Non-Interventional Study Protocol
B1931024

Special Investigation of
BESPONSA® Injection 1 mg

Statistical Analysis Plan

Version: 6.0

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Date: 02-Sep-2024

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1. REVISION HISTORY

Version/ Date/ Author(s)	Summary of Changes/Comments
6.0 02-Sep-2024 PPD	○ Section 5.4: Some subgroup factors and their categories were added. ◯Section 8.2.2: Histogram classes were changed. ◯Section 8.2.2: Analysis of correlation between age and patient characteristics was added. ◯Section 8.2.3.1: The factors explored in the "Exploration of factors associated with the occurrence of VOD/SOS" were changed. ◯Section 8.2.3.4: Specifications and factors for subgroup analyses of adverse drug reactions were added. ◯Section 8.2.3.4: Analysis of adverse events was deleted from the subgroup analyses of adverse drug reactions. ◯Section 8.2.4.1: The categorization for the summary of hematologic response data by cycle was changed. ◯Section 8.2.4.4: Analysis of deaths and causes of death were added. ○ Section 9: Some listings were added and specifications were changed. ◯Editorial revisions
5.0 30-Nov-2023 PPD	○ Section 2.1: A description was added to reflect that the continuation of the survey with registration only will be terminated in the future. ○ Section 5.2: Some terms used for the exclusion criterion h to define the effectiveness analysis set was changed in accordance with the revision to the Guidance for Adoption/Rejection Criteria for Analysis Populations and Handling of Data in Special Investigation, Ver 3. ○ Sections 5.4, 8.2.2, and 8.2.3.4: The analysis set for the analysis of pregnancy was changed. ○ Sections 5.4 and 8.2.3.4: Categories were added for subgroups. ○ Sections 5.4 and 8.2.3.4: The two factors for the safety subgroup analyses, namely, Prophylactic injection to reduce infusion reaction and Prophylactic treatment to prevent/reduce tumor lysis syndrome were deleted. (This is because, although information regarding present/absent of administration defined in the case report form during the observation period [starting from the start of administration to Day 28 post-final dose] should be collected, sufficient information will not be obtained to perform these safety subgroup analyses during the period thereof.) ○ Section 6.1: The descriptions of the definition of adverse events was revised to align with the protocol. There is no change in the assessment and analysis methods for adverse events. ◯Section 8.2.1: Drawing for the follow-up period after the start of this drug and the follow-up period after HSCT was deleted. ◯Section 8.2.1: In "Continuation/discontinuation of survey (treatment period and

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	follow-up period)", categories for the definition of the timing 1 were added. ○Section 8.2.2: A description was deleted to change the population for making listings to reported cases. (The description in Section 9 was unchanged.) ○Section 8.2.2: Drawing for the period from the HSCT (the most recent before the start of this drug) to the start of this drug was deleted. ○Section 8.2.2: Categories for the time from the date of final dose of this drug to the first HSCT after the start of this drug were changed. ○Section 8.2.2: Part of the tabulation plan for the summary of individual drug therapies for the target disease and individual non-drug therapies for the target disease was deleted. ○Section 8.2.3: The period for collecting data to summarize occurrence of VOD/SOS was changed. ○Section 8.2.3.1: The tabulation plan for serious adverse drug reactions was deleted. ○Section 8.2.3.1: Items to be included in the tabulation for the occurrence of VOD/SOS were changed. ○Section 8.2.3.1: The specifications for the drawing concerning the occurrence of VOD/SOS were changed. ○Section 8.2.3.2: The summary of adverse events was changed so as to be performed only for serious adverse events and for non-serious adverse events, with analysis specifications added. ○Section 8.2.3.4: Subgroup analyses for myelosuppression, infection, and hemorrhage were added. ○ Section 9: The listing specifications were changed. ○Editorial revisions
4.0 28-Oct-2022 PPD	○Section 2.1: The starting point for the 52 week follow-up after HSCT was explicitly stated. ○ Section 5.1: For the safety analysis set, an exclusion condition was added so that patients whose case report forms at the original hospital has not been fixed are excluded. ○ Sections 5.3 and 8.2: Definitions and handling were added for the Safety Analysis Set with Informed Consent and the Effectiveness Analysis Set with Informed Consent. ○ Sections 5.4, 8.2.2, and 8.2.3.4: Changes were made for the terms used to describe the administration at a dosage of > 1.8 mg/m^2/cycle. ○ Section 6.1: The units used to present the time to death after HSCT were changed. ○ Sections 6.1, 6.2, and 6.3: The description for the patients included in each analysis was deleted, because it was determined that they are to be specified in separate sections. ○Sections 6.1, 6.3, 8.2.1, and 8.2.3: In the definition of the times to be assessed, it was specified that the first HSCT after the start of this drug will be considered, because multiple HSCTs may be performed. ○ Sections 6.1, 6.2, 7, 8.2.3.3, and 8.2.4.4: The censoring date was changed for death after HSCT, transplant-related death after HSCT (non-relapse death), transplant-unrelated death

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	after HSCT (relapse death), overall survival, and overall survival after the last dose of this drug in patients who underwent HSCT. ○ Section 8.1.4: The method used to estimate the standard error for the cumulative incidence rates at each time point that take into account competing risks was specified. ○ Section 8.2.2: ・The period during which data of concomitant anti-malignant tumor agents are collected was specified. ・For individual drug therapies for the target disease and individual non-drug therapies for the target disease, analyses of only those started by the end of the treatment period were added. ○ Section 8.2.3.1 ・The analysis plan was changed taking into account that records with unknown CTCAE Grade may exist. ・Summary of adverse drug reactions by present/absent of causal relationship with this drug was deleted. ・The priority order of outcomes in summary of adverse drug reactions by outcome was changed. ・Summary of serious adverse drug reactions by outcome was added. ○ Section 8.2.3.3: What population is used for the analysis of deaths after HSCT was specified, and at which time points the mortality after HSCT is estimated was added. ○ Section 8.2.4.4: What population is used for the analysis of overall survival and of overall survival after the final dose of this drug in HSCT recipients was added. ○ Section 9: Some listings were deleted or added. ◯Editorial revisions

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3.0 01-Sep-2021 PPD	○ Section 6.2: The category "other" was added for the endpoint hematologic response. ○ Section 8.2.1: The category "entire period" was added for the summary by time period concerning completion/discontinuation of treatment and continuation/discontinuation of survey (treatment period and follow-up period). ○ Section 8.2.2: Listing of off-label diseases was added (added to Section 9) ○ Section 8.2.2: Summary and a listing of concomitant anti-malignant tumor agents used for the target disease (not all drugs used for the target disease) was added (added to Section 9). ○ Section 8.2.3.1: The summary plan for patients who experienced the events identified in the safety specification was updated to include summary by CTCAE Grade. ○ Section 8.2.3.4: Control by proportion was removed from the subgroup analyses of adverse drug reactions by factor. ○ Section 8.2.4.1: In the summary plan for hematologic response, an analysis of data excluding "not performed" was added. ○ Section 8.2.4.2: In the summary plan for minimal residual disease, an analysis of data excluding "not performed" was added. ○ Section 9: Listing of off-label diseases and listing of concomitant anti-malignant tumor agents were added. ○ Section 9: The listing plan was updated to use day as the unit to express some kinds of time in combination with month. ○ Other: Editorial revisions

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2.0 17-Aug-2020 PPD	○ Section 2.1: Changes were made for the survey and observation periods in accordance with lifting of approval conditions for all-case survey ○ Section 7: The last observation date was defined and the imputation method for missing or partial dates of death was specified. ○ Section 8.2.1: ・Summary by founder was deleted (due to deletion of the corresponding item in Attached Form 16). ・Time intervals used for the summary of completion/discontinuation of treatment was defined. ・The method of summarizing data of continuation/discontinuation of survey was changed. ○ Section 8.2.2: Summary of present/absent of pregnancy in the follow-up period was deleted (because it was deleted from the case report form). ○ Section 8.2.3.1: ・In the analyses of onset timing of adverse drug reactions and VOD/SOS, what data will be analyzed was changed. ・Handling of patients who did not experience VOD/SOS (definition of cut-off date) was changed. ○ Sections 8.2.3.3 and 8.2.4.4: What patients will be included in the analyses of mortality after HSCT and overall survival was changed and how patients who finished survey alive will be handled (definition of censoring date) was changed. ○ Section 8.2.4.1: ・The categories for the analysis of best overall response of hematologic response were changed. ・An analysis of the timing of achieving CR or CRi was added. ○ Section 9: ・Some listings were deleted (due to duplication or being unnecessary for this survey) ・Listing of hematopoietic stem cell transplants and listing of patients with adverse events of VOD/SOS were added. ○ Other: Editorial revisions
1.0 10-Apr-2018 PPD	Original version

2. INTRODUCTION

This statistical analysis plan (SAP) is for the Special Investigation of BESPONSA® Injection 1 mg (hereinafter, this drug). In this SAP, texts quoted from the corresponding protocol are shown in *italics*.

2.1. Study Design

- **Target population**

All patients who received this drug will be included in this survey.

- **Survey period**

The scheduled periods of this survey are as follows:

*Survey period: From the date of launch of this drug to 5 years**

*Registration period: From the date of launch of this drug to the time of lifting of approval conditions for all-case survey**

**: Patients who started to receive this drug on or after May 1, 2020 will only be registered.*

The protocol may be changed to terminate the registration only period, but this change will not affect the SAP.

