Protocol B1931030

A PHASE 4, OPEN-LABEL, RANDOMIZED STUDY OF TWO INOTUZUMAB OZOGAMICIN DOSE LEVELS IN ADULT PATIENTS WITH RELAPSED OR REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA ELIGIBLE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION AND WHO HAVE RISK FACTOR(S) FOR VENO-OCCLUSIVE DISEASE

Statistical Analysis Plan (SAP)

Version: 3.0

Date: 29-Apr-2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-inotuzumab ozogamicin antibodies
AE	adverse event
AEoSI	adverse events of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BSA	body surface area
BMI	body mass index
CI	confidence interval
CR	complete remission
CRi	complete remission with incomplete hematologic recovery
CRF	clinical report form
CTCAE	Common Terminology Criteria for Adverse Events
DI	dose intensity
DoR	duration of remission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDISH	evaluation of drug-induced serious hepatotoxicity
EOT	end of treatment
HR	heart rate
HSCT	hematopoietic stem cell transplantation
IOTA	investigator overall tumor assessment
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
Nab	neutralizing antibodies
NCI	National Cancer Institute
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PP	Per-Protocol
PT	preferred term
PMAR	population modeling analysis report
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcB	QTc corrected using Bazett's formula
QTcF	QTc corrected using Fridericia's formula
RDI	relative dose intensity
RR	R is a point corresponding to the peak of the QRS complex of ECG wave and RR is the interval between successive Rs
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	System Organ Class
TEAE	treatment emergent adverse event
ULN	upper limit of normal
VOD	veno-occlusive disease

1. VERSION HISTORY

This amended Statistical Analysis Plan (SAP) for Study B1931030 is the second amendment of the original SAP version 1.0 dated 29 May 2018. This amendment is based on the original version of the protocol (dated 23 May 2018).

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	• The data cutoff for the primary analysis was revised to 12 months following randomization of the last patient; • The time intervals for summarizing safety endpoints were clarified in Section 3.1.2 for VOD rate and Section 3.4 for AEs and laboratory abnormalities; • Minor revisions were incorporated for PK analyses (Section 3.2) and PK/Immunogenicity analysis set (Section 4.4 and 4.5) for clarification purpose; • Tumor assessment was revised to ALL disease assessment in Section 5.2.5; • Methods for handling ECG data not being collected in triplicate was added in Section 5.3.3; • More details were added in summary of patient disposition in Section 6.5.2.1; • Summary of exposure to inotuzumab in Section 6.5.3.1 was revised to account for its administration schedule; • A summary of post-HSCT SAEs was added in Section 6.6.1; • A section for AE summaries (required for basic results disclosure in EU and US) in Section 6.6.1 was removed; • Summaries of PR and QRS were removed in Section 6.6.5; • Explicit references to any specific CRF pages were removed.	• Considering the clinical circumstances where nearly all post-SCT VOD would occur within 100 days of transplant the sponsor expected that all data to assess CR/CRi and nearly all VOD cases are likely to occur within one year from the last patient randomized; • To align with the protocol
3	General • Replaced “during study treatment” with “on-treatment” for the primary safety endpoint. • Added Appendix 2 to document additional analyses that may be undertaken to assess the impact of COVID-19 pandemic. Table 1 • Modified rationale for primary analysis cutoff time change for version 2. Section 3.1	• Remove the unnecessary analyses • Clarify the endpoint definitions and analysis details. • Incorporating clinical consideration for primary analysis cutoff time change.

	• Clarified that primary efficacy endpoint only accounted for CR/CRi prior to EOT. Section 3.2 • Changed the start dates for PFS/OS from date of randomization to date of first dose. • Removed the secondary endpoint PFS according to standard definition. Added a sensitivity analysis of PFS with an alternative censoring rule in Section 6.2.3, which is equivalent to the analysis of PFS according to standard definition. • Clarified the definition of DoR, PFS, OS, rate of HSCT, post-HSCT relapse, post-HSCT mortality, post-HSCT non-relapse mortality, and post-HSCT relapse-related mortality. Section 3.3 • Clarified the definition of baseline. • Clarified baseline variables for the analysis. • Moved the definition of study treatment exposure variables from Section 6.5.3 to Section 3.3.3. • Clarified lab parameters for the analysis in Section 3.4.2. • Added definitions of other safety endpoints in Section 3.4.3. Section 4.2 • Clarified the definition of per-protocol analysis set. Section 5.2 • Removed unnecessary details on Pfizer standard methods for data derivation. Section 5.3 • Clarified the approach for imputing missing ECG data. Section 6 • Removed unnecessary details on Pfizer standard analyses. • Added details for the non-standard analyses. Section 6.1.2 • Added analyses of association of baseline and patient characteristics at the time of HSCT with occurrence of VOD post-HSCT.	

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data to be collected in Study B1931030. This document may modify the plan outlined in the protocol;

however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Any deviations from this SAP will be described in the clinical study report (CSR).

The data cutoff for the primary analysis will be 12 months following randomization of the last patient. All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives of the study are to evaluate the rates of veno-occlusive disease (VOD) and hematologic remission (complete remission [CR]/complete remission with incomplete hematologic recovery [CRi]) following treatment at 2 inotuzumab ozogamicin dose levels in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) who are eligible for hematopoietic stem cell transplantation (HSCT) and who are at higher risk for developing VOD post-HSCT after inotuzumab ozogamicin treatment.

The study analyses will be descriptive only, without conducting formal hypothesis testing.

The primary endpoints include the following:

- Rate of VOD (total, during study treatment, and post-HSCT); and
- Rate of hematologic remission (CR/CRi).

2.1.2. Secondary Objectives

The secondary objectives of the study are to evaluate the safety and efficacy following treatment at 2 inotuzumab ozogamicin dose levels.

The secondary endpoints include the following:

- Adverse events (AEs) and laboratory abnormalities (grade, timing, seriousness, relatedness) during study treatment and post-HSCT;
- Minimal residual disease (MRD) negativity in patients achieving CR/CRi;
- Duration of remission (DoR) in patients achieving a CR/CRi;
- Progression-free survival (PFS);
- Overall survival (OS);
- Rate of HSCT;
- Post-HSCT relapse;

- Post-HSCT mortality;
- Post-HSCT non-relapse mortality;
- Post-HSCT relapse-related mortality;
- Pharmacokinetic (PK) exposure-response relationships for efficacy and safety; and
- Immunogenicity testing for anti-inotuzumab ozogamicin antibodies (ADA) and neutralizing antibodies (Nab).

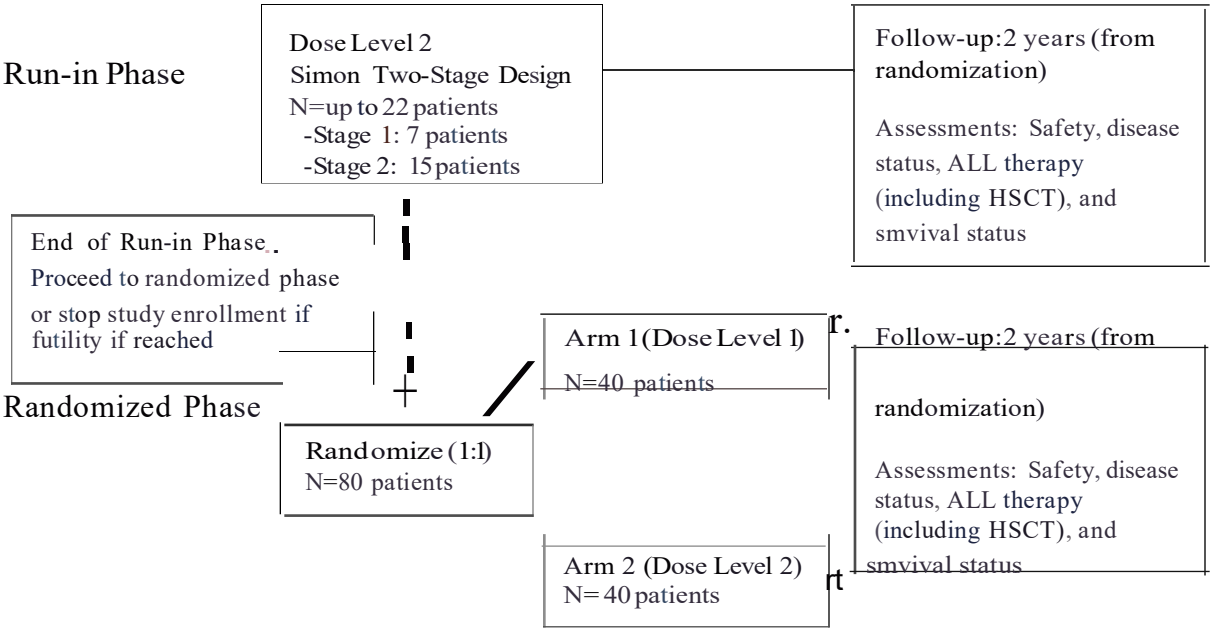
2.2. Study Design

This open-label study will evaluate 2 inotuzumab ozogamicin dose levels in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT after inotuzumab ozogamicin treatment. Figure 1 shows the study design.

