A PHASE 4, OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY OF INOTUZUMAB OZOGAMICIN IN CHINESE ADULT PATIENTS WITH RELAPSED OR REFRACTORY CD22-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Study Intervention Number:	PF-05208773
Study Intervention Name:	Inotuzumab Ozogamicin
United States (US) Investigational New Drug (IND) Number:	NA
European Clinical Trials Database (EudraCT) Number:	NA
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Pediatric Investigational Plan Number:	NA
Protocol Number:	B1931034
Phase:	Phase 4

Brief Title: A Phase 4 ,open-label, single-arm, multicenter study in Chinese patients with relapsed or refractory CD22-positive B-cell acute lymphoblastic leukemia (ALL)

Document History

Document	Version Date
Amendment 2	15 May 2023
Amendment 1	03 March 2022
Original protocol	02 December 2019

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 2 (15 May 2023)

Overall Rationale for the Amendment: Added the appendix for alternative measures during public emergencies to facilitate compliance with national COVID-19 measures in China.

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Title page	Change the US IND number to NA and added NCT number	US IND number is not applicable.	Non-substantial
Sections 1.1 and 4.1	Add the definition of salvage therapy.	Clarify the targeted patient population.	Non-substantial
Sections 1.1 and 4.1	Add the description to limit enrolling Ph+ ALL patients	Keep this PAC study's population and prior regimen consistent with B1931022 Phase 3 study, in which the Ph+ percentage also represents clinical practice.	Non-substantial
Sections 1.1, 4.1, 8.3.5, and 9.5.2	Add Hy's law cases for HEAC	HEAC will also review Hy's law cases.	Non-substantial
Sections 1.1	H0: CR/CRi rate per investigator's assessment should be "≤37%" instead of "≥37%".	Correct the typo	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 1.3	Add description of laboratory assessment window	Clarify visit window of laboratory assessment	Non-substantial
Section 1.3	Add enrollment process	Consistent with practice	Non-substantial
Section 1.3	Add the note "or CT by clinical request" to Chest X-ray	Consistent with practice	Non-substantial
Section 1.3 footnotes 3-7, 9, 14	Update the wording accordingly	Consistent with practice	Non-substantial
Section 2.2.1	Add approval country	Inotuzumab ozogamicin was approved in China	Non-substantial
Section 5.1 Inclusion 2	Remove M2 or M3 marrow	Consistent with practice	Non-substantial
Section 8.4.1	Deletion of the "Medical occurrences that……,not the AE section".	To be consistent with context.	Non-substantial
Sections 1.1, 6, 7.1, 7.2, 8, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.12, 10.13	Update the wording accordingly	To align with Pfizer's protocol template	Non-substantial
Table 8	Formatting	Correct the formatting errors	Non-substantial
Section 1.3 and Section 8.8 (PACL dated 30 Aug 2022)	Deletion of "A peripheral blood sample must be provided if a patient has an inadequate aspirate at screening."	Peripheral blood sample will not be required by central laboratory.	Non-substantial
Appendix 11 (PACL dated 30 Aug 2022)	Added Appendix 11 Alternative Measures During Public Emergencies	Make sure the study team will approach questions from study sites due to the	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
		COVID-19 pandemic in a consistent manner.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A PHASE 4, OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY OF INOTUZUMAB OZOGAMICIN IN CHINESE ADULT PATIENTS WITH RELAPSED OR REFRACTORY CD22-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Brief Title:

A Phase 4 ,open-label, single-arm, multicenter study in Chinese patients with relapsed or refractory cluster of differentiation (CD)-22-positive B-cell acute lymphoblastic leukemia (ALL).

Rationale

This study is a post approval commitment study to confirm the efficacy, safety, and pharmacokinetics (PK) of inotuzumab ozogamicin in patients with relapsed or refractory B cell ALL from mainland China.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:		
• To evaluate the efficacy of inotuzumab ozogamicin based on a primary endpoint of complete remission [CR]/complete remission with incomplete hematologic recovery [CRi] per Investigator's assessment in Chinese adult patients with relapsed/refractory B-cell ALL.	• The treatment effect of inotuzumab ozogamicin from the time of first dose until end of treatment for all patients who received at least one dose of inotuzumab ozogamicin regardless of tolerability and duration on treatment.	• CR/CRi per investigator's assessment.
Secondary:		
• To evaluate the efficacy of inotuzumab ozogamicin.		• Duration of remission (DoR). • Minimal residual disease (MRD) negativity in patients achieving CR/CRi. • Progression-free survival (PFS). • Overall survival (OS). • Hematopoietic stem cell transplant (HSCT).

Objectives	Estimands	Endpoints
• To evaluate the safety of inotuzumab ozogamicin. • To evaluate PK of inotuzumab ozogamicin. • To evaluate the immunogenicity of inotuzumab ozogamicin.		• AEs and laboratory abnormalities by type, frequency, severity (as graded by NCI CTCAE v5.0), timing, seriousness, and relationship to study therapy, including veno-occlusive disease [VOD] (total, during study treatment, and post-HSCT). • Inotuzumab ozogamicin maximum observed concentration (C_{max}) and trough plasma concentration (C_{trough}). • Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb).

Overall Design

This is an open-label, single-arm, multicenter study in Chinese patients with relapsed or refractory CD22-positive B-cell ALL. The objective of the study is to confirm the efficacy, safety, and PK of inotuzumab ozogamicin in patients with relapsed or refractory B-cell ALL from mainland China.

Approximate 44 mainland Chinese adult (≥18 years) patients who intend to receive either Salvage 1 or 2 therapy with relapsed or refractory CD22-positive, Philadelphia chromosome positive (Ph+) or Philadelphia chromosome-negative (Ph-) B-cell ALL will be enrolled in the study. To reflect the general relapsed/refractory ALL patient population, the number of patients with Ph+ disease will be capped at approximately 20% of the entire trial population.

- Salvage 1: Morphological relapse after initial treatment or resistant disease (no CR/CRi) after initial treatment;
- Salvage 2: Morphological relapse after salvage 1 therapy or resistant disease after salvage 1;

For this study, morphologic relapse or resistant/refractory disease will be defined as ≥5% blast by morphologic marrow assessment (or by the presence of circulating blasts if bone marrow was not assessed). Therapy modification(s) resulting from isolated molecular relapse, in the absence of morphologic relapse, will not be considered a salvage therapy.

The dosing regimen for inotuzumab ozogamicin in this study will be the same as that used in National Medical Products Administration (NMPA) -approved labeling. Patients will be treated with inotuzumab ozogamicin for a maximum dose of 1.8 mg/m^2 per cycle with a split dose regimen using weekly administrations. Patients will receive 0.8 mg/m^2 on week 1, followed by 0.5 mg/m^2 on weeks 2 and 3 every 21-28 days cycle. In Cycle 2 and beyond, the

inotuzumab ozogamicin dose administered on week 1 will be reduced to 0.5 mg/m^2 in patients achieving CR/CRi (for a total cycle dose of 1.5 mg/m^2).

Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment. For patients planning to receive an HSCT, it is recommended that treatment with inotuzumab ozogamicin be limited to 2 cycles of induction, a third cycle may be given if CR/CRi and minimal residual disease (MRD) negativity is not achieved after 2 cycles. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered.

Patients who achieve a response to treatment and who have a suitable donor may undergo stem-cell transplantation at the discretion of the investigator. No association between the time from last dose of inotuzumab ozogamicin to HSCT and outcomes after HSCT has been observed. The potential risk of relapse after the last dose of inotuzumab ozogamicin must be balanced against the potential risk of toxicity associated with beginning HSCT soon after the last dose of inotuzumab ozogamicin.

All cases of VOD/sinusoidal obstruction syndrome (SOS) irrespective of causality or severity will be reported as serious adverse events (SAEs) for up to 2 years after the first dose of inotuzumab ozogamicin. An independent hepatic event adjudication committee will evaluate safety for potential VOD/SOS events and Hy's law cases. Survival will be followed up to 2 years from first dose.

PK samples will be collected for all 44 patients in the study to describe population PK profiles.

Number of Participants

Approximately 44 mainland Chinese adult (≥18 years) patients who intend to receive either Salvage 1 or 2 therapy with relapsed or refractory CD22-positive, Ph+ or Ph- B-cell ALL will be enrolled in the study. The statistical consideration for the sample size is described in Section 9.2.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention.

Study Population

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male or female participants, age 18 years or older at screening.

2. Relapsed or refractory CD22-positive ALL (≥5% marrow blasts, assessed by morphology) due to receive either salvage 1 or salvage 2 therapy and for which treatment with inotuzumab ozogamicin offers a reasonable treatment option.

3. Ph+ ALL patients must have failed treatment with at least 1 tyrosine kinase inhibitor and standard multi-agent induction chemotherapy.

4. Patients in Salvage 1 with late relapse should be deemed poor candidates for reinduction with initial therapy.

5. Patients with lymphoblastic lymphoma and bone marrow involvement ≥5% lymphoblasts by morphologic assessment.

6. ECOG performance status 0-2.

7. Adequate liver function, including total serum bilirubin ≤1.5 × ULN unless the patient has documented Gilbert syndrome, and aspartate and alanine aminotransferase (AST and ALT) ≤2.5 × ULN. If organ function abnormalities are considered due to tumor, total serum bilirubin must be ≤2 × ULN and AST/ALT ≤2.5 × ULN.

8. Serum creatinine ≤1.5 × upper limit of normal (ULN) or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min.

9. Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for a minimum of 8 months (females) and 5 months (males) after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active. Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

    a Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level confirming the postmenopausal state;

    b Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions:

1. Isolated extramedullary relapse (ie, testicular or central nervous system [CNS]).
2. Burkitt's or mixed phenotype acute leukemia based on the World Health Organization (WHO) 2008 criteria.
3. Active CNS leukemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF), use of CNS-directed local treatment for active disease within the prior 28 days, symptomatic CNS leukemia (ie, cranial nerve palsies or other significant neurologic dysfunction) within 28 days. Prophylactic intrathecal medication is not a reason for exclusion.
4. Major surgery within ≤4 weeks before Cycle 1 Day 1.
5. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function or unstable pulmonary condition).
6. Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or localized prostate cancer that has been definitely treated with radiation or surgery. Patients with previous malignancies are eligible provided that they have been disease free for ≥2 years.
7. Cardiac function, as measured by left ventricular ejection fraction (LVEF) that is less than 45%, or the presence of New York Heart Association (NYHA) stage III or IV congestive heart failure.
8. Patients with active heart disease (NYHA class ≥3 as assessed by history and physical examination).
9. Myocardial infarction ≤6 months before Cycle 1 Day 1.
10. History of clinically significant ventricular arrhythmia, or unexplained syncope not believed to be vasovagal in nature, or chronic bradycardic states such as sinoatrial block or higher degrees of atrioventricular (AV) block unless a permanent pacemaker has been implanted.
11. Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (eg, hypokalemia, hypocalcemia, hypomagnesemia).
12. History of chronic liver disease (eg, cirrhosis) or suspected alcohol abuse.
13. History of hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS).

14. Evidence of uncontrolled current serious active infection (including sepsis, bacteremia, fungemia) or patients with a recent history (within 4 months) of deep tissue infections such as fascitis or osteomyelitis.

15. Patients who have had a severe allergic reaction or anaphylactic reaction to any humanized monoclonal antibodies.

16. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

17. Prior chemotherapy within 2 weeks before enrollment with the following exceptions:

    a. To reduce the circulating lymphoblast count or palliation: steroids, hydroxyurea or vincristine;

    b. For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine, and/or tyrosine kinase inhibitors.

18. Patients must have recovered from acute non hematologic toxicity (to ≤Grade 1) of all previous therapy prior to enrollment.

19. Prior monoclonal antibodies within 6 weeks of enrollment, with the exception of rituximab which must be discontinued at least 2 weeks prior to Cycle 1 Day 1.

20. Prior allogeneic hematopoietic stem cell transplant (HSCT) or other anti-CD22 immunotherapy ≤4 months before enrollment. Patients must have completed immunosuppression therapy for treatment of graft versus host disease (GvHD) prior to enrollment. At enrollment, patients must not have ≥Grade 2 acute GvHD, or extensive chronic GvHD.

21. Administration of live vaccine ≤6 weeks before enrollment.

Prior/Concurrent Clinical Study Experience:

22. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer).

Diagnostic Assessments:

23. Peripheral absolute lymphoblast count ≥10,000 /μL (treatment with hydroxyurea and/or steroids/vincristine is permitted within 2 weeks of Cycle 1 Day 1 to reduce the white blood cell [WBC] count).

24. Known systemic vasculitides (eg, Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as human immunodeficiency virus [HIV] infection or severe inflammatory disease).

25. Current or chronic hepatitis B or C infection as evidenced by hepatitis B surface antigen and anti-hepatitis C antibody positivity, respectively, or known seropositivity for HIV. HIV testing may need to be performed in accordance with local regulations or local practice.

26. QTcF >470 msec (based on the average of 3 consecutive electrocardiograms [ECGs]).

Other Exclusions:

27. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

28. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use highly effective contraception as outlined in this protocol for the duration of the study and for a minimum of 8 months (females) and 5 months (males) after the last dose of investigational product.

Study Arms and Duration

The dosing regimen for inotuzumab ozogamicin in the China post approval study will be the same as that used in NMPA-approved labeling as summarized below:

- Cycle 1: 1.8 mg/m^2 inotuzumab ozogamicin (Day 1: 0.8 mg/m^2, Day 8 and Day 15: 0.5 mg/m^2), Cycle 1 consists of 3 weeks. However, the duration may be extended to 4 weeks if the patient achieves a CR or CRi and/or to allow toxicity recovery.

- For subsequent cycles (4 weeks in duration):

  - In patients who achieve a CR or CRi: 1.5 mg/m^2 per cycle (Days 1, 8, and 15: 0.5 mg/m^2), subsequent cycles are 4 weeks in duration.

  - In patients who do not achieve a CR or CRi: 1.8 mg/m^2 per cycle (Day 1: 0.8 mg/m^2, Days 8 and 15: 0.5 mg/m^2). Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment.

- For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve CR or CRi and MRD negativity after 2 cycles.

- For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered.

Following the discontinuation from the treatment, patients will be followed for:

1. Disease progression for up to 2 years from the first dose, unless the disease progressed during the treatment;

2. Potential VOD/SOS cases, irrespectively of grade or causality for up to 2 years from the first dose;

3. Survival for up to 2 years from the first dose.

Statistical Methods

The statistical methods and analyses for the study will be described detail in the statistical analysis plan (SAP).

Specifically, the study will test the null hypothesis H_0: CR/CRi rate per investigator's assessment $\leq$37% vs the alternative hypothesis H_a: CR/CRi rate $\geq$61% where both hypotheses are consistent with those from study B1931022.

A sample size of 44 patients is planned to provide at least 90% power to reject the null hypothesis when the true CR/CRi rate $\geq$61% under the 1-sided significance level 0.025.

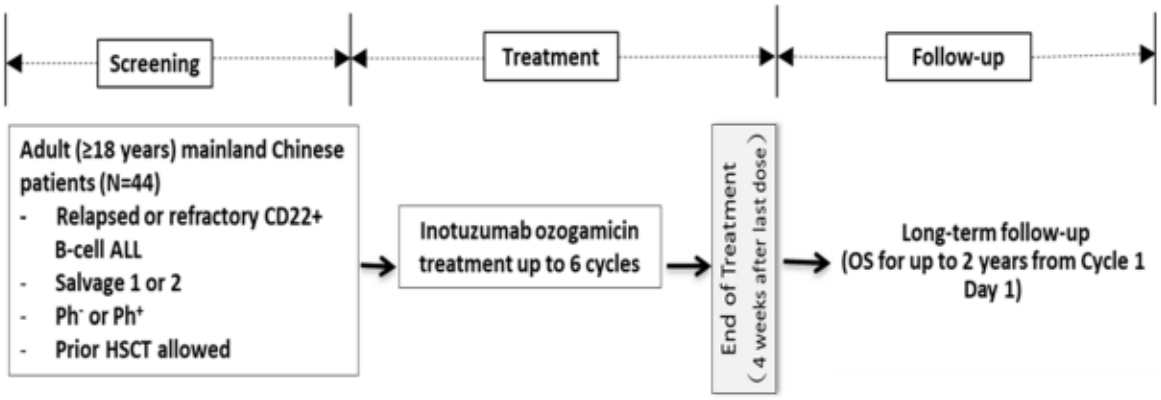
All other secondary endpoints will be descriptively summarized. Kaplan-Meier method will be used to summarize the time-to-event variables including duration of remission (DoR), progression-free survival (PFS) and overall survival (OS).