- **Observation period**

Observation period: The observation period is to be 52 weeks for patients who did not undergo hematopoietic stem cell transplant (HSCT) within 52 weeks after the start of the treatment with this drug and up to 52 weeks after HSCT for patients who underwent HSCT within 52 weeks after the start of this drug. If patients who started to receive this drug on or before April 30, 2020 are transferred to another hospital during the observation period, the transferred hospitals will be requested to conclude a contract for the conduct of this survey, and the information at the transferred hospitals will be collected as much as possible.

[1] Treatment Period

From the start of treatment to Day 28 post-final dose: For assessments of safety (e.g., adverse events) and effectiveness (hematologic response, survival time)

[2] Follow-up period

For 52 weeks from 29 days after the final dose (for patients who did not undergo HSCT by 52 weeks after the start of treatment) or for 52 weeks after HSCT (for patients who underwent HSCT by 52 weeks after the start of treatment): For assessments of safety (VOD/SOS) and effectiveness (survival time)

The starting point for the 52 week follow-up after HSCT is the day of the last HSCT performed within 52 weeks after the start of this drug.

- **Safety specification**

See Protocol Section 7.1.

- **Sample size and its rationale**

Of the patients who have received this drug, a total of 176 patients with relapsed or refractory CD22 positive (CD22+) acute lymphocytic leukemia (ALL) will be included in the safety analysis set. In consideration of dropouts during the survey, 200 patients will be registered.

A sample size of 176 patients was selected so as to be able to evaluate potential risk factors associated with the occurrence of VOD/SOS. In clinical studies (Studies B1931022 and B1931010), the incidence of VOD/SOS was 12.3% (26/212 patients).

The sample size was determined so as to be able to confirm the effects of the risk factors identified in clinical studies on the occurrence of VOD/SOS in routine clinical practice and explore other potential risk factors. Assuming that the true incidence in the overall population is 12.3%, the true relative risk of the onset of events in subgroups is 3.0 (corresponding to assuming that the incidence in the high-risk group and in the low-risk group is 18.5% and 6.2%, respectively), and the ratio of the sample size in each subgroup is 1:1, the sample size of 176 patients has 80.4% power in a chi-square test with a significance level of 0.1 (two-sided), assuming the probability of detecting a statistically significant relative risk as the power.

2.2. Study Objectives

To investigate the following items in patients treated with this drug under post-marketing routine uses.

[1] Occurrence of adverse events, including the investigation of following factors:

Background factors that may affect the occurrence of liver disorder including VOD/SOS, myelosuppression, infection, hemorrhage, and Grade ≥ 3 events based on Common Terminology Criteria for Adverse Events (CTCAE) *version 4.0; and risk factors for early death in HSCT recipients after treatment with this drug.*

[2] Effectiveness (hematologic response rate, survival)

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for periodic safety update reports will be performed periodically. Among analysis items defined in this SAP, only the analysis items necessary for periodic safety reports will be analyzed at the time of interim analysis. In addition, a final analysis to support the re-examination application will be performed. All analyses specified in this SAP will be performed at the time of the final analysis.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Since this study is not a confirmatory study, statistical testing should be positioned as exploratory. The p-value of a statistical test will be evaluated as a descriptive statistic and the significance level will not be specified, but a threshold may be set in a post-hoc manner for screening purpose.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set (SAS) is defined as the full analysis set (FAS) that is as close as possible to all patients treated with this drug. Specifically, the SAS consists of all registered or reported patients except those who meet any of the following conditions:

a. The case report form could not be collected at all. (Indicated as "CRF not collected" in the survey report.)

b. There was a violation or flaw in the study contract. (Indicated as "Contract violation/flaw" in the survey report.)

c. There was a violation in the registration. (Indicated as "Invalid registration" in the survey report.)

d. Administration of the survey drug was not reported at all. (Indicated as "No dosing information" in the survey report.)

e. The case report form at the original hospital before patient transfer has not been fixed. (Indicated as "No dosing information - dosing information unconfirmed") * This condition applies only to cases where information of the original hospital and that of the transferred hospital are linked. If the original hospital refuses continued survey or information from the original hospital becomes uncollectible, this exclusion condition is considered not met (the patient will not be excluded because of this exclusion criterion).

f. Information on adverse events was not reported at all - no visits after the first prescription. (Indicated as "No information on adverse events - no visits" in the survey report.)

g. Information on adverse events was not reported at all - there is a visit(s) after the first prescription but no record of information. (Indicated as “No information on adverse events - no record” in the survey report.)

For details of each criterion other than e, see the Guidance for Adoption/Rejection Criteria for Analysis Populations and Handling of Data in Special Investigation.

5.2. Effectiveness Analysis Set

The effectiveness analysis set (EAS) consists of all patients in the SAS except those who meet any of the following conditions:

h. Effectiveness cannot be appropriately evaluated because some of the necessary conditions for evaluating effectiveness are missing. (Indicated as "Unable to evaluate effectiveness" in the survey report.)

i. Disease is outside the scope of survey. (Indicated as "Disease outside the scope" in the survey report.)
This survey includes the following exclusion criterion: Patients whose condition is not relapsed or refractory CD22+ acute lymphocytic leukemia (ALL)

5.3. Other Analysis Sets

5.3.1. Safety analysis set with informed consent

The safety analysis set with informed consent (SASIC) is defined as all registered or reported patients with informed consent, excluding those who meet any of the conditions in Section 5.1.

5.3.2. Effectiveness analysis set with informed consent

The effectiveness analysis set with informed consent (EASIC) is defined as all patients in the SASIC, excluding those who meet any of the conditions in Section 5.2.

5.4. Subgroups

Subgroup analyses of safety will be performed for the following patient characteristics. The subgroups defined for each background factor are shown in the squared brackets [] with the reference for the calculation of risk ratio/difference being underlined:

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Disease name [Relapsed CD22+ acute lymphocytic leukemia (ALL), refractory CD22+ ALL, other ALL, other]
- Chromosome karyotype [normal, t (4;11), unknown]
- Chromosome karyotype [Philadelphia chromosome positive, negative, unknown]* Philadelphia chromosome is considered positive if the chromosome karyotype is t(9;22).
- Hepatic impairment [absent, present] {According to the Procedure of Extracting Patients with Hepatic Impairment/Renal Impairment in Post-Marketing Surveillance and its Attachment, the version of Medical Dictionary for Regulatory Activities Terminology (MedDRA) used for analysis should be followed.}
- Renal impairment [absent, present] (According to the Procedure of Extracting Patients with Hepatic Impairment/Renal Impairment in Post-Marketing Surveillance and its Attachment, the MedDRA version used for analysis should be followed.)
- Medical history (past) - VOD/SOS [absent, present]
- Medical history (past) - Graft versus host disease (GVHD) [absent, present]
- Medical history (past) - Hepatitis or hepatic disease [absent, present]

- Medical history (present) - VOD/SOS [absent, present]
- Medical history (present) - GVHD [absent, present]
- Medical history (present) - Hepatitis or hepatic disease [absent, present]
- Eastern Cooperative Oncology Group performance status (ECOG PS) before the start of this drug [0, 1, ≥ 2, not performed]
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels immediately before the start of this drug [≤1.5 × the institutional upper limit of normal range (IULN), either > 1.5 × IULN, not performed]
- γ-glutamyl transpeptidase (γ-GTP) level immediately before the start of this drug [≤ 50 IU/L, > 50 IU/L, not performed]
- Total bilirubin level immediately before the start of this drug [≤ the institutional upper limit of normal range (IULN), >IULN, not performed]
- Hemoglobin level immediately before the start of this drug [< 10 g/dL, ≥ 10 g/dL, not performed]
- White blood cell count immediately before the start of this drug [< 4000/mm^3, ≥ 4000/mm^3, not performed]
- Neutrophil count immediately before the start of this drug [< 2000/mm^3, ≥ 2000/mm^3, not performed]
- Platelet count immediately before the start of this drug [< 10 × 10^4/μL, ≥ 10 × 10^4/μL, not performed]
- Peripheral blast count immediately before the start of this drug [≤ 1000 /μL, > 1000 /μL, not performed]
- Myeloblast count immediately before the start of this drug [≤ 50%, > 50%, not performed]
- Salvage line of the induction treatment with this drug [Initial induction, 1st, 2nd, 3rd or later]
- HSCT before the start of this drug [not performed, performed]

Subgroup analyses of safety will be performed also for the following factors:

- HSCT after the start of this drug [not performed, performed]
- Type of the first HSCT after the start of this drug [autologous transplant, allogeneic hematopoietic stem cell transplant with myeloablative conditioning, allogeneic hematopoietic stem cell transplant with nonmyeloablative conditioning, unknown]
- Donor of the first HSCT after the start of this drug [alternative donor, matched related donor]
- Conditioning with alkylating agent for the first HSCT after the start of this drug [≤ 1 agent (including no conditioning), ≥ 2 agents]
- Conditioning with busulfan for the first HSCT after the start of this drug [not performed (including no conditioning), performed]
- ECOG PS before conditioning for the first HSCT after the start of this drug [0, 1, ≥ 2, not performed]
- AST and ALT levels before conditioning for the first HSCT after the start of this drug [≤ 1.5 × the institutional upper limit of normal range (IULN), either > 1.5 × IULN, not performed]
- γ-GTP level before conditioning for the first HSCT after the start of this drug [≤ 50 IU/L, > 50 IU/L, not performed]

