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

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PROTOCOL SUMMARY

Indication

Adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Background and Rationale

Inotuzumab ozogamicin (BESPONSA™) is a CD22-targeted antibody-drug conjugate (ADC) that is currently approved in the United States (US), the European Union (EU), Switzerland (approvals granted in 2017), and Japan (approval granted in 2018). Approval was based on demonstration of a positive benefit/risk for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The approved dosing regimen is a starting dose of 1.8 mg/m^2/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/cycle (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 duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve CR/CRi and minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT, up to a maximum of 6 cycles may be administered.

The activity of inotuzumab ozogamicin using this dosing regimen was demonstrated in a randomized, 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. The study had 2 primary endpoints: hematologic remission (CR/CRi, evaluated based on the first 218 patients randomized, per Endpoint Adjudication Committee assessment) and overall survival (OS; based on all 326 randomized patients after 252 OS events were observed). The study met the primary objective of CR/CRi, with rates of 80.7% versus 29.4% for inotuzumab ozogamicin and control arms, respectively (p-value <0.0001). The analysis of OS did not meet the pre-specified 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 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%] versus 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.

This Phase 4 study (B1931030) is a post-marketing requirement (PMR) that was requested by the US Food and Drug Administration and is designed to evaluate the safety and efficacy of 2 inotuzumab ozogamicin dose levels in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT.

Objectives

Primary Objective

The primary objectives are to evaluate the rates of VOD and hematologic remission (CR/CRi) for 2 inotuzumab ozogamicin dose levels in adult patients with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT. The study analysis will be descriptive only, without formal hypothesis testing.

The primary endpoints are:

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

Secondary Objective

The secondary objectives are to evaluate the safety and efficacy of 2 inotuzumab ozogamicin dose levels. Secondary endpoints include the following: adverse events and laboratory abnormalities, MRD negativity in patients achieving CR/CRi, duration of remission (DoR) in patients achieving a CR/CRi, progression-free survival (PFS), OS, rate of HSCT, post-HSCT relapse, post-HSCT mortality, post-HSCT non-relapse mortality, post-HSCT relapse-related mortality, pharmacokinetic (PK) exposure-response relationships for efficacy and safety, and immunogenicity testing for anti-drug antibodies, including neutralizing antibodies.

Study Design

This is an open-label, study of inotuzumab ozogamicin in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who have risk factor(s) for developing VOD with inotuzumab ozogamicin treatment.

The study will be conducted in 2 phases: a run-in phase and a randomized phase. In total, up to approximately 102 patients will be enrolled in the study across the 2 phases.

Run-in phase: a total of up to 22 patients will be enrolled to receive the starting dose of 1.2 mg/m^2/cycle (dose level 2). A Simon Two-Stage optimal design will be used. If acceptable efficacy (CR/CRi and MRD negativity) is observed in the run-in phase, the study will enter the randomized phase.

Randomized phase: if acceptable efficacy is observed in the run-in phase, the study will enter the randomized phase. A total of approximately 80 patients will be randomized (1:1) to 1 of 2 dose levels of inotuzumab ozogamicin (40 patients per dose level). Patients will be stratified at randomization based on age (<55 vs ≥55 years), salvage status (Salvage 1 vs ≥2), and prior HSCT (yes vs no).

The treatment period is expected to last, on average, approximately 3 months (ie, 2-3 cycles). Safety and disease assessments and PK sample collection will be conducted throughout the treatment period.

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

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

Study Treatments

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

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

Statistical Methods

This study will evaluate the safety and efficacy of 2 inotuzumab ozogamicin dose levels. Descriptive analyses, for each dose level will be provided for the primary and secondary endpoints. Other than the Simon Two-Stage Design in the run-in phase, no formal hypothesis testing will be conducted.

A total of up to 22 patients will be enrolled in the run-in phase. In order to minimize the expected number of patients enrolled in the event that the lower dose level (1.2 mg/m^2/cycle of inotuzumab ozogamicin, dose level 2) proves to be of minimal efficacy benefit, a Simon Two-Stage optimal design will be used for the run-in phase. The run-in phase will test the null hypothesis (H_0) that the CR/CRi rate is ≤31.2% versus the alternative hypothesis (Ha) that the CR/CRi rate is ≥57% (ie, predicted based on the exposure response model) with a significance level of 0.10 and 80% power.