The 2 dose levels are as follows:

- Dose Level 1: Patients will be treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2/cycle administered over 3 divided doses. After CR/CRi is achieved, the dose will be reduced to 1.5 mg/m^2/cycle administered over 3 divided doses. For patients proceeding to HSCT, 2 cycles are recommended; a third cycle may be considered for those patients who do not achieve CR/CRi and MRD-negativity after 2 cycles. Patients who do not achieve CR/CRi within 3 cycles should discontinue treatment. The cycle length will be 21-28 days.
- Dose Level 2: Patients will be treated with inotuzumab ozogamicin at a starting dose of 1.2 mg/m^2/cycle administered over 3 divided doses. After CR/CRi is achieved, the dose will be reduced to 0.9 mg/m^2/cycle administered over 3 divided doses. For patients proceeding to HSCT, 2 cycles are recommended; additional cycles may be considered for those patients who do not achieve CR/CRi and MRD-negativity after 2 cycles (maximum of 4 cycles). Patients who do not achieve CR/CRi within 4 cycles should discontinue treatment. The cycle length will be 21-28 days.

Figure 1. Study B1931030: Study Design



The study will be conducted in 2 phases: a nm-in phase and a randomized phase. Up to approximately 102 patients will be enrolled in the study across these 2 phases.

Run-in phase: Up to 22 patients will be enrolled and receive a staiiing dose of 1.2 mg/m^2/cycle (dose level 2). A Simon Two-Stage optimal design will be used. Ifacceptable efficacy (CR/CRi and MRD-negativity) is observed in the nm-in phase, patients will be enrolled into the randomized phase (see Section 5.1.2).

Randomized phase: Ifacceptable efficacy is observed in the nm-in phase (see Section 5.1.2), patients will be randomized (1:1) to 1of 2 dose levels of inotuzumab ozogamicin (40 patients per dose level):

- Ann 1 of Randomized Phase: Dose level 1;
- Ann 2 of Randomized Phase: Dose level 2.

A total of approximately 80 patients will be strntified at randomization based on age (<55 vs 55 yeais), salvage status (Salvage 1 vs 2), and prior HSCT (yes vs no).

Patients will receive an average of approximately 3 months (i.e., 2-3 cycles) of inotuzumab ozogamicin treatment. Safety assessments, disease assessments, and PK sample collections will be conducted throughout the treatment period.

After inotuzumab ozogamicin treatment, patients will be followed for at least 2 years from the time of randomization. During the follow-up period, safety and disease assessments will be conducted, and information about subsequent ALL treatments (including HSCT) and survival status will be collected. All known cases of VOD, regardless of causality and severity, will be reported as serious adverse events (SAEs) throughout the follow-up period.

This study will be conducted at approximately 50 clinical sites and is expected to be completed (last patient last visit) in approximately 6 years.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Efficacy

The primary efficacy endpoint is CR/CRi rate. CR/CRi rate is defined as the percentage of patients with a best overall response of CR or CRi until the End of Treatment (EOT) based on investigator assessments (according to the modified Cheson Criteria defined in Study B1931030 Protocol Appendix 1). Patients without a documented CR or CRi until the EOT will be considered as non-responders.

3.1.2. Safety

The primary safety endpoint is VOD rate. The criteria for VOD are defined in Study B1931030 Protocol Section 8.4.

VOD rate will be summarized based on patients experiencing VOD by overall study period, on-treatment or in follow-up without HSCT period and post-HSCT period. The definitions of those periods are described in Section 3.4.

3.2. Secondary Endpoints

Secondary endpoints include, and are defined, as follows:

Adverse Events (AEs) and Laboratory Abnormalities

- Definition: AEs and laboratory abnormalities characterized by grade, timing, seriousness, relatedness, and time of occurrence (i.e., on-treatment or post-HSCT) (see Section 3.4).
    - All known cases of VOD, regardless of causality and severity, will be reported as serious adverse events (SAEs) throughout the follow-up period.

MRD Negativity

- Definition: In patients who achieve CR/CRi, a patient will be considered to be MRD negative if the minimum MRD (%) between the date of achieving CR/CRi and the EOT test is <0.01%.

DoR

- Definition: Time from date of first response in responders (patients who achieved CR/CRi) to the date of disease progression (i.e., objective progression, relapse from CR/CRi, including post-study treatment follow-up disease assessments) or death due to any cause, whichever occurs first.

- Censorship:

  - Patients without a DoR event at time of analysis will be censored at the date of last adequate post-baseline disease assessment including follow-up disease assessment.

  - Patients with documentation of a DoR event after an unacceptably long interval (>28 weeks) since the previous adequate post-baseline disease assessment will be censored at the date of the previous assessment.

  - Adequate post-baseline disease assessment is defined as an assessment where a response has been provided and analyzed by the investigator. Timepoints at which the response is not evaluable, or no assessment was performed will not be used for determining the censoring date.

- Duration (months): [date of event/ censoring−date of first response+1]/30.4375.

PFS

- Definition: Time from date of first dose of study treatment to the date of disease progression (i.e., objective progression, relapse from CR/CRi, including post-study treatment follow-up disease assessments), death due to any cause, or starting new induction therapy/post-therapy HSCT without achieving CR/CRi, whichever occurs first.

- Censorship:

  - Patients without a PFS event at time of analysis will be censored at the date of last adequate post-baseline disease assessment.

  - Patients with documentation of a PFS event after an unacceptably long interval (>28 weeks if there was adequate post-baseline disease assessment, or >12 weeks if there was no adequate post-baseline assessment) since the previous adequate disease assessment will be censored at the date of the previous assessment (date of first dose of study treatment if no adequate post-baseline assessment).

  - Patients without adequate baseline assessment will be censored at the date of first dose of study treatment.

  - Adequate baseline is defined using the following criteria:

    - All baseline assessments must be within 28 days prior to and including the date of first dose of study treatment,

    - Bone marrow biopsy or aspirate with blasts ≥5%, OR hematology test with presence of blast cells (% or absolute).

  - Adequate post-baseline disease assessment is defined as an assessment where a response has been provided and analyzed by the investigator. Timepoints at which the response is not evaluable, or no assessment was performed will not be used for determining the censoring date.

- For patients in the randomized phase who did not receive the randomly assigned study treatment, the date of first dose of study treatment will be missing. This missing date will be imputed using the date of randomization and such patient will be censored at the date of randomization.

- Duration (months): [date of event/ censoring−date of first dose +1]/30.4375.

OS

- Definition: Time from date of first dose of study treatment to death due to any cause.

- Censorship: Patients without confirmation of death will be censored at the date that the patient is last known to be alive (see Section 5.2.4 for derivation of date of last contact).

- For patients in the randomized phase who did not receive the randomly assigned study treatment, the date of first dose of study treatment will be missing. This missing date will be imputed using the date of randomization and such patient will be censored at the date of randomization.

- Duration (months): [date of death/ last known to be alive−date of first dose +1]/30.4375.

Rate of HSCT

- Definition: Percentage of patients who undergo HSCT after inotuzumab ozogamicin treatment and prior to post induction therapy.

Post-HSCT Relapse

- Definition: Time from date of first HSCT after inotuzumab ozogamicin treatment to the date of first relapse post-HSCT.

    - Event: first relapse post-HSCT.

    - Competing event: any deaths post-HSCT without prior relapse.

    - If a cause of death is relapse/progression, it should be assumed that relapse occurred prior to death.

- Censorship: Patients without confirmation of relapse/death will be censored at the date that the patient was last known to be alive (see Section 5.2.4 for derivation of date of last contact).

- Duration (months): [date of event/ competing event/ last known to be alive−date of first transplant after study treatment +1]/30.4375.

Post-HSCT Mortality

- Definition: Time from date of first HSCT after inotuzumab ozogamicin treatment to death due to any cause.

- Censorship: Patients without confirmation of death will be censored at the date that the patient was last known to be alive (see Section 5.2.4 for derivation of date of last contact).

- Duration (months): [date of death/ last known to be alive−date of first transplant after study treatment +1]/30.4375.

Non-relapse Mortality

- Definition: Time from date of first HSCT after inotuzumab ozogamicin treatment to death due to any cause without prior relapse.

    - Event: Death post-HSCT without any prior relapse.

    - Competing event: Relapse post-HSCT or any death post-HSCT related to relapse, whichever occurs first.

    - If a cause of death is relapse/progression, it should be assumed that relapse occurred prior to death.

- Censorship: Patients without confirmation of death will be censored at the date that the patient was last known to be alive (see Section 5.2.4 for derivation of date of last contact).

- Duration (months): [date of event/ competing event/ last known to be alive−date of first transplant after study treatment +1]/30.4375.

Relapse-related Mortality

- Definition: time from date of first HSCT after inotuzumab ozogamicin treatment to death due to any cause with prior relapse.

  - Event: Death post-HSCT with prior relapse.
  - Competing event: Death post-HSCT without any prior relapse/progression.
  - If a cause of death is relapse/progression, it should be assumed that relapse occurred prior to death.
- Censorship: Patients without confirmation of death will be censored at the date that the patient was last known to be alive (see Section 5.2.4 for derivation of date of last contact).
- Duration (months): [date of event/ competing event/ last known to be alive−date of first transplant after study treatment +1]/30.4375.

PK Exposure-Response Relationships for Efficacy and Safety

- PK serum concentrations for inotuzumab ozogamicin and unconjugated calicheamicin.
- Relationships between PK exposure and efficacy endpoints, including CR/CRi and MRD-negativity. This will be provided separately as part of a population modeling analysis report (PMAR).
- Relationships between PK exposure and safety endpoints, including rate of VOD and hepatic events (i.e., Grade ≥3 and/or serious hepatotoxicity) as well as Grade ≥3 elevated bilirubin, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), thrombocytopenia, and neutropenia rate. This will be provided separately as part of a PMAR.

Immunogenicity

- Incidence and titer of ADA, including Nab.
- Impact of ADA/Nab on inotuzumab ozogamicin clearance, safety, and efficacy, if data permit.