- Total bilirubin level before conditioning for the first HSCT after the start of this drug [≤ institutional upper limit of normal range (IULN), > IULN, not performed]
- Hemoglobin level before conditioning for the first HSCT after the start of this drug [< 10 g/dL, ≥ 10 g/dL, not performed]
- Platelet count before conditioning for the first HSCT after the start of this drug [< $10 \times 10^4/\mu L$, ≥ $10 \times 10^4/\mu L$, not performed]
- Peripheral blast count before conditioning for the first HSCT after the start of this drug [≤ 1000 /μL,> 1000 /μL, not performed]
- Myeloblast count before conditioning for the first HSCT after the start of this drug [≤ 50%, > 50%, not performed]
- Time from the date of final dose of this drug to the date of the first HSCT after the start of this drug [< 4 weeks, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks to < 16 weeks, ≥ 16 weeks]
- Treatment cycles [1 cycle, 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 cycles, > 6 cycles]
- Treatment cycles [≤ 3 cycles, ≥ 4 cycles]
- Dosing of > 1.8 mg/m^2 per cycle [absent, present] (Considered to be present, if there is a cycle of > 1.8 mg/m^2 per cycle during the treatment period.)
- Pregnancy [absent, present] * Pregnancy during the treatment period. Limited to cases in which information on pregnancy is collected
- Best overall response [complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), progression or relapse, indeterminate/other, not performed]
- Minimal residual disease (MRD) [negativity achieved, negativity not achieved, test not performed] * Irrespective of the result of best overall response.
- Best overall response and MRD [CR/CRi achieved and negativity achieved, CR/CRi achieved and negativity not achieved, progression/relapse and negativity achieved, progression/relapse and negativity not achieved] * "Indeterminate/other" and "not performed" are excluded.
- Adverse drug reactions that occurred during the treatment period - liver disorder as a safety specification [absent, present]

Subgroup analyses of hematologic response and MRD will be performed for the following patient characteristics and other factors:

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Disease name [Relapsed CD22+ acute lymphocytic leukemia (ALL), refractory CD22+ ALL]
- Chromosome karyotype [normal, t (4;11), unknown]
- Chromosome karyotype [Philadelphia chromosome positive, negative, unknown]* Philadelphia chromosome is considered positive if the chromosome karyotype is t(9;22).
- Hemoglobin level immediately before the start of this drug [< 10 g/dL, ≥ 10 g/dL, not performed]
- Platelet count immediately before the start of this drug [< $10 \times 10^4/\mu L$, ≥ $10 \times 10^4/\mu L$, not performed]

- Peripheral blast count immediately before the start of this drug [≤ 1000 /μL,> 1000 /μL, not performed]
- Myeloblast count immediately before the start of this drug [≤ 50%, > 50%, not performed]
- Salvage line of the induction treatment with this drug [Initial induction, 1st, 2nd, 3rd or later]
- HSCT before the start of this drug [not performed, performed]
- Pregnancy [absent, present] * Pregnancy during the treatment period. Limited to cases in which information on pregnancy is collected

Subgroup analyses of overall survival (OS) will be performed for the following patient characteristics and other factors:

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Disease name [Relapsed CD22+ acute lymphocytic leukemia (ALL), refractory CD22+ ALL]
- Chromosome karyotype [normal, t (4;11), unknown]
- Chromosome karyotype [Philadelphia chromosome positive, negative, unknown]* Philadelphia chromosome is considered positive if the chromosome karyotype is t(9;22).
- Hemoglobin level immediately before the start of this drug [< 10 g/dL, ≥ 10 g/dL, not performed]
- Platelet count immediately before the start of this drug [< 10×10^4/μL, ≥ 10×10^4/μL, not performed]
- Peripheral blast count immediately before the start of this drug [≤ 1000 /μL,> 1000 /μL, not performed]
- Myeloblast count immediately before the start of this drug [≤ 50%, > 50%, not performed]
- Salvage line of the induction treatment with this drug [Initial induction, 1st, 2nd, 3rd or later]
- HSCT before the start of this drug [not performed, performed]
- Pregnancy [absent, present] * Pregnancy during the treatment period. Limited to cases in which information on pregnancy is collected
- Best overall response [CR or CRi, progression or relapse, indeterminate or other, not performed]
- Best overall response [CR, CRi]* "Progression", "relapse", "indeterminate/other" and "not performed" are excluded.
- MRD [negativity achieved, negativity not achieved, test not performed] * Irrespective of the result of best overall response.
- Best overall response and MRD [CR/CRi achieved and negativity achieved, CR/CRi achieved and negativity not achieved, progression/relapse and negativity achieved, progression/relapse and negativity not achieved] * "Indeterminate/other" and "not performed" are excluded.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse events: All undesirable or unintended signs or symptoms that occurred after administration of this drug, regardless of causal relationship

- Adverse drug reactions: Adverse events assessed as causally related to this drug by the physician

- Serious adverse events or serious adverse drug reactions: Adverse events or adverse drug reactions assessed as serious by the physician

- Death after HSCT:

  - Time to death after HSCT: Days and weeks from the date of first HSCT after the start of this drug to the date of death
  - Event: Death (for any cause)
  - Censoring: The patient is confirmed alive at the time of completion or discontinuation of the survey. The endpoint will be censored on the day when patient's survival was last confirmed.

  Early death after HSCT is defined as the above event that occurred within 100 days after the first HSCT after the start of this drug. Early death is supposed to be absent if the patient died on 101 days or later, or was confirmed alive at the time of completion/discontinuation of the survey.

- Transplant-related death after HSCT (non-relapse death):

  - Time to transplant-related death after HSCT: Days and weeks from the date of first HSCT after the start of this drug to the date of death.
  - Event: Death due to non-tumor-related causes, resulting from worsening of the target disease of this drug
  - Competing risks: Death due to tumor-related causes, resulting from worsening of the target disease of this drug
  - Censoring: The patient is confirmed alive at the time of completion or discontinuation of the survey. The endpoint will be censored on the day when patient's survival was last confirmed.

  Early transplant-related death after HSCT (non-relapse death) is defined as the above event that occurred within 100 days after the first HSCT after the start of this drug. Early death is supposed to be absent if the patient died on 101 days or later, or was confirmed alive at the time of completion/discontinuation of the survey.

- Transplant-unrelated death after HSCT (relapse death):

  - Time to transplant-unrelated death after HSCT: Days and weeks from the date of first HSCT after the start of this drug to the date of death.
  - Event: Death due to tumor-related causes, resulting from worsening of the target disease of this drug
  - Competing risks: Death due to non-tumor-related causes, resulting from worsening of the target disease of this drug
  - Censoring: The patient is confirmed alive at the time of completion or discontinuation of the survey. The endpoint will be censored on the day when patient's survival was last confirmed.

  Early transplant-unrelated death after HSCT (relapse death) is defined as the above event that occurred within 100 days after the first HSCT after the start of this drug. Early death is supposed to

be absent if the patient died on 101 days or later, or was confirmed alive at the time of completion/discontinuation of the survey.

- Safety specification: Events included in safety specification will be specified separately.

6.2. Effectiveness Endpoints

- Hematologic response. This is assessed as one of the following categories based on the best overall hematologic response: CR, CRi, progressive disease (PD), relapse, indeterminate, other, assessment not performed. "Other" corresponds to the cases where the clinical assessment of hematologic response was performed but the result did not fall into any of the categories described in the case report form, while "assessment not performed" corresponds to the cases where the clinical assessment was not performed.

- MRD. This is assessed as one of the following categories based on the MRD status: negativity achieved, negativity not achieved, unknown, test not performed.

- Overall survival:

  - Overall survival: Defined as the months from the start of this drug to all-cause death.
  - Event: Death
  - Censoring: The patient is confirmed alive at the time of completion or discontinuation of the survey. The endpoint will be censored on the day when patient's survival was last confirmed.

- Overall survival after the final dose of this drug in patients who underwent HSCT:

  - Overall survival: Defined as the months from the date of final dose of this drug to all-cause death.
  - Event: Death
  - Censoring: The patient is confirmed alive at the time of completion or discontinuation of the survey. The endpoint will be censored on the day when patient's survival was last confirmed.

6.3. Other Endpoints

- Duration of follow-up after the start of this drug: Period from the start date of this drug to the end date of this survey

- Duration of follow-up after HSCT: Period from the date of the first HSCT after the start of this drug to the end date of this survey

6.4. Covariates

Potential risk factors identified from available data including those from clinical studies conducted to date that are associated with development of liver disorders including VOD/SOS as safety specification include:

  - Past history of hepatitis or hepatic disease

- Presence/absence of hepatic impairment
- Peripheral blast count immediately before the start of this drug
- ECOG PS before the start of this drug
- Salvage line of the induction treatment with this drug
- Number of treatment cycles of this drug
- HSCT status (performed or not performed)
- Peripheral blast count before conditioning for HSCT

Potential risk factors associated with the occurrence of safety specification events of VOD/SOS include:

- Age
- Past history of hepatitis or hepatic disease
- Platelet count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- Number of treatment cycles of this drug
- HSCT status (performed or not performed)
- Conditioning with alkylating agents or busulfan
- Total bilirubin, AST, and ALT levels before conditioning for HSCT

Potential prognostic factors associated with achieving hematologic remission include:

- Age
- ALL Status (relapsed or refractory)
- Chromosome karyotype
- Hemoglobin, platelet count, peripheral blast count, and myeloblast count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT status (performed or not performed)

Potential prognostic factors associated with overall survival include:

- Age
- ALL Status (relapsed or refractory)
- Chromosome karyotype
- Hemoglobin, platelet count, peripheral blast count, and myeloblast count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT status (performed or not performed)
- Hematologic response, MRD

7. HANDLING OF MISSING VALUES

The last observation date is defined as the latest full date among the following:

- Date of administration/discontinuation of this drug

- Date of onset/outcome of adverse event
- Date of assessment of hematologic response
- Date of MRD, laboratory tests, or ECG
- Date of ECOG PS assessment
- Date of hematopoietic stem cell transplant
- Start date of drug therapy or non-drug therapy for the target disease
- Date of survival assessment
- Date of last confirmed survival

If the date of death is missing or partial, it will be imputed based on the date of the last confirmed survival and the last observation date:

- If the date of death is missing, the date of the last confirmed survival will be used. If it is also missing, the last observation date will be used. If the day or month + day of the last confirmed survival is missing, the last observation date or the following date, whichever comes later, will be used.
  - If the day of the date of the last confirmed survival is missing: First day of the month and year when survival was last confirmed.
  - If the month + day of the date of the last confirmed survival are missing: January 1 of the year when survival was last confirmed.
- If the day or month + day of the date of death is missing, the date of the last confirmed survival, the last observation date, or the following date, whichever comes latest, will be used.
  - If the day is missing: First day of the month and year of death.
  - If the month and day are missing: January 1 of the year of death.