Seven (7) patients will be enrolled in Stage 1. If ≤2 CR/CRi responders are observed in Stage 1, accrual will be stopped for further evaluation. Once at least 3 (ie, 42.9%) CR/CRi responders are documented, an additional 15 enrolled patients will be evaluated in Stage 2. If ≥10 CR/CRi responders are observed in the total of 22 patients from both stages, it will be concluded that the true CR/CRi rate for the lower dose is higher than the historical control (31.2% for Study B1931022 control arm subgroup of patients with risk factors for VOD post-HSCT).

The expected MRD negativity rate among the patients who achieve CR/CRi is ≥70%. With ≥10 CR/CRi responders expected at the end of Stage 2, the expected number of patients with MRD negativity among the 22 patients in the run-in phase is ≥7. Given a CR/CRi rate of 57%, predicted by the exposure response model, and ≥70% expected MRD negativity rate among CR/CRi responders, 40% is the expected MRD negativity rate among all patients enrolled in the run-in phase. Twenty-two (22) patients will also provide 80% power to reject the null hypothesis of the MRD negativity rate ≤20% when the alternative hypothesis of the true MRD negativity rate is ≥40% with significance level of 0.10. There will be 84% probability to observe a minimum of 7 patients who have achieved MRD negativity if the true MRD negativity rate is at least 40%.

To review the totality of the efficacy data, DoR will also be analyzed for the run-in phase. Safety data will also be reviewed for the run-in phase.

Once at least 10 CR/CRi responders and at least 7 patients achieving MRD negativity are documented among the 22 patients in the run-in phase, patients enrolled in the randomized phase will then be evaluated, with approximately 80 patients randomized (1:1) to the approved dose level of 1.8 mg/m^2/cycle (dose level 1, Arm 1) or the lower dose level of 1.2 mg/m^2/cycle (dose level 2, Arm 2).

Until analyses for decision-making are completed, enrollment will continue between Stage 1 and Stage 2 of the run-in phase and between the run-in and randomized phases of the study.

At the end of the study, descriptive analyses will be conducted. For the randomized phase, a sample size of 40 patients per arm will provide the estimated VOD rate in each dose level with a maximum standard error (SE) of 0.08. The maximum SE estimated for other binary endpoints in each dose level (eg, CR/CRi rate) will also be 0.08. In addition, for summary of dose level 2, patients in the run-in phase will be combined with Arm 2 of the randomized phase, for a sample size of approximately 62 patients (ie, 22 patients enrolled in the run-in

phase and 40 patients enrolled in Arm 2 in the randomized phase) to provide the above-mentioned estimated rates with a maximum SE of 0.06.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections 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 on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Schedule of Activities

Activity	**Screen**[1] -28 days from randomization	**Inotuzumab Ozogamicin Treatment Cycle**			**End of Treatment (EOT)**[2] (All patients: 4 -6 weeks from the last dose of study drug)
		Study Visit (Window, days)			
		Day 1 (± 2)	**Day 8** (± 2)	**Day 15** (± 2)	**EOT** (± 3)
Informed Consent[1]	X				
Review study eligibility (inclusion and exclusion criteria)	X				
CD22 Immunophenotyping[3]	X				
Antibodies to inotuzumab[4]		X			X
Medical History (including cancer history and prior treatments and therapies)	X				
Weight/height[5]	X	X			X
Vital Signs and Physical Examination[6]	X	X	X	X	X
ECOG PS	X				X
Hematology[7]	X	X	X	X	X
Blood Chemistry[7]	X	X	X	X	X
Coagulation[8]	X	X			X
Pregnancy test[9]	X	X			X
Contraception check[10]	X	X			X
HbsAg and anti-HCV[11]	X				
ECG[12]	X (3-28 days prior to randomization)	X			X
Pharmacokinetics		See Table 3 for time points			
Randomization[13]	X				
Premedications		X	X	X	