3.3. Baseline Variables

- Start and end dates of study treatment
  - The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of the study drug.
  - The date of last dose of study treatment is the latest date of non-zero dosing of the study drug.
- Definition of baseline:

- For efficacy endpoints and baseline characteristics associated with disease assessments, unless otherwise specified, the last assessment prior to first dose of study treatment will serve as the baseline assessment.

    - For post-HSCT efficacy endpoints, the last assessment prior to first transplant after study treatment will serve as the baseline assessment.

- For safety (including Eastern Cooperative Oncology Group [ECOG] performance status) and immunogenicity, unless otherwise specified, the last assessment performed on or prior to the date of the first dose of study treatment will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline will be considered as 'missing'.

- For electrocardiograms (ECGs), as triplet ECG will be collected; therefore the baseline for each ECG measurement is the average of the measurements prior to the first dose of study treatment.

Notes:

- No 'windowing' will be applied when defining baseline. Values from the assessments performed outside the protocol-specified window will not be excluded when determining baseline assessments. Any deviations from the protocol-specified window will be documented as protocol deviations.

3.3.1. Baseline Covariates

1. Demographic characteristics including age, race, sex, and ethnicity, where age is calculated following Pfizer data standards as age in years.

2. Physical measurements at baseline include height (cm), body weight (kg), body mass index (BMI), and body surface area (BSA), where baseline is defined as the last assessment prior to first dose of study treatment.

    - BMI (kg/m^2) will be computed as Height (cm)/Weight (kg) x 100.

    - BSA (m^2) will be computed using Du Bois Formula: 0.007184 x Weight $(kg)^{0.425}$ x Height $(cm)^{0.725}$.

3. Other baseline patient characteristics, including:

    - Enrollment geographical region (eg, North America, Western Europe, Eastern Europe, and Asia) and country within each region.

    - VOD risk factors collected at the screening visit, including age (<55, ≥55 years), salvage status (Salvage 1, ≥2), prior HSCT (yes, no) and ongoing/prior hepatic disease (yes, no).

- ECOG performance status collected at the screening visit.

4. Significant medical history, including diseases or syndromes that are ongoing at, or stopped before, the screening visit. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code the disease/syndrome.

    - Medical history for hepatic medical conditions, including ascites, cholelithiasis, gallbladder disorder, hepatic steatosis, nodular hepatic disease, VOD/SOS and neoplasm not otherwise specified (NOS).

5. Disease characteristics, including:

    - Duration since onset (months), defined as (date of first dose – date of onset of current episode)/30.4375.

    - Local/central CD22 expression in percentage at the screening visit.

    - Local cytogenetics including number of metaphases analyzed, karyotype (abnormal, normal, not evaluable), and chromosomal abnormality, at the screening visit.

6. Prior anticancer therapy, including:

    - Prior systemic/induction/radiation therapy for primary diagnosis.

    - Responses to most recent prior induction regimen, to prior regimen 1 and 2.

    - Duration of first remission (months), defined as (date of relapse – date of best overall response +1)/30.4375 in the first regimen with best overall response of CR.

3.3.2. Stratification Factors

In the randomized phase, randomization will be stratified by the following VOD risk factors collected at the screening visit,

- Age (<55 vs ≥55 years),

- Salvage status (Salvage 1 vs ≥2),

- Prior HSCT (yes vs no).

Unless otherwise specified, stratified analyses will utilize strata as defined in the randomization system.

3.3.3. Study Treatment Exposure

Inotuzumab ozogamicin will be administered at a starting dose of 1.8 mg/m^2/cycle (Dose Level 1) or 1.2 mg/m^2/cycle (Dose Level 2) over 3 divided doses (Section 2.2). The cycle length will be 21-28 days.

1. Treatment exposure to inotuzumab ozogamicin, including

    - Treatment cycles,
    - Treatment duration (weeks), defined as (last dose date – first dose date + 1)/7,
    - Actual overall dose (mg/m^2), defined as the sum of the actual dose that the patient received across all cycles,
        - Actual dose (mg/m^2) in a cycle is defined as total dose administered within a cycle[mg]/BSA [m^2], where BSA will be calculated based on the last available weight on or prior to the date of first dose of a cycle.
    - Actual dose intensity (mg/m^2/cycle), defined as [actual overall dose (mg/m^2)]/[number of cycles],
    - Relative dose intensity (%), defined as the actual dose intensity divided by the planned dose intensity.
        - Planned dose intensity (mg/m^2/cycle) is defined as [planned overall dose (mg/m^2)]/[number of cycles].

2. Dose modification, including

    - Dose reduction, defined as a nonzero dose that is less than the prior dose.
    - Dose delay, defined as ≥3 days of delay of the actual to the planned treatment administration day relative to the previous treatment administration date (1-2 days of delays will not be considered as dose delay).

3.4. Safety Endpoints

AEs and laboratory abnormalities, including the VOD rate, will be summarized based on the overall study period. The overall study period will be defined as the period starting with the first dose of study treatment through end of study follow-up (including on-treatment period and post-HSCT period).

- On-treatment period will be defined as the period starting with the first dose of study treatment drug through 63 days after last dose or one day before start day of new anti-cancer therapy, whichever occurs first.

- Post-HSCT will be defined as the period starting from the first transplant after inotuzumab ozogamicin treatment and including the entire duration of subsequent follow-up; this assessment will not be applicable for patient not proceeded to HSCT after study treatment.

Other safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

3.4.1. Adverse Events

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (v3.0). For other Aes without specific NCI CTCAE v3.0 definitions, results will be identified according to NCI CTCAE v3.0 "other" categories.

In both dose levels, patients will be followed for AEs for a minimum of 9 weeks (63 calendar days) after the last dose of study treatment. All AEs will be followed until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator assuming Pfizer concurs with that assessment.

All known cases of VOD, regardless of causality or severity, will be reported in the clinical report form (CRF) and as SAEs for the entire duration of study participation and the follow-up period.

An AE will be considered treatment related if the investigator considers the AE to be related to the study treatment.

3.4.1.1. Treatment Emergent Adverse Events

Treatment emergent AEs (TEAEs) will be defined as AEs that commence on or after Cycle 1 Day 1 but within 63 days of last dose (non-related) or any time after Cycle 1 Day 1 (treatment-related). All VOD events within 2 years of randomization date regardless of causal attribution to study treatment will be included.

3.4.1.2. Adverse Events of Special Interest

AEs of special interest (AESI) are as follows:

- GRADE ≥3 HEPATOTOXICITY AND/OR SERIOUS HEPATOTOXICITY, INCLUDING VOD/SOS;
- MYELOSUPPRESSION/CYTOPENIA (including Infections and Haemorrhage);
- INTERSTITIAL LUNG DISEASE;
- INFLAMMATORY GASTROINTESTINAL EVENT;

- PANCREATITIS;
- SECONDARY PRIMARY MALIGNANCY;
- REPRODUCTIVE AND DEVELOPMENT TOXICITY;
- NEPHROTOXICITY; and
- NEUROTOXICITY.

These events are defined in Appendix 1.

Note: Prior to data analysis, the AEoSI list may be updated if required.

3.4.2. Laboratory Data

Relevant hematology and chemistry parameters (on-treatment and post-HSCT) will be programmatically graded according to the NCI CTCAE v3.0. Parameters which cannot be graded will be summarized relative to the normal range (i.e., higher or lower than normal range). Additional details are provided in Section 6.6.3.

3.4.3. Other Safety Endpoints

- Physical examination: if any finding on the physical examination is considered by the investigator to be 'clinically significant', the event is to be recorded as medical history (preexisting) or an AE (treatment emergent), as appropriate.
- Vital signs: vital sign parameters include body weight, height, body temperature, pulse rate, and blood pressure (systolic and diastolic).
- Electrocardiogram (ECG): triplicate ECGs produce the following parameters: heart rate, PR, QT, QRS complex, corrected QT intervals (QTcB corrected using Bazett's formula, and QTcF corrected using Fridericia's formula), and RR.
    - Triplicate ECGs will be performed at screening, at baseline (prior to dose on Day 1), prior to the start of each cycle, and at the EOT. A 12 lead tracing will be used for all ECGs, including measurements of PR interval, QT interval, QRS complex and, RR interval.
- Hospitalization: status and date as collected in the CRF.

4. ANALYSIS SETS

This study is designed to enroll patients who are eligible for HSCT. Patients must be eligible for HSCT at the time of randomization (see Study B1931030 Protocol Section 4.1). Patients who are eligible for HSCT at randomization but who subsequently are not able to proceed to HSCT will not be replaced. Analyses will be performed based on the intent-to-treat (ITT) population (full

analysis set), Per-Protocol population (per protocol analysis set), and Safety population (safety analysis set) as described below.

4.1. Full Analysis Set

The Full Analysis Set will be based on the ITT population which will include all patients who are randomized into the study with study drug assignment based on randomization.

4.2. Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be based on the PP population which will be a subset of the ITT population and will include all patients who meet all of the following criteria:

- Patients who were randomized and received at least one dose of study drug with treatment assignments designated according to actual treatment received.
- Patients with no major protocol violations; major violations include,
  - Failure to satisfy major entry criteria, include the following: Inclusion criteria 1, 2, 6, 11; exclusion criteria 1, 2, 3, 13, 19.
  - Life-threatening dosing error, defined as taking wrong study treatment (ie, randomized to Dose Level 1 but took study drug for Dose Level 2; OR randomized to Dose Level 2 but took study drug for Dose Level 1).
- Patients with an adequate baseline disease assessment. A patient will have an adequate baseline disease assessment if the patient has one of the following two procedures at screening:
  - Bone marrow biopsy or aspirate with blasts ≥5%,
  - Hematology test with presence of blast cells (% or absolute).
- Patients who proceed to follow-up HSCT.