If the survival confirmation date is missing or partial, it will be imputed based on the last observation date:

- If the survival confirmation date is missing, the last observation date will be used.
- If the day or month + day of the survival confirmation date is missing, the last observation date or the following date, whichever comes later, will be used:
  - If the day is missing: First day of the month and year of the day of survival confirmation.
  - If the month and day are missing: January 1 of the year of the day of survival confirmation.

If for an adverse event, its seriousness, action made, or outcome is missing, it will be handled as "unknown" when summarizing data.

Cleaning-uncompleted data will be in principle handled as follows.

- Items with missing values: They will be handled as missing (or "unknown" for categorical variables) in both summary and listing.
- Items with inconsistent values: They will be handled as missing in both summary and listing. A list of how data were handed will be prepared separately.

- No signature: Descriptions in the case report form with no signature of contract physician (including cases with only signature of an individual other than contract physician) will be handled as missing in both summary and listing. If, despite the existence of a field for the date of signature, no date or inconsistent date (e.g. a date before the start of treatment or future date) is filled in, the descriptions in the case report form will be regarded as lacking signature.

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Continuous variables

For continuous variables, summary statistics (number of patients [n], mean, standard deviation, median, maximum, and minimum) will be calculated. For body surface area, quartiles (first and third quartiles) will also be calculated.

8.1.2. Categorical variables

For categorical variables, results of each categorization will be summarized in terms of frequency and proportion.

8.1.3. Binary variables

For binary variables, patients falling into each binary category will be summarized in terms of frequency (n) and proportion. If a confidence interval (CI) is determined for a proportion, the two-sided 95% CI will be determined using the exact method.

For a comparison of proportion between subgroups, the risk ratio (RR) and its 95% CI will be determined. In addition, the RRs and their 95% CIs will be graphically presented.

For statistical tests, Fisher's exact test will be performed to test correlations in nominal scale data, and Cochran-Armitage test (exact method) to test correlations in ordinal scale data. If, however, it is difficult to use the exact method, chi-square test or Cochran-Armitage test with normal approximation will be used as an alternative to the exact method.

8.1.4. Time-to-event data

For time-to-event data, the median, 1st quartile, and 3rd quartile will be determined using the Kaplan-Meier method. The rate at each time point will also be determined. To estimate CIs, log-log transformation will be used (this corresponds to specifying loglog under the conftype option in the proc lifetest statement of the SAS® lifetest procedure). In addition, Kaplan-Meier plots will be presented.

When time data are compared between subgroups using the Kaplan-Meier method, the hazard ratio of event occurrence and its 95% CI will be determined using the Cox proportional hazards model (ties handled by the Breslow method). In addition, the hazard ratio and its 95% CI will be presented graphically.

In the analysis of time data with competing risks, the cumulative incidence rate at each time point that takes into account competing risks will be determined (this corresponds to using the event code option in the time statement of the SAS® lifetime procedure). The standard error is to be estimated by the delta method. In addition, the time course of cumulative incidence will be graphically presented.

8.2. Statistical Analyses

Analyses similar to those in the SAS and the EAS will also be performed in the SASIC and the EASIC; details of these analyses will be separately specified. When performing these analyses, the SAS and the EAS should be read as the SASIC and the EASIC, respectively.

8.2.1. Summary of patients

- **Disposition**

The registered patients, survey-completed patients, patients included in the SAS, and patients included in the EAS will be counted in the population of registered patients. In addition, case report form-uncollected patients, patients excluded from the SAS, and patients excluded from the EAS will also be counted. For those excluded from the SAS/EAS, patients will also be counted by reason for exclusion.

- **Follow-up period**

For the SAS and EAS, the follow-up period after the start of this drug and the follow-up period after HSCT will be analyzed.

  - For the follow-up period (weeks) after the start of this drug:
    - Patients included in the analysis: The SAS and the EAS
    - Subgroup analyses: In addition to the summary with all patients in each analysis set above, patients will also be summarized by the conditions where patients underwent HSCT after the start of this drug and patients did not.
    - What are analyzed:
      - Summary statistics for the follow-up period (calculated as per Section 8.1.1)
      - Number of patients by follow-up duration (< 12 weeks, ≥ 12 weeks to < 24 weeks, every 12 weeks thereafter; and < 13 weeks, ≥ 13 weeks to < 26 weeks, and every 13 weeks thereafter) (calculated as per Section 8.1.2)
      - Number of patients who were being followed up at each time point (Week 12, Week 24, and every 12 weeks thereafter; and Week 13, Week 26, and every 13 weeks thereafter) (calculated as per Section 8.1.2)

  - For follow-up period after HSCT (weeks) = follow-up period after the first HSCT after the start of this drug:
    - Patients included in the analysis: patients in the SAS/EAS who underwent HSCT after the start of this drug
    - What are analyzed: Same as those for the follow-up period after the start of this drug

- **Summary of patients with completed/discontinued status**

For the SAS and EAS, patients with the following kinds of completed/discontinued status will be summarized in terms of n and proportion by timing. In addition, patients will also be summarized in terms of n and proportion by reason. To calculate the proportion of patients falling into each reason in each timing, the number of patients who completed or discontinued treatment/survey in the relevant timing will be used as the denominator.

Completion/discontinuation of treatment

Definition of the timing 1 of completion/discontinuation of treatment: < 4 weeks after the start of this drug, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks to < 16 weeks, ≥ 16 weeks to < 20 weeks, ≥ 20 weeks to < 24 weeks, ≥ 24 weeks, entire period

Definition of the timing 2 of completion/discontinuation of treatment: Cycle 1 ongoing or started but the next cycle not started, the same with Cycle 2, the same with Cycle 3, the same with Cycle 4, the same with Cycle 5, the same with Cycle 6, after the start of the subsequent cycle, entire period

Continuation/discontinuation of survey (treatment period and follow-up period)

Definition of the timing 1: < 4 weeks after the start of this drug, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks to < 16 weeks, ≥ 16 weeks to < 20 weeks, ≥ 20 weeks to < 24 weeks, ≥ 24 weeks to < 52 weeks, ≥ 52 weeks, entire period

Definition of the timing 2: < 4 weeks after the end of this drug, ≥ 4 weeks to < 12 weeks, ≥ 12 weeks to < 24 weeks, ≥ 24 weeks to < 48 weeks, ≥ 48 weeks, entire period

- **Transfer to another hospital**

A patient is defined to have been transferred, if the patient's information at the transferred hospital is linked to the patient's information at the original hospital through the case report form prepared at the transferred hospital. For the SAS and EAS, patients will be summarized by each of the following factors, as per Section 8.1:

  - Transfer to another hospital [absent, present]
  - Timing of transfer (treatment period, follow-up period) * The timing will be determined referring to the record of survey continuation/discontinuation in the original hospital's case report form. The denominator will be the number of patients with transfer.

- **Summary of excluded patients**

Patients excluded from the SAS, those excluded from the EAS, and reasons for exclusion will be listed.

8.2.2. Patient characteristics and treatment history

- **Patient characteristics**

For the SAS and EAS, patients will be summarized by each of the following patient characteristics, as per Section 8.1:

- Sex [male, female]
- Age (continuous)
- Age [< 15 years, ≥ 15 years, ≥ 15 years to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 years, ≥ 18 years to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 years, ≥ 15 years to < 40 years, ≥ 40 years]
- Body surface area (continuous)
- Disease name [Relapsed or refractory CD22+ acute lymphocytic leukemia (ALL), relapsed CD22+ ALL, refractory CD22+ ALL, other ALL, other, individual names included in the "other"]
- WHO classification [B-lymphoblastic leukemia/lymphoma, unspecified type, B-lymphoblastic leukemia/lymphoma with recurrent gene abnormalities, T-lymphoblastic leukemia/lymphoma, other, individual names included in the "other"]
- Chromosome karyotype [normal, abnormal, unknown]* Chromosome karyotype is to be considered abnormal if any of the following conditions is met: t (9; 22), t (4; 11), Complex, Karyotype (5 or more chromosomal abnormalities), other
- Chromosome karyotype [normal, t (9; 22), t (4; 11), Complex, Karyotype (5 or more chromosomal abnormalities), other, unknown]
- Chromosome karyotype [Philadelphia chromosome positive, negative, unknown]* Philadelphia chromosome is considered positive if the chromosome karyotype is t(9;22).
- Disease duration [< 3 months, ≥ 3 months to < 6 months, ≥ 6 months to < 9 months, ≥ 9 months to < 12 months (1 year), ≥ 1 year to < 2 years, ≥ 2 years]
- Hepatic impairment [absent, present] (According to the Procedure of Extracting Patients with Hepatic Impairment/Renal Impairment in Post-Marketing Surveillance and its Attachment, the MedDRA version used for analysis should be followed.)
- Renal impairment [absent, present] (According to the Procedure of Extracting Patients with Hepatic Impairment/Renal Impairment in Post-Marketing Surveillance and its Attachment, the MedDRA version used for analysis should be followed.)
- Medical history (past) [absent, present]
- Medical history (past) - VOD/SOS [absent, present]
- Medical history (past) - GVHD [absent, present]
- Medical history (past) - Hepatitis or hepatic disease [absent, present]
- Medical history (present) [absent, present]
- Medical history (present) - VOD/SOS [absent, present]
- Medical history (present) - GVHD [absent, present]
- Medical history (present) - Hepatitis or hepatic disease [absent, present]
- ECOG PS before the start of this drug [0, 1, 2, 3, 4, not performed]
- ECOG PS before the start of this drug [0, 1, ≥ 2, not performed]
- AST level immediately before the start of this drug [≤ 1.5 × the institutional upper limit normal range (IULN), > 1.5 × IULN, not performed]
- ALT level immediately before the start of this drug [≤ 1.5 × IULN, > 1.5 × IULN, not performed]
- AST and ALT levels immediately before the start of this drug [≤ 1.5 × IULN, either > 1.5 × IULN, not performed]
- γ-GTP level immediately before the start of this drug [≤ 50 IU/L, > 50 IU/L, not performed]
- Total bilirubin level immediately before the start of this drug [≤ IULN, > IULN, not performed]

- Hemoglobin level immediately before the start of this drug [< 10 g/dL, ≥ 10 g/dL, not performed]
- Platelet count immediately before the start of this drug [$< 10 \times 10^4/\mu L$, $\geq 10 \times 10^4/\mu L$, not performed]
- Peripheral blast count immediately before the start of this drug [≤ 1000 /μL,> 1000 /μL, not performed]
- Myeloblast count immediately before the start of this drug [≤ 50%, > 50%, not performed]
- Salvage line of the induction treatment with this drug [Initial induction, 1st, 2nd, 3rd or later]

For the SAS, patients falling into the following categories will be summarized in terms of n and proportion by System Organ Class (SOC) and Preferred Term (PT):

- Medical history (past)
- Medical history (past) - hepatitis or hepatic disease
- Medical history (present)
- Medical history (present) - hepatitis or hepatic disease

For the SAS and EAS, patients falling into the following categories defined for HSCT performed before the start of this drug will be summarized in terms of n and proportion. Note that only patients who underwent HSCT before the start of this drug will be included in this summary, except for "HSCT before the start of this drug [not performed, performed]":

- HSCT before the start of this drug [not performed, performed]
- Number of HSCTs before the start of this drug [1, ≥ 2]
- Type of HSCT before the start of this drug (regardless of the number of HSCTs) [autologous transplant, allogeneic hematopoietic stem cell transplant with myeloablative conditioning, allogeneic hematopoietic stem cell transplant with nonmyeloablative conditioning, unknown]
- Type of the HSCT immediately before the start of this drug [same as above]
- Type of the conditioning drug for HSCT before the start of this drug (regardless of the number of HSCTs) [busulfan (BSF, BUS), cyclophosphamide (CPA), melphalan (LPAM), cytarabine (Ara-C), fludarabine phosphate (F-ara-AMP), etoposide (ETP, VP-16), other]
- Type of the conditioning drug for the HSCT immediately before the start of this drug [same as above]
- Time from the date of the HSCT immediately before the start of this drug to the date of the start of this drug (continuous)

Listings will also be prepared.

For the SAS and EAS, patients falling into the following categories defined for remission induction therapies performed before the start of this drug will be summarized in terms of n and proportion. Note that only patients who received remission induction therapy before the start of this drug will be included in this summary, except for "Remission induction chemotherapy before the start of this drug [not performed, performed]":

- Remission induction chemotherapy before the start of this drug [not performed, performed]

- Induction chemotherapy regimen and response before the start of this drug (regardless of line of therapy)
- Regimen of the induction chemotherapy immediately before the start of this drug (by line of treatment)
- Regimen and response of the induction chemotherapy immediately before the start of this drug

For the SAS and EAS, summary will be performed for anti-malignant tumor agents (drug code 42x) started by the day of the final dose of this drug that are recorded as concomitant anti-malignant tumor agents used for the target disease. Listings will also be prepared.

For the SAS and EAS, patients falling into the following categories defined for HSCT performed after the start of this drug will be summarized in terms of n and proportion. Note that only patients who underwent HSCT after the start of this drug will be included in this summary, except for "HSCT after the start of this drug [not performed, performed]":

- HSCT after the start of this drug [not performed, performed]
- Number of HSCTs after the start of this drug [1, ≥ 2]
- Type of HSCT after the start of this drug (regardless of the number of HSCTs) [autologous transplant, allogeneic hematopoietic stem cell transplant with myeloablative conditioning, allogeneic hematopoietic stem cell transplant with nonmyeloablative conditioning, unknown]
- Type of the first HSCT after the start of this drug [same as above]
- Donor of HSCT after the start of this drug (regardless of the number of HSCTs) [alternative donor, matched related donor]
- Donor of the first HSCT after the start of this drug [same as above]
- Type of conditioning drug for HSCT after the start of this drug (regardless of the number of HSCTs) [busulfan (BSF, BUS), cyclophosphamide (CPA), melphalan (LPAM), cytarabine (Ara-C), fludarabine phosphate (F-ara-AMP), etoposide (ETP, VP-16), other]
- Type of conditioning drug for the first HSCT after the start of this drug [same as above]
- Conditioning with alkylating agent for the first HSCT after the start of this drug [≤ 1 agent (including no conditioning), ≥ 2 agents]
- Conditioning with busulfan for the first HSCT after the start of this drug [not performed (including no conditioning), performed]
- ECOG PS before conditioning for the first HSCT after the start of this drug [0, 1, 2, 3, 4, not performed]
- ECOG PS before conditioning for the first HSCT after the start of this drug [0, 1, ≥ 2, not performed]
- AST level before conditioning of the first HSCT after the start of this drug [≤ 1.5 × the institutional upper limit of normal range (IULN), > 1.5 × IULN, not performed]
- ALT level before conditioning of the first HSCT after the start of this drug [≤ 1.5 × IULN, > 1.5 × IULN, not performed]
- AST and ALT levels before conditioning for the first HSCT after the start of this drug [≤ 1.5 × IULN, either > 1.5 × IULN, not performed]
- γ-GTP level before conditioning for the first HSCT after the start of this drug [≤ 50 IU/L, > 50 IU/L, not performed]

- Total bilirubin level before conditioning for the first HSCT after the start of this drug [≤ IULN, > IULN, not performed]
- Hemoglobin level before conditioning for the first HSCT after the start of this drug [< 10 g/dL, ≥ 10 g/dL, not performed]
- Platelet count before conditioning for the first HSCT after the start of this drug [< 10×10^4/μL, ≥ 10×10^4/μL, not performed]
- Peripheral blast count before conditioning for the first HSCT after the start of this drug [≤ 1000 /μL, > 1000 /μL, not performed]
- Myeloblast count before conditioning for the first HSCT after the start of this drug [≤ 50%, > 50%, not performed]
- Time from the start date of this drug to the date of the first HSCT after the start of this drug (continuous)
- Time from the start date of this drug to the date of the first HSCT after the start of this drug [< 4 weeks, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks to < 16 weeks, ≥ 16 weeks to < 20 weeks, ≥ 20 weeks to < 24 weeks, ≥ 24 weeks to < 28 weeks, ≥ 28 weeks]
- Time from the date of final dose of this drug to the date of the first HSCT after the start of this drug (continuous)
- Time from the date of final dose of this drug to the date of the first HSCT after the start of this drug [< 4 weeks, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks to < 16 weeks, ≥ 16 weeks to < 20 weeks, ≥ 20 weeks to < 24 weeks, ≥ 24 weeks]

Data for the time from the start of this drug to the first HSCT after the start of this drug will be summarized in a histogram with the 1st class being from 0 to 4 weeks and a class width of 4 weeks thereafter (the longitudinal axis is frequency). Data for the time from the date of final dose of this drug to the first HSCT after the start of this drug will also be summarized in the same manner. Listings concerning HSCT will also be prepared.

For the SAS and EAS, patients will be summarized in terms of n and proportion by each of the following factors:

- Individual drug therapies for the target disease (started by the end of the treatment period [i.e., by Day 28 post-final dose])
- Prophylactic injection to reduce infusion reactions [not performed, performed]
- Prophylactic treatment to prevent/reduce tumor lysis syndrome [not performed, performed]

- **Relationship between age and patient characteristics**

For the patient population aged 15 years or older, patients aged 65 years or older will be summarized in terms of n and proportion by each of the following factors selected from those specified in Section 5.4. In addition, statistical testing and risk ratio estimation will be performed according to Section 8.1.3.

- Hepatic impairment
- Medical history (past) - Hepatitis or hepatic disease
- Medical history (present) - Hepatitis or hepatic disease
- AST and ALT levels immediately before the start of this drug

- γ-GTP level immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug

Similar analysis will be performed for patients aged < 15 years in the patient population aged < 65 years.