Activity	**Screen**[1] -28 days from randomization	**Inotuzumab Ozogamicin Treatment Cycle**			**End of Treatment (EOT)**[2] (All patients: 4 -6 weeks from the last dose of study drug)
		Study Visit (Window, days)			
		Day 1 (± 2)	**Day 8** (± 2)	**Day 15** (± 2)	**EOT** (± 3)
Study Treatments		See Protocol Section 5.0			
Bone marrow aspirate and clinical disease assessments[14]	X	See table footnote 14			X
Karyotyping/ Immunophenotyping/ MRD / Bone marrow biopsy[15]	X	Done in patients with suspected CR and/or CRi[15]			
Radiological Assessment[16]	X	As clinically indicated. See Appendix 1.			
Assessment of CNS disease[17]	X	As clinically indicated			
AE/SAE and concomitant medications[18]	X	Assessed throughout the study until 9 weeks from last dose of inotuzumab ozogamicin			
[redacted] CCI		[redacted]			

Abbreviations: AE=adverse event, ANC=absolute neutrophil count; antiHCV=antibody to hepatitis C virus; APTT=activated partial thromboplastin time; β-HCG=beta-human chorionic gonadotropin; BM=bone marrow; BSA=body surface area; CBC = complete blood count; CD22=cluster of differentiation-22; CNS=central nervous system; CR=complete remission; CRF=case report form; CRi=complete remission with incomplete count recovery; CT=computerized tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EMD=extramedullary disease; EOT=end of treatment; FACS=fluorescence activated cell sorting; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HSCT = hematopoietic stem cell transplant; ICD=informed consent document; IEC = independent ethics committee; IHC= immunohistochemistry; IRB = institutional review board; MRD=minimal residual disease; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK=pharmacokinetic(s); PT=prothrombin time; RNA=ribonucleic acid; SAE=serious adverse event; SOC= standard of care; VOD=veno-occlusive disease.

Additional procedures or samples may be undertaken as medically required at the discretion of the Investigator. These data may be recorded on the CRF (eg, local MRD analysis if done at the site).

1. Assessment(s) and test(s) done according to SOC 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. Results will be recorded in the CRF. However, before any collected sample is sent to the central vendor, the patient must be consented for study participation.
2. EOT visits should be performed before starting a new anti-leukemic therapy (including before subsequent 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 to 6 weeks after the last dose of study drug.
3. CD22 immunophenotyping performed at screening on peripheral blood or bone marrow aspirate by local laboratories. Surface CD22 expression should be measured by FACS; IHC analysis is allowed in patients with 1) dry tap or 2) inadequate BM aspirate and/or with insufficient circulating blasts for FACS.
4. 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 EOT visit. Analysis will be performed by a central laboratory.
5. Height required only at screening; patients must be weighed up to 72 hours prior to Day 1 of each cycle and EOT visit. 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.
6. Physical examination performed at screening and at Day 1, 8 and 15 of every cycle prior to inotuzumab ozogamicin administration. Vital signs (pulse, blood pressure, temp) required on every day of dosing for every regimen (see Section 6).

7. Serum chemistry and Hematology (see Table 1): performed at screening to determine eligibility, up to 3 days prior to randomization and up to 3 days before Day 1 of Cycle ≥2 and on 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.
8. Coagulation (see Table 4): PT/INR collected at screening, up to 72 hours predose of Day 1 of each cycle and EOT. APTT required at screening and EOT visits only.
9. For women of childbearing potential, β-HCG serum or urine pregnancy test will be performed at screening, up to 72 hours prior to Cycle 1 Day 1, at all subsequent cycles prior to dosing, and EOT. Additional pregnancy tests may be done as required by local regulations and/or IEC/IRBs.
10. Inform the patient of the need to use highly effective contraception consistently and correctly (see Section 4.3).
11. Hepatitis B (HbsAg) and C tests. Antibody to HCV and/or HCV ribonucleic acid testing may be done to confirm or rule out current HCV infection.
12. ECGs will be done at screening, prior to each cycle, and EOT. Screening ECG will be done approximately 3-28 days prior to randomization. Additional ECGs can be done if clinically required.
13. Patients must be treated within 3 days from randomization. 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.
14. Bone marrow aspirate and disease assessments (see Appendix 1) will be performed at screening, once at Day 16-28 of Cycles 1 and 2, or until CR/CRi and MRD negativity are achieved, then after every 1-2 cycles as clinically indicated, and at EOT visit (unless previously done within 28 days). Bone marrow aspirates will be analyzed at the study site. No bone marrow aspirate is necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation or radiological/clinical assessment. 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 randomization and every 24 weeks (±2 weeks) between year 1 and 2, and whenever clinically indicated, until progression (see Table 2). All disease assessment results will be captured in the CRF, even if unplanned or not required by protocol.
15. Immunophenotyping/MRD: Bone marrow aspirate, collected at screening and for remission status, will be sent to the central vendor, for immunophenotyping and assessment of MRD. MRD will be assessed by flow cytometry for cell surface markers associated with B-ALL. The leukemia phenotype and/or genotype may also be evaluated by other test methods at the discretion of the Sponsor. MRD analysis will be done at least once in patients with prior assessment of CR or CRi. A peripheral blood sample must be provided to the central vendor if a patient has an inadequate aspirate at screening.