4.3. Safety Analysis Set

The Safety Analysis Set will be based on the safety population which includes all randomized patients who receive at least 1 dose of study drug, with treatment assignments designated according to actual treatment received.

Safety will also be evaluated post-HSCT in the HSCT safety population. The HSCT safety population will include all randomized patients who receive at least 1 dose of study drug, with treatment assignments designated according to actual treatment received, and who undergo HSCT after inotuzumab ozogamicin treatment. In addition, subgroup analysis will be performed for patients who undergo HSCT directly without new induction therapy.

4.4. PK Analysis Set

The PK Analysis Set will be based on the PK population which includes all treated patients who received at least 1 dose of study drug and had at least one PK sample collected and analyzed.

4.5. Immunogenicity Analysis Set

The Immunogenicity Analysis Set will be based on the immunogenicity population which includes all treated patients who received at least 1 dose of study drug and had at least one ADA/Nab sample collected and analyzed for immunogenicity.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

A total of up to approximately 102 patients will be enrolled in the study: up to 22 patients in the run-in phase (dose level 2) and 80 patients (40 patients per dose level) in the randomized phase if acceptable efficacy is observed at dose level 2 in the run-in phase.

5.1.1.1. Run-in Phase

The primary objective of the run-in phase is to allow for the potential to stop the study early if insufficient efficacy (see Section 5.1.2) is observed at the lower dose level (1.2 mg/m^2/cycle [dose level 2]).

The run-in phase is designed to test:

- The null hypothesis H_{10}: CR/CRi rate ≤31.2% versus the alternative hypothesis H_{1a}: CR/CRi rate ≥57%;
- The null hypothesis H_{20}: MRD-negativity rate ≤20% versus the alternative hypothesis H_{2a}: MRD-negativity rate ≥40%.

In Phase 3 Study B1931022, patients that had ≥1 factor for a higher risk of VOD post-HSCT had an observed CR/CRi rate of 70.5% in the inotuzumab ozogamicin arm and 31.2% in the control arm.

In the current study, based on the exposure-response modeling from Study B1931022 and depending on the actual prognostic factors of the enrolled patients, the true response rates for patients that have ≥1 factor for a higher risk of VOD post-HSCT might be as low as 57%. Therefore, in the current study, the null hypothesis H_{10} has been selected to be 31.2% and the alternative hypothesis H_{1a} has been selected to be 57%.

In the current study, the MRD-negativity rate among patients who achieve CR/CRi is expected to be ⩾70%. Given an expected CR/CRi rate of 57% and an expected MRD-negativity rate of ⩾ 70% among CR/CRi responders, the MRD-negativity rate among all the patients enrolled in the

run-in phase is expected to be 40%. Therefore, an MRD-negativity rate of 40% has been selected as the alternative hypothesis H_{2a}.

A total of up to 22 patients will be enrolled in the run-in phase. This sample size will provide 80% power to reject the null hypothesis with a significance level of 0.10 if the true CR/CRi rate is 57%. This sample size will also provide 80% power to reject the null hypothesis of an MRD-negativity rate of $\leqslant$20% when the alternative hypothesis for the true MRD-negativity rate is $\geqslant$ 40% with a significance level of 0.10.

5.1.1.2. Randomized Phase

The primary purpose of the randomized phase is to evaluate the safety and efficacy of two inotuzumab ozogamicin dose levels through descriptive analyses. There is no hypothesis testing for either primary or secondary endpoints.

Assuming the study proceeds beyond the run-in phase to the randomized phase, approximately 80 patients will be randomized (1:1) to either 1.8 mg/m^2/cycle (dose level 1, Arm 1) or 1.2 mg/m^2/cycle (dose level 2, Arm 2). A sample size of 40 patients per dose level will provide the estimated VOD rates shown in Table 2 at each dose level with a maximum standard error (SE) of 0.08. The maximum SE estimated for other binary endpoints in each dose level (e.g., CR/CRi rate) will also be 0.08.

In addition, for dose level 2, data from patients included in the run-in phase (i.e., who were treated with 1.2 mg/m^2/cycle) will be combined with data from patients from Arm 2 of the randomized phase, leading to a sample size of approximately 62 patients (i.e., 22 patients enrolled in the run-in phase and 40 patients enrolled in Arm 2 in the randomized phase) to provide the above-mentioned estimated rates with a maximum SE of 0.06.

Table 2 shows the possible estimated VOD rates and CR/CRi rates with 95% confidence interval (CI) with a sample size of 40 patients and 62 patients, respectively.

Table 2. 95% CI for Different Estimated VOD Rates and CR/CRi Rates

VOD/Sample Size	VOD Rate % (95% CI)	Responders/Sample Size	CR/CRi rate % (95% CI)
40 patients			
4/40	10 (2.8-23.7)	16/40	40% (24.9-56.7)
6/40	15 (5.7-29.8)	20/40	50% (33.8-66.2)
8/40	20 (9.1-35.6)	24/40	60% (43.3-75.1)
10/40	25 (12.7-41.2)	28/40	70% (53.5-83.4)
12/40	30 (16.6-46.5)	32/40	80% (64.4-90.9)
62 patients			
6/62	10 (3.6-19.9)	25/62	40% (28.1-53.6)
9/62	15 (6.9-25.8)	31/62	50% (37.0-63.0)
13/62	21 (11.7-33.2)	37/62	60% (46.4-71.9)
16/62	26 (15.5-38.5)	44/62	71% (58.1-81.8)
19/62	31 (19.6-43.7)	50/62	81% (68.6-89.6)

Table 2. 95% CI for Different Estimated VOD Rates and CR/CRi Rates

VOD/Sample Size	VOD Rate % (95% CI)	Responders/Sample Size	CR/CRi rate % (95% CI)

Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; VOD=veno-occlusive disease.

5.1.2. Decision Rules

Overall, the study is designed have a run-in phase to assess for potential futility at the lower inotuzumab ozogamicin dose level (1.2 mg/m^2/cycle, dose level 2) and a follow-up randomized phase (descriptive analyses) in which patients will receive inotuzumab ozogamicin dose levels of 1.8 mg/m^2/cycle or 1.2 mg/m^2/cycle.

For the run-in phase, a Simon Two-Stage optimal design will be used to minimize the expected number of patients enrolled if the lower dose proves to have insufficient efficacy. Therefore, overall, the study is designed to have 2 interim analyses for futility.

The first interim analysis will be performed at the end of Stage 1 of the run-in phase, i.e. after 7 patients have been enrolled with a minimum of 3 months follow-up from randomization. Meanwhile, patient enrollment will continue between Stage 1 and Stage 2 until analyses for decision-making are completed. Once ≥3 (i.e., 42.9%) CR/CRi responders being documented, an additional 15 enrolled patients will be evaluated in the second interim analysis. If, at the first interim analysis, <3 CR/CRi responders are documented for the 7 patients enrolled in Stage 1, patient enrollment will be stopped for further evaluation (see Section 7 for the derivations).

If the decision is made to proceed after the first interim analysis, enrollment will continue, and the second interim analysis will be conducted.

The second interim analysis will be performed at the end of the run-in phase, i.e. after a total of 22 patients have been enrolled with a minimum of 3 months follow-up from randomization. Meanwhile, patient enrollment will continue into the randomized phase while analyses for decision-making are being completed. If there are ≥10 CR/CRi responders and ≥7 patients achieving MRD-negativity documented among the 22 patients in the run-in phase, the enrollment will further continue until randomized phase has completed. Subsequently, patients enrolled in the randomized phase will be evaluated in the final analysis. If, at the second interim analysis, <10 CR/CRi responders or <7 patients achieving MRD-negativity are documented for the 22 patients enrolled in the run-in phase, patient enrollment will be stopped for further evaluation (see Section 7 for the derivations). DoR and safety will also be analyzed at the end of the run-in phase.

If the decision is made to proceed after the second interim analysis, enrollment will continue, and the final analysis will be conducted as planned.

5.2. General Methods

All analyses will be based on descriptive statistics without hypothesis testing and with 95% CI provided for each of the estimate. No p-values will be provided. Additional analyses may be performed if deemed appropriate.

5.2.1. Pooling of Data by Center

In order to provide overall estimates of treatment effects, data will be pooled across centers (clinical sites). A variable for 'center' will not be included in statistical models or for subset analyses since it is anticipated that there will be a high number of participating centers with a small number of patients randomized/treated at each center.

5.2.2. Nominal Timepoints

For all algorithms and analyses, visit labels as specified on the clinical report form (CRF) will be used as the nominal timepoint (i.e. assessment will not be slotted).

5.2.3. Definition of Study Day

The study day for assessments occurring on or after the first dose of study treatment (e.g., adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event – start date of study treatment + 1.

The start date of study treatment is the date of Cycle 1 Day 1.

The study day for assessments occurring prior to the first dose of study treatment (e.g., baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event – start date of study treatment.

The study day will be displayed in all relevant data listings.

5.2.4. Date of Last Contact

The date of last contact will be derived for patients not known to have died at the data cutoff date using the latest complete date (i.e., imputed dates will not be used in the derivation) among the following:

- All patient assessment dates (e.g., blood draws [laboratory, PK]), vital signs, physical exam, performance status, ECG, disease assessments);
- Start and stop dates of concomitant therapies including non-drug treatments or procedures;
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation including systemic therapy, radiation, and surgeries;

- AE start and end dates;
- Last date of contact collected by subsequent follow-up (do not use date of survival follow-up assessment unless status is 'alive');
- Study treatment start and end dates;
- Randomization date;
- Date of discontinuation (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed, or dates data were entered into the CRF will not be used. Assessment dates after the data cutoff date will not be applied to derive the last contact date.