- **Status of the treatment with this drug**

For the SAS, status of the treatment with this drug will be summarized with respect to the following factors. Similar summarys will also be performed by absence/presence of HSCT after the start of this drug:

- Number of treatment cycles (continuous)
- Number of treatment cycles [1 cycle, 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 cycles, > 6 cycles]
- Number of treatment cycles [≤ 3 cycles, ≥ 4 cycles]
- Dose amount in each cycle (continuous)
- Total dose amount (continuous)
- Dosing of > 1.8 mg/m^2 per cycle [absent, present] (Considered to be present, if there is a cycle of > 1.8 mg/m^2 per cycle during the treatment period.)

- **Pregnancy**

For the SAS, pregnancy status will be summarized:

- Pregnancy [absent, present] * Pregnancy during the treatment period. Limited to cases in which information on pregnancy is collected

8.2.3. Safety analyses

Adverse drug reactions (ADRs) and adverse events (AEs) that occurred in the following periods will be collected for summary: for ADRs and AEs other than VOD/SOS, those that occurred from the start of this drug to 28 days after the final dose of this drug will be collected; for ADRs and AEs of VOD/SOS in patients who did not undergo HSCT within 52 weeks after the start of this drug, those that occurred within 52 weeks after the start of this drug will be collected; for ADRs and AEs of VOD/SOS in patients who underwent HSCT within 52 weeks after the start of this drug, those that occurred within 52 weeks after the last HSCT will be collected. The listings will include all events reported in this survey.

8.2.3.1. Adverse drug reactions

- **All adverse drug reactions**

The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT.

- **Details of adverse drug reactions**

ADRs categorized by each of the following factors will be summarized in terms of number and proportion of patients with ADRs by SOC and PT:

- Seriousness [serious, non-serious]
- Known/Unknown [known, unknown]
- Action taken (additional treatment for the AE) [performed, not performed]
- Action taken [discontinuation of treatment, temporary suspension or dose reduction, none]
- Outcome [fatal, not recovered, recovered with sequelae, recovering, resolved/recovered, unknown]
- CTCAE Grade (1) [1, 2, 3, 4, 5, unknown]
- CTCAE Grade (2) [< 3, ≥ 3, unknown]

Multiple occurrences of the same adverse drug reaction (with the same PT) in the same patient will be handled as follows in the summary:

- Seriousness: If both serious and non-serious events of the same AR occurred in the same patient, the patient will be counted as one with a serious reaction.
- Known/Unknown: If both known and unknown events of the same AR occurred, the patient will be counted as one with an unexpected reaction.
- Action taken: If multiple types of actions were taken for the same AR in the same patient, one action will be adopted in the order of priority of "discontinuation of treatment", "temporary suspension or dose reduction", and "none".
- Outcome: See below
- CTCAE Grade: If there are multiple grades, the highest grade will be used.

In the summary by outcome, multiple events of the same AR in the same patient will be handled as follows:

- Outcome: If multiple different outcomes were reported, one category of outcome will be adopted from "fatal", "not recovered", "unknown", "recovered with sequelae", "recovering", and "resolved/recovered" with priority in this order.

Each SOC and PT of serious ADRs will be summarized by outcome.

- **Safety specification**

Patients who experienced the events identified as the safety specification will be summarized in terms of n and proportion. Similar summary will also be performed by CTCAE Grade [< 3, ≥ 3, unknown].

In addition, events identified as the safety specification will be summarized in terms of number and proportion of patients with such events for each SOC and PT by actions taken and outcome thereof.

- **Timing of onset of adverse drug reactions**

For ADRs that occurred in at least 10% of patients, number and proportion of patients with the ADRs will be summarized for each SOC and PT by category of timing of initial onset [< 4 weeks after the start of treatment, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks to < 16 weeks, ≥ 16 weeks to < 20 weeks, ≥ 20 weeks to < 24 weeks, ≥ 24 weeks].

In addition, time to event will be summarized as per Section 8.1.4 with event being the first onset of the AR. The analysis will be performed with the following specifications:

- Analysis set: SAS
- Handling of patients with no AR: Censored at 28 days after the final dose of this drug.
- Time points for rate estimation: Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24

- **Occurrence of adverse drug reactions by inclusion/exclusion in the safety analysis set**

For the population of patients whose case report form was collected, a listing of ADRs in patients excluded from the SAS will be prepared. In addition, excluded patients with ADRs will be summarized by SOC and PT.

- **VOD/SOS**

Events of VOD/SOS reported as AR will be analyzed. Events included in each analysis will not be limited to events of initial onset. Unless otherwise specified, VOD/SOS events will be summarized respectively for each of the following categories.

- VOD/SOS that occurred after the start of this drug (Use the SAS as the analysis set.)
- VOD/SOS that occurred with absence of HSCT after the start of this drug (Same as above): Here, "absence of HSCT" means that VOD/SOS occurred with no HSCT or occurred before any HSCT.
- VOD/SOS that occurred with presence of HSCT after the start of this drug (Patients in the SAS who underwent HSCT after the start of this drug will be analyzed)

Occurrence of VOD/SOS: The number of patients with VOD/SOS and its proportion will be summarized. Among the factors listed in "Details of adverse drug reactions" in Section 8.2.3.1, n and proportion will be summarized with respect to each of the following factors: Action taken [discontinuation, temporary suspension or dose reduction, none], Outcome [fatal, not recovered, recovered with sequelae, recovering, resolved/recovered, unknown], CTCAE Grade (1) [1, 2, 3, 4, 5, unknown], and CTCAE Grade (2) [< 3, ≥ 3, unknown].

Timing of onset of VOD/SOS: To analyze the timing of onset of VOD/SOS, summary statistics will be performed as per Section 8.1.1, for the following kinds of time.

- Time from the final dose of this drug: Time (weeks) from the final dose of this drug to the onset of VOD/SOS
- Time from HSCT: Time (weeks) from the first HSCT after the start of this drug to the onset of VOD/SOS. Only VOD/SOS events that occurred with presence of HSCT after the start of this drug will be included in this analysis (Similar limitation shall also apply to the analysis set).

Patients with VOD/SOS will be counted by each of the following timing factors. For each timing factor, data will also be summarized in a histogram (The longitudinal axis is frequency. The width of each onset period will depend on the actual duration of the period).

- Time from the final dose of this drug: < 2 weeks, ≥ 2 weeks to < 4 weeks, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks to < 16 weeks, ≥ 16 weeks
- Time from HSCT 1: < 2 weeks, ≥ 2 weeks to < 4 weeks, ≥ 4 weeks to < 6 weeks, ≥ 6 weeks to < 8 weeks, ≥ 8 weeks. This time is defined as the time starting from the first HSCT after the start of this drug.
- Time from HSCT 2: ≤ 3 weeks, > 3 weeks. This time is defined as the time starting from the first HSCT after the start of this drug.

Regarding the timing of onset of events described in "Timing of onset of adverse drug reactions" in Section 8.2.3.1, data will be analyzed with the following specifications.

- Analysis set: Patients who finished the survey (Patients who are recorded as discontinued in the "Record of continued/discontinued survey [treatment period]" in the case report form or patients for whom "Record of continued/discontinued survey [follow-up period]" in case report form is filled in. The latter means the survey is discontinued and completed for the patient.)
- Handling of patients who did not experience ADRs: If the survey had been discontinued for the patient, data shall be censored on the date of discontinuation based on the "Record of continued/discontinued survey" in the case report form; if the survey had been completed for the patient, data shall be censored on the last observation date defined in Section 7.
- Time points for rate estimation: Every 4 weeks from Week 4 to Week 52

For individual patients who experienced VOD/SOS, graphs will be prepared to indicate the start of this drug, the date(s) of HSCT after the start of this drug (only for those who underwent HSCT), the onset of VOD/SOS, the death (only for those who died), and timing of completion of the observation period or discontinuation of the survey, using the date of the last dose of this drug as the origin and using month as the time unit. The graphs will be displayed in ascending order of the time from the last dose of this drug to the onset of VOD/SOS.

Performance of HSCT: Performance of HSCT and occurrence of VOD/SOS will be summarized in terms of n and proportion with respect to the following specifications. The denominator of a proportion is the number of patients included in the 1-step higher itemization level.

- Safety Analysis Set
  - ➢ HSCT not performed (not performed before and after the start of this drug)
  - ➢ HSCT performed
    - ✧ HSCT performed before the start of this drug
      - ● HSCT not performed after the start of this drug
    - ✧ HSCT performed after the start of this drug
      - ● HSCT not performed before the start of this drug
      - ● HSCT performed before the start of this drug (performed both before and after the start of this drug)
  - ➢ VOD/SOS occurred
    - ✧ HSCT not performed before the start of this drug
    - ✧ HSCT performed before the start of this drug

- ✧ Occurred with no HSCT performed after the start of this drug or occurred before HSCT
  - ● HSCT not performed before the start of this drug
  - ● HSCT performed before the start of this drug
- ✧ Occurred after HSCT performed after the start of this drug
  - ● HSCT not performed before the start of this drug
  - ● HSCT performed before the start of this drug (performed both before and after the start of this drug)

Exploration of factors associated with the occurrence of VOD/SOS (subgroup analyses): Patients who experienced VOD/SOS after the start of this drug and patients who experienced VOD/SOS with HSCT performed after the start of this drug will be summarized in terms of n and proportion by each of the following factors selected from those specified in Section 5.4. In addition, risk ratios for the proportion of patients with the AR for different subgroups will be determined as per Section 8.1.3 and presented graphically. If, however, there is a category with less than 10 patients and after reconsideration it is considered difficult to determine the risk ratio for the category, it will not be determined for the relevant category. To investigate correlation between factors and occurrence of the ADR, statistical tests specified in Section 8.1.3 will be performed.

