		
DS-3201b administration (k)		X							X	X						X	X	X	X	X	X			
Blood sample for DS-3201a PK (l) (m)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
Blood collection for histamine (n)		X		X	X		X		X	X						X								
Blood collection for protein binding determination (l) (m)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
Serum collection for AAG		X								X														
Dispense DS-3201b									X	X						X	X	X	X	X	X			
Pill diaries dispensed/reviewed									X	X						X	X	X	X	X	X	X		

Cycle (1 cycle = 28 days) (a)	Pre-Cycle	1														2		3	4 and beyond	Post-Cycle		LTFU
Visit Number	1	2						3	4						5	6	7	8	9	10 and beyond	TBD		TBD
Visit Description	Screening	Exam and 1st Dose						Exam	Exam						Exam	Exam	Exam	Exam	Exam	Exam	EOT (b)	EOS F/U *	LTFU (q)
Cycle Day(s)	-14 to -1	1						2	8						15	22	1	15	1	1	ND	ND	ND
Visit Window (days)									± 2						± 2	± 2	± 4	± 4	± 4	± 4			
Time post-dose (hours)		Pre-dose	0.5	1	2	4	6	8	Pre-dose	0.5	1	2	4	6	8								
Medication compliance reviewed									X							X	X	X	X	X	X	X		
Optional marrow re-biopsy (o)																						X		
Reason for treatment discontinuation recorded																						X		
Survival status assessed																							X	X
Unused meds & bottles collected																							X	
Subsequent AML/ALL treatments and results																								X (r)

a: Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.

b: End-of-treatment visit will occur within 30 days after the last administration of DS-3201b. If the subject begins another form of anticancer therapy before the end of the 30 day period, every effort will be made to complete all the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution or confirmed stability of the abnormality.

c: Pregnancy test will be performed in female subjects of childbearing potential at screening, Cycle 3/Day 1, and EOT visit.

d: Clinical laboratory samples for Day 1 pre-dose (complete blood count with differential and absolute neutrophil counts, reticulocyte counts, and peripheral blood blasts, serum chemistry, urinalysis, and coagulation profile) can be collected within 72 hours before the first dose. Creatinine clearance will be calculated at screening.

e: Urinalysis will be performed for the indicated visits up to Cycle 3/Day 1 and at EOT visit.

f: Electrocardiograms will be performed pre-dose at Cycle 1/Days 1, 2, 8, 15, and 22, Cycle 2/Day 1, Cycle 3/Day 1, and EOT, and additionally at 1, 2, 4, and 8 hours post-dose on Cycle 1/Days 1 and 8. Procedure window is ± 1 hour. Electrocardiograms will be performed in triplicate (5 minutes apart). Whenever there are time matched ECGs and PK sampling, ECGs should be done first. PK samples should be collected within 15 minutes of ECG collection.

g: If the ECG at 8 hours post-dose is not possible, then ECG may be performed at 6 hours (± 10 minutes) post-dose.

h: All unscheduled bone marrow assessments of disease burden performed on non-visit days must be reported as unscheduled visits and samples for flow cytometry and/or mass cytometry, cytogenetics, and other biomarkers should be obtained.

i: Perform a bone marrow assessment if Cycle 2/Day 1 bone marrow revealed aplasia.

j: Blood samples drawn pre-dose at Cycle 1/Days 1, 2, 8, 15, and 22, Cycle 2/Day 1, and EOT visit for exploratory biomarker analysis.

k: DS-3201b is administered per protocol at the clinical site at the indicated time. Subjects should avoid food for 2 hours before and 1 hour after drug administration.

l: Blood samples for DS-3201a PK measurements and protein binding will be collected pre-dose at the indicated visits (Cycle 1/Days 1, 2, 8, 15, and 22, and Cycle 2/Day 1), at the indicated time points on Cycle 1/Days 1 and 8, and at EOT. Subjects will be instructed not to take their dose until after sample has been collected on clinic days. Additional samples will be collected at the indicated time points. The window for sample collection will be ± 15% of the specified time. Based on the PK profile established from the initial subjects treated in the study, sample collection time points may be modified upon notification by the Sponsor. Blood samples should be collected within 15 minutes of ECG collection on days with time matched ECGs and blood sampling.

m: If moderate or strong CYP3A and/or P-gp inhibitors are co-administered with DS-3201b, blood samples for DS-3201a PK measurements and protein binding should be collected on the first day of moderate or strong CYP3A and/or P-gp inhibitor dosing at pre-dose, 4 hours, and 8 hours post-dose of DS-3201b; and within 28 days after last day of moderate or strong CYP3A and/or P-gp inhibitor dosing at pre-dose, 4 hours, and 8 hours post-dose of DS-3201b.

n: Blood for histamine measurement will be obtained at the indicated time points (pre-dose and 1, 2, and 6 hours post-dose on Cycle 1/Day 1 and pre-dose on Cycle 1/Days, 2, 8, and 15).

o: A bone marrow re-biopsy may be performed within 30 days of the last dose of DS-3201b in subjects who have achieved an initial complete remission/partial remission to DS-3201b by revised IWG response criteria or NCCN response criteria but later developed progressive disease while on therapy.

p: Based on the Investigator's clinical judgment, the frequency of bone marrow biopsies/aspirates can be reduced to once every 3 cycles after Cycle 3/Day1 until Cycle 12/Day1 (eg, Day 1 of Cycles 6, 9, and 12). After Cycle 12/Day1, the frequency of bone marrow biopsies/aspirates can be reduced up to once every 6 cycles (eg, Day 1 of Cycles 18, 24, etc).

q: LTFU will occur every 3 months after EOS Follow-up via telephone until death, loss to follow-up, or termination of study by the Sponsor.

r: Information on AML/ALL treatment (including stem cell transplants), HCT and HCT-relevant information (if performed), and response to treatment should be collected.