5.2.5. ALL Disease Assessment Date

The ALL disease assessment date at each nominal timepoint will be utilized for respective analyses.

5.2.6. Unscheduled Assessments

Unless otherwise specified, unscheduled assessments will not be displayed in summary tables by nominal visit/timepoint. Unscheduled assessments will be used when deriving baseline and worst case on-treatment for safety (except where noted for baseline ECGs). Additionally, unscheduled assessments will be used for efficacy analyses (e.g. defining date of progression/censoring, hematologic remission, date of last contact).

5.2.7. Standard Derivations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Percentages will be reported to 1 decimal place. Rounding will be performed to the closest integer/first decimal using the common mid-point between 2 consecutive values e.g., 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.8. Analyses of Continuous Endpoints

Continuous variables will be summarized using descriptive statistics i.e., mean, standard deviation, median, minimum, maximum and number of patients. The difference in mean values between two arms with CI calculated based on the t-distribution will be displayed.

5.2.9. Analyses of Categorical Endpoints

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category. In addition, appropriate Cis will be calculated using the normal approximation or the exact method (Collett D, 1991).

The difference in percentages between two arms with CI calculated using the normal approximation or the exact method (Collett D, 1991) will be displayed.

5.2.10. Analyses of Time to Event Endpoints

Time to event endpoints (i.e., DoR, OS, PFS and post-HSCT mortality) will be summarized using the Kaplan-Meier method and estimated time to event curves will be displayed graphically when appropriate. The median, quartiles, and probabilities of an event at a particular timepoint will be estimated using the Kaplan-Meier method. CIs for medians and quartiles will be calculated using the method described by Brookmeyer R and Crowley J (1982). CIs for the estimated probability of event at a particular timepoint will be generated using the log(-log) method with back transformation to a CI on the untransformed scale. Summaries of the number and percentages of patients with an event will also be provided in summary tables and figures.

5.2.11. Competing-Risks Analyses of Time to Event Endpoints

Time to event endpoints associated with competing events (i.e., post-HSCT relapse, non-relapse mortality and relapse-related mortality) will be summarized using competing-risks analyses and estimated cumulative incidence plot will be displayed graphically when appropriate. Cumulative incidence rates of an event at a particular timepoint will be estimated with the CI calculated based on the cumulative incidence function using the method described by Kalbfleisch RL and Prentice JD (1980). Summaries of the number and percentages of patients with an event and patients with a competing event will also be provided in summary tables and figures, respectively.

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Any imputations will occur at the analysis dataset level. In all patient data listings imputed values will be presented and flagged as imputed.

5.3.1. Missing Dates

For time to event endpoints, missing date will be handled by censoring as described in their definitions in Section 3.2.

For purposes of data listings, dates will reflect only the information provided by the Investigator on the CRF.

If start dates for AEs or concomitant medications are completely missing, a worst case approach will be taken whereby the events will be considered treatment emergent and the medications will be considered concomitant. If only partial information are available (e.g. only a month and year or only a year) and the partial information provide sufficient information to indicate the dates are prior to the start of study treatment (e.g. month/year less than month/year of first dose), then these will be considered to have started prior to treatment; otherwise a similar worst case approach will apply and these will be considered to have started after treatment.

No imputation will be done for first dose date. The date of last dose of study treatment, if unknown or partially unknown, will be imputed as follows:

- If the last date of study treatment is completely missing and there is no End of Treatment (EOT) visit and no death date, the patient should be considered to be ongoing and use the data cutoff date for the analysis as the last dosing date; or

- If the last date of study treatment is completely or partially missing and there is EITHER an EOT visit OR a death date available (on or prior to the data cutoff date), then impute this date as the last dose date:

    - = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date);

    - = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date); or

    - = min (EOT date, death date), for all other cases.

Missing or partial death dates will be imputed based on the last contact date:

- If the entire date is missing it will be imputed as the day after the date of last contact (see derivation of date of last contact in Section 5.2.3); or

- If the day or month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:

    - Missing day: 1st day of the month and year of death; or

    - Missing day and month: January 1st of the year of death.

Incomplete dates for new anti-cancer therapy will be imputed as follows and will be used to determine censoring dates for efficacy analyses:

- The end date of new anti-cancer therapy will be included in the imputation for start date of new anti-cancer therapy if the end data of new anti-cancer therapy is:

    - Completely missing then it will be ignored in the imputations below;

  - Partially missing with only year available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy; or

  - Partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy.

- For patients who have not discontinued study treatment at the time of the data cutoff date, the last dose of study treatment will be set to the data cutoff date in the imputations below.

- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy will be:

  - = 31DECYYYY, if only Year is available and Year < Year of min [max (progression/relapse date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy];

  - = Last day of the month, if both Year and Month are available and

    - Year = Year of min [max (progression/relapse date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    - Month < Month of min [max (progression/relapse date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

  - = min [max (progression/relapse date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], for all other cases.

The following imputation rules apply if the event is unique for a patient or it is the first of a series of similar events; otherwise, the AE Onset Date will not be imputed:

- If the AE Collection Date is not missing, is less than the Date of First Exposure to Treatment, and is less than the AE Stop Date, then AE Onset Date will be set to the Date of AE Collection;

- If the Previous Visit Date is greater than the Date of First Exposure to Treatment and less than the AE Stop Date, the AE Start Date will be set to the previous visit date;

- If the Date of First Exposure to Treatment is greater than the previous visit date and less than the AE Stop Date, the AE Onset Date will be set to the Date of First Exposure to Treatment;

- Otherwise the AE Onset date will be set to the AE Stop date.

Ongoing events will have the AE Stop Date set to 1 of the following values:

- Date of Death, if the patient died and a date of death exists;

- Maximum of Patient Withdraw Date, AE Onset Date, or AE Collection Date if the patient withdrew from the study and a date of withdraw exists;

- Maximum of AE Onset Date, Subject Summary Collection Date, or AE Collection Date if a date of subject summary collection exists but a date of withdraw does not exist;

- Maximum of Last Treatment Date or AE Onset Date if a date of subject summary collection does not exist.

Imputation will only occur if event is unique for the patient, or it is the last of a series of similar events; otherwise the Stop Date will not be imputed. AEs are deemed similar if they have the same verbatim term.

Resolved events will have the AE Stop Date set to the maximum of the AE collection date and the AE Onset date.

Imputation methods for other partial dates will be as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date;

- If both the day and month are missing, the first day of the year will be used;

- For stop dates, the last day of the month, or last day of the year will be used if the day or day and month are missing, respectively;

- If the date is completely missing, no imputation will be performed.

5.3.2. Missing Toxicity Grade of Adverse Events

Prior to Study Treatment: If no toxicity grade is available or the grade is reported as unknown for an adverse event prior to the first study treatment, then Grade 1 will be assumed for purposes of defining a baseline grade for assessing if further occurrences are treatment emergent. However, if the patient experiences multiple episodes of the same AE prior to study treatment, then the maximum toxicity grade observed prior to study treatment will be utilized in assessing if further occurrences are treatment emergent.

During Study Treatment: If no toxicity grade is available or the grade is reported as unknown for an adverse event during the study treatment, then the event will be considered treatment emergent unless a baseline event was reported as Grade 4.

In summaries which present maximum toxicity grade, the maximum of non-missing grades will be displayed. Missing grade will only be displayed for cases where a patient reported only 1 event and the grade is missing.

5.3.3. Missing ECG Data

For QTc analyses, no values will be imputed for missing data. If one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a timepoint for an ECG parameter, no values will be imputed for this timepoint. If the triplicate needs to be repeated because of an artifact, then the repeated triplicate will be reported on an unscheduled CRF page. Based on a review of the data these unscheduled assessments may be used in place of the assessments at the nominal time. Data review and consultation with the study team is required to flag these cases.

6. ANALYSES AND SUMMARIES

This study is designed to have 2 phases, the run-in phase and the randomized phase. All efficacy and safety analyses will be done by dose level and by study phase (i.e., the run-in phase, Arm 1 of the randomization phase (Dose Level 1), and Arm 2 of the randomization phase (Dose Level 2) will be summarized separately). In addition, patients enrolled in the run-in phase will be combined with Arm 2 of the randomization phase for the summary of Dose Level 2.

6.1. Primary Endpoints

6.1.1. CR/CRi Rate

6.1.1.1. Primary Analysis

The primary analysis of CR/CRi rate will be based on the ITT population.

The frequency (number and percentage) of patients with CR, and CRi, and not met CR or CRi will be tabulated for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined). Not met CR or CRi includes three categories,

1. Not post baseline samples: define as patients did not have any post baseline aspirate collected (non-response confirmed by peripheral blasts only),

2. Patients with ≥5% blasts,

3. Patients with <5% blasts: define as patients with less than 5% bone marrow blasts but did not meet criteria for CR or CRi due to the presence of peripheral blasts, EMD, or missing assessments.

CR/CRi rate will be calculated along with the two-sided 95% CI using the normal approximation or the exact method (Collett D, 1991) for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined). The unstratified and stratified difference in response rates between two dose levels of the randomized phase (Dose Level 1 – Dose Level 2) along with the 2-sided 95% CI for the difference will be provided as a descriptive statistic.