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Hepatic impairment
- Medical history (past) - VOD/SOS
- Medical history (past) - Hepatitis or hepatic disease
- Medical history (present) - VOD/SOS
- Medical history (present) - Hepatitis or hepatic disease
- ECOG PS before the start of this drug [0, 1, ≥ 2, not performed]
- AST and ALT levels immediately before the start of this drug
- γ-GTP level immediately before the start of this drug
- Total bilirubin level immediately before the start of this drug
- Platelet count immediately before the start of this drug
- Peripheral blast count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug
- HSCT after the start of this drug

Similarly, VOD/SOS that occurred with HSCT performed after the start of this drug will be analyzed with respect to the following factors:

- Type of the first HSCT after the start of this drug
- Donor of the first HSCT after the start of this drug
- Conditioning with alkylating agent for the first HSCT after the start of this drug
- Conditioning with busulfan for the first HSCT after the start of this drug

- ECOG PS before conditioning for the first HSCT after the start of this drug [0, 1, ≥ 2, not performed]
- AST and ALT levels before conditioning for the first HSCT after the start of this drug
- γ-GTP level before conditioning for the first HSCT after the start of this drug
- Total bilirubin level before conditioning for the first HSCT after the start of this drug
- Platelet count before conditioning for the first HSCT after the start of this drug
- Peripheral blast count before conditioning for the first HSCT after the start of this drug
- Time from the date of final dose of this drug to the date of the first HSCT after the start of this drug
- Treatment cycles [1 cycle, 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 cycles, > 6 cycles]
- Treatment cycles [≤ 3 cycles, ≥ 4 cycles]

Listings that account for the occurrence of VOD/SOS and other features in patients who experienced VOD/SOS will be prepared.

8.2.3.2. Adverse events

- **Serious and non-serious adverse events**

The number (n) and proportion of patients with serious adverse events (SAEs) will be tabulated by SOC and PT. Similar summary will also be performed for non-serious adverse events (AEs), but a threshold will be set for the proportion as necessary, and summary will be performed only for events that are associated with a proportion at or above the threshold.

8.2.3.3. Other endpoints

- **Death after HSCT**

To investigate early deaths after HSCT (see Section 6.1 for definition), the following kinds of patient data will be summarized as per Section 8.1.2. The denominator of a proportion is the number of patients included in the 1-step higher itemization level.

- Patients in the SAS who underwent HSCT after the start of this drug and have finished the survey (Patients who are recorded as discontinued in the "Record of continued/discontinued survey [treatment period]" in the case report form or patients for whom "Record of continued/discontinued survey [follow-up period]" in case report form is filled in. The latter means the survey is discontinued and completed for the patient.)
  - ➢ Death after HSCT
    - ✧ Death within 100 days post-HSCT
    - ✧ Death after > 100 days post-HSCT
    - ✧ Transplant-related death (non-relapse death)
      - ● Death within 100 days post-HSCT
      - ● Death after > 100 days post-HSCT
    - ✧ Transplant-unrelated death (relapse death)
      - ● Death within 100 days post-HSCT
      - ● Death after > 100 days post-HSCT

➢ Survival confirmed at the time of discontinuation of the survey

- **Mortality after HSCT**

Time to death after HSCT, time to transplant-related death after HSCT, and time to transplant-unrelated death after HSCT (see Section 6.1 for definitions) will be analyzed as per Section 8.1.4 (Although the time to death after HSCT does not have any competing risk, the same analysis with competing risks will be performed for the variable). Those who included in the analysis are patients in the SAS who underwent HSCT after the start of this drug and finished the survey (Patients who are recorded as discontinued in the "Record of continued/discontinued survey [treatment period]" in the case report form or patients for whom "Record of continued/discontinued survey [follow-up period]" in case report form is filled in. The latter means the survey is discontinued and completed for the patient.). The cumulative incidence will be estimated at Week 4, Week 8, Week 12, Day 100, Week 24, Week 36, Week 48, Week 52, Week 78, and Week 104.

- **Exploration of factors associated with early death after HSCT (subgroup analyses)**

Patients with early death after HSCT will be summarized in terms of n and proportion by each of the following factors selected from those specified in Section 5.4. In addition, risk ratios for the proportion of patients who died for different subgroups will be determined as per Section 8.1.3 and presented graphically. If, however, there is a category with less than 10 patients and after reconsideration it is considered difficult to determine the risk ratio for the category, it will not be determined for the relevant category. To investigate correlation between factors and death, statistical tests specified in Section 8.1.3 will be performed. Similar analyses will also be performed for early transplant-related death after HSCT (non-relapse death).

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Disease name
- Chromosome karyotype [normal, t (4;11)]
- Chromosome karyotype [Philadelphia chromosome positive, negative] * Philadelphia chromosome is considered positive if the chromosome karyotype is t(9;22).
- Hepatic impairment
- Medical history (past) - VOD/SOS
- Medical history (past) - GVHD
- Medical history (past) - Hepatitis or hepatic disease
- Medical history (present) - VOD/SOS
- Medical history (present) - GVHD
- Medical history (present) - Hepatitis or hepatic disease
- ECOG PS before the start of this drug [0, 1, ≥ 2, not performed]
- Hemoglobin level immediately before the start of this drug
- Platelet count immediately before the start of this drug
- Peripheral blast count immediately before the start of this drug

- Myeloblast count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug
- Type of the first HSCT after the start of this drug
- Donor of the first HSCT after the start of this drug
- Conditioning with alkylating agent for the first HSCT after the start of this drug
- Conditioning with busulfan for the first HSCT after the start of this drug
- ECOG PS before conditioning for the first HSCT after the start of this drug [0, 1, ≥ 2, not performed]
- Hemoglobin level before conditioning for the first HSCT after the start of this drug
- Platelet count before conditioning for the first HSCT after the start of this drug
- Peripheral blast count before conditioning for the first HSCT after the start of this drug
- Myeloblast count before conditioning for the first HSCT after the start of this drug
- Time from the date of final dose of this drug to the date of the first HSCT after the start of this drug
- Treatment cycles [1 cycle, 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 cycles, > 6 cycles]
- Treatment cycles [≤ 3 cycles, ≥ 4 cycles]
- Best overall response
- MRD
- Best overall response and MRD
- Adverse drug reactions that occurred during the treatment period - liver disorder as a safety specification

8.2.3.4. Subgroup analyses

Patients who experienced at least one AR will be summarized in terms of n and proportion by each of the following factors selected from those specified in Section 5.4. To investigate the correlation between patient characteristics and occurrence of ADRs, statistical tests specified in Section 8.1.3 and risk ratio estimation will be performed.

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 years to < 40 years, ≥ 40 years]
- Disease name
- Chromosome karyotype
- Chromosome karyotype * Philadelphia chromosome is considered positive if the chromosome karyotype is t(9;22).
- Hepatic impairment
- Renal impairment
- Medical history (past) - VOD/SOS
- Medical history (past) - GVHD
- Medical history (past) - Hepatitis or hepatic disease
- Medical history (present) - VOD/SOS
- Medical history (present) - GVHD
- Medical history (present) - Hepatitis or hepatic disease

- ECOG PS before the start of this drug
- AST and ALT levels immediately before the start of this drug
- γ-GTP level immediately before the start of this drug
- Total bilirubin level immediately before the start of this drug
- Hemoglobin level immediately before the start of this drug
- Platelet count immediately before the start of this drug
- Peripheral blast count immediately before the start of this drug
- Myeloblast count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug
- Pregnancy * Pregnancy during the treatment period. Limited to cases in which information on pregnancy is collected

Furthermore, patients who experienced ADRs will be summarized in terms of n and proportion for each SOC and PT by each of the following factors selected from those specified in Section 5.4. In addition, risk ratios for the proportion of patients with ADRs for different subgroups will be determined as per Section 8.1.3 and presented graphically. If, however, there is a category with less than 10 patients and after reconsideration it is considered difficult to determine the risk ratio for the category, it will not be determined for the relevant category. To investigate the correlation between patient characteristics and occurrence of ADRs, statistical tests specified in Section 8.1.3 will be performed.

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Hepatic impairment
- Renal impairment
- HSCT before the start of this drug
- Total dose per cycle > 1.8 mg/m^2
- Pregnancy * Pregnancy during the treatment period. Limited to cases in which information on pregnancy is collected

Similarly, ADRs meeting definition of liver disorder including safety specification events of VOD/SOS will be analyzed by each of the following factors. Similar analyses will also be performed for ADRs of Grade 3 or higher based on CTCAE v4.0.

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Hepatic impairment
- Medical history (past) - VOD/SOS
- Medical history (past) - Hepatitis or hepatic disease
- Medical history (present) - VOD/SOS
- Medical history (present) - Hepatitis or hepatic disease
- ECOG PS before the start of this drug

- AST and ALT levels immediately before the start of this drug
- γ-GTP level immediately before the start of this drug
- Total bilirubin level immediately before the start of this drug
- Platelet count immediately before the start of this drug
- Peripheral blast count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug

Similarly, ADRs meeting definition of safety specification events of myelosuppression will be analyzed by each of the following factors. Similar analyses will also be performed for ADRs of Grade 3 or higher based on CTCAE v4.0.

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Hepatic impairment
- Renal impairment
- Total dose per cycle > 1.8 mg/m^2
- ECOG PS before the start of this drug
- White blood cell count immediately before the start of this drug
- Neutrophil count immediately before the start of this drug
- Platelet count immediately before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug

Similarly, ADRs meeting definition of safety specification events of infection will be analyzed by each of the following factors. Similar analyses will also be performed for ADRs of Grade 3 or higher based on CTCAE v4.0.