All safety analysis will be performed on the safety population. The number and percentage of patients with adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, preferred term, relationship to study drug, and severity.

Analyses of the PK data will be conducted on the PK concentration population. Descriptive summary statistics will be provided.

The anti-drug antibody (ADA) and NAb data are to be listed and summarized through frequency and percentage.

1.2. Schema



1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Schedule of Activities

Protocol Activity	Screen[17] -28 days from enrollment	Cycles 1-6			End of Treatment (EOT)[19] (All patients: 4 weeks from the last dose of study drug)
		Day 1	Day 8	Day 15	
Study Visit Window (Days)		±2	±2	±2	±3
Informed consent & Participant ID number & Distribute emergency contact card	X				
Eligibility criteria	X				
Contraception check	X	X			X
CD22 Immunophenotyping[1]	X				
Antibodies to inotuzumab[2]		X			X
Demography/Medical History	X				
Weight/height[4]	X	X			X
Vital Signs and Physical Examination[3]	X	X	X	X	X
ECOG performance status (PS)	X				X
Laboratory Assessments: During the treatment period, all laboratory assessments must be done within 72 hours prior to dosing.					
Hematology[5]	X	X	X	X	X
Blood Chemistry[5]	X	X	X	X	X
Urinalysis[7]	X				X
Coagulation[8]	X	X			X
Pregnancy test[9]	X	X			X
HbsAg and anti- hepatitis C virus (HCV)[6]	X				

Table 1. Schedule of Activities

Protocol Activity	Screen[17] -28 days from enrollment	Cycles 1-6			End of Treatment (EOT)[19] (All patients: 4 weeks from the last dose of study drug)
		Day 1	Day 8	Day 15	
Chest X-ray (or CT by clinical request)	X				
ECG (in triplicate)[10]	X (3-28 days prior to enrollment)	See Table 3 for additional time points			X
Pharmacokinetics		See Table 3 for time points			
LVEF[11]	X				
Premedications		X	X	X	
Study Treatments[12]		See protocol Section 6			
Bone marrow aspirate and clinical disease assessments[13]	X	See Table 1 footnote[13]			X
Karyotyping/FISH/ Immunophenotyping/Minimal residual disease (MRD)/Bone marrow biopsy[14]	X	Done in patients with suspected CR and/or CRi[14]			
Radiological Assessment[15]	X	As clinically indicated. See Appendix 7.			
Assessment of CNS disease[18]	X[18]	As clinically indicated[18]			
AE/SAE and concomitant medications[16]	X	Assessed throughout the study until 9 weeks from last dose of inotuzumab ozogamicin			

Additional procedures or samples may be undertaken as medically required at the discretion of the Investigator. Data may be recorded on the CRF (eg, local MRD analysis if done at the site). Additional blood samples may be taken, or additional tests conducted in existing samples, for analyses at central or local laboratories in order to provide the best possible guidance on improving the medical management of study patients on emerging safety findings during the conduct of the study.

1. CD22 immunophenotyping performed at screening on peripheral blood or bone marrow aspirate. Surface CD22 expression should be measured by FACS; immunohistochemistry (IHC) analysis is allowed in patients with 1) dry tap or 2) if BM aspirate was inadequate and/or with insufficient circulating blasts for FACS..
2. Immune response testing to inotuzumab ozogamicin: blood sample will be collected at Day 1 of every cycle prior to the beginning of inotuzumab ozogamicin infusion and at the end-of-treatment visit. Analysis will be performed by central laboratory.
3. Physical examination (PE) performed at screening and at Day 1, 8 and 15 of every cycle prior to study drug administration. Vital signs (pulse, blood pressure, temp) required on every day of dosing. Record vital signs prior to each infusion and 1 hour (±15 minutes) after the end of each infusion. Vital signs will be also recorded 2 hours (±15 minutes) after the end of inotuzumab ozogamicin infusion at Cycle 1 Day 1 dose.
4. Height required only at screening; patients must be weighed up to 72 hours prior to Day 1 of each cycle and end-of-treatment. If the patient experiences a weight loss or gain >10% from the prior weight obtained, the BSA and the amount of inotuzumab ozogamicin required for dose preparation must be re-calculated.
5. Serum chemistry and Hematology: performed at screening to determine eligibility, up to 72 hours prior to Day 1, Days 8 and 15 of every cycle. Additional (unscheduled) assessments should be done if laboratory values are abnormal (or if clinically indicated) and repeated until resolution, until return to baseline, or until NCI CTCAE Grade ⩽1. A CBC with platelets and differential must accompany each bone marrow assessment.

Table 1. Schedule of Activities

Protocol Activity	Screen[17] -28 days from enrollment	Cycles 1-6			End of Treatment (EOT)[19] (All patients: 4 weeks from the last dose of study drug)
		Day 1	Day 8	Day 15	

6. Hepatitis B (HbsAg) and C (anti-HCV) tests. A recombinant immunoblot assay (RIBA) or nucleic acid test (NAT) may be done to confirm or rule out HCV infection as clinically indicated.
7. Urinalysis: conducted at screening, within 72 hours prior to dosing of Cycle 4 Day 1, and the end-of-treatment visit. Urine protein to creatinine ratio will be calculated at screening and End of treatment only.
8. Coagulation: PT/INR collected at screening, up to 72 hours predose of Day 1 of each cycle and EOT. PTT or APTT required at screening and end-of-treatment visits only
9. For women of childbearing potential, beta-human chorionic gonadotropin (β-HCG) serum or urine pregnancy test will be performed at screening, up to 72 hours prior to dosing at Day 1 each cycle, and EOT. Additional pregnancy tests may be done as required by local regulations and/or EC/IRBs.
10. ECGs will be done in triplicate (3 consecutive ECGs approximately 2 minutes apart) in all patients at screening, during treatment Cycles 1, 2 and 4, and EOT. Screening ECG will be done approximately 3-28 days prior to enrollment.
11. LVEF will be assessed at screening either by echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA). Additional assessments may be done during the study if clinically required.
12. Patients must be treated within 3 days from enrollment. If extenuating circumstances prevent a patient from beginning treatment within this time, the patient may begin treatment only with written permission by the Pfizer Clinician.
13. Bone marrow aspirate and disease assessments will be performed at screening, at Day 16-28 of Cycles 1, 2, or until CR/CRi and MRD negativity are achieved. Then after every 1- 2 cycle as clinically indicated, and at EOT visit (unless previously done within 28 days). Bone marrow aspirates will be analyzed at the study site. A CBC with platelets and differential must accompany each bone marrow assessment. Disease assessments will include clinical evaluation of liver and spleen, and other sites of prior or suspected extramedullary disease. Disease assessments will continue until progression. For those who have not progressed at EOT, disease will be assessed every 12 weeks (±1 week) up to 1 year from enrollment and every 24 weeks (±2 weeks) between year 1 and 2, and whenever clinically indicated, until progression. All disease assessment results will be captured in the CRF, even if unplanned or not required by protocol.
14. Minimal residual disease (MRD): Bone marrow aspirate will be collected at screening, investigator suspected CR/CRi, achievement of CR/CRi until MRD negativity before EOT. MRD will be assessed using NGS for rearranged IgH, IgK, and IgL receptor gene sequences at a central laboratory.

    Immunophenotyping: performed on peripheral blood or bone marrow aspirate with flow cytometry at screening and will be done in patients with suspected CR and/or CRi. IHC is allowed in patients with a dry tap or otherwise inadequate bone marrow aspirate in the absence of circulating blasts. The leukemia phenotype and/or genotype may also be evaluated by other test methods at the discretion of the investigator.

    FISH: Bone marrow aspirates may be analyzed by fluorescence in situ hybridization analysis (FISH) for detection of chromosomal aberrations at screening according to standard of care.

    Karyotyping[28]: in all patients, at screening and at least once in patients achieving CR or CRi who had abnormal cytogenetics at baseline. It is recommended that 20 or more metaphases be counted for cytogenetics analysis.

    Bone Marrow Biopsy: required at least once, to assess cellularity, in patients with CRi by investigator assessment (ANC <1 ×109/L and/or platelets <100 × 109/L) and as clinically indicated per local standard of care. Biopsies may be also required for inadequate aspirate samples

Table 1. Schedule of Activities

Protocol Activity	Screen[17] -28 days from enrollment	Cycles 1-6			End of Treatment (EOT)[19] (All patients: 4 weeks from the last dose of study drug)
		Day 1	Day 8	Day 15	

15. Radiological assessments (ie, computed tomography scan or MRI) will be done at screening for patients with suspected extramedullary disease, during study as clinically indicated and to confirm CR or CRi in patients with extramedullary disease at screening. Please use the same method of assessment for each evaluation. Computed tomography scan with contrast is the preferred method of assessment.
16. AEs will be followed until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, or longer if requested by the sponsor. The AE reporting period continues until 9 weeks after the last dose of investigational drug. However, VOD/SOS events, irrespective of the grade, causality, will be reported in the CRF for up to 2 years from first dose and will also be reported as SAEs.
17. Assessment(s) and test(s) done according to standard of care at the institution prior to the patient signing the ICD can be used to determine patient eligibility if collected within the timeframe specified in this protocol, e.g. procedures conducted within 28 days (ECG 3-28 days) prior to enrollment. Results will be recorded in the CRF. However before any collected sample (e.g. ECG, BM aspirate for disease assessment) is sent to the central vendor, the patient must be consented for study participation.
18. Assessment of CNS disease (eg, lumbar puncture) is required at screening in any patient with a prior history of CNS disease or if CNS disease is suspected due to clinical signs and/or symptoms. If a complete CNS assessment is not feasible due to comorbidities, the patient cannot be included in the study. If additional assessments are done at the site, as clinically indicated, results must be collected in the CRF. Patients with history of CNS disease who achieve a CR or CRi must have a CNS assessment to confirm complete response.
19. EOT visits should be performed before starting a new anti-leukemic therapy (including before subsequent hematopoietic stem cell transplant (HSCT) conditioning, other form of consolidation/intensification or maintenance therapy). If a new anti-leukemia therapy will be started, the EOT visit should occur as close as possible to 4 weeks after the last dose of study drug.

Table 2. Long Term Follow-Up

Study Procedures	Disease Follow-up[1]	Survival Follow-up[2]
Study Visit	Every 12-24 weeks[1]	Every 12 weeks
Serum chemistry[3]	X	
Hematology[3]	X	
Coagulation test (INR/PT)[3]	X	
ECOG performance status	X	
Bone marrow aspirate and disease assessments[4]	X	
Other anticancer therapy[5]	X	X
Survival status[2]	X	X

1. Disease follow-up: For patients who have discontinued treatment but have not progressed, (including patients undergoing stem-cell transplant or other subsequent anti-leukemic therapy), starting approximately 12 weeks after the last disease assessment, until disease progression for up to 2 years after Day 1 Cycle 1, disease will be assessed every 12 weeks (±1 week) up to 1 year from Cycle 1 Day 1 and every 24 weeks (±2 weeks) between year 1 and 2, and whenever clinically indicated, until relapse.
2. Survival follow-up: All patients (including patients undergoing stem-cell transplant or other subsequent anti-leukemic therapy) starting approximately 12 weeks (±1 week) after documented disease progression and continuing approximately every 12 weeks (±1 week) for up to 2 years after Day 1 cycle 1 for each patient. It can be conducted by telephone or email.
3. Coagulation, hematology and serum chemistry (limited to total bilirubin, alkaline phosphatase, ALT, AST, GGT, LDH and albumin) required for one year after Cycle 1 Day 1 or until new anti-cancer treatment, whichever occurs first. For patients in disease follow up beyond a year from Cycle 1 Day 1, CBC with differential and platelets required until disease progression.
4. Bone marrow aspirate and extramedullary disease assessments. Performed every 12 weeks (±1 week) for 1 year from Cycle 1 Day 1, and every 24 weeks (±2 weeks) between year 1 and 2, and whenever clinically indicated. Disease assessments include liver and spleen assessments. No bone marrow aspirate is necessary if non-response or progressive disease/relapse can be diagnosed from peripheral blood evaluation.
5. To include anticancer medications, cancer-related radiotherapy, and cancer-related surgical therapies. Start/stop date will be collected for 2 years (total, relative to the day of enrollment). Also at least the first post-study salvage therapy (re-induction) and response to the first post study salvage therapy (re-induction) will be reported in the CRF (refractory or responsive disease). Post-study transplant information including conditioning treatments will be collected for up to 2 years from enrollment. Select concomitant medications including antifungals, prophylaxis/treatment for graft vs host disease, and prophylaxis/treatment for VOD will be collected for up to at least 100 days after HSCT.

PK samples will be collected for all patients and ECG in triplicate will be done for all patients.

Table 3. Pharmacokinetics and ECG Monitoring Flowchart

Cycle 1										
Cycle Day	1				4	8			15	
Time (h) relative to the start of inotuzumab ozogamicin administration	0	1	2	4	72	0	1	6	0	1
PK sample collection[a]	X[b]	X[c]	X	X	X	X[b]	X[c]	X	X[b]	X[c]
ECGs[d]	X	X								

Cycle 2					
Cycle Day	1			8	
Time (h) relative to the start of inotuzumab ozogamicin administration	0	1	2	0	2
PK sample collection[a]	X[b]	X[c]	X	X[b]	X
ECGs[d]	X	X			

Cycle 4			
Cycle Day	1		8
Time (h) relative to the start of inotuzumab ozogamicin administration	0	1	0
PK sample collection[a]	X[b]	X[c]	X[b]
ECGs[d]	X	X	

Table 3. Pharmacokinetics and ECG Monitoring Flowchart

Abbreviations. h=hour; PK=pharmacokinetics; ECG=electrocardiogram

a. PK samples: Consult the laboratory manual for volume of blood needed and sample preparation. To avoid contamination, samples must not be taken from the same lumen that is used for drug infusion. Only in extenuating circumstances may the PK sample(s) be collected from the same lumen. If the same lumen has been used for a PK sample collection it must be documented in the CRF. The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF). Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

b. Sample to be drawn before the start of inotuzumab ozogamicin infusion.

c. Sample to be drawn immediately before end of inotuzumab ozogamicin infusion.

d. Electrocardiograms (ECGs) are collected in triplicate (3 consecutive ECGs approximately 2 minutes apart) and will be done immediately (within 15 minutes) before each corresponding PK sample collection. Predose ECGs to be performed after premedications and before the start of drug infusion.

2. INTRODUCTION

2.1. Study Rationale

This is a Phase 4, open-label, single-arm, multicenter study in Chinese patients with relapsed or refractory CD22-positive B-cell ALL. This study is a post approval commitment study to confirm the efficacy, safety, and PK of inotuzumab ozogamicin in patients with relapsed or refractory B-cell ALL from mainland China.