    Karyotyping: to be performed locally, 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: Bone marrow biopsy recommended at the time of bone marrow aspirate, and is required at least once during treatment, to assess cellularity, in patients with CRi by Investigator assessment (ANC <1 x10^9/L and/or platelets <100 x 10^9/L) and as clinically indicated per local standard of care.
16. Radiological assessments (ie, CT 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. CT scan with contrast is the preferred method of assessment. See Appendix 1.
17. 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.
18. 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. All known cases of VOD (also known as sinusoidal obstruction syndrome [SOS]), regardless of causality or severity, will be reported in the CRF and as SAEs for the entire duration of study participation, including the Follow-up period (Table 2, Section 8).

CCI [redacted]

Table 2. Follow-Up

Study Procedures	Disease Follow-up[1]	Survival Follow-up[2]
Study Visit	every 12-24 weeks[1]	every 12 weeks
Serum chemistry (*limited*)[3]	X	
Hematology[3]	X	
Bone marrow aspirate and disease assessments[4]	X	
Other anticancer therapy, including HSCT, and select concomitant medications[5]	X	X
Survival status[2]	X	X
VOD reporting[6]	X	X

Abbreviations: ALT=alanine aminotransferase; AST= aspartate aminotransferase; CBC=complete blood count; CRF=case report form; HSCT=hematopoietic stem cell transplant; GGT=gamma-glutamyl transpeptidase; SAE=serious adverse event; VOD=veno-occlusive disease (VOD).

1. Disease Follow-up: For patients who have discontinued treatment but have not progressed, starting approximately 12 weeks after the last disease assessment, disease will be assessed every 12 weeks (±1 week) up to 1 year from randomization and every 24 weeks (±2 weeks) between year 1 and 2, and whenever clinically indicated, until relapse.
2. Survival follow-up: starting approximately 12 weeks (±1 week) after documented disease progression and continuing approximately every 12 weeks (±1 week) for at least 2 years after randomization. Can be conducted by telephone or email.
3. Hematology and serum chemistry (limited to total bilirubin, alkaline phosphatase, ALT, AST, GGT, and albumin) required for 1 year after randomization or until new anti-cancer treatment. For patients in disease follow up beyond a year from randomization, CBC with differential and platelets required until disease progression.
4. Bone marrow aspirate and extramedullary disease assessments (see Appendix 1). Performed every 12 weeks (±1 week) for 1 year from randomization, and every 24 weeks (±2 weeks) between year 1 and 2, and whenever clinically indicated. Disease assessments to 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 randomization). Also at least the first post study salvage therapy (re-induction) and response (refractory or responsive disease) will be reported in the CRF. HSCT information including conditioning treatments will be collected for up to 2 years from randomization. Select concomitant medications including antifungals, prophylaxis/treatment for graft versus host disease, and prophylaxis/treatment for VOD will be collected for up to at least 100 days after HSCT.
6. All known cases of VOD, also known as sinusoidal obstruction syndrome (SOS), regardless of causality or severity, will be reported on the CRF and as SAEs throughout the follow-up period (see Section 8.4.3).

Table 3. Pharmacokinetics Flowchart

Cycle 1										
Cycle Day	**1**				**4**	**8**			**15**	
Time (hours) relative to the start of inotuzumab ozogamicin administration	0	1	2	4	72	0	1	6	0	1
PK sample collection	X[1]	X[2]	X	X	X	X[1]	X[2]	X	X[1]	X[2]
Cycle 2										
Cycle Day	**1**			**8**						
Time (hours) relative to the start of inotuzumab ozogamicin administration	0	1	2	0	2					
PK sample collection	X[1]	X[2]	X	X[1]	X					
Cycles 3 and 4[3]										
Cycle Day	**1**		**8**							
Time (hours) relative to the start of inotuzumab ozogamicin administration	0	1	0							
PK sample collection	X[1]	X[2]	X							

Abbreviations: PK=pharmacokinetic.