* Note: The EOS Follow-up will occur 30 (± 5) days after the last administration of DS-3201b. Follow-up information will be collected via a phone call or site visit. If the subject begins another form of anticancer therapy before the end of the 30 (± 5)-day period, every effort will be made to complete all of the following EOS assessments prior to commencing the new therapy: assessment of AEs, current medications, subject survival status, and collection of any empty bottle(s) along with any unused medication.

AAG = alpha 1-acid glycoprotein; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia ; CYP = cytochrome P450; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG-PS = Eastern Cooperative Oncology Group – Performance Status; EOS = End-of-study; EOT = End-of-treatment; F/U = follow-up; IWG = International Working Group; LTFU = Long-term Follow-up; NCCN = National Comprehensive Cancer Network; ND = not determined; P-gp = P-glycoprotein; PK = pharmacokinetics; TBD = to be determined.

17.9. Extension Phase

17.9.1. Extension Phase Synopsis

Objective of the Extension Phase:	The primary objective of the Extension Phase is to allow continuation of DS-3201b study treatment for those subjects in the DS-3201b Phase 1 study who have tolerated the drug and whose disease has not progressed (ie, stable disease [SD] or better) at the time of closure of the main study phase.
Design of the Extension Phase:	This is an open-label, nonrandomized extension phase of the main study phase which is designed to allow subjects who have tolerated DS-3201b and demonstrated clinical benefit (SD or better) at the time of study closure during the main study phase to continue with DS-3201b monotherapy. Subjects will continue with the same dose of DS-3201b monotherapy treatment as in the main study phase until they commence new cancer therapy, experience unacceptable toxicity, withdraw consent, or have progressive disease. If study drug is withheld for toxicity, periodic visits should continue to occur as clinically indicated. These visits should include any procedures needed to ensure subject safety. Subjects enrolled in the Extension Phase will be assessed as outlined in Table 17.4. Data collected will be recorded in the individual, subject-specific eCRF. The extent or frequency of data collection into the eCRFs may be reduced for the Extension Phase.
Duration of the Extension Phase:	The start of the Extension Phase is when all the subjects in Part 1 and Part 2 of the study have completed at least 6 months of treatment and the main study phase is being closed. Subjects who are receiving clinical benefit (SD or better) and have tolerated DS-3201b will continue to receive the drug. It is not possible to predict the duration of the Extension Phase because subjects may continue treatment until disease progression, unacceptable toxicity, starting of new cancer therapy, or withdrawal of consent.

Subject Eligibility:	Subjects must have tolerated DS-3201b and demonstrated clinical benefit (SD or better) at the time of closure of the main study phase (Part 1 and Part 2) in order to be eligible for this extended use phase of the study.
Safety Evaluations:	Safety evaluations include documentation of adverse events, serious adverse events, clinical laboratory evaluations, physical examinations, vital signs, and electrocardiograms, as needed.
Dose:	Subjects who participate in the Extension Phase will continue to take DS-3201b at the same dose as was taken in the main study phase.
Statistical Analyses:	Data collected during the Extension Phase will be listed and appended to the Clinical Study Report.

Table 17.4: Schedule of Events (Extension Phase)

Assessment	All Cycles, Day 1 (a)	End-of-treatment Visit (b)
Visit Window (Days)	**28 days ± 4 days from Day 1 of previous cycle**	**30 to 45 days after last dose**
Physical examination	X	X
Vital signs (c)	X	X
Adverse events	X	X
CBC (with differential and platelet count)	X (d)	X
Serum chemistries	X (d)	X
DS-3201b administration (e)	X	
Bone marrow assessment	X (f)	

[a] Assessments and laboratory tests indicated on Day 1 will occur before administration of DS-3201b.
[b] End-of-treatment visit will occur 30 to 45 days after the last administration of DS-3201b in the Extension Phase. If there is a clinically significant laboratory abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution of the abnormality or until it is considered stable.
[c] The subject's weight will be recorded as part of the vital signs assessment.
[d] Clinical safety laboratory tests include hematology, chemistry, CBC, and platelet count. The tests described in Section 9.7 will be conducted on Day 1 of all cycles and as clinically indicated by the Investigator.
[e] DS-3201b is to be administered at the same dosing schedule as during the main study phase.
[f] Marrow assessment will be performed as clinically indicated.
CBC = complete blood count; EOT = End-of-treatment