2.2. Background

Over 5300 new ALL patients >18 years are diagnosed annually in the US, with >90% of B cell ALL patients expressing CD22.[1,2] Similar numbers of ALL patients are diagnosed annually in the European Union (EU) with an annual incidence of 1.3 per 100,000 individuals.[3] In China, the incidence rate of ALL is similar to US and EU with a rate of 1.5 per 100,000 individuals for males and 1.2 per 100,000 individuals for females.[4]

Treatment of relapsed or refractory Ph- B-cell ALL typically includes a variety of induction regimens (ie, there is no single standard of care). Acceptable regimens can include induction therapies based on a backbone of vincristine, corticosteroids, and anthracyclines, hyper cyclophosphamide, vincristine, adriamycin-, and dexamethasone (hyper-CVAD), cytarabine-based (Ara-C) regimens such as high-dose Ara-C (HIDAC), fludarabine plus Ara-C plus granulocyte-colony stimulating factor (FLAG) ±idarubicin, methotrexate based regimens, HSCT, and other chemotherapy regimens.[16]

All these agents are considered to have limited treatment benefits in the relapsed or refractory ALL setting and carry significant toxicity risks with the vast majority of patients not achieving long-term survival. Complete response rates in the front-line setting can range from 80% to 90%; however, only approximately 30 – 40% of adults achieve long-term disease-free survival (DFS), with the primary reason for failure being disease recurrence.[5] Despite the associated mortality and morbidity, allogeneic hematopoietic cell transplantation after salvage therapy offers the best opportunity for long-term survival in patients with a suitable donor and a response to salvage therapy. However, the prognosis for these patients remains poor with only 30% expected to have a complete response after 1st salvage therapy with a median overall survival (OS) of approximately 5 months and with only a quarter of patients alive at 1 year.[6] Complete responses and prognosis are even poorer in the second and third salvage setting. A retrospective review of 288 second salvage patients treated at a single institution was notable for a CR rate of 18%, a median CR duration of 7 months, and a median overall survival of only 3 months.[7] While allogeneic transplant is standard in the salvage setting, a significant number of patients do not have a suitable donor, or their age or other comorbidities preclude this option. Approximately one quarter of adult ALL patients are older than 60 years of age, with these older patients having worse outcomes with median overall survival (OS) durations ranging from 3 – 14 months.[8] Furthermore, patients with Philadelphia chromosome-positive ALL and other high-risk cytogenetic abnormalities do more poorly, with 3 – 5 years DFS rates of <10%.[5]

Approved therapies for the treatment of relapsed ALL include Clofarabine (Clolar/Elvoltra®), Dasatinib (Sprycel®) and Imatinib is currently approved for relapsed pediatric ALL patients in the United States and EU. Approval of clofarabine was based on the results of a phase 2 study in refractory/relapsed ALL (both B and T cell ALL) showing a complete remission rate (CR+CRp) of 20% and an overall response rate (including CR, CRp, and partial response [PR]) of 30% in 61 pediatric patients.[9] Dasatinib and imatinib are also approved for adult patients with relapsed or refractory Philadelphia-chromosome positive ALL worldwide including Japan.[10] For patients with Ph- B-cell ALL, more recent US FDA-approved treatment approaches include:Tisagenlecleucel, a CD19-directed genetically modified autologous T-cell immunotherapy was granted regular approval by FDA in August 2017 for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.[17] Blinatumomab, a bispecific anti-CD3/CD19 monoclonal antibody, was granted accelerated approval by the FDA in 2014 for the treatment of Ph- patients with relapsed or refractory B-cell precursor ALL and was granted full approval by FDA in July 2017 for the treatment of relapsed or refractory B-cell precursor in adults and children; full approval included treatment of Ph+ patients. In March 2018, blinatumomab was granted accelerated approval for the treatment of B-cell precursor (ALL) in first or second CR with MRD ≥0.1% in adults and children.[18] Liposomal vincristine was granted accelerated approval by the FDA in 2012 for treatment of patients in second or later salvage.[19]

Therefore, there is a significant population of pediatric and adult patients with relapsed/refractory ALL in which current therapies are suboptimal in terms of remission induction and durability of remission.

Inotuzumab ozogamicin, an antibody targeting CD22 and conjugated with a cytotoxic antitumor antibiotic (calicheamicin), has been evaluated as a single agent or in combination with rituximab in phase 1/2 studies in relapsed/refractory CD22-positive non-Hodgkin's lymphoma (NHL). Significant clinical activity has been noted at doses starting at 0.8 mg/m^2 every 3 weeks with objective responses observed across all dosing cohorts and multiple NHL subtypes.[11] In these initial studies, the maximum tolerated dose of inotuzumab ozogamicin given alone or in combination with rituximab in over 300 patients, was identified at 1.8 mg/m^2 every 4 weeks.

Acute lymphocytic leukemia would be expected to be a good therapeutic target for inotuzumab ozogamicin due to CD22 positivity on B cell lymphoblasts, and presence of the target in the systemic circulation. In part, some of the theoretical concerns regarding access of an antibody conjugate to penetrate into large bulky solid tumor are mitigated.

2.2.1. Inotuzumab Ozogamicin

Inotuzumab ozogamicin is a CD22 directed antibody drug conjugate (ADC) consisting of 3 components: 1) the recombinant humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody inotuzumab, specific for human CD22, 2) N-acetyl gamma calicheamicin that causes double stranded deoxyribonucleic acid (DNA) breaks, and 3) an acid cleavable linker composed of the condensation product of 4 (4-acetylphenoxy) butanoic acid (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently

attaches N-acetyl gamma calicheamicin to inotuzumab. Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22 expressing tumor cells, followed by internalization of the ADC CD22 complex, and the intracellular release of N-acetyl gamma calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker1. Activation of N-acetyl gamma calicheamicin dimethylhydrazide induces double strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

Inotuzumab ozogamicin (BESPONSA®) is currently approved in the United States (US), the European Union (EU), Switzerland (approvals granted in 2017), and Japan (approval granted in 2018), and China (approval granted in 2021). Approval was based on demonstration of a positive benefit/risk for the treatment of adults with relapsed or refractory B cell precursor ALL. The approved dosing regimen is a starting dose of 1.8 mg/m^2 per cycle (administered as 3 divided doses on Day 1 [0.8 mg/m^2], Day 8 [0.5 mg/m^2], and Day 15 [0.5 mg/m^2]) which is reduced to 1.5 mg/m^2 per cycle (administered as 3 divided doses on 0.5 mg/m^2 on Day 1, 8, and 15) once complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) is achieved. Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves a CR/CRi, and/or to allow recovery from toxicity. Subsequent cycles are 4 weeks in duration. For patients proceeding to hematopoietic stem cell transplantation (HSCT), the recommended treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve CR/CRi and MRD negativity after 2 cycles. For patients not proceeding to HSCT, up to a maximum of 6 cycles may be administered.

2.2.2. Clinical Overview

2.2.2.1. Phase 3 Study B1931022

2.2.2.1.1. Efficacy

The activity of the currently approved inotuzumab ozogamicin dosing regimen was demonstrated in a randomized (1:1), open-label, international Phase 3 study (B1931022). Study B1931022 compared inotuzumab ozogamicin- to Investigator's choice of chemotherapy (control) as Salvage 1 or 2 therapy in adults with relapsed or refractory CD22 positive B-cell ALL. Investigator's choice of chemotherapy was fludarabine + cytarabine + granulocyte colony stimulating factor (FLAG), high-dose cytarabine (HIDAC), or mitoxantrone + cytarabine (MXN/Ara-C). Patients with Ph+ disease must have failed treatment with at least 1 tyrosine kinase inhibitor (TKI) and standard chemotherapy. Patients were stratified at randomization based on duration of first remission (<12 vs ≥12 months), line of salvage (Salvage 1 vs 2), and age (<55 vs ≥55 years).[12,13]

The study had 2 primary endpoints: hematologic remission (CR/CRi, evaluated based on the first 218 patients randomized (intent-to-treat (ITT) 218 population), per Endpoint Adjudication Committee assessment) and overall survival (OS; based on all 326 randomized patients). The secondary efficacy endpoints included MRD negativity (defined as <1 abnormal cell/10^4 nucleated cells by flow cytometry per central laboratory analysis), duration of remission (DoR), progression-free survival (PFS), and HSCT rate.[12,13]

The study met the primary objective of CR/CRi, with rates of 80.7% vs 29.4% for the inotuzumab ozogamicin and control arms, respectively (p-value <0.0001) (Table 4). Among responders in the ITT218 population, MRD negativity was higher and DoR was longer for the inotuzumab ozogamicin arm compared to the control arm (MRD negativity, 78.4% vs 28.1%, respectively; median DoR, 5.4 months vs 3.5 months, respectively, Table 4). Remission, DoR, and MRD negativity results in all 326 randomized patients were consistent with those for the first 218 randomized patients (Table 4).[12,13]

Table 4. Study B1931022: Efficacy Findings for CR/CRi, DoR and MRD Negativity

	First 218 Patients Randomized[1]		All 326 Patients Randomized[2]	
	Inotuzumab Ozogamicin (N=109)	Control: HIDAC, FLAG, or MXN/Ara-C (N=109)	Inotuzumab Ozogamicin (N=164)	Control: HIDAC, FLAG, or MXN/Ara-C (N=162)
Responding (CR/CRi) patients				
n (%) [95% CI]	88 (80.7) [72.1 87.7]	32 (29.4) [21.0 38.8]	120 (73.2) [65.7 79.8]	50 (30.9) [23.9 38.6]
p-value[3]	<0.0001 (primary endpoint)		<0.0001	
DoR in responding (CR/CRi) patients[4]				
N	84	32	120	50
Median, months [95% CI]	5.4 [4.2-8.0]	3.5 [2.9-6.6]	5.3 [4.2-7.0]	3.6 [2.9-5.2]
p value[3]	0.0031		0.0052	
MRD negativity in responding (CR/CRi) patients[5]				
N	69	9	92	19
Rate[6](%) [95% CI]	69/88 (78.4) [68.4-86.5]	9/32 (28.1) [13.7-46.7]	92/120 (76.7) [68.1-83.9]	19/50 (38.0) [24.7-52.8]
p-value	<0.0001		<0.0001	

Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DoR=duration of remission; EAC=Endpoint Adjudication Committee; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high-dose cytarabine; MRD=minimal residual disease; MXN/Ara-C=mitoxantrone + cytarabine; N/n=number of patients; PFS=progression free survival.

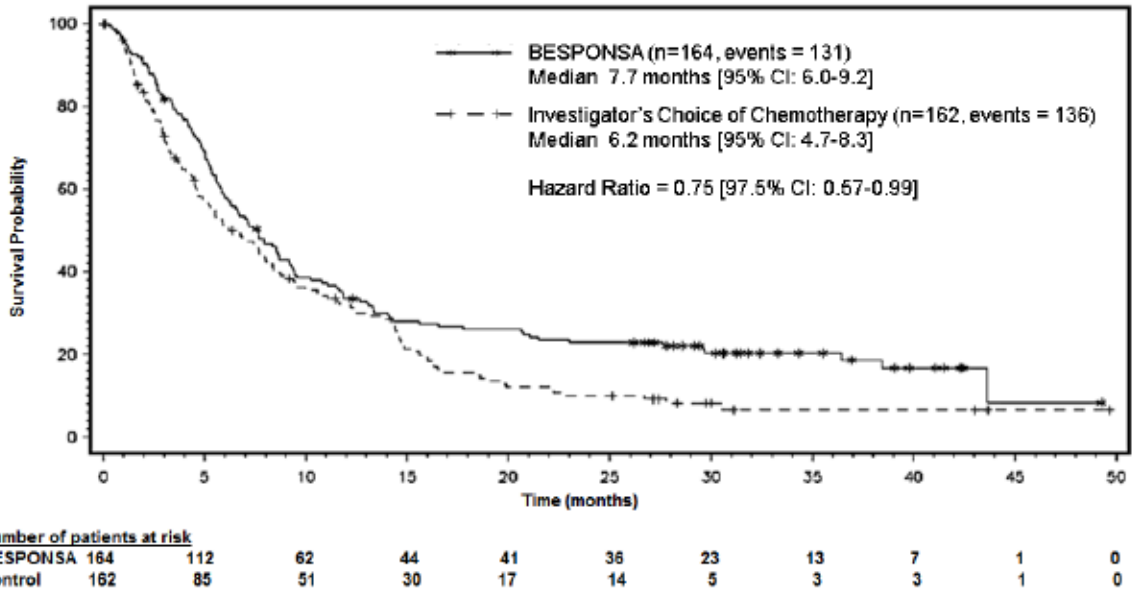
1. CR/CRi per EAC assessment. CR was defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥100 × 10^9/L and absolute neutrophil counts [ANC] ≥1 × 10^9/L) and resolution of any extramedullary disease. CRi was defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets <100 × 10^9/L and/or ANC <1 × 10^9/L) and resolution of any extramedullary disease. CR/CRi and MRD negativity results from planned interim analysis (data cutoff date 02 October 2014).
2. CR/CRi per Investigator's assessment. Data cutoff date 08 March 2016.
3. 1-sided p-value using Chi-squared test or Fisher's exact test (if any Chi-squared cell count <5).
4. DoR, based on a later cutoff date than the CR/CRi (data cutoff date 08 March 2016), was defined for patients who achieved CR/CRi per Investigator's assessment as time since first response of CR/CRi per Investigator's assessment to the date of a PFS event or censoring date if no PFS event was documented.
5. MRD negativity was defined by flow cytometry as leukemic cells comprising <1 × 10^{-4} (<0.01%) of bone marrow nucleated cells.
6. Rate was defined as the number of patients who achieved MRD negativity divided by the total number of patients who achieved CR/CRi per EAC (first 218 randomized patients) or per Investigator assessment (all 326 randomized patients).

In all randomized patients (N = 326) at study completion (last patient last visit), the estimated hazard ratio (HR) for PFS was 0.450 (95% confidence interval [CI]: 0.336-0.602) with 1-sided p<0.0001 in favor of inotuzumab ozogamicin over control based on a stratified analysis.

Overall, 79/164 patients (48%) in the inotuzumab ozogamicin arm and 35/162 patients (22%) in the control arm had a follow-up HSCT.[13] Among the 79 patients in the inotuzumab ozogamicin arm who underwent a follow-up HSCT, 71 patients proceeded to HSCT directly after inotuzumab ozogamicin- treatment (without any intervening induction therapy) with a median gap of 4.9 weeks (range: 1-19 weeks) between the last dose of inotuzumab ozogamicin- and HSCT.

The other primary objective of the study was to compare OS between the 2 treatment arms. To protect the type I error, alpha was split between the two primary endpoint CR/CRi rate per Endpoint Adjudication Committee (EAC) and OS. At the final analysis of OS based on data cutoff date of 08 March 2016, the estimated HR (inotuzumab ozogamicin vs the Investigator's choice of chemotherapy arm) was 0.770 (97.5% CI: 0.578-1.026; 1-sided p=0.0203) based on the stratified analysis, indicating an overall 23% reduction in the risk of death in favor of inotuzumab ozogamicin. Therefore, there was a clinically meaningful trend towards improved OS in the inotuzumab ozogamicin arm compared with the Investigator's choice of chemotherapy arm, but this did not reach prespecified statistical significance at a 1-sided significance level of 0.0104 due to the split alpha design and alpha spending at the 2 interim analyses. At study completion (last patient last visit), the estimated HR for OS was 0.75 (97.5% CI: 0.57-0.99, 1 sided p-value 0.0105) (Figure 1).[13]

Figure 1. Study B1931022: Kaplan Meier Curve for Overall Survival (Intent to Treat Population)



2.2.2.1.2. Pharmacokinetic

Based on PK data from 163 patients in Study B1931022, mean peak and trough exposures of inotuzumab ozogamicin increased with each cycle, due to its long steady state elimination half life (12.3 days). Mean peak concentrations in serum were observed at or near the end of infusion with a highest observed mean peak concentration of 308 ng/mL by Cycle 4 Day 1 and the highest observed mean trough concentration of 91.3 ng/mL, by Cycle 4 Day 8, compared to a peak of 211 ng/mL at Cycle 1 Day 1 and a trough of 6.84 ng/mL at Cycle 1 Day 8.

Based on the exposure response analyses of the safety and efficacy data from Phase 3 Study B1931022 and Phase 1/2 Study B1931010, there was a statistically significant ($p<0.0001$) relationship between inotuzumab ozogamicin average serum concentration up to the time of response (C_{avg}) and the probability of CR/CRi and MRD negativity. Furthermore, there was a statistically significant ($p<0.05$) relationship between inotuzumab ozogamicin cumulative total serum exposure during Cycle 1 ($cAUC_{P1}$) and the probability of VOD (VOD per assessment of the independent Hepatic Events Adjudication Board (HEAB) for Phase 3 Study B1931022).

2.2.2.1.3. Safety

In Study B1931022, 164 patients received inotuzumab ozogamicin. The median duration of treatment was 8.9 weeks (range: 0.1-26.4 weeks), with a median of 3 treatment cycles started in each patient. The most common (≥2%) serious adverse events reported for patients who received inotuzumab ozogamicin were infection, febrile neutropenia, hemorrhage, abdominal pain, pyrexia, fatigue, and VOD.[13]

2.2.2.1.3.1. Hepatotoxicity, Including Veno-occlusive Disease (VOD; also known as sinusoidal obstruction syndrome)

Hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD was observed in 23/164 patients (14%) during or following inotuzumab ozogamicin. As described below, most cases of VOD occurred after subsequent HSCT (following completion of inotuzumab ozogamicin treatment).[13]

VOD was reported in 5/164 patients (3%) during study therapy or in follow-up without an intervening HSCT. For these 5 patients, VOD was reported up to 56 days after the last dose of inotuzumab ozogamicin.[13]

Among the 79 inotuzumab ozogamicin treated patients who proceeded to a subsequent HSCT, VOD was reported in 18/79 patients (23%). The median time from subsequent HSCT to onset of VOD was 15 days (range: 3-57 days). Five (5) cases of VOD post-HSCT were fatal.[13] While VOD is a toxicity known to be associated with the hepatotoxic conditioning regimens used in HSCT,[14] the frequency of VOD post -HSCT was higher in the inotuzumab ozogamicin arm compared to the control arm (23% vs 3/34 [9%] patients, respectively).