1. Sample drawn before start of inotuzumab ozogamicin infusion.
2. Sample drawn immediately before end of inotuzumab ozogamicin infusion.
3. Cycle 4 for Arm 2 (dose level 2) only.

Table 4. Safety Laboratory Requirements

Hematology Panel:	Chemistry Panel:	Coagulation Panel[2]:	Hepatitis Screening:
White blood cell (WBC) count with differential including **blast count**[1]	Sodium	INR or prothrombin time (PT)	Hepatitis B surface antigen (HbsAg)
Hemoglobin	Potassium	Activated partial thromboplastin time (APTT) (heparin absorbed if done through central venous line)	Antibody to hepatitis C virus (anti-HCV) and/or hepatitis C ribonucleic acid testing
Platelet count	Magnesium		
	Calcium		
	Creatinine		
	Albumin		
	Alanine aminotransferase (ALT)		
	Aspartate aminotransferase (AST)		
	Glucose		
	Phosphorus		
	Total Bilirubin		
	Direct bilirubin only if total is elevated		
	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[3]		

1. Preferably absolute values will be recorded in the Case Report Form (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 3 days prior to day 1 of each cycle, and end-of-treatment visit). APTT required at screening and end-of-treatment visits.
3. 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.

1. INTRODUCTION

1.1. Indication

Adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

1.2. Background and Rationale

1.2.1. 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 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 linker.[1] 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). Approval was based on demonstration of a positive benefit/risk for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The approved dosing regimen is a starting dose of 1.8 mg/m^2/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/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 minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT, up to a maximum of 6 cycles may be administered.

1.2.2. Phase 3 Study B1931022

1.2.2.1. 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 B1930122 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/AraC). Patients with Philadelphia chromosome-positive

(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 versus ≥12 months), line of salvage (Salvage 1 versus 2), and age (<55 versus ≥55 years).[2,3]

The study had 2 primary endpoints: hematologic remission (CR/CRi, evaluated based on the first 218 patients randomized (ITT218 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.[2,3]

The study met the primary objective of CR/CRi, with rates of 80.7% versus 29.4% for the inotuzumab ozogamicin and control arms, respectively (p-value <0.0001) (Table 5). 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% versus 28.1%, respectively; median DoR, 5.4 months versus 3.5 months, respectively, Table 5). Remission, DoR, and MRD negativity results in all 326 randomized patients were consistent with those for the first 218 randomized patients (Table 5).[2,3]

Table 5. Study B1931022: Efficacy Findings for CR/CRi, DoR, and MRD Negativity

	First 218 Patients Randomized[a]		**All 326 Patients Randomized**[b]	
	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[c]	**<0.0001** ***(primary endpoint)***		<0.0001	
DoR in responding (CR/CRi) patients[d]				
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[c]	0.0031		0.0052	
MRD negativity in responding (CR/CRi) patients[e]				
N	69	9	92	19
Rate[f] (%) [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[c]	<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/AraC=mitoxantrone + cytarabine; N/n=number of patients; PFS=progression-free survival.

a. 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 × 109/L and absolute neutrophil counts [ANC] ≥ 1 × 109/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 × 109/L and/or ANC < 1 × 109/L) and resolution of any extramedullary disease. CR/CRi and MRD negativity results from planned interim analysis (data cutoff date 02 October 2014).

b. CR/CRi per Investigator's assessment. Data cutoff date 08 March 2016.

c. 1-sided p-value using Chi-squared test or Fisher's exact test (if any Chi-squared cell count <5)

d. 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.

e. MRD negativity was defined by flow cytometry as leukemic cells comprising < 1 × 10-4 (< 0.01%) of bone marrow nucleated cells.