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]
- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Hepatic impairment
- Renal impairment
- Total dose per cycle > 1.8 mg/m^2
- ECOG PS before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug

Similarly, ADRs meeting definition of safety specification events of hemorrhage will be analyzed by each of the following factors. Similar analyses will also be performed for ADRs of Grade 3 or higher based on CTCAE v4.0.

- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Age [< 18 years, ≥ 18 to < 55 years, ≥ 55 years]

- Age [< 15 years, ≥ 15 to < 40 years, ≥ 40 years]
- Hepatic impairment
- Renal impairment
- Total dose per cycle > 1.8 mg/m^2
- ECOG PS before the start of this drug
- Salvage line of the induction treatment with this drug
- HSCT before the start of this drug

Similarly, patients who experienced GVHD will be analyzed by each of the following factors. GVHD events included in the analysis will be events of which PT includes GVHD according to the version of MedDRA used for the analysis.

- Medical history (past) - GVHD
- Medical history (present) - GVHD

Similar analyses will be performed for serious ADRs.

8.2.3.5. Exploratory analyses

Additional analyses may be performed as necessary. Results of exploratory analyses will be reported only if the analyte provide important interpretation.

8.2.4. Effectiveness analyses

8.2.4.1. Hematologic response

For patients who achieved the following responses based on the best overall response of hematologic response, their proportion and its confidence interval will be determined as per Section 8.1.3. Patients who underwent no clinical assessment of hematologic response will also be included in the analysis, but another analysis in patients except them will also be performed.

- CR or CRi
- CR
- CRi

Cycles in which CR or CRi was achieved for the first time will be analyzed by determining the proportion of patients as per Section 8.1.2. The relevant cycle is determined based on the assessment date for which CR or CRi was determined and shall include the date of the most recent past dose of this drug. If the assessment date is 29 days after the last dose or later, however, the cycle should be determined to be post-treatment; the following categories will be used for this analysis.

- Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle > 6, post-treatment

8.2.4.2. Minimal residual disease

For categories based on MRD status, proportions will be calculated according to Section 8.1.2. In addition, patients categorized by the following factor will be analyzed by determining their proportions and

confidence intervals as per Section 8.1.3. Patients who underwent no MRD assessment will also be included in the analysis, but another analysis in patients except them will also be performed.

- Achievement of MRD negativity (achieved, not achieved, not performed)* Irrespective of the result of best overall response.

Similar analyses will also be performed using the following populations. For the handling of the populations, see Section 8.2.4.1.

- CR or CRi achieved
- CR achieved
- CRi achieved

8.2.4.3. Hematopoietic stem cell transplant

The proportion of patients who underwent HSCT after the start of this drug and its confidence interval will be determined as per Section 8.1.3. Similar analyses will also be performed using the following populations. See Sections 8.2.4.1 and 8.2.4.2 for the handling of the populations.

- CR or CRi achieved
- MRD negativity achieved
- CR or CRi achieved and MRD negativity achieved
- CR or CRi achieved and MRD negativity not achieved

8.2.4.4. Overall survival

Percentages of deaths and their causes of death will be summarized as per Section 8.1.2.

Overall survival (OS) will be analyzed using the entire analysis set and also by HSCT performed or not performed after the start of this drug, as per Section 8.1.4. Those who included in the analysis are patients in the EAS who finished the survey (Patients who are recorded as discontinued in the "Record of continued/discontinued survey [treatment period]" in the case report form or patients for whom "Record of continued/discontinued survey [follow-up period]" in case report form is filled in. The latter means the survey is discontinued and completed for the patient.). The time points for rate estimation will be at Months 3, 6, 9, and 12 for the entire analysis set and patients who did not undergo HSCT, and at Months 3, 6, 9, 12, 18, and 24 for patients who underwent HSCT. Results of the analysis for the entire analysis set should be interpreted with caution, because the planned observation period for this survey differs for patients who did and did not undergo HSCT after the start of this drug (see Section 2.1).

The OS after the final dose of this drug in patients who underwent HSCT will also be analyzed in the same manner. Those who included in the analysis are patients in the EAS who underwent HSCT after the start of this drug and finished the survey (Patients who are recorded as discontinued in the "Record of continued/discontinued survey [treatment period]" in the case report form or patients for whom "Record of

continued/discontinued survey [follow-up period]" in case report form is filled in. The latter means the survey is discontinued and completed for the patient.).

8.2.4.5. Subgroup analyses

Subgroup analyses for hematologic response and MRD will be performed by each of the factors defined in Section 5.4. In addition, hematological response rate ratio and MRD negative rate ratio (corresponds to risk ratio in the SAS) for different subgroups will be determined as per Section 8.1.3, and presented graphically. If, however, there is a category with less than 10 patients and after reconsideration it is considered difficult to determine the ratios for the category, it will not be determined for the each of the relevant category.

In addition, subgroup analyses of OS will also be performed for each of the factors defined in Section 5.4. Hazard ratios for the occurrence of events for different subgroups will be determined as per Section 8.1.4 and graphically presented. If, however, there is a category with less than 10 patients and after reconsideration it is considered difficult to determine the hazard ratio for the category, it will not be determined for the relevant category. The OS after the final dose of this drug in patients who underwent HSCT will also be analyzed in the same manner. Results of the analysis for the entire analysis set should be interpreted with caution, because the planned observation period for this survey differs for patients who did and did not undergo HSCT after the start of this drug (see Section 2.1). The above subgroup analyses of OS will also be performed by HSCT performed or not performed after the start of this drug.

8.2.4.6. Exploratory analyses

Additional analyses may be performed as necessary. Results of exploratory analyses will be reported only if the analyte provide important interpretation.

9. LISTINGS

The following data will be listed in tabular form:

- All patients
- Off-label diseases
- Dosing records
- Reasons for completion/discontinuation of treatment * Only for "other" reasons.
- Concomitant anti-malignant tumor agents
- Hematopoietic stem cell transplants (before and after the start of this drug)
- Patients with AEs
- Patients with ADRs
- Patients with ADRs who were excluded from the safety analysis
- ADRs with data deleted
- Patients with serious ADRs
- Patients with serious AEs
- Patients with AEs of VOD/SOS
- Patients with ADRs in the population with hepatic impairment

- Patients with ADRs in the population with renal impairment
- Elderly patients with ADRs
- Patients with ADRs by event included in the safety specification
- Laboratory test values

The descriptions included in the listing of "Off-label diseases" are as follows:

- Disease name (as recorded by the physician)
- ADRs

The descriptions included in the listing of "Dosing records" are as follows:

- Items in the "Record of the Treatment with This Drug" page of the case report form
- Number of treatment cycles of this drug
- Number of doses and total dose of this drug in each cycle
- Total dose amount of this drug

The descriptions included in the listing of "Reasons for completion/discontinuation of treatment" are as follows:

- Details of the "other" reasons for the completion/discontinuation of treatment

The descriptions included in the listing of "Concomitant anti-malignant tumor agents" are as follows:

- Drug code
- Drug name [code-based name]
- Drug name [generic name]
- Drug name (product name) [as per physician's description]
- Start date

The descriptions included in the listing of "Hematopoietic stem cells transplants (before and after the start of this drug)" are as follows:

- Disease name (as per physician's description), salvage line number, and presence/absence of resumption of this drug
- Items in the "Hematopoietic Stem Cell Transplant (before the start of the treatment with this drug)" page of the case report form
- Items in the "Hematopoietic Stem Cell Transplant (treatment and follow-up periods)" page of the case report form. In addition, the following items will also be presented:
  - Months (days) from the start of this drug to the day of transplant
  - Months (days) from the date of the final dose of this drug to the day of transplant
  - Occurrence of VOD/SOS * This item describes ADRs in the events recorded in the "Adverse Events (VOD/SOS)" page of the case report form.
    - Presence or absence of occurrence
    - Months (days) from the date of transplant to the date of onset after transplant
    - Outcome

The descriptions included in the listing of "Patients with AEs of VOD/SOS" are as follows:

- Disease name (as per physician's description), salvage line number, and presence/absence of resumption of this drug
- Items in the "Adverse Events (VOD/SOS)" page of the case report form
- Risk factors (those listed in "Section 8.2.3.1. Exploration of factors associated with the occurrence of VOD/SOS [subgroup analyses]")
- Months (days) from the start date of this drug to the onset of VOD
- Months (days) from the end date of this drug to the onset of VOD
- Months (days) from the onset of VOD to the date of death
- HSCT (before the start of this drug) status* "Hematopoietic Stem Cell Transplant (before the start of the treatment with this drug)" page of the case report form
- HSCT (treatment and follow-up periods) status* "Hematopoietic Stem Cell Transplant (before the start of the treatment with this drug)" page of the case report form
  - HSCT status (performed or not performed)
  - Type of HSCT
  - Donor characteristics
  - Conditioning
  - Months (days) from the date of transplant to the first onset of VOD after transplant

In addition, the following tables corresponding to the Attachment Forms for periodic safety update reports will be prepared:

- Attachment Form 12 (Occurrence of Adverse drug reactions/Infections in Additional Pharmacovigilance Plans)
- Attached Form 15 (Occurrence of Adverse drug reactions/Infections in Post-Marketing Surveillance, etc.)
- Attached Form 16 (List of Case Summaries in Post-Marketing Surveillance, etc.)

10. REFERENCES

1. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863-71.