In addition, time to remission (in months), defined as time from the date of first dose of study treatment to the date of first remission (CR/CRi), will be summarized using descriptive statistics for patients achieving CR/CRi for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined). Length of duration (months) will be calculated as [date of first remission−date of first dose+1]/30.4375.

6.1.1.2. Sensitivity Analysis

A sensitivity analysis will be performed based on the PP population to explore the robustness of the primary analysis results. CCI [redacted] The sensitivity analysis will be a repeat of the primary analysis described in Section 6.1.1.1.

6.1.2. VOD Rate

The primary analysis of VOD rate will be based on the Safety population for the following periods:

- Overall study period,
- On-treatment or in follow-up without HSCT period, and
- Post-HSCT period.

VOD rate will be calculated along with the 2-sided 95% CI using the normal approximation or the exact method (Collett D, 1991) for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined). The difference (unstratified) in incidence between two dose levels of overall patients of the randomized phase (Dose Level 1 – Dose Level 2) along with the two-sided 95% CI for the difference will be provided as a descriptive statistic.

In addition, similar analyses will be conducted for VOD rate for the two subsets:

1. HSCT safety population,
2. Patients who proceed to HSCT directly after inotuzumab ozogamicin treatment without an intervening induction therapy in the HSCT safety population.

Time to VOD post-HSCT (from date of first HSCT after inotuzumab ozogamicin treatment) will be summarized using descriptive statistics for patients having experienced VOD post-HSCT in the above two subsets.

Subset Analyses by VOD Risk Factors

For Dose Level 1 (randomized) and Dose Level 2 (randomized), the VOD rates by dose levels and rate differences (Dose Level 1 – Dose level 2) along with the 2-sided 95% CI will be provided for

1. Safety population,

2. HSCT safety population, and

3. Patients who proceed to HSCT directly after inotuzumab ozogamicin treatment without an intervening induction therapy in the HSCT safety population,

respectively, in subsets per VOD risk factors as listed below:

- Age <55 years vs ≥55 years,
- Salvage 1 vs ≥2,
- Prior HSCT (yes vs no),
- Prior history of liver disease/hepatitis (yes vs no).

Analyses of Association of Baseline Characteristics and Patient Characteristics at the Time of HSCT with Occurrence of VOD Post-HSCT

Both univariate and multivariate logistic regression analyses will be performed to evaluate the potential influences of baseline characteristics and patient characteristics at the time of HSCT with occurrence on VOD occurrence post-HSCT for HSCT safety population. The covariates for baseline characteristics of interest are:

- Age (<55 years, ≥55 years),
- Salvage status (1, ≥2),
- Prior HSCT (yes, no),
- Prior history of liver disease/hepatitis (yes, no),
- Number of treatment cycles received (continuous).

The covariates for patient characteristics at the time of HSCT of interest are:

- Use of HSCT conditioning regimens containing alkylating agents (single, dual),
- Last bilirubin prior to conditioning therapy (<ULN, ≥ULN),
- Last bilirubin prior to follow-up HSCT (<ULN, ≥ULN).

Covariates for other baseline characteristics and patient characteristics at the time of HSCT, if interested, may be included in the univariate and multivariate logistic regression analyses.

For each univariate analysis, number of patients, number of patients in each subset if the covariate is binary, estimated odds ratio along with the 95% CI and two-sided p-values will be provided for Dose Level 1 (randomized), Dose Level 2 (runin & randomized) and all patients

combined from 2 dose levels (in this case, an additional covariate of dose level will be included in the analysis).

For each multivariate analysis, a stepwise selection procedure will serve to identify these covariates of potential prognostic values. Covariates are entered into and removed from the model in such a way that each forward selection step can be followed by one or more backward elimination steps. The stepwise selection process terminates if no further covariate can be added to the model or if the covariate just entered into the model is the only covariate removed in the subsequent backward elimination. The level of significance for an explanatory variable to enter the model is set to 0.3 and the significance level for removing it is set to 0.1. For Dose Level 1 (randomized) and Dose Level 2 (runin & randomized), those covariates selected by the stepwise procedure will be reported using number of patients in each subset if the covariate is binary, and estimated odds ratio along with the 95% CI and two-sided p-values.

6.2. Secondary Endpoints

The primary analyses of the follow secondary endpoints will be based on the ITT population. In addition, the sensitivity analyses will be performed to explore the robustness of the primary analyses results. CCI The sensitivity analyses will repeat the primary analyses on the PP population.

6.2.1. MRD-Negativity

MRD-negativity per central lab (qualitative result) will be summarized using frequency (counts and percentages) with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined) in patients achieving CR/CRi. The difference (unstratified) in percentages between two dose levels of the randomized phase (Dose Level 1 – Dose Level 2) along with the 2-sided 95% CI for the difference will be provided as a descriptive statistic.

Patients without any post-baseline central MRD results up to end of treatment will be summarized using frequency (counts and percentages) in patients achieving CR/CRi for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Minimum MRD percentage per central lab (quantitative result) from post-baseline to 7 days post-EOT will be summarized using descriptive statistics in patients achieving CR/CRi for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Same summary will be performed in patients achieving CR and CRi separately.

6.2.2. DoR

Number and percentage of patients with a remission (CR/CRi), and remission status (in patients with a remission) will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose

Level 2 (randomized), and Dose Level 2 (run-in & randomized combined). Remission statuses include,

- Patients with a remission (CR/CRi) and subsequently progressed or died due to any cause while on study, and
- Patients with a remission (CR/CRi) who had not progressed or died due to any cause while on study.

Median Q1, and Q3 of DoR will be estimated using the Kaplan-Meier method and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The Kaplan-Meier curves for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined) will be displayed graphically.

Additional sensitivity analyses for DoR will be performed in both ITT population and PP population where patients without a DoR event at time of analysis will be censored at the date of last valid disease assessment (including follow-up disease assessment) or the date of last laboratory test showing no blasts, whichever occurs last.

6.2.3. PFS

Number and percentage of patients with events (including type of event) and patients censored (including reason for censoring) will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Median, Q1 and Q3 of PFS will be estimated using the Kaplan-Meier method and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

PFS rates will be computed at months 3, 6, 9, 12 and 15 using the Kaplan-Meier method, and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The Kaplan-Meier curves will be displayed graphically for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Additional sensitivity analyses for PFS will be performed in both ITT population and PP population where patients experiencing events of starting new induction therapy/post-therapy HSCT without achieving CR/CRi will be censored at the date of starting new induction therapy/post-therapy HSCT.

6.2.4. OS

Number and percentage of patients with events and patients censored (including reason for censoring) will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Median, Q1 and Q3 of OS will be estimated using the Kaplan-Meier method and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Survival probabilities will be computed at months 6, 12 and 24 using the Kaplan-Meier method, and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The Kaplan-Meier curves will be displayed graphically for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

6.2.5. Rate of HSCT

Patients who undergo HSCT and patients who undergo HSCT directly without new induction therapy will be summarized using frequency counts and percentages in the ITT population for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Type of transplant (allogeneic and autologous) and type of conditioning therapy (myeloablative and reduced intensity) will be summarized using frequency counts and percentages in patients who undergo HSCT for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

No sensitivity analysis will be performed in the PP population.

6.2.6. Post-HSCT Relapse

Number and percentage of patients who undergo HSCT and patients with post-HSCT relapse adjusted for competing risk will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence rate of post-HSCT relapse will be computed at Day 180 and other clinical meaningful timepoints using a method adjusting competing-risks and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence plot will be displayed for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

6.2.7. Post-HSCT Mortality

Number and percentage of patients who undergo HSCT and patients with post-HSCT mortality will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence rate of post-HSCT mortality will be computed at Day 180 and other clinical meaningful timepoints using the Kaplan-Meier method and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence plot (i.e., 1 minus the Kaplan-Meier curve) will be displayed for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

6.2.8. Non-Relapse Mortality

Number and percentage of patients who undergo HSCT and patients with post-HSCT non-relapse mortality adjusted for competing risk will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence rate of non-relapse mortality will be computed at Day 180 and other clinical meaningful timepoints using a method adjusting competing-risks and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence plot will be displayed for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

6.2.9. Relapse-Related Mortality

Number and percentage of patients who undergo HSCT and patients with post-HSCT relapse-related mortality adjusted for competing risk will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence rate of relapse-related mortality will be computed at Day 180 and other clinical meaningful timepoints using a method adjusting competing-risks and will be reported with 2-sided 95% CI for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

The cumulative incidence plot will be displayed for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

6.2.10. Immune Response to Inotuzumab

In patients who test positive for anti-inotuzumab ozogamicin antibodies and neutralizing antibodies, the effect of anti-inotuzumab ozogamicin antibodies and neutralizing antibodies on inotuzumab ozogamicin safety, efficacy, and clearance will be examined and descriptively summarized.

6.3. PK Exposure-Response for Efficacy and Safety Endpoints

Analysis of bioanalytical measures for inotuzumab ozogamicin (and unconjugated calicheamicin, if possible) will be performed using a nonlinear mixed effects model and a previously defined base model structure of drug disposition which accounts for the nonlinear drug disposition which has been observed following inotuzumab ozogamicin administration.

Using a Bayesian post-hoc approach, individual patient PK parameters based on the final population PK model and individual patient contributions to the model may be generated. These parameters would serve as input for PK predictions and for exposure response analyses with respect to key safety (e.g., VOD, ALT, AST, bilirubin) and efficacy (CR/CRi, MRD-negativity) endpoints.