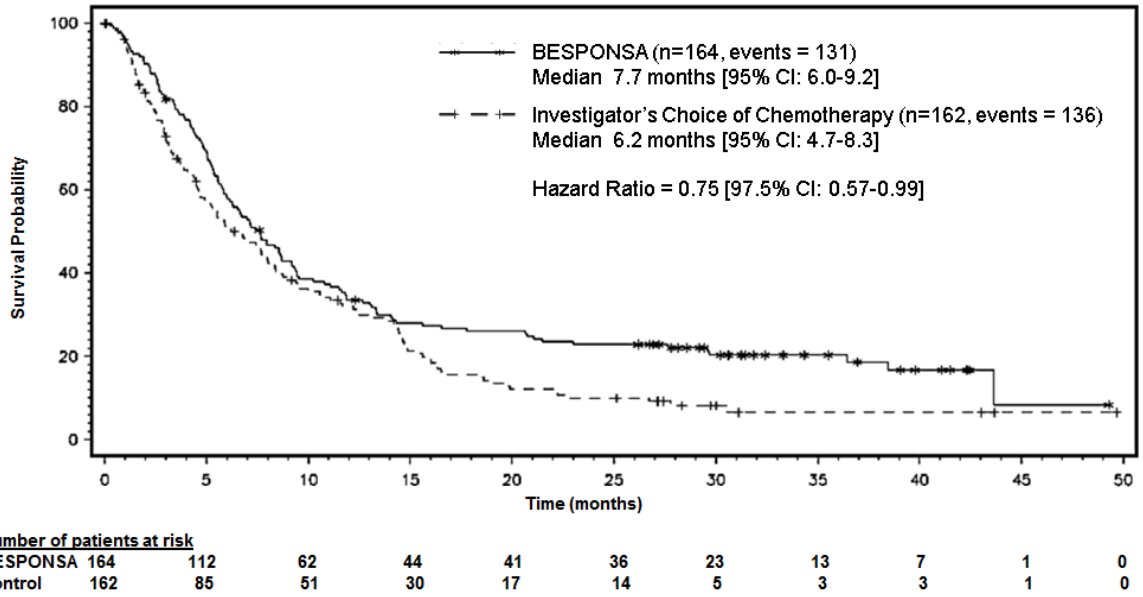
f. Rate was defined as the number of patients who achieved MRD negativity divided by the total number of patients who achieved CR/CRi per EAC (first 218 randomized patients) or per Investigator assessment (all 326 randomized patients).

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.[3] 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 analysis of OS did not meet the pre-specified boundary for statistical significance. 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).[3]

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



1.2.2.2. Pharmacokinetics

Based on pharmacokinetic (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 PK exposure-response analyses of the safety and efficacy data from Phase 3 Study B1931022 and Phase 1/2 Study B1931010 (see Section 1.2.3), 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 (cAUCP1) and the probability of VOD (VOD per assessment of the independent Hepatic Events Adjudication Board for Phase 3 Study B1931022).

1.2.2.3. 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.[3]

1.2.2.3.1. 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).[3]

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.[3]

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.[3] While VOD is a toxicity known to be associated with the hepatotoxic conditioning regimens used in HSCT,[4] the frequency of VOD post-HSCT was higher in the inotuzumab ozogamicin arm compared to the control arm (23% versus 3/34 [9%] patients, 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 (Table 6).

Table 6. Study B1931022: Association of Patient Baseline Characteristics with Occurrence of VOD Post-HSCT in Inotuzumab Ozogamicin Treated Patients

	Subsets, n	Estimate (SE)	Odds Ratio	95% CI	P-value
Univariate Analysis (N=79)					
Prior HSCT (yes, no)	11, 68	1.26 (0.68)	3.526	0.931, 13.358	0.064
Salvage status (2 or more, 1)[1]	20, 58	0.83 (0.58)	2.301	0.744, 7.117	0.148
Age (≥55, <55 years)	17, 62	1.18 (0.59)	3.245	1.012, 10.406	0.048
Prior history of liver disease/hepatitis (yes, no)	21, 58	1.08 (0.57)	2.954	0.970, 8.994	0.057

Abbreviations: CI:=confidence interval; HSCT=hematopoietic stem cell transplant; SE=standard error.
Baseline characteristics to be used in Logistic Regression model may include prior SCT (Yes, No), ALT/AST/bilirubin elevation (Yes, No), Salvage Status (2 or more, 1), age (>=55, <55), prior history of liver disease/hepatitis (Yes, No), baseline ECOG performance status (2, 0/1).
Data cutoff date 01 September 2016.

1. Salvage status missing for 1 patient.

The rates of VOD post-HSCT for inotuzumab ozogamicin treated patients with and without potential baseline risk factors is shown in Table 7.