The risk of VOD was greater in patients who underwent HSCT after BESPONSA treatment; use of HSCT conditioning regimens containing 2 alkylating agents (eg, busulfan in combination with other alkylating agents) and last total bilirubin level greater than or equal to the upper limit of normal (ULN) before HSCT are significantly associated with an increased risk of VOD. Other risk factors for VOD in patients treated with BESPONSA included ongoing or prior liver disease, prior HSCT, increased age, later salvage lines, and a greater number of BESPONSA treatment cycles. Patients who have experienced prior VOD or have serious ongoing hepatic liver disease (eg, cirrhosis, nodular regenerative hyperplasia, active hepatitis) are at an increased risk for worsening of liver disease, including developing VOD, following treatment with BESPONSA. Among the 79 inotuzumab ozogamicin treated patients who had a subsequent HSCT, 11 (13.9%) patients received dual-alkylating conditioning regimens including 5 patients who received busulfan and thiotepa containing regimens, and 2 patients who received busulfan and cyclophosphamide containing regimens.

Other hepatotoxicity reported for inotuzumab ozogamicin treated patients included abnormal liver tests: Grade 3/4 increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin occurred in 7/160 (4%), 7/161 (4%), and 8/161 patients (5%), respectively.[13]

2.2.2.1.3.2. Post HSCT Non-Relapse Mortality

While the overall percentage of patients surviving after HSCT was similar in both arms (35.4% vs 34.3%), post HSCT non-relapse mortality (NRM) rate was higher in the inotuzumab ozogamicin- arm compared to the control arm (39% vs 23%, respectively, Table 5). The most common causes of post HSCT NRM for inotuzumab ozogamicin treated patients included VOD and infections. Five (5) of the 18 VOD events that occurred post- HSCT were fatal. Among patients with ongoing VOD at time of death, 6 patients died due to multiorgan failure (MOF) and/or infection (3 patients died due to MOF, 2 patients died due to infection, and 1 patient died due to MOF and infection).[13]

Table 5. Study B1931022: Post HSCT Non Relapse Mortality Rate by Arm

	Rate of VOD Post-HSCT	
	Inotuzumab ozogamicin (N=164)	Control (N=162)
Number of patients who had follow-up HSCT	79 (48.2)	35 (21.6)
Number of patients with post-HSCT non-relapse mortality adjusting for competing risks[a,b]	31 (39.2)	8 (22.9)
Estimated mortality rate at end of Day 100 (95% CI)	20.25 (12.19, 29.77)	5.71 (0.99, 16.93)
Estimated mortality rate at end of Month 12 (95% CI)	36.71 (26.14, 47.31)	14.54 (5.18, 28.48)

Patients may have had more than 1 reported reason for the cause of death. MedDRA (v18.1) coding dictionary was applied.
Data cutoff date 01 September 2016.
Abbreviations: CI=confidence interval; HSCT=hematopoietic stem cell transplant; N=number of patients.

a. Number of patients with post-transplant was used for percent calculation.
b. Competing risk was defined as relapse from CR/CRi after post HSCT, or death where mechanism of death = disease progression/relapse. Events that occurred after competing risk were not included in the calculation of cumulative incidence rate.

2.2.2.1.3.3. Myelosuppression

Myelosuppression was observed in patients who received inotuzumab ozogamicin.

Thrombocytopenia and neutropenia were reported in 83/164 (51%) patients and 81/164 (49%) patients, respectively. Grade 3 thrombocytopenia and neutropenia were reported in 23/164 (14%) patients and 33/164 (20%) patients, respectively. Grade 4 thrombocytopenia and neutropenia were reported in 46/164 (28%) patients and 45/164 (27%) patients, respectively. Febrile neutropenia, which may be life-threatening, was reported in 43/164 (26%) patients. For patients who were in CR/CRi at the end of treatment, the recovery of platelet counts to >50,000/mm^3 was later than 45 days after the last dose in 15/164 (9%) patients who received inotuzumab ozogamicin and 3/162 (2%) patients who received control therapy (Investigator's choice of chemotherapy).[13]

Complications associated with myelosuppression (including infections and bleeding/hemorrhagic events) were observed in inotuzumab ozogamicin treated patients. Infections, including serious infections, some of which were life-threatening or fatal, were reported in 79/164 (48%) patients. Fatal infections, including pneumonia, neutropenic sepsis, sepsis, septic shock, and pseudomonal sepsis, were reported in 8/164 (5%) patients; the frequency of fatal infections was the same in the control arm (7/143 patients, 4.9%). Bacterial, viral, and fungal infections were reported.[13]

Hemorrhagic events were reported in 54/164 (33%) patients who received inotuzumab ozogamicin. Grade 3 or 4 hemorrhagic events were reported in 8/164 (5%) patients. One Grade 5 (fatal) hemorrhagic event (intra-abdominal hemorrhage) was reported in 1/164 (1%) patients. The most common hemorrhagic event was epistaxis which was reported in 24/164 (15%) patients.[13]

2.2.2.1.3.4. Infusion Related Reactions

Infusion related reactions were observed in patients who received inotuzumab ozogamicin.

Infusion related reactions (all Grade 2) were reported in 4/164 (2%) patients (reported symptoms included fever, chills, and hypotension). Infusion related reactions generally occurred in Cycle 1 shortly after the end of the inotuzumab ozogamicin infusion and resolved spontaneously or with medical management.[13]

2.2.2.1.3.5. QT Interval Prolongation

Increases in QT interval corrected for heart rate using Fridericia's formula (QTcF) of ≥60 msec from baseline were measured in 4/162 (3%) patients who received inotuzumab ozogamicin. No patients had QTcF values greater than 500 msec. Grade 2 QT prolongation was reported in 2/164 (1%) patients. No ≥ Grade 3 QT prolongation or events of Torsade de Pointes were reported in inotuzumab ozogamicin treated patients. In the control arm, QTcF ≥60 msec from baseline were measured in 3/124 (2%) patients, and 1/124 (1%) patients had QTcF values >500 msec.[13]

Central tendency analysis of the QTcF interval changes from baseline showed that the highest mean (upper bound of the 2-sided 90% CI) for QTcF was 15.3 (21.1) msec, which was observed at Cycle 4/Day 1/1 hour in the inotuzumab ozogamicin- arm.[13] Based on the latest exposure response analysis, although there was a positive correlation between corrected QT (QTc) interval with inotuzumab ozogamicin serum concentration, the upper bound of the 95% confidence interval for the predicted changes from baseline in QTcF and QT interval corrected for heart rate using a population specific method (QTcS-), at therapeutic and supratherapeutic (1.5 fold therapeutic) concentrations, remained below the 10 msec threshold (4.92-8.28 msec).

2.2.2.2. Phase 1/2 Study B1931010

Study B1931010 was a Phase 1/2 single-arm, 2-stage, multicenter, open-label study evaluating -single agent inotuzumab ozogamicin for the treatment of relapsed or refractory ALL. Results from this study helped to inform the inotuzumab ozogamicin dosing regimen used in Phase 3 Study B1931022. -Key eligibility criteria included age ≥18 years and relapsed or refractory CD22 positive ALL. -For the Phase 2 part of the study, the patients must have been due to receive Salvage ≥2 therapy. Patients with Ph+ ALL had to have failed treatment with at least 1 TKI.[15]

The Phase 1 dose escalation portion of Study B1931010 was designed to determine the recommended Phase 2 dose (RP2D) of weekly inotuzumab ozogamicin. -Twenty four (24) patients were treated with inotuzumab ozogamicin- at dose levels of 1.2 mg/m^2/cycle (n=3), 1.6 mg/m^2 per cycle (n=12), or 1.8 mg/m^2/cycle (n=9).[15]

Remissions (CR/CRi) were observed across all dose levels: the CR/CRi rate was 2/3 (66.7%) for 1.2 mg/m^2 per cycle, 9/12 (75.0%) for 1.6 mg/m^2 per cycle, and 8/9 (88.9%) for 1.8 mg/m^2 per cycle MRD negativity was also achieved among responders in each dose level; time to MRD negativity was longest for the 1.2 mg/m^2 per cycle group.[15]

Table 6. Study B1931010: Summary of Hematologic Remission, Time to Hematologic Remission, MRD Negativity and Time to MRD Negativity for Phase 1 Dose Escalation Cohorts

	Phase 1, Dose Escalation		
	1.2 mg/m^2	1.6 mg/m^2	1.8 mg/m^2
Number of Patients	**(N=3)**	**(N=12)**	**(N=9)**
Hematologic remission rate (CR/CRi)			
n (%)	2 (66.7)	9 (75.0)	8 (88.9)
95% CI[a]	(9.4, 99.2)	(42.8, 94.5)	(51.8, 99.7)
Time to remission (CR/CRi) (days)			
N	2	9	8
Mean	39.0	35.3	42.8
SD	24.0	12.6	19.9
Median	39.0	29.0	38.0
Range	22-56	22-59	22-78
MRD negativity			
n/N (%)[b]	2/2 (100)	8/9 (88.8)	8/8 (100)
Time to MRD negativity (days)			
Median (range)	98.5(98-99)	32.0(22-64)	30.0(22-141)

Abbreviations: CI=confidence interval; CR=complete response; CRi=complete response with incomplete count recovery; N/n=number of patients SD=standard deviation.
Final data from completed study.
a. CI created by Exact Binomial approximation.
b. Percentages were based on the number of patients with CR/CRi.

2.3. Benefit/Risk Assessment

The benefit and risk are demonstrated in previous studies. The principal evidence for the clinical efficacy and safety of inotuzumab ozogamicin in patients with relapsed or refractory B-cell ALL is derived from pivotal Phase 3 randomized Study B1931022 and supportive Phase 1/2 single-arm Study B1931010.

Study B1931022 compared inotuzumab ozogamicin to Investigator's choice of chemotherapy (control) as Salvage 1 or 2 therapy in adults with relapsed or refractory CD22 positive B cell ALL. The study met the primary objective of CR/CRi, with rates of 80.7% vs 29.4% for inotuzumab ozogamicin and control arms, respectively (p value <0.0001). The analysis of OS did not meet the prespecified boundary for statistical significance. At study completion, the estimated hazard ratio (HR) for OS was 0.75 (97.5% confidence interval [CI]: 0.57-0.99, 1-sided p-value 0.0105). The most comment (≥20%) all-causality TEAEs in the inotuzumab ozogamicin arm were Thrombocytopenia (49.4%), Neutropenia (48.8%), Anaemia (33.5%), Nausea (32.3%), Pyrexia (31.7%), Leukopenia (28.7%), Headache (27.4%), Febrile neutropenia (26.8%), Fatigue (25.6%), AST increased (22.6%), and gamma glutamyl transpeptidase (GGT) increased and hyperbilirubinaemia (21.3% each).

The frequency of hepatic veno-occlusive disease (VOD) (also known as sinusoidal obstruction syndrome [SOS]) after a subsequent HSCT was higher in the inotuzumab ozogamicin arm compared to the control arm (18/79 patients [23%] vs 3/34 patients [9%], respectively). Baseline characteristics that were identified as potential risk factors for VOD post HSCT in inotuzumab ozogamicin treated patients included ongoing or prior liver disease, prior HSCT, increased age, and later salvage lines. The use of HSCT conditioning regimens containing 2 alkylating agents, total bilirubin level greater than or equal to the upper limit of normal before HSCT, and a greater number of inotuzumab ozogamicin cycles were also associated with greater risk of VOD.

Based on the comprehensive data of inotuzumab ozogamicin from previous studies, it is proposed that inotuzumab ozogamicin has a favorable benefit-risk profile that justifies this study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of Inotuzumab ozogamicin may be found in the approved package insert, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:		
• To evaluate the efficacy of inotuzumab ozogamicin based on a primary endpoint of complete remission [CR]/complete remission with incomplete hematologic recovery [CRi] per Investigator's assessment in Chinese adult patients with relapsed/refractory B-cell ALL.	• The treatment effect of inotuzumab ozogamicin from the time of first dose until end of treatment for all patients who received at least one dose of inotuzumab ozogamicin regardless of tolerability and duration on treatment.	• CR/CRi per investigator's assessment.

Objectives	Estimands	Endpoints
Secondary:		
• To evaluate the efficacy of inotuzumab ozogamicin.		• Duration of remission (DoR). • Minimal residual disease (MRD) negativity in patients achieving CR/CRi. • Progression-free survival (PFS). • Overall survival (OS). • Hematopoietic stem cell transplant (HSCT).
• To evaluate the safety of inotuzumab ozogamicin.		• AEs and laboratory abnormalities by type, frequency, severity (as graded by NCI CTCAE v5.0), timing, seriousness, and relationship to study therapy, including VOD (total, during study treatment, and post-HSCT).
• To evaluate PK of inotuzumab ozogamicin		• Inotuzumab ozogamicin C_{max} and C_{trough}.
• To evaluate the immunogenicity of inotuzumab ozogamicin		• Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb).

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-arm, multicenter study in Chinese patients with relapsed or refractory CD22-positive B-cell ALL. The objective of the study is to confirm the efficacy, safety, and PK of inotuzumab ozogamicin in patients with relapsed or refractory B-cell ALL from mainland China.

Approximately 44 mainland Chinese adult (≥18 years) patients who intend to receive either Salvage 1 or 2 therapy with relapsed or refractory CD22-positive, Ph+ or Ph- B-cell ALL will be enrolled the study. To reflect the general relapsed/refractory ALL patient population, the number of patients with Ph+ disease will be capped at approximately 20% of the entire trial population.

- Salvage 1: Morphological relapse after initial treatment or resistant disease (no CR/CRi) after initial treatment;

- Salvage 2: Morphological relapse after salvage 1 therapy or resistant disease after salvage 1;

For this study, morphologic relapse or resistant/refractory disease will be defined as ⩾5% blast by morphologic marrow assessment (or by the presence of circulating blasts if bone marrow was not assessed). Therapy modification(s) resulting from isolated molecular relapse, in the absence of morphologic relapse, will not be considered a salvage therapy.

The primary endpoint is CR/CRi and secondary efficacy endpoints include DoR, MRD negativity in patients with CR/CRi, OS, PFS, HSCT, Adverse events and laboratory abnormalities (CTCAE v5.0 grade, timing, seriousness and relatedness), VOD (total, during study treatment, and post-HSCT), PK parameter and immunogenicity.

The dosing regimen for inotuzumab ozogamicin in the China post approval study will be the same as that used in NMPA-approved labeling. Patients will be treated with inotuzumab ozogamicin for a maximum dose of 1.8 mg/m^2 per cycle with a split dose regimen using weekly administrations. Patients will receive 0.8 mg/m^2 on week 1, followed by 0.5 mg/m^2 on weeks 2 and 3 every 21-28 days cycle. In Cycle 2 and beyond, the inotuzumab ozogamicin dose administered on week 1 will be reduced to 0.5 mg/m^2 in patients achieving CR/CRi (for a total cycle dose of 1.5 mg/m^2).

Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment. A third cycle may be considered for those patients who do not achieve CR or CRi and MRD negativity after 2 cycles. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered.

All cases of VOD/SOS irrespective of causality or severity will be reported as SAEs for up to 2 years after the first dose of inotuzumab ozogamicin. An independent hepatic event adjudication committee will evaluate safety for potential VOD/SOS events and Hy's law cases. Survival will be followed up to 2 years from first dose.

PK samples will be collected for all 44 patients in the study to describe population PK profiles.

4.2. Scientific Rationale for Study Design

Inotuzumab ozogamicin is an antibody directed against the CD22 antigen, conjugated with a cytotoxic antitumor antibiotic (calicheamicin) in development for the treatment of B cell malignancies such as non-Hodgkin's lymphoma (NHL) and ALL. CD22 is expressed on the malignant cells of the majority of B-lymphocyte malignancies, including on the surface of B cell ALL blasts in the vast majority of patients (>90%).[2]

Inotuzumab ozogamicin (BESPONSA®) is currently approved in the United States (US), the European Union (EU), Switzerland (approvals granted in 2017), and Japan (approval granted in 2018), and China (approval granted in 2021). Approval was based on demonstration of a positive benefit/risk for the treatment of adults with relapsed or refractory B-cell precursor

ALL. On 20 Dec 2021, Besponsa was approved by NMPA for the treatment of adults with relapsed or refractory B-cell precursor ALL.