The results of population PK analysis and exposure response analyses with respect to safety and efficacy endpoints of interest will be provided separately as part of a population modeling analysis report. However, the exposure response analyses described previously will be only performed if the study moves into its randomized phase.

The listings and descriptive statistics for the observed concentrations of the inotuzumab ozogamicin and unconjugated calicheamicin by dose level, cycle, day, and nominal time will be provided as part of the CSR.

6.4. Subset Analyses

Subgroup analysis for safety will be conducted for all patients in the HSCT safety population as well as only patients who undergo HSCT directly without new induction therapy.

6.5. Baseline and Other Summaries

6.5.1. Baseline Summaries

Baseline demographic and baseline variables will be summarized for ITT population.

6.5.1.1. Demographic and Baseline Characteristics

1. Demographic characteristics will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall. Age categories to display are ≥18 to <45 years, ≥45 to 65 years, and ≥65 years.

2. Enrollment geographical region and country will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall.

3. Baseline physical measurement (including height, body weight, BMI, and BSA) will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall, according to Pfizer data standards.

4. Baseline VOD risk factors and ECOG performance status will be summarized using number and percentage for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall.

6.5.1.2. Medical History

Significant medical history and medical history for hepatic medical conditions will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall according to Pfizer data standards.

6.5.1.3. Disease Characteristics

1. Duration since onset (months) will be summarized using descriptive statistics for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall.

2. Baseline local/central CD22 expression (%) will be summarized using descriptive statistics for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall.

3. Baseline cytogenetics listed below will be summarized using number and percentage for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall.

    - Total number of metaphases analyzed in categories of ≥20, ≥10 to <20, <10, and missing/unknow,

    - Karyotype per local lab (normal, abnormal, not evaluable, missing), and

    - Chromosomal abnormality for Ph+, t(4:11), and others.

6.5.1.4. Prior Anti-Cancer Therapies

The following categories will be summarized using number and percentage for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall:

- Salvage status (derived): 1, 2, 3, 4, 5, etc (derived based on the number of relapses and treatment failures of prior induction therapies)

- Prior induction therapy for primary diagnosis: yes, no,

    - Number of regimens: 1, 2, 3, etc.

- Prior radiation therapy for primary diagnosis: yes, no,

- Responses to most recent prior induction regimen, to first induction regimen, to prior induction regimen 2: CR, PR, treatment failure, N/A (adjuvant only),

- Duration of first remission: <12 months and ≥12 months.

6.5.2. Study Conduct and Patient Disposition

6.5.2.1. Patient Disposition

1. The number of randomized participants in the below analysis sets/populations (defined in Section 4) will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall according to Pfizer data standards,

   - ITT population,

   - PP population,

   - Safety population,

   - Post-HSCT safety population,

   - PK population,

   - Immunogenicity population.

2. Patient disposition at screening, end of treatment, and disease/survival follow-up will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall, according to Pfizer data standards.

3. Medication errors will be listed according to Pfizer data standards.

6.5.2.2. Protocol Deviations

Protocol deviations will be compiled prior to database closure and will be summarized by categories (number and percentage) for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall, according to Pfizer data standards. Categories will be assigned by the study clinician.

6.5.3. Study Treatment Exposure

Exposure will be summarized for the safety population.

6.5.3.1. Exposure to Inotuzumab Ozogamicin

1. Number of cycles started and duration of treatment (weeks) will be summarized using descriptive statistics for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized). Number and percentage will be provided for

   - Duration categories (weeks): 0 -<4, 4 -<8, 8 -<12, 12 -<16, 16 -<20, 20 -<24, and >24,

- Cycle number categories: any cycle, 1 cycle, 2 cycles, 3 cycles, 4, cycles, ≥5 cycles.

2. The actual overall dose (mg/m^2), actual dose intensity (mg/m^2/cycle) and the relative dose intensity (%) of inotuzumab ozogamicin will be summarized using descriptive statistics for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized).

6.5.3.2. Dose Reductions and Delays

Number and percentages will be provided for patients with dose reduction and dose delay for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized).

6.5.4. Concomitant Medications

Concomitant drug treatments received by patients during the study will be summarized by Anatomical Therapeutic Chemical Classification level 2 (ATC2) and preferred term (PT) for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall, according to Pfizer data standards.

6.5.5. Follow-up Systemic Therapies

The number and percentage of patients with follow-up systemic therapies (overall and induction therapy only), and number of regimens (1, 2 , ≥3) , will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized).

Follow-up systemic therapy (overall and induction therapy only) medications will be coded using the WHO Drug coding dictionary and will be tabulated by ACT2 and PT in descending order of frequency for Dose Level 2 (run-in), Dose Level 1 (randomized), Dose Level 2 (randomized), and overall according to Pfizer data standards.

Follow-up HSCT will be summarized as described in Section 6.2.4.

6.6. Safety Summaries and Analyses

Safety endpoints will be analyzed by dose level based on the safety population for overall safety, the HSCT safety population and subpopulation only including patients who undergo HSCT directly without new induction therapy for safety post-HSCT. No adjustment for multiple comparisons will be made when analyzing safety endpoints.

6.6.1. Adverse Events

AEs will be coded using the MedDRA dictionary. Toxicity will be graded according to the NCI CTCAE v3.0. All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in Section 3.4. AEs not considered treatment emergent will be flagged in data listings.

Overview of TEAEs, all causality and treatment-related, will be provided using number and percentage for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined) according to Pfizer data standards.

Incidence of TEAEs, all causality and treatment-related, during the on-treatment period will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined) by

- SOC, PT and maximum CTCAE grade,
- PT and maximum CTCAE grade of any grade in ≥10% patients by the categories of all grades and grade ≥3 (in decreasing order based on the observed frequencies of all grades in Dose Level 1).

Incidence of TEAEs, all causality and treatment-related, leading to permanent discontinuation/dose reduction/ dose interruption of study drug and death will be summarized by PT for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Incidence of SAEs (all causality and treatment-related) and post-HSCT SAEs will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined), by

- SOC and PT,
- PT in ≥10% patients (in decreasing order based on the observed frequencies in Dose Level 1).

Each patient will be counted only once within each SOC and PT.

6.6.1.1. Adverse Events of Special Interest

AEoSI (see Section 3.4.1.2) will be summarized to present the incidence of patients with all-causality events for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

6.6.2. Deaths

The number and percentage of patients in the safety population who died and who died within 63 days after last dose of study treatment as well as the primary reason for death, will be tabulated.

The date and cause of death will be provided in an individual patient data listing together with selected dosing information (study treatment received, date of first/last administration, dose).

6.6.3. Laboratory Data

Laboratory results will be converted to units using the International System of Units (Système International d'unités [SI]) which will be used for applying toxicity grades and for all summaries.

Quantitative data will be summarized by dose level using simple descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change

from baseline for each nominal visit over time (i.e., unscheduled assessments will be excluded). Summary will only include data from local laboratories. The total number of patients for change from baseline will include all patients who have both a baseline and a value at the nominal visit.

Results collected as strict inequalities (e.g., >10, <10) will be converted to numeric values subtracting a factor of 0.001. Expressions of the form "≥" or "≤" will be converted to the end point. These numeric values will be evaluated for clinically significant abnormalities but will not be included in calculations of summary statistics.

Laboratory abnormalities will be summarized and programmatically classified according to NCI CTCAE v3.0. Additional laboratory results that are not part of NCI CTCAE will be presented according to the following categories: below normal limit, within normal limits, and above normal limits. All summaries will be based on local laboratory data.

Change from baseline in hematology and chemistry parameters during on-treatment period will be summarized using shift tables for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined) according to Pfizer data standards,

- By maximum CTCAE grade for all grades at baseline to all grades post-baseline,
- By maximum CTCAE grade for Grade ≤2 at baseline to Grade 3 or 4 post-baseline, and
- By worst on-treatment assessment for no CTCAE criteria.

Parameters of liver function test during the on-treatment period will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined) according to Pfizer data standards.

A plot showing an evaluation of drug-induced serious hepatotoxicity (eDISH) for liver function tests, as defined in Study B1931030, Protocol, Section 8.4, will be presented according to Pfizer data standards.

6.6.4. Vital Signs and Physical Examination

No specific data summaries will be provided for vital signs and physical examinations. Any findings considered by the investigator to be 'clinically significant' will be recorded as adverse events and will be included in the adverse event summaries.

6.6.5. Electrocardiograms

Triplicate ECGs were required at each assessment. ECG summaries will include all ECG assessments during on-treatment period.

Absolute values and changes from baseline in ECG parameters during on-treatment period will be summarized for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined) by the categories,

- HR interval:
  - ≤50 bpm and decrease from baseline ≥20 bpm,
  - ≥220 bpm and increase from baseline ≥20 bpm.
- QTc interval:
  - Increase from baseline >30 msec,
  - Increase from baseline >60 msec,
  - >450 to 480 msec,
  - >480 to 500 msec,
  - >500 msec.
- QTcB interval: Same as QTc interval.
- QTcF interval: Same as QTc interval.
- QRS complex:
  - Increase from baseline >30 msec,
  - Increase from baseline >60 msec,
  - ≥120 msec.
- PR interval: ≥220 msec and increase from baseline ≥20 msec.

Values of ECG parameters in the above categories will be listed according to Pfizer data standards.

6.6.6. Other Safety Analysis

Number and percentage of patients with hospitalization from first dose of study treatment until the end of Cycle 1 and until the EOT will be provided for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

Hospitalization duration from first dose of study treatment until the end of Cycle 1 and until the EOT will be summarized using descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) for Dose Level 2 (run-in), Dose Level 1 (randomized), and Dose Level 2 (randomized), and Dose Level 2 (run-in & randomized combined).