Table 7. Study B1931022: Rate of VOD Post-HSCT for Inotuzumab Ozogamicin Treated Patients by Baseline Risk Factors for VOD Post-HSCT

Baseline Risk Factor for VOD post-HSCT	Rate of VOD Post-HSCT	
	Yes % (n/N)	No % (n/N)
Prior HSCT	45.5% (5/11)	19.1% (13/68)
Salvage status >1[1]	35.0% (7/20)	19.0% (11/58)
Age (≥55 years)	41.2% (7/17)	17.7% (11/62)
Prior history of liver disease/hepatitis	38.1% (8/21)	17.2% (10/58)

Abbreviations: HSCT=hematopoietic stem cell transplant; N=number of subjects who had follow-up HSCT and in each specified category; n=the number of subjects who had VOD as specified among the N patients. Percentage is calculated based on N of each category.
Data cutoff date 01 September 2016.

1. Salvage status missing for 1 patient.

Other characteristics that were identified as potential risk factors for VOD post-HSCT in inotuzumab ozogamicin treated patients included 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. 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.[3]

1.2.2.3.2. 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% versus 23%, respectively, Table 8). 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).[3]

Table 8. 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.

1.2.2.3.3. 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).[3]

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.[3]

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.[3]

1.2.2.3.4. 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.[3]

1.2.2.3.5. 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.[3]

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.[3] Based on the latest exposure response analysis, although there was a positive correlation between 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).

1.2.3. 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.[5]

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/cycle (n=12), or 1.8 mg/m^2/cycle (n=9).[5]

Remissions (CR/CRi) were observed across all dose levels: the CR/CRi rate was 2/3 (66.7%) for 1.2 mg/m^2/cycle, 8/16 (75.0%) for 1.6 mg/m^2/cycle, and 8/9 (88.9%) for 1.8 mg/m^2/cycle (Table 9). MRD negativity was also achieved among responders in each dose level (Table 9); time to MRD negativity was longest for the 1.2 mg/m^2/cycle group.[5]

Table 9. 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.

1.2.4. Phase 4 Study B1931030

Study B1931030 is a post-marketing requirement (PMR) requested by the US Food and Drug Administration (FDA). The study will evaluate the safety and efficacy of 2 inotuzumab ozogamicin dose levels in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT.

In this study, the currently approved inotuzumab ozogamicin dosing regimen and an alternative dosing regimen, examining a lower total dose per cycle, will be evaluated to assess whether a lower dose improves safety, and specifically reduces the rate of VOD post-HSCT, and is efficacious for patients at higher risk for VOD post-HSCT.

1.2.4.1. Selection of Dose Levels

Dose level 1 (starting dose, 1.8 mg/m^2/cycle, administered in 3 divided doses) was chosen to evaluate the safety and efficacy of inotuzumab ozogamicin at the approved starting dose in patients with a higher risk of developing VOD post-HSCT. In Study B1931022, among all enrolled patients treated with inotuzumab ozogamicin (N=164), the CR/CRi rate was 73.2% and the percentage of responding patients who achieved MRD negativity was 76.7%. In Study B1931022, the percentage of patients who developed VOD post-HSCT was 23%. Among the subgroup of Study B1931022 inotuzumab ozogamicin treated patients with ≥1 risk factors for VOD post-HSCT (prior HSCT, Salvage status >1, age ≥55 years, and/or prior history of liver disease/hepatitis [N=105]), the CR/CRi and VOD post-HSCT rates were 70.5% and 31.1% (14 /45 patients who underwent HSCT after inotuzumab ozogamicin treatment), respectively.

Dose level 2 (starting dose, 1.2 mg/m^2/cycle, administered in 3 divided doses) was chosen to evaluate the safety and efficacy of inotuzumab ozogamicin at a lower dose than the approved starting dose in order to assess whether a lower dose improves safety, and in particular reduces the risk of VOD post-HSCT, and is efficacious in patients with a higher risk of developing VOD post-HSCT. This starting dose was examined in Phase 1/2 Study B1931010. In Study B1931010, activity of 1.2 mg/m^2/cycle was shown as 2 of 3 patients treated at this dose level achieved CR/CRi (Table 9). The time to achieve CR/CRi was similar across each of the dose groups (1.2 mg/m^2/cycle, 1.6 mg/m^2/cycle, and 1.8 mg/m^2/cycle, Table 9). Both patients who achieved CR/CRi with 1.2 mg/m^2/cycle treatment