The activity of the currently approved inotuzumab ozogamicin dosing regimen was demonstrated in a randomized (1:1), open label, international Phase 3 study (B1931022). Study B1931022 compared inotuzumab ozogamicin to Investigator's choice of chemotherapy (control) as Salvage 1 or 2 therapy in adults with relapsed or refractory CD22 positive B-cell ALL. Investigator's choice of chemotherapy was fludarabine + cytarabine + granulocyte colony stimulating factor (FLAG), high dose cytarabine (HIDAC), or mitoxantrone + cytarabine (MXN/Ara-C). Patients with Ph+ disease must have failed treatment with at least 1 tyrosine kinase inhibitor (TKI) and standard chemotherapy. The primary endpoints were CR/CRi, assessed by a blinded independent EAC, and OS. The secondary endpoints included MRD-negativity, DoR, HSCT rate, and PFS.

The analysis of CR/CRi based on the ITT population (data cutoff date 08 March 2016) and a subgroup analysis in Asian patients (by race and geographic region) and mainland Chinese patients.

- *All (ITT) patients:* At this later cutoff date (08 March 2016), the improvement in CR/CRi per Investigator's assessment in the ITT population was consistent with the previous (ITT218) analysis. Inotuzumab ozogamicin demonstrated a statistically significant and clinically meaningful improvement in CR/CRi (per Investigator's assessment) compared to Investigator's choice of chemotherapy (73.2% vs 30.9% for a rate difference of 42.3% [97.5% CI: 31.1, 53.5] with 1-sided $p<0.0001$).

- *Mainland Chinese patients:* In mainland Chinese patients, 5 out of 6 (83.3%) patients responded to inotuzumab ozogamicin treatment while 2 out of 6 (33.3%) patients responded to the Investigator's choice of chemotherapy.

- *Asian patients:* In Asian patients, a consistent and clinically meaningful improvement in CR/CRi compared to Investigator's choice of chemotherapy was also observed. In Asian (by race) patients, CR/CRi was 71.0% vs 20.8% (rate difference of 50.1% [97.5% CI: 24.1-76.2]) and in Asian (by geographic region) patients, CR/CRi was 73.1% vs 29.4% (rate difference of 43.7% [97.5% CI: 12.1, 75.2]).

The primary analysis of OS based on the ITT population (data cutoff date 08 March 2016) and a subgroup analysis in Asian patients (by race and region) and mainland Chinese patients.

- *All (ITT) patients:* In the ITT population (data cutoff date 08 March 2016), the median OS was 7.7 months vs 6.7 months and an estimated HR=0.770 (97.5% CI: 0.578-1.026; 1-sided p=0.0203) based on the stratified analysis and HR=0.748 (97.5% CI: 0.563, 0.993; 1-sided p=0.0104) based on the unstratified analysis.

- *Mainland Chinese patients:* In mainland Chinese patients, OS was consistent with the overall results in the ITT population recognizing the wide CIs for the HR, due to the small sample size (n=12); which overlapped with the ITT population. In mainland Chinese patients, median OS was 6.0 months vs 8.0 months and HR=0.797 (97.5% CI: 0.170, 3.735) based on the unstratified analysis.

- *Asian patients:* In Asian patients, OS findings were consistent with the overall results in the ITT population (which show a clinically meaningful improvement in OS) recognizing the wide CIs for the HRs, due to small sample sizes (n=55 [Asian by race] and 43 [Asians by geographic region]), which overlapped with the ITT population. In Asians (by race) patients, median OS was 5.8 months vs 3.9 months and HR = 0.815 (97.5% CI: 0.409, 1.624). In Asian (by geographic region) patients, median OS was 6.5 months vs 5.3 months and HR=1.230 (97.5% CI: 0.537, 2.818) based on the unstratified analysis.

For China, based on the comprehensive data available on inotuzumab ozogamicin, and the similarities in efficacy, safety, and PK between races and geographic regions, China Center for Drug Evaluation (CDE) agency has agreed to Pfizer's proposal to submit a clinical trial waiver (CTW) at the time of the new drug application (NDA) submission and conduct a clinical trial in Chinese patients as a post approval commitment (PAC) to support the registration of inotuzumab ozogamicin for the treatment of patients with relapsed or refractory B-cell ALL in China. The study design refers to the global Phase 3 B1931022 study. PAC study population will be the same as that used in global pivotal Phase 3 Study B1931022. Mainland Chinese adult (≥18 years) patients who intend to receive either Salvage 1 or 2 therapy with relapsed or refractory CD22-positive, Ph(+) or Ph (-) B-cell ALL will be enrolled in this study. Approved dosing regimen of inotuzumab ozogamicin will be used in this study.

4.3. Justification for Dose

Inotuzumab ozogamicin dose selection in this study was same as used in the global Phase 3 study (B1931022) and was approved by NMPA.

Dose modification is allowed in the event of toxicity, the specific deification see Section 6.6.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including screening, treatment period, disease follow up and survival follow up. For each patient survival follow up will start after documented disease progression and continuing for up to 2 years from the first dose (Day 1 Cycle 1).

The end of the study is defined as the date of the last participant completion of survival follow up, it will be up to 2 years from first dose of the last patient. Survival follow up can be conducted by telephone or email.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants, age 18 years or older at screening.

Type of Participant and Disease Characteristics:

2. Relapsed or refractory CD22-positive ALL (≥5% marrow blasts, assessed by morphology) due to receive either salvage 1 or salvage 2 therapy and for which treatment with inotuzumab ozogamicin offers a reasonable treatment option.

3. Ph+ ALL patients must have failed treatment with at least 1 tyrosine kinase inhibitor and standard multi-agent induction chemotherapy.

4. Patients in Salvage 1 with late relapse should be deemed poor candidates for reinduction with initial therapy.

5. Patients with lymphoblastic lymphoma and bone marrow involvement ≥5% lymphoblasts by morphologic assessment.

6. ECOG performance status 0-2.

7. Adequate liver function, including total serum bilirubin ≤1.5 × ULN unless the patient has documented Gilbert syndrome, and aspartate and alanine aminotransferase (AST and ALT) ≤2.5 × ULN. If organ function abnormalities are considered due to tumor, total serum bilirubin must be ≤2 × ULN and AST/ALT ≤2.5 × ULN.

8. Serum creatinine ≤1.5 × upper limit of normal (ULN) or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min.

9. Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for a minimum of 8 months (females) and 5 months (males) after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator,

he/she is biologically capable of having children and is sexually active. Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level confirming the postmenopausal state;

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

Informed Consent:

10. Capable of giving signed informed consent as described in Section 10.1, Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Isolated extramedullary relapse (ie, testicular or central nervous system [CNS]).

2. Burkitt's or mixed phenotype acute leukemia based on the World Health Organization (WHO) 2008 criteria.

3. Active CNS leukemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF), use of CNS-directed local treatment for active disease within the prior 28 days, symptomatic CNS leukemia (ie, cranial nerve palsies or other significant neurologic dysfunction) within 28 days. Prophylactic intrathecal medication is not a reason for exclusion.

4. Major surgery within ≤4 weeks before Cycle 1 Day 1.

5. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function or unstable pulmonary condition).

6. Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or localized prostate cancer that has been definitely treated with radiation or surgery. Patients with previous malignancies are eligible provided that they have been disease free for ≥2 years.

7. Cardiac function, as measured by left ventricular ejection fraction (LVEF) that is less than 45%, or the presence of New York Heart Association (NYHA) stage III or IV congestive heart failure.

8. Patients with active heart disease (NYHA class ≥3 as assessed by history and physical examination).

9. Myocardial infarction ≤6 months before Cycle 1 Day 1.

10. History of clinically significant ventricular arrhythmia, or unexplained syncope not believed to be vasovagal in nature, or chronic bradycardic states such as sinoatrial block or higher degrees of atrioventricular (AV) block unless a permanent pacemaker has been implanted.

11. Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (eg, hypokalemia, hypocalcemia, hypomagnesemia).

12. History of chronic liver disease (eg, cirrhosis) or suspected alcohol abuse.

13. History of hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS).

14. Evidence of uncontrolled current serious active infection (including sepsis, bacteremia, fungemia) or patients with a recent history (within 4 months) of deep tissue infections such as fascitis or osteomyelitis.

15. Patients who have had a severe allergic reaction or anaphylactic reaction to any humanized monoclonal antibodies.

16. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

17. Prior chemotherapy within 2 weeks before enrollment with the following exceptions:

    a. To reduce the circulating lymphoblast count or palliation: steroids, hydroxyurea or vincristine;

    b. For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine, and/or tyrosine kinase inhibitors.

18. Patients must have recovered from acute non hematologic toxicity (to ≤Grade 1) of all previous therapy prior to enrollment.

19. Prior monoclonal antibodies within 6 weeks of enrollment, with the exception of rituximab which must be discontinued at least 2 weeks prior to Cycle 1 Day 1.

20. Prior allogeneic hematopoietic stem cell transplant (HSCT) or other anti-CD22 immunotherapy ≤4 months before enrollment. Patients must have completed immunosuppression therapy for treatment of graft versus host disease (GvHD) [26, 27] prior to enrollment. At enrollment, patients must not have ≥Grade 2 acute GvHD, or extensive chronic GvHD.

21. Administration of live vaccine ≤6 weeks before enrollment.

Prior/Concurrent Clinical Study Experience:

22. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer).

Diagnostic Assessments:

23. Peripheral absolute lymphoblast count ≥10,000 /µL (treatment with hydroxyurea and/or steroids/vincristine is permitted within 2 weeks of Cycle 1 Day 1 to reduce the white blood cell [WBC] count).

24. Known systemic vasculitides (eg, Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as human immunodeficiency virus [HIV] infection or severe inflammatory disease).

25. Current or chronic hepatitis B or C infection as evidenced by hepatitis B surface antigen and anti-hepatitis C antibody positivity, respectively, or known seropositivity for HIV. HIV testing may need to be performed in accordance with local regulations or local practice.

26. QTcF >470 msec (based on the average of 3 consecutive electrocardiograms [ECGs]).

Other Exclusions:

27. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

28. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use highly effective contraception as outlined in this protocol for the duration of the study and

for a minimum of 8 months (females) and 5 months (males) after the last dose of investigational product.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Section 10.4.4 Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Patients who are screened and meet the exclusion criteria or fail to fulfill the inclusion criteria could be re-screened once, during the open screening period of the study. There is no requirement for a waiting period between the screen-failure date and the re-screening date, and a different patient identification number will be issued. Patients who are re-screened must sign a new consent form, and all screening procedures must be repeated.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and non-investigational medicinal products/auxiliary medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to inotuzumab ozogamicin.

6.1. Study Intervention(s) Administered

Table 7. Study Intervention Administered

Intervention Name	Inotuzumab ozogamicin.
ARM Name	Single arm.
Type	Intervention Type: Drug.
Dose Formulation	The inotuzumab ozogamicin drug product is prepared as a lyophilized powder. The drug product is formulated with 20 mM tromethamine (pH 8.0), 5% (w/v) sucrose, 0.01 % (w/v) polysorbate 80, and 10 mM sodium chloride.
Unit Dose Strength(s)	1 mg/vial.
Dosage Level(s)	See Section 6.1.1.
Route of Administration	Intravenous (IV).
Use	Experimental
Investigational Medicinal Product (IMP) or Noninvestigational Medicinal Product (NIMP)	IMP.
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Inotuzumab ozogamicin is provided in China commercial presentation as a lyophilized, unpreserved white to off-white powder in an amber vial for intravenous injection. Each vial will be labeled as required per country requirement.

6.1.1. Administration

See the Investigational Product Manual for instructions on how to administer inotuzumab ozogamicin.

Premedication is required for all subjects. Pre-medicate with a corticosteroid, antipyretic, and antihistamine. Premedication may also include antiemetics.

Patients should be observed during and for at least 1 hour after the end of study intervention infusion for symptoms of infusion related reactions. In cases of infusion related reactions, interrupt the infusion and institute appropriate medical management. Depending on the severity of the infusion related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue treatment.

Prophylactic CNS chemotherapy (intrathecal) is strongly recommended during study participation.

The starting dose of inotuzumab ozogamicin is 1.8 mg/m^2 per cycle (administered in 3 divided doses). After CR/CRi is achieved, the dose is reduced to 1.5 mg/m^2 per cycle (administered in 3 divided doses). The cycle length will be 21-28 days. Inotuzumab ozogamicin is administered on Days 1, 8, and 15.

For patients proceeding to HSCT, 2 cycles of inotuzumab ozogamicin 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 a CR/CRi within 3 cycles should discontinue treatment.

The dosing schedule is shown in Table 8.

Table 8. Dosing Schedule: Inotuzumab Ozogamicin Starting Dose of 1.8 mg/m^2/cycle (administered in 3 divided doses)

	Day 1	Day 8[a]	Day 15[a]
Dosing regimen for Cycle 1 (1.8 mg/m^2/cycle)			
All patients:			
Dose[b]	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	21 days[c]		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR[d] or CRi[e] (1.5 mg/m^2/cycle)			
Dose[b]	0.5 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days[f]		
Patients who have not achieved a CR[d] or CRi[e] (1.8 mg/m^2/cycle)			
Dose[b]	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days[f]		

Abbreviations: CR=complete remission; CRi=complete remission with incomplete hematologic recovery.

a. ±2 days (maintain minimum of 6 days between doses).

b. Dose is based on the patient's body surface area (m^2).

c. For patients who achieve a CR or a CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (ie, 7-day treatment free interval starting on Day 21).

d. CR is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥100 × 10^9/L and absolute neutrophil counts [ANC] ≥1 × 10^9/L) and resolution of any extramedullary disease.

e. CRi is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets <100 × 10^9/L and/or ANC <1 × 10^9/L) and resolution of any extramedullary disease.

f. 7-day treatment free interval starting on Day 21.

Infusions of inotuzumab ozogamicin must be completed according to time frames specified in the IP manual.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a

minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IP manual for instructions how to prepare inotuzumab ozogamicin for administration.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product manual (IP manual). All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the Investigational Product Manual for instructions on how to prepare inotuzumab ozogamicin for administration. Inotuzumab ozogamicin should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

6.3. Assignment to Study Intervention

This is an open-label, single-arm study; randomization codes will be distributed to sites manually by sponsor, and the investigators at the sites will record the randomization codes on the CRF. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Investigational product will be dispensed at the study visits summarized in the SoA.

Returned investigational product must not be redispensed to the participants.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

The site will complete the required dosage Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6. Dose Modification

6.6.1. Recommended Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule. In the event of toxicity, dosing may be delayed as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur as follows:

Within a cycle: dose interruption until adequate recovery or omission of a dose during a given treatment cycle. Between cycles: next cycle administration may be postponed due to toxicity in the previous cycle. In the next cycle: dose reduction based on worst toxicity observed in the previous cycle.

6.6.2. Dose Reductions

Dose reductions may be required based on the worst toxicity experienced in the previous cycle. Dose reductions or omissions of drug should be based on institutional guidelines or standard of care. Patients experiencing a treatment interruption due to test article-related toxicity ≥14 days will resume dosing with a single 25% reduction in inotuzumab ozogamicin for the subsequent cycle (0.5 mg/m2, to 0.375 mg/m2) once adequate recovery is achieved. If further dose modification is indicated after a 25% dose reduction, the number of doses within the cycle should be reduced to two for subsequent cycles. Dose reduction of inotuzumab ozogamicin by 25% is recommended for patients with CRi, whose platelet counts have not recovered to those values obtained prior to the start of the previous cycle.

Once a participant has a dose reduction for a drug-related toxicity, the dose will not be re-escalated. Participants who are unable to tolerate a 25% dose reduction followed by a decrease in the number of doses per cycle to two doses will be withdrawn from treatment unless otherwise agreed between the investigator and the sponsor.

6.7. Continued Access to Study Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

6.8. Treatment of Overdose

For this study, any dose of inotuzumab ozogamicin greater than the 110% of 0.8 mg/m^2 within a 24-hour time period ±2 hours will be considered an overdose.

There is no specific antidote for an overdose of inotuzumab ozogamicin and treatment of overdose should therefore consist of general supportive measures.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until inotuzumab ozogamicin can no longer be detected systemically (at least 9 weeks).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

Overdose will be recorded in the CRF related page.