7. INTERIM ANALYSES

This study is designed to have two interim analyses to allow the potential for the study to be stopped early due to insufficient efficacy at the lower dose level (1.2 mg/m^2/, dose level 2).

The first interim analysis will be performed at the end of Stage 1 of the run-in phase, i.e. after 7 patients have been enrolled with a minimum of 3 months follow-up from randomization. Meanwhile, patient enrollment will continue between Stage 1 and Stage 2 until analyses for decision-making are completed. Once ≥3 CR/CRi responders are documented, an additional 15 enrolled patients will be evaluated in the second interim analysis. If, at the first interim analysis, <3 CR/CRi responders are documented for the 7 patients enrolled in Stage 1, patient enrollment will be stopped for further evaluation.

As the run-in phase is a Simon Two-Stage optimal design (with 22 patients being enrolled and the hypothesis test H_{10}: CR/CRi rate ≤31.2% versus H_{1a}: CR/CRi rate ≥57%), the number of enrolled patients and the decision rule for Stage 1 (i.e., the first interim analysis) are set at 7 and ≥3/7, respectively, so that the expected sample size of the run-in phase will be minimized if dose level 2 has insufficient efficacy subject to constraints that the hypothesis test H_{10} versus H_{1a} for the run-in phase will have 80% power to reject H_{10} with significance level of 0.10 if the true CR/CRi rate is 57%.

If the decision is made to proceed after the first interim analysis, enrollment will continue and the second interim analysis will be conducted.

The second interim analysis will be performed at the end of the run-in phase, i.e. after a total of 22 patients have been enrolled with a minimum of 3 months follow-up from randomization. Meanwhile, patient enrollment will continue into the randomized phase while the analyses for decision-making are being completed. If there are ≥10 CR/CRi responders and ≥7 patients achieving MRD-negativity documented among the 22 patients in the run-in phase, patient enrollment will further continue until randomized phase has completed. Subsequently, patients in the randomized phase will be evaluated in the final analysis. If, at the second interim analysis, <10 CR/CRi responders or <7 patients achieving MRD-negativity are documented for the 22 patients enrolled in the run-in phase, patient enrollment will be stopped for further evaluation.

Based on H_{1a} (i.e., CR/CRi rate ≥57%), the decision rule per CR/CRi is set at ≥10/22 for the second interim analysis, so that there will be less than 10% chance of observing <10 responders out of 22 patients if the true response rate is at least 57% using the exact binomial distribution.

As the MRD-negativity rate among CR/CRi responders is expected to be ≥70% in the current study, the number of patients achieving MRD-negativity among the 22 enrolled patients in the run-in phase is expected to be ≥7 if there are ≥10 CR/CRi responders documented in those patients. Therefore, the decision rule per MRD-negativity is set at ≥7 patients achieving MRD-negativity in the second interim analysis. In addition, there will be 84% probability to observe a minimum of 7 patients achieving MRD-negativity if the true MRD-negativity rate is at least 40% (per H_{2a}).

DoR and safety data will also be analyzed at the end of the run-in phase.

8. REFERENCES

Brookmeyer R and Crowley J. A Confidence Interval for the Median Survival Time. Biometrics. 1982:38: 29–41.

Collett D. Modelling Binary Data, London: Chapman & Hall, 1991.

Kalbfleisch RL and Prentice JD. The Statistical Analysis of Failure Time Data, New York: Willey, 1980.

9. APPENDICES

Appendix 1. Definitions of Adverse Events of Special Interest

IMPORTANT IDENTIFIED RISKS

- **Grade ≥3 hepatotoxicity and/or serious hepatotoxicity, including VOD/SOS**

  GRADE ≥3 HEPATOTOXICITY AND/OR SERIOUS HEPATOTOXICITY, INCLUDING VOD/SOS AEs will be defined as:

  - Grade ≥3 AEs and/or SAEs retrieved by applying the following MedDRA SMQs : Cholestasis and jaundice of hepatic origin (SMQs narrow); Hepatic failure, fibrosis, cirrhosis, and other liver damage related conditions (SMQs narrow); Hepatitis, non-infections (SMQs narrow); Liver related investigations signs and symptoms (SMQs narrow and broad)

  - Grade ≥3 AEs and/or SAEs encoded to the following MedDRA PTs: Hepatic vein occlusion, Hepatic vein thrombosis, Portal vein thrombosis, Budd-Chiari Syndrome, Chronic graft-versus-host disease in liver, and Acute graft-versus-host disease in liver

  - All AEs encoded to the following MedDRA PTs: Venoocclusive liver disease and Venoocclusive disease

- **Myelosuppression/cytopenia**

  MYELOSUPPRESSION/CYTOPENIA AEs will be defined as:

  - Any reported PTs retrieved by applying the following MedDRA SMQs: Haematopoietic thrombocytopenia (SMQ narrow and broad), Haematopoietic leukopenia (SMQ narrow), Haematopoietic erythropenia (SMQ narrow and broad), and Haematopoietic cytopenias affecting more than one type of blood cell (SMQ narrow)

  INFECTION AEs (not considered a separate risk, but considered to be complications of myelosuppression/cytopenia) will be defined as:

  - Any reported PTs retrieved by applying the MedDRA SOC: Infections and Infestations

  HAEMORRHAGE AEs (not considered a separate risk, but considered to be complications of myelosuppression/cytopenia) will be defined as:

  - Any reported PTs retrieved by applying the MedDRA SMQ: Haemorrhage terms (excluding laboratory terms) (SMQ narrow)

IMPORTANT POTENTIAL RISKS

- **Interstitial lung disease (ILD)**

INTERSTITIAL LUNG DISEASE AEs will be defined as

- Any reported PTs retrieved by applying the MedDRA SMQ: Interstitial lung disease (SMQ narrow)
- All AEs encoded to the following MedDRA PT: Graft versus host disease in lung

- **Inflammatory gastrointestinal events**

  INFLAMMATORY GASTROINTESTINAL EVENT AEs will be defined as

  - Any reported PTs retrieved by applying the MedDRA Version SMQ Gastrointestinal nonspecific inflammation (SMQ narrow),
  - All AEs retrieved by applying the MedDRA higher level term (HLT) Colitis (excluding infective) (all paths) and Stomatitis and ulceration (all paths)
  - All AEs encoded to the following MedDRA PTs: Oral pain, Oropharyngeal pain, and Mucosal inflammation

- **Pancreatitis**

  PANCREATITIS AEs will be defined as

  - Any reported PTs retrieved by applying the MedDRA Version SMQ: Acute pancreatitis (SMQ narrow)
  - All AEs encoded to the following MedDRA PTs: Amylase abnormal, Amylase creatinine clearance ratio abnormal, Amylase increased, Lipase abnormal, Lipase increased, Lipase urine increased, Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, and Pancreatic enzymes increased

- **Second primary malignancy**

  SECONDARY PRIMARY MALIGNANCY AEs will be defined as:

  - Any reported PTs retrieved by applying the MedDRA SOC: Neoplasms benign, malignant and unspecified (including cysts and polyps).
  - Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding)

  REPRODUCTIVE AND DEVELOPMENT TOXICITY AEs will be defined as

  - Any reported PTs retrieved by applying the following MedDRA SMQs: Termination of pregnancy and risk of abortion (SMQ narrow), Fertility disorders (SMQ narrow and

broad), Foetal disorders (SMQ narrow and broad), Neonatal disorders (SMQ narrow and broad), Congenital, familial, and genetic disorders (SMQ narrow)

- All AEs encoded to the following MedDRA PTs: Pregnancy of partner, Exposure via father, Foetal exposure during pregnancy, and Maternal exposure during pregnancy

- **Nephrotoxicity**

  NEPHROTOXICITY AEs will be defined as:

  - Any reported PTs retrieved by applying the following MedDRA SMQ: Acute renal failure (SMQ narrow and broad)

- **Neurotoxicity**

  NEUROTOXICITY AEs will be defined as

  - Any reported PTs retrieved by applying the following MedDRA SMQs: Demyelination (SMQ narrow and broad) and Peripheral neuropathy (SMQ narrow and broad) and by searching for the following specific PTs under the higher level term: Cranial nerve disorders NEC (all paths)

Appendix 2. Analyses to Assess the Impact of COVID-19 Pandemic

The study enrollment started before the COVID-19 pandemic period and the study is ongoing during the pandemic period. The following data summaries and analyses may be performed to assess the impact of COVID-19 on the trial population and study data. Additional analyses may be added in a SAP amendment if they are considered necessary to evaluate the outcome of the trial. Details of these summaries and analyses are included in the respective sections.

- A listing of all participants affected by COVID-19 related study disruption.
- A listing of protocol deviations related to COVID-19.
- COVID-19 related AEs and deaths.
- Summary of missing ALL disease assessments due to COVID-19.

If additional analyses are needed to assess the impact of COVID-19 on the trial population and the study data, an anchor date will be used as a start date for COVID-19 pandemic related periods based on Pfizer guidance and standard operating procedure (SOP):

- For global pandemic reference date: Use the date the World Health Organization designated COVID-19 as a global pandemic - March 11, 2020.

- For China reference date: Use the date COVID-19 was identified as the causative agent of outbreak in Wuhan by the China Center for Disease Control and Prevention - January 9, 2020.

When producing data summaries intended to show the potential impacts of COVID-19 on the study, data will be presented as “before” and “during,” where the anchor date is included in the “during” group.

A different anchor date may be used for purposes of regulatory submission should the regulatory authority requests.