6.9. Prior and Concomitant Therapy

6.9.1. Concomitant Medications

The start date, stop date, and indication for all concomitant treatments and/or therapies, including vaccines, blood products, as well as nondrug interventions received by participants from screening until 4 weeks after the last dose of investigational product (ie, through end of treatment visit) will be recorded on the case reports form (CRF). Treatment and/or therapies for adverse events will be recorded on the CRF up through 9 weeks after the last dose of inotuzumab ozogamicin (see Section 1.3). In the Follow-up period, select concomitant medications including antifungals, prophylaxis/treatment for GvHD, and prophylaxis/treatment for VOD (including ursodeoxycholic acid or defibrotide) will be collected in the CRF for up to at least 100 days after a subsequent HSCT (Section 1.3). Also, in case of severe liver toxicity following subsequent HSCT warranting an SAE report, include details regarding these concomitant medications such as the actual dose used, start and stop dates and clinical response to their use. Data collected in the context of their use will be provided as part of the final clinical study report.

6.9.2. Permitted Concomitant Medications

Any medication for a concurrent medical condition is permitted and will be supplied by the study site.

During the treatment period, the use of hydroxyurea is permitted for temporary control of WBC elevations in patients with aggressive disease both prior and during the first 5 days of study treatment. Reduction of peripheral blast counts to at least 10,000/μL is required for enrollment and may improve the initial PK profile of inotuzumab ozogamicin. Hydroxyurea may be given at 1 to 5 grams daily for up to 5 days in Cycle 1.

Concurrent therapy for CNS prophylaxis/treatment is strongly encouraged (eg, intrathecal methotrexate).

Growth factors such as granulocyte colony stimulating factor (G-CSF), including pegfilgrastim, and granulocyte macrophage colony stimulating factor (GM-CSF) may be used in accordance with local guidelines and medical practice.

Platelet transfusions should be given if clinically indicated but cannot be used to meet dosing criteria prior to the start of subsequent cycles.

Corticosteroids are allowed for cytoreduction, CNS prophylaxis/treatment, as premedication for up to 1 day, to treat hypersensitivity reactions for up to 1 day, and as antiemetic for up to 8 days/cycle as supportive care. Intranasal, inhaled, or topical corticosteroids are allowed, as are low doses of corticosteroids (10 mg or less of prednisone or equivalent/day) throughout study participation. Higher doses of steroids are discouraged if alternative therapy is available. It is crucial to enter dosing details for systemic corticosteroids administered in the CRF due to their possible influence on the study endpoints.

6.9.3. Prohibited Concomitant Medications

Craniospinal radiation (CSXRT) is prohibited during study treatment. If CSXRT is clinically indicated, the patient should be withdrawn from study therapy.

Anti-cancer therapy other than as defined/allowed in this protocol and other investigational agents are prohibited throughout the treatment period of the study.

6.9.4. Discouraged Concomitant Medications

Patients should be strongly encouraged to avoid herbal supplements throughout the treatment period of the study.

Concomitant use of inotuzumab ozogamicin with drugs known to prolong the QT interval or induce Torsades de Pointes may increase the risk of a clinically significant QTc interval prolongation. Discontinue or use alternative concomitant drugs that do not prolong QT/QTc interval during inotuzumab ozogamicin treatment. When it is not feasible to avoid concomitant use of drugs known to prolong QT/QTc, obtain ECGs and electrolytes prior to the start of treatment, after initiation of any drug known to prolong QTc, and periodically monitor as clinically indicated during treatment. See Section 10.8, Appendix 8 for a list of medications.

At clinically relevant concentrations, N-acetyl-gamma-calicheamicin (which is released from inotuzumab ozogamicin following hydrolytic cleavage of the ADC linker) had a low potential to inhibit or induce cytochrome P450 enzymes, inhibit uridine glucuronyltransferase (UGT) enzymes, or inhibit drug transporters (p-glycoprotein, breast cancer resistance protein (BCRP), organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3. At clinically relevant concentrations, inotuzumab ozogamicin had a low potential to inhibit or induce cytochrome P450 enzymes.

6.9.5. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with inotuzumab ozogamicin; standard medical supportive care must be provided to manage AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Per the study estimands, if investigational product is permanently discontinued, the participant will remain in the study and continue to be followed for protocol specified follow up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information.

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Objective disease progression;
- Lack of efficacy
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety, disease assessments, subsequent anticancer therapies, and survival. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further\ receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

Following the discontinuation from the treatment, patients will be followed for:

1. Disease progression for up to 2 years from the first dose, unless the disease progressed during the treatment.
2. Potential VOD/SOS cases, irrespective of grade or causality for up to 2 years from the first dose.
3. Survival for up to 2 years from the first dose.

7.1.1. Temporary Discontinuation

7.1.1.1. Redosing Criteria and Dose Delays

Unless patients meet the following criteria prior to the start of each cycle, all study therapy will be delayed.

1. No evidence of progressive disease. See Appendix 7 for outcome definitions. Study treatment may be continued in patients with isolated CNS relapse, at the investigator's discretion.

2. Decrease in blast percentage or stable disease (ie, not more than a 50% increase in blast percentage) based on the most recent peripheral blood counts and bone marrow evaluation.

3. Recovery to grade 1 or baseline for non-hematologic study intervention-related toxicity (except alopecia) (prior to each dose of inotuzumab ozogamicin).

4. Total serum bilirubin $\leq$1.5 × ULN (or if elevated due to tumor, total serum bilirubin $\leq$2 × ULN), and AST, ALT $\leq$2.5 × ULN irrespective of the causality (prior to each dose of inotuzumab ozogamicin). Exception: Hyperbilirubinemia in the setting of documented Gilbert's syndrome or hemolysis.

5. Serum creatinine $\leq$2 × ULN or estimated creatinine clearance $\geq$40 mL/min as calculated using the method standard for the institution (prior to each dose of inotuzumab ozogamicin).

6. For patients with pre-treatment (C1D1) absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L: ANC$\geq 1 \times 10^9$/L.

7. For patients with pre-treatment (C1D1) platelets $\geq 50 \times 10^9$/L: platelets $\geq 50 \times 10^9$/L.

8. For patients with baseline ANC $< 1 \times 10^9$/L and/or platelets $< 50 \times 10^9$/L: ANC and platelets must recover at least to baseline values obtained for the last cycle, or ANC $\geq 1 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L, or the most recent bone marrow must demonstrate stable or improved disease, and the ANC and platelets are believed to be low due to disease, not investigational product.

9. QTcF $\leq$470 msec (average of 3 ECGs). Note: QTcF must be confirmed prior to dosing on Day 1 of Cycles 1, 2 and 4 only (irrespective of the causality, dosing must be held if average QTcF >470 msec).

10. Any hypocalcemia, hypokalemia, or hypomagnesemia must be corrected according to standard of care prior to dosing.

While doses given within a treatment cycle (ie, Days 8 and/or 15) need not be delayed due to neutropenia or thrombocytopenia, dose delays within a cycle are required for non-hematologic toxicity (see #s 3, 4, 5, 9, and 10 above). Platelet transfusions should be given if

clinically indicated but cannot be used to meet dosing criteria prior to the start of subsequent cycles.

Inotuzumab ozogamicin dosing should be permanently discontinued for any patient with possible, probable or confirmed VOD/SOS or other severe liver toxicity. For inotuzumab ozogamicin, dose delays due to test article-related toxicity ≤7 days during a treatment cycle are permitted. If dose delay is >7 days, it will result in omission of the next dose within the cycle; the patient remains eligible to receive the subsequent planned dose assuming all dosing criteria are met. If a dose within a cycle is delayed (ie, Day 8 or 15 dose is delayed), the next dose should also be delayed. A minimum of 6 days should be maintained between doses. Reason for any dose delays must be reported on dosing CRF. If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be considered Day 1 of the next cycle. If the beginning of the next cycle is delayed by more than 28 days due to test article-related toxicity/ies (Delay of Day 1 dosing beyond 42 days from prior cycle Day 15 dosing) , study treatment will be permanently discontinued unless otherwise agreed by sponsor and investigator. All toxicity grades are according to National Cancer Institute version 5.0 (NCI CTCAE v5.0).

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Withdrawal by participant;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent:

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Section 10.1 Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's standard of care and obtained before signing of the ICD may be utilized for eligibility provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.2. Efficacy Assessments

Assessment of response and progression status will be evaluated according to a modified Cheson Criteria described in Section 10.7 Appendix 7. Disease assessments are determined using information from bone marrow evaluations, laboratory assessments (eg, hematology), clinical and radiological information (eg, extramedullary disease). No bone marrow aspirate is necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation or radiological/clinical assessment. Patients with extramedullary disease prior to first dose will have radiographic assessment (computed tomography [CT] or magnetic resonance imaging [MRI]) to confirm a CR or CRi using the same method of assessment, unless contraindicated. CT scan with contrast is the preferred method of assessment.

Bone marrow aspirates (or biopsies if clinically indicated) and disease assessments (See Section 10.7, Appendix 7) will be performed at screening, at day 16-28 of cycles 1, 2 or until CR/CRi and MRD negativity are achieved. Then after every 1, 2 cycles as clinically indicated, and at end-of-treatment (EOT) visit (unless previously done within 28 days).

Bone marrow aspirates will be analyzed at the study site. A bone marrow (BM) biopsy will be done in patients achieving CRi by the investigator's assessment to evaluate cellularity.

Complete blood count (CBC) with differential and platelets, bone marrow aspirate, bone marrow biopsy as clinically indicated, plus re-evaluation of pre-existing or suspected extramedullary disease as clinically indicated should be completed at the time of each disease assessment. If a CNS disease assessment was indicated during screening, reassessments will be done as clinically indicated. (Table 1).

At any time point, an additional aspirate or biopsy may be required if the original aspirate is inadequate for disease assessment.

- For patients requiring baseline cytoreduction or palliation (eg, hydroxyurea, steroids and/or vincristine), a post-cytoreduction BM assessment is not required prior to enrollment.
- If a patient receives a more aggressive chemotherapy regimen (ie, another salvage attempt), the patient must repeat the entire screening process and must meet all eligibility criteria prior to enrollment.
- G-CSF should be discontinued at least 72 hours prior to every bone marrow assessment.

Immunophenotyping by flow cytometry will be performed in all patients at screening and will be done in patients with suspected CR and/or CRi. The leukemia phenotype and/or genotype may also be evaluated by other test methods at the discretion of the investigator.

Fluorescence in situ hybridization (FISH) analysis may be done in all patients at screening.

Karyotyping will be performed in all patients at screening and at least once in patients achieving morphologic CR or CRi and who had abnormal cytogenetics at baseline. It is recommended that 20 or more metaphases be counted for local cytogenetics analysis.

OS is the time from the first day of the first cycle to date of death due to any cause. Censorship: Patients last known to be alive are censored at date of last contact.

For determination of MRD, BMA samples will be sent to a central laboratory and evaluated by next generation sequencing (NGS) to identify and quantify the rearranged genetic sequences (eg, IgH, IgK, and IgL receptor gene sequences).

8.3. Safety Assessments

Safety endpoints include adverse events (graded according to the NCI CTCAE, version 5.0), clinical examination (including blood pressure and pulse), laboratory tests (hematology, chemistry, coagulation and urinalysis) and ECGs run in triplicate.

Additional procedures or samples may be undertaken as medically required at the discretion of the Investigator. In addition to the local laboratory tests, additional blood samples may be taken, or additional tests may be conducted in existing samples, for analyses at either central or local laboratories in order to provide the best possible guidance on improving the medical management of study patients on emerging safety findings during the conduct of the study.

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.3.1. Physical Examinations

A brief physical examination will include, at a minimum, assessments of skin, head/eyes/ears/nose/throat, heart, lungs, testes, abdomen, extremities, neurological, back/spinal, liver, spleen, and lymph nodes; Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Vital signs include blood pressure, pulse and temperature. Performed on all day's test article (inotuzumab ozogamicin) is administered for all cycles (predose and 1 hour [±15 minutes] after the end of each inotuzumab ozogamicin infusion; also performed 2 hours [±15 minutes] after the end of inotuzumab ozogamicin infusion for Cycle 1 Day 1 dose).

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Electrocardiograms

ECGs will be collected in all patients as described in Table 3. The ECGs will be collected in triplicate (3 consecutive ECGs approximately 2 minutes apart). Predose ECGs will be performed prior to dosing, but after administration of premedications. ECGs will be done immediately prior to the end of infusion prior to PK sample collection (within 15 minutes).

ECG values of potential clinical concern are listed in Section 10.6 Appendix 6.

8.3.4. Clinical Safety Laboratory Assessments

See Section 10.2 Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 9 weeks after the last dose of study intervention, unless a new anti-cancer therapy is given, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential DILI. See Appendix 12 for instructions for laboratory testing to monitor kidney function and report laboratory test abnormalities.

No need to repeat a clinical laboratory assessment on Cycle 1 Day 1 if the baseline assessment was performed within 72 hours prior to that date.

8.3.5. Hepatic Events Adjudication Commitee

The study will also use an external HEAC. This Adjudication Commitee will review safety data with respect to the potential cases of VOD/SOS and Hy's law.

8.3.6. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in woman of childbearing potential (WOCBP) at the times listed in the SoA (Table 1).

Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study treatment.

Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRB)/ECs or if required by local regulations.

8.4. Adverse Events,Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Section 10.3 Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the inotuzumab ozogamicin (see Section 7).

During the active collection period as described in Section 8.4.1, each participant/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study related procedure and/or receiving study intervention, through and including a minimum of 9 weeks after the last administration of the study intervention, except as indicated below, after the last administration of the study intervention.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

The "active collection period" for VOD/SOS is the entire duration of study participation, including the long term follow-up period, regardless of whether new anti-cancer treatment is initiated. All cases of VOD/SOS will be reported in the CRF for up to 2 years from Cycle 1 Day 1 and must be reported as SAEs (recorded on the CRF and CT SAE Report Form).

Follow-up by -the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed, and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above indicated active collection period. Note that a switch to a

commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Section 10.3 Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. Environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 8 months after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in

the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in participants with ALL independent of exposure to study intervention, can be serious/life threatening:

- Febrile neutropenia;
- Neutropenic sepsis;
- Disease progression.
- The following occurring post HSCT and after discontinuation of inotuzumab ozogamicin:
  - Acute GvHD;
  - Infection requiring IV antibiotics;
  - Hemorrhage/bleeding;
  - Weight loss/anorexia;
  - Acute kidney injury;

- Nausea/vomiting/diarrhea;
- Thrombocytopenia/anemia.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE, unless the Investigator believes that there is a causal relationship between the investigational product. These events will be recorded on the corresponding CRF page in the participant's CRF within the appropriate time frame.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.
- Grade 5 (or with an outcome of fatal).

8.4.8. Adverse Events of Special Interest

AESI constitute AEs (serious or non-serious) of scientific and medical concern in the evaluation of inotuzumab ozogamicin, for which in addition to ongoing monitoring, rapid communication by the Investigator to the Sponsor is considered appropriate. Such events may require further investigation in order to characterize and understand them. AESI may be added or removed during a study by Protocol Amendment.

Reporting of AESI With Immediate Notification

Investigator should notify the sponsor immediately (ie, within 24 hours) of the following events, as per SAE notification and/or using the pregnancy form (whichever is applicable):

- Hy's Law cases (see Section 10.5)
- Potential VOD/SOS Cases (see Section 8.4.8.2)
  - All suspected cases of hepatic SOS, irrespective of timing, causality and severity, should be reported in the AE CRF. If the event is deemed serious by the investigator, the SAE reports should include a complete list of all anticancer therapy administered before, during and after study therapy, including pre- and post-study HSCT conditioning, GVHD prophylaxis and treatment, and all concomitant medications used for prevention of hepatic toxicity (eg, ursodiol, defibrotide, low molecular weight heparin) and/or for the treatment of SOS (ie, defibrotide).

- Exposure during Pregnancy (see Section 8.4.5.1)
- Second primary malignancy

Reporting of AESI Without Immediate Notification (unless assessed as SAE [see Section 8.4.1.1 for reporting timeframe])

- Neurotoxicity
- Nephrotoxicity
- QT abnormalities (defined as Grade 3, 4, prolongation or QTcF post-baseline absolute value of >500 msec)
- Interstitial lung disease
- Pancreatitis
- Myelosuppression/cytopenia including Infections and Hemorrhages

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.8.2. Potential VOD/SOS Cases

All cases of VOD, also known as SOS, regardless of causality, severity and treatment arm must also be reported as an SAE for the entire duration of study participation up to 2 years after the first dose of inotuzumab ozogamicin, including the Follow-up period (Table 1). Events of VOD which occur thereafter should be reported following the SAE reporting criteria. In the event of serious or severe hepatic adverse events, patients should have a hepatology consultation and workup including (but not limited to), weights, infectious hepatitis testing (A, B, C). When evaluating liver toxicity, inform the radiologist of the potential for hepatic vascular disease. When VOD is in the differential diagnosis, a right upper quadrant ultrasound with color flow doppler (including resistive indices to hepatic

artery flow and evaluation of hepatic venous outflow) should be performed. In addition, the radiology report should describe common bile duct, the degree of gall bladder wall thickening in millimeters, and the volume of ascites should be estimated as closely as possible (ie, small and localized, moderate and generalized, or large and generalized). Assessment of abdominal tumor(s); collection of alcohol use information (historical, current); prior hepatitis or a related condition (either infectious or noninfectious, including nonalcoholic steatohepatitis [NASH, also known as nonalcoholic fatty liver or NAFL] and alcoholic steatohepatitis [ASH]), laboratory tests (including, but not limited to, conventional liver function tests, INR/ prothrombin time (PT), albumin, and ammonia levels), and information from liver biopsy or autopsy if performed.

Results of all assessments, signs and symptoms should be recorded in the CRF (including imaging results, biopsy results, vital signs [including changes in weight], detailed pertinent physical exam, laboratory values, nonstudy medications [including herbal supplements and herbal teas, if applicable], sites of disease other adverse events particularly recent and/or concurrent infections, and other nonstudy treatments); unplanned CRF pages can be used if necessary. Assessment (recording) of weights in a patient experiencing any hepatic event is important because it can help in the differential diagnosis, given the association of fluid retention with portal hypertension and VOD. One of the major distinctions between most acute liver disorders in oncology patients and VOD is the presence of portal hypertension, which leads to renal retention of salt and water, and thus, to abrupt gains in weight.

For this study, criteria for VOD (also known as SOS) are defined as:[20]

a. Classical VOD (first 21 days after HSCT):

   - Bilirubin ≥2 mg/dL and two (or more) of the following criteria must also be present;
     - Painful hepatomegaly;
     - Weight gain >5%;
     - Ascites.

b. Late onset VOD (>21 days after HSCT):

   - Classical VOD beyond Day 21;

   or

   - Histologically proven VOD;

   or

   - Two or more of the following criteria must be present:

- Bilirubin >2 mg/Dl;
- Painful hepatomegaly;
- Weight gain >5%;
- Ascites.

AND hemodynamical and/or ultrasound evidence of VOD.

For this study, severity of VOD is defined as follows (Table 9).

Table 9. VOD Severity Grading (Patients Belong to the Category that Fulfills Two or More Criteria)[a]

	Mild (Grade 1)[b]	Moderate (Grade 2)[b]	Severe (Grade 3)	Very severe (Grade 4)[c]
Time since first clinical symptoms[d]	>7 days	5-7 days	≤4 days	Any time
Bilirubin (mg/dL)	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin (umol/L)	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics			doubling ≤48 hr	
Transaminases	≤2 × ULN	>2 and ≤5 × ULN	>5 and ≤8 × ULN	>8 × ULN
Weight increase	<5%	≥5% and <10%	≥5% and <10%	>10%
Renal Function	<1.2 × baseline at HSCT	≥1.2 and <1.5 × baseline at HSCT	≥1.2 and <1.5 × baseline at HSCT	≥2 × baseline at HSCT or other signs of MOD/MOF

Abbreviations:hr=hour; HSCT=hematopoietic stem cell transplant; MOD=multi-organ dysfunction; MOF=multi-organ failure; ULN=upper limit of normal.
a. If patients fulfill two or more criteria in two different categories, they must be classified in the most severe category. Patients weight increase ≥5% and <10% is considered by default as a criterion for severe VOD; however, if patients do not fulfill other criteria for severe VOD, weight increase ≥5% and <10% is therefore considered as a criterion for moderate VOD.
b. In the case of presence of two or more risk factors for VOD, patients should be in the upper grade.
c. Patients with multi-organ dysfunction must be classified as very severe.
d. Time from the date when the first signs/symptoms of VOD began to appear (retrospectively determined).and the date when the symptoms fulfilled VOD diagnostic criteria.

See also Section 10.10 Appendix 10 for guidance about recommendation for patients proceeding to HSCT and potential VOD cases.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study interevntion;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 1.35 mL of serum, will be collected for measurement of serum concentrations of inotuzumab ozogamicin and free calicheamicin as specified in the SoA (Table 1). Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF). Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

Samples will be used to evaluate the PK of inotuzumab ozogamicin and free calicheamicin. Each serum sample will be divided into three aliquots (1 for inotuzumab ozogamicin and 2 for free calicheamicin). Samples collected for analyses of inotuzumab ozogamicin and free calicheamicin concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Samples collected for measurement of serum concentrations of inotuzumab ozogamicin and free calicheamicin will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6. Genetics

8.6.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7. Biomarkers

Unless prohibited by local regulations (HGRAC, etc.) or ethics committee decision(s), the following samples will be collected from all participants in this study as specified in the SoA.

Bone marrow aspirate (BMA) for minimal residual disease (MRD): BMA sampling will be collected at time points specified in the SoA. MRD will be evaluated using next generation sequencing (NGS) to identify and quantify the rearranged genetic sequences (eg, IgH, IgK, and IgL receptor gene sequences) at a central laboratory. This unique immunoglobulin receptor repertoire defines the patient-specific malignant B lymphocyte clone and is used as a baseline reference for comparison to subsequent samples. On-treatment BMA samples are used to monitor for the identified clones. MRD analysis will be done at least once in patients with prior assessment of CR or CRi.

CD22 immunophenotyping performed at screening on peripheral blood or bone marrow aspirate. Surface CD22 expression should be measured by fluorescence-activated cell sorter (FACS); immunohistochemistry (IHC) analysis is allowed in patients with 1) dry tap or 2) if BM aspirate was inadequate and/or with insufficient circulating blasts for FACS.

FISH: Bone marrow aspirates may also be analyzed by fluorescence in situ hybridization analysis (FISH) for detection of chromosomal aberrations at screening.

Karyotyping will be performed in all patients, at screening and at least once in patients achieving CR or CRi who had abnormal cytogenetics at baseline. It is recommended that 20 or more metaphases be counted for cytogenetics analysis.

8.8. Immunogenicity Assessments

8.8.1. Analysis of Anti-Inotuzumab Ozogamicin Antibodies and Neutralizing Anti-Inotuzumab Ozogamicin Antibodies

Blood samples will be collected for determination of ADA and NAb against inotuzumab ozogamicin as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample collection will be recorded on the CRF.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. Unless prohibited by local regulations or ethics committee decision, these data will be used for internal exploratory purposes.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

The primary objective of this study is to evaluate the treatment effect with inotuzumab ozogamicin, by demonstrating a greater CR/CRi rate than that observed with historical

control. The statistical hypotheses for the primary endpoint CR/CRi per investigator's assessment are the same as those used in global pivotal Phase 3 Study B1931022, where based on review of the literature published historical data, the expected CR/CRi rate with historical control in the combined first and second salvage setting was approximately 37%. The observed results in the control arm in Study B1931022 didn't exceed 37% either. The study will test the null hypothesis H0: CR/CRi rate per investigator's assessment ≤37% vs the alternative hypothesis Ha: CR/CRi rate ≥61% where both hypotheses are consistent with those from study B1931022.

9.1.1. Primary Estimands

The primary estimand is the treatment effect of inotuzumab ozogamicin from the time of first dose until end of treatment regardless of tolerability, duration on treatment. The estimands includes the following 4 attributes:

- Population: Patients who meet the criteria for As-treated (Section 9.3).
- Variable: the incidence of a patient with a best overall response of CR or CRi from date of the first dose to the end of treatment per Investigator's assessment according to a modified Cheson Criteria (See Section 10.7 Appendix 7).
- Intercurrent event(s): All data collected after an intercurrent event of subsequent anti-cancer therapy are excluded.

Population-level summary: Percentage of CR/CRi among the As-treated population.

9.2. Sample Size Determination

- A single-stage design will be used to test the null hypothesis (H0) with 1-sided 0.025 significance level that CR/CRi is ≤37%.
- A sample size of 44 patients is planned to provide at least 90% power to reject the null hypothesis (H0: CR/CRi rate ≤37%) when the true CR/CRi rate ≥61% under the 1-sided significance level 0.025, based on single binomial proportion test under normal approximation with empirical estimate for variance.
- Assuming exactly 44 patients are enrolled and treated, the null hypothesis will be rejected and it will be concluded that the study has demonstrated that the true CR/CRi rate exceeds 37% if 23 or more responders are observed. However, at the time of the analysis, the testing will depend on the actual number of patients enrolled.

A sufficient number of participants will be screened to achieve 44 participants enrolled and received at least one dose of inotuzumab ozogamicin.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Per Protocol Population	All patients who meet all of the following criteria: 1. Receive at least one dose of investigational product (inotuzumab ozogamicin). 2. No major protocol violations. Major violations include failure to satisfy major entry criteria or life-threatening dosing error. 3. An adequate baseline disease assessment.
Safety/As-Treated	All participants who take at least 1 dose of investigational product.
PK concentration	Subset of the As-Treated analysis set and will include participants who have at least one post-dose concentration measurement above the lower limit of quantitation.
Immunogenicity	Subset of the As-Treated analysis set and will include participants who receive at least 1 dose of investigational product (inotuzumab ozogamicin) and have at least 1 ADA sample collected and analyzed for immunogenicity

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	**CR/CRi per investigator's assessment** • Using normal approximation method with empirical estimate for variance to test the hypothesis H_0: CR/CRi rate ≤37% vs H_a: CR/CRi rate ≥61%. • Estimate the CR/CRi rate per investigator's assessment and corresponding two-sided 95% CI using normal approximate method for all participants received at least one dose of investigational product from the time of first dose until the end of treatment. • This analysis is based on As-Treated population. Patients with death prior to first post-baseline assessment, inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders. Data collected after the end of treatment will be excluded from the analysis. • Sensitivity analysis may be conducted in the per-protocol analysis set.
Secondary	**DoR** • DoR will be defined as the time from date of first response in responders (CR/CRi) to the date of disease progression (ie, objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), death due to any cause, whichever occurs first (including post-study treatment follow-up disease assessments). • Using the Kaplan-Meier method, plot the estimation of the survival function and estimate its associated statistics on DoR (including the median DoR with two-sided 95% CI) for responders to investigational product without regard to discontinuation from treatment. This analysis is based on responders in the As-Treated population. Patients with an event more than 28 weeks after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment that documented no progression. The CI for the median DoR will be calculated according to Brookmeyer and Crowley method. **MRD negativity in patients achieving CR/CRi.** • The percentage of patients who achieve MRD-negativity between the date of CR/CRi and end of treatment will be

Endpoint	Statistical Analysis Methods
	analyzed. And the MRD-negativity will be defined as malignant B lymphocytes occurring at a frequency of $<10^{-4}$. • The number and percentage of patients with MRD negativity in patients achieving CR/CRi will be summarized descriptively with corresponding two-sided 95% CI. This analysis is based on responders in the As-Treated population. **PFS** • PFS will be defined as the time from date of first dose to the date of disease progression (ie, objective progression, relapse from CR/CRi), or death due to any cause, whichever occurs first. • Using the Kaplan-Meier method, plot the estimation of the survival function and estimate its associated statistics on PFS (including the median PFS with two-sided 95% CI, the PFS rates at clinical meaningful timepoints with two-sided 95% CI) for all participants received at least one dose of investigational product without regard to discontinuation from treatment. This analysis is based on As Treated population. Patients without a PFS event at time of analysis will be censored at the date of last valid disease assessment. Patients with documentation of a PFS event after an unacceptably long interval (>28 weeks if there was post-baseline disease assessment, or >12 weeks if there was no post-baseline assessment) since the previous disease assessment will be censored at the date of the previous assessment (date of first dose if no postbaseline assessment). The CI for the median PFS will be calculated according to Brookmeyer and Crowley method, and the CIs for the survival function estimates at the timepoints will be derived using the log(-log) method • A sensitivity analysis of PFS will be based on defining PFS as the time from date of first dose to the date of disease progression (ie, objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), death due to any cause, or starting new induction therapy/post-therapy HSCT without achieving CR/CRi, whichever occurs first (including post-study treatment follow-up disease assessments). **OS** • OS will be defined as the time from first dose to death due to any cause. • Using the Kaplan-Meier method, plot the estimation of the survival function and estimate its associated statistics on OS

Endpoint	Statistical Analysis Methods
	(including the median OS with two-sided 95% CI, the OS rates at clinical meaningful timepoints with two-sided 95% CI) for patients received at least one dose of investigational product without regard to discontinuation from treatment and start of new anti-cancer therapy. This analysis is based on As-Treated population. Patients without confirmation of death will be censored on date of last contact. The CI for the median OS will be calculated according to Brookmeyer and Crowley method, and the CIs for the survival function estimates at the timepoints will be derived using the log(-log) method. **HSCT** • HSCT post inotuzumab ozogamicin will be summarized by descriptive analyses (ie, the number, percent of patients underwent HSCT along with 2-sided 95% CI). This analysis is based on As Treated population.

9.4.2. Safety Analyses

The safety analysis will be conducted on the safety population. AEs will be presented with and without regard to causality based on the Investigator's judgment. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described. Additional summaries will be provided for AEs that are observed with higher frequency.

Rate of VOD/SOS (total, on-study treatment, and post-HSCT) will be summarized in the safety population. Descriptive analyses (ie, the number, percent of patients with VOD along with 2-sided 95% CI) will be presented. A subgroup analysis will also be conducted for VOD in patients who undergo HSCT in the safety population. Analyses in this subgroup will include an assessment of VOD in all patients with a subsequent HSCT as well as in patients who proceed to HSCT directly after inotuzumab ozogamicin treatment (without an intervening induction therapy). All known cases of VOD, regardless of causality and severity, will be reported as SAEs for the entire duration of study participation, including the Follow-up period.

Drug exposure will be summarized using descriptive statistics.

Laboratory data will be summarized by the type of laboratory test. Summary of Laboratory abnormalities will be presented by maximum CTCAE Grade. A shift summary of baseline grade by maximum post-baseline grade will also be presented. Parameters which cannot be graded will be summarized relative to the normal range (ie, higher or lower than normal range). Vital signs data will be summarized using descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (ie, unscheduled assessments will be excluded).

The number and percentage of patients with abnormal findings in physical examination will be summarized by body system for each nominal assessment timepoint.

Exploratory analysis may be performed to assess relationship between CD22 and efficacy (including MRD) and/or safety outcomes if data permit, the details will be decrypted in the SAP.

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetics Analysis

Analyses of the PK data will be conducted on the PK concentration population.

Descriptive summary statistics will be provided for plasma concentration at scheduled visits. Plasma concentration value below the limit of quantitation will be treated as zero in the descriptive statistics calculation. N, mean, standard deviation, percent coefficient of variation (%CV), median, range, geometric mean and geometric %CV will be presented by cycle, day and nominal time in tabular form.

9.4.3.2. Population Pharmacokinetic (PK) Analysis Modeling

PK data from this study may be analyzed using compartmental modeling approaches and may also be pooled with data from other studies to investigate any association between inotuzumab ozogamicin exposure and biomarkers or significant safety and/or efficacy endpoints. The results of these modeling analyses, if performed, will be reported separately from the clinical study report.

9.4.3.3. Immunogenicity Analysis

The percentage of patients with positive ADA and NAb will be summarized. The magnitude (titer), time of onset and duration of ADA/NAb will also be described if data permit.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

9.5.2. Hepatic Events Adjudication Commitee (HEAC)

The study will also use a HEAC. This adjudication committee will review safety data with respect to the potential cases of veno-occlusive disease and Hy's law cases. Additional information is in HEAC charters maintained by the Sponsor.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or his/her legally authorized representative must be informed that his/her personal study related data will be used by the sponsor in accordance with local data protection law.The level of disclosure must also be explained to the participant or his/her legally authorized representative.

The participant or his/her legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current IRB/EC version of the ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative (if allowed by local regulations).

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient level data or full CSRs for the purposes of "bona fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including the definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data is to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly

provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data, and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered into the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Pfizer intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the study team on demand (SToD) system.

To facilitate access to the investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant, and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site..

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 10. Protocol-Required Safety Laboratory Assessments

Hematology Panel	Chemistry Panel	Coagulation Panel[2]	Urinalysis[3]	Hepatitis Screening	Pregnancy Tests
WBC count with differential including **blast count**[1]	Sodium	INR or prothrombin time (PT)	pH	Hepatitis B surface antigen (HbsAg)	For female participants of childbearing potential, beta-human chorionic gonadotropin (ß-HCG) serum or urine pregnancy test
	Potassium	Activated partial thromboplastin time or partial thromboplastin time (APTT or PTT)	Protein or albumin	Antibody to hepatitis C virus (anti-HCV)	
Hemoglobin	Magnesium		Urine protein to creatinine ratio[3,5]		
Platelet count	Calcium		Blood/hemoglobin		
	Creatinine		Ketones or acetone		
	Albumin				
	Alanine aminotransferase (ALT)				
	Aspartate aminotransferase (AST)				
	Glucose				
	Phosphorus				
	Total Bilirubin				
	Direct bilirubin only if total is elevated				

Table 10. Protocol-Required Safety Laboratory Assessments

Hematology Panel	Chemistry Panel	Coagulation Panel[2]	Urinalysis[3]	Hepatitis Screening	Pregnancy Tests
	Blood urea nitrogen (BUN) or urea				
	Uric acid or urate				
	Alkaline phosphatase				
	Lactate dehydrogenase (LDH)				
	Gamma-glutamyl transpeptidase (GGT)				
	Total protein				
	Amylase and/or Lipase[4]				

1. Preferably absolute values will be recorded in the CRF. Percentage will be recorded only if the absolute value is not reported at the local laboratory.
2. Coagulation: includes PT/INR (collected at screening, up to 72 hours predose of day 1 of each cycle and EOT). PTT or APTT required at screening and end-of-treatment visits only.
3. Urinalysis: conducted at screening, within 72 hours prior to dosing of Cycle 4 Day 1, and the end-of-treatment visit. Urine protein to creatinine ratio will be calculated at screening and End of treatment only.
4. Both amylase and lipase are required. However, at sites where one or the other is not performed, either the amylase or lipase test will be done. The same test will be performed throughout the study.
5. In the event the site laboratory does not perform urine protein measurements, a urine albumin to creatinine ratio will be obtained and recorded in the CRF.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms;
  - Requires additional diagnostic testing or medical/surgical intervention;
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or

outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) , that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study, the event leading to death must be recorded as an

AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section) if it occurs during the active collection period.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting SAE information is not the same as the AE page of the CRF. When the same data is collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
**__EDB__ is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
***__Environmental or occupational exposure:__ AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and grade it according to the NCI-CTCAE (Version 5.0)

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the SRSD(s) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 5 months after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s)

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 8 months after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential and Non-Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
     - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone releasing system (IUS).
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral;
    - intravaginal;
    - transdermal.
2. Progestogen only hormone contraception associated with inhibition of ovulation:
    - oral;
    - injectable.

Sexual abstinence

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be

evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a TBili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, GGT, PT/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New onset type I second degree- (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New onset left bundle branch block (QRS complex >120 msec).
• New onset right bundle branch block (QRS complex >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm),

and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).

- Type II second degree (Mobitz II) AV block.
- Complete (third degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second or third degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia is classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.7. Appendix 7. Outcome Definitions

The below outcome definitions will be used for reporting of disease assessments:[21]

- Complete response (CR) is defined as a disappearance of leukemia as indicated by<5% marrow blasts and the absence of peripheral blood leukemic blasts, with recovery of hematopoiesis defined by ANC ≥1000/µL and platelets ≥100,000/µL. C1 extramedullary disease status is required.

- Complete response with incomplete count recovery (CRi) is defined as CR except with ANC <1000/µL and/or platelets <100,000/µL.

- Partial response (PR) is defined as an improved or no worsening of ALL as indicated by no peripheral blood blasts, neutrophils ≥1000/µL, platelets ≥100,000/µL, and either or both of the following:

  - At least a 50% decrease in the marrow blast percentage, compared to the pretreatment value, and marrow blast percentage ≥5% and ≤25%;

  - C2 extramedullary disease status.

- Treatment failures are defined as patients who fail to achieve CR, CRi or PR will be classified according to the type of failure:

  - Resistant disease: Patient survives ≥7 days following completion of initial treatment course and has persistent leukemia in the most recent peripheral blood smear or bone marrow and/or persistent disease involvement at any extramedullary site after completion of therapy.

  - Death during aplasia: Patient survives ≥7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow without leukemic blasts.

- Indeterminate:

  - Patient survives <7 days after completion of initial treatment course.

  - Patient survives ≥7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination or extramedullary disease examination.

- Relapse from CR or CRi:

  - Appearance of leukemic blasts in the peripheral blood.

  - Appearance of extramedullary disease.

- ≥5% blasts in the bone marrow not attributable to another cause (eg, recovery of normal cells following chemotherapy-induced aplasia). If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is ≥5% but <20%, then a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage is 5% is necessary to establish relapse.

- Progressive disease is defined as a doubling of peripheral blasts with an absolute increase of $>5 \times 10^9$/L and/or appearance of or progression of extramedullary disease.

The following criteria will be used for evaluation of extramedullary disease:

- Measurable extramedullary disease: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), or other conventional technique and a greatest transverse diameter (GTD) of 1 cm or greater; or palpable lesions with both diameters ≥2 cm. Note: although computed tomography scans remain the standard for evaluation of nodal disease, radiographic scans are not required for patients with easily palpable/superficial nodes.

- Non-measurable extramedullary disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques or disease documented by indirect evidence only (eg, lab values).

Extramedullary disease status:

- C1: Complete disappearance of all measurable and non-measurable extramedullary disease with the exception of lesions for which the following must be true: For patients with at least one measurable lesion, all nodal masses >1.5 cm in GTD at baseline must have regressed to ≤1.5 cm in GTD and all nodal masses ≥1 cm and ≤1.5 cm in GTD at baseline must have regressed to <1 cm GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. All diseases must be assessed using the same technique as at baseline.

- C2: Patient does not qualify for C1 status.

10.8. Appendix 8: List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S.®
Escitalopram	Lexapro®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondensetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sevoflurane	Ulane®, Sojourn®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Zactima®

Reference: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://crediblemeds.org/everyone/composite-list-all-qtdrugs. See website for current list and refer to the relevant package insert.
* Zofran: intravenous (IV) dose >16 mg (reference, 29Jun2012 US FDA Drug Safety Communication; US FDA website http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm).

10.9. Appendix 9. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

10.10. Appendix 10. Recommendation for Patients Proceeding to Transplant and Potential VOD Cases

- For patients planning to receive HSCT, it is recommended that treatment with inotuzumab ozogamicin be limited to 2 cycles; a third cycle may be given for patients not achieving CR/CRi with MRD negativity after 2 cycles.
- The risk of relapse must be balanced against the potential risk of toxicity associated with beginning HSCT soon after the last dose of inotuzumab ozogamicin. In Phase 3 Study B1931022, the median time between last dose of inotuzumab ozogamicin and HSCT for patients proceeding directly to HSCT was 4.9 weeks (range: 1- 19 weeks).
- Healthcare providers should use their clinical judgment to determine the most appropriate course of therapy for prophylactic treatment of VOD before the start of conditioning therapy according to standard of care (eg, prophylactic ursodeoxycholic acid* [proprietary names include Actigall®, Urso®, and Ursodiol®] at 12-15 mg/kg/day), beginning 2 weeks before the start of conditioning therapy.[22,23]
- Use the least hepatotoxic conditioning regimen and, specifically, avoid using regimens that contain 2 alkylating agents and or that combine an alkylating agent with higher dose total body irradiation (TBI) (defined as >12 Gy).
- If using a busulfan containing conditioning regimen, please consider using pharmacokinetically dosed busulfan.[24]
- When possible, avoid the concomitant use of hepatotoxic drugs peri transplant.
- If significant liver toxicity occurs, consult a gastroenterology and/or hepatology service.
- When evaluating liver toxicity, inform the radiologist of the potential for hepatic vascular disease. When VOD is in the differential diagnosis, a right upper quadrant ultrasound with color flow doppler (including resistive indices to hepatic artery flow and evaluation of hepatic venous outflow) should be performed. In addition, the radiology report should describe the degree of gall bladder wall thickening in millimeters and the volume of ascites should be estimated as closely as possible (ie, small and localized, moderate and generalized, or large and generalized).
- Defibrotide** may be used in the setting of severe VOD.[25] In Phase 3 Study B1931022, 4/8 inotuzumab ozogamicin treated patients who had Grade 3 or 4 VOD after a follow up HSCT and who were treated with defibrotide recovered. The median duration of defibrotide treatment was 20 days. Of note, inotuzumab ozogamicin treated patients with Grade 3 or 4 VOD after a follow up HSCT and not treated with defibrotide did not recover.
- If a patient will proceed to HSCT under the care of different physicians, this recommendation should be reviewed with the new treating physicians.

*Ursodeoxycholic acid is authorized for use by regulatory authorities in China.

**Defibrotide is not authorized for use in China.

10.11. Appendix 11. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This section applies for the duration of the COVID-19 pandemic in China and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business-as-usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.11.1. Eligibility

While COVID-19/SARS-CoV-2 testing is not mandated for entry into this study, testing should follow local clinical practice standards. If a participant has a positive test result for COVID-19/SARS-CoV-2 infection within 14 days prior to enrollment, is known to have asymptomatic infection or is suspected of having COVID-19/SARS-CoV-2, they are excluded.

10.11.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow-up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments may be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to study protocol Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.11.3. Alternative Facilities for Safety Assessments

10.11.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The safety laboratory evaluations may be performed at a local laboratory, including pregnancy testing.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.11.3.2. Imaging

If the participant is unable to visit the study site for CT scans or MRI, the participant may visit an alternative facility to have the CT scans, MRI, or wholebody bone scan performed, after discussion with the sponsor. Qualified study site personnel must order, receive, and review results.

10.11.3.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results. The ECG may be repeated if lead placements are reversed or incorrect.

10.11.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

The following is recommended for the administration of study intervention for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) COVID-19/SARS-CoV-2 infection:

- For symptomatic participants with active COVID-19/SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of COVID-19/SARS-CoV-2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and COVID-19/SARS-CoV-2 -related symptoms should have recovered to ≤Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in study protocol Section 6.9 for any concomitant medication administered for treatment of COVID-19/SARS-CoV-2 infection.

10.11.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the SoA. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit, if permitted by local regulations:

- All safety assessments
- Required blood samples

10.11.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the medical monitor.

10.11.7. COVID-19 Vaccines

COVID-19 vaccines (approved or given by emergency use authorization) are permitted and should be recorded in the CRF. The timing of vaccine administration relative to study intervention is at the discretion of the investigator although, if possible, it is best to avoid vaccine administration during the study intervention period. COVID-19 vaccines received prior to study enrollment and during study participation will be collected in the CRF.

10.11.8. COVID-19 Infection

Participants with ALL are at increased risk of severe disease and complications from COVID-19 infection (Chari et al, 2020; Terpos et al, 2020). Participants should be regularly educated on the continuing risk and symptoms of COVID-19 infection, best practices to reduce the risk of infection including mask usage, and the importance of regular testing including at home. Participants are to be tested for COVID-19 upon exposure to COVID-19 and at signs or symptoms of COVID-19 infection (eg. new or worsening fever, cough, sore throat, shortness of breath or fatigue). Frequent reflex testing is encouraged. A positive COVID-19 test result should be immediately reported to the study investigator and documented as an AE.

Participants who develop COVID-19 infection while on study should be managed in accordance with their treating healthcare provider's standard of care and local and/or regional guidelines, considering all treatments available to study participants, including PAXLOVID™ and monoclonal antibody treatments. In accordance with standard of care

practice, it is expected that initiation of treatment will start as soon as possible and ideally within 24 hours following a positive COVID-19 test. Where feasible, the sponsor will supply PAXLOVID™ that may be used for treatment of COVID-19 in accordance with prescribing information.

10.12. Appendix 12. Kidney Safety: Monitoring Guidelines

10.12.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline (Scr measurement to eGFR [Scr-based eGFR]) or eCrCl. Baseline and post baseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.12.2. Age-Specific Kidney Function Calculation Recommendations

10.12.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021; 385:1737-49.

10.12.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to CTCAE criteria.

10.13. Appendix 13. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	2 December 2019	Not applicable (N/A)
Amendment 1	3 March 2022	This amendment is making the following changes to the original protocol: a) Remove the description of IVRS/IWRS in Section 5.4. Screen Failures. b) Remove the description of IRT in Section 6.3.1. Allocation to Investigational Product. c) Remove the description of bone marrow aspirate in Section 8.5.1. d) Updated biomarker testing assay in Section 8.8 and throughout. e) Updated the definition of secondary endpoint of MRD negativity in patients achieving CR/CRi. f) Clarifications were made throughout, including the SoA. g) The dosing regimen for inotuzumab ozogamicin in this study has been updated to be the same as that used in the NMPA-approved labeling to align with China local approval labeling.

10.14. Appendix 14: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AcBut	butanoic acid
ADA	anti-drug antibodies
ADC	antibody drug conjugate
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
Ara-C	cytosine arabinoside
ASH	alcoholic steatohepatitis
AST	aspartate aminotransferase
AV	atrioventricular
B-ALL	B-lineage ALL
BCRP	breast cancer resistance protein
β-HCG	beta-human chorionic gonadotropin
BM	bone marrow
BMA	bone marrow aspirate
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
$cAUC_{pl}$	inotuzumab ozogamicin cumulative total serum exposure during Cycle 1
C_{avg}	average serum concentration up to the time of response
CBC	complete blood count
CD	cluster of differentiation
CDE	China Center for Drug Evaluation
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{max}	maximum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete remission
CRF	case report form
CRi	incomplete hematologic recovery
CRp	CR with incomplete platelet recovery
CSF	cerebrospinal fluid

Abbreviation	Term
CSXRT	craniospinal radiation
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough plasma concentration
CTW	Clinical Trial Waiver
CV	coefficient of variation
DFS	disease-free survival
DILI	drug induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of remission
EAC	endpoint adjudication committee
EC	ethics committee
ECG	Electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EOT	End-of-treatment
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence-activated cell sorter
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLAG	fludarabine + cytarabine + granulocyte colony stimulating factor
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma glutamyl transferase
GM-CSF	macrophage-colony stimulating factor
GTD	greatest transverse diameter
GvHD	graft versus host disease
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEAC	Hepatic Events Adjudication Committee
HGRAC	Human Genetic Resource Administration of China
HIDAC	high dose cytarabine
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant

Abbreviation	Term
Hyper-CVAD	hyper cyclophosphamide, vincristine, adriamycin, and dexamethasone
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IgG4	immunoglobulin class G subtype 4
IgH	immunoglobulin heavy chain
IgK	immunoglobulin kappa light chain
IgL	immunoglobulin lambda light chain
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IP manual	investigational product manual
IPM	investigational product manual
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MOF	multiorgan failure
msec	millisecond
MRD	minimal residual disease
MUGA	Multigated Acquisition Scan
MXN	mitoxantrone
N/A	not applicable
NAb	neutralizing antibodies
NAFL	non-alcoholic fatty liver
NASH	non-alcoholic steatohepatitis
NCI	National Cancer Institute
NDA	new drug application
NGS	next generation sequencing
NHL	non-Hodgkin's lymphoma
NIMP	Non investigational medicinal product
NMPA	National Medical Products Administration
NRM	non-relapse mortality

Abbreviation	Term
NYHA	New York Heart Association
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
PAC	post approval commitment
PD	pharmacodynamic(s)
PE	physical examination
PFS	progression free survival
Ph+	Philadelphia chromosome positive
Ph-	Philadelphia chromosome negative
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QTcS	QT interval corrected for heart rate using a population specific method
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SOS	sinusoidal obstruction syndrome
SPD	sum of products of greatest diameters
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TBI	total body irradiation
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TOC	table of content
UGT	uridine glucuronyltransferase
ULN	upper limit of normal
US	United States
VOD	veno-occlusive disease

Abbreviation	Term
WBC	white blood cell
WOCBP	woman of childbearing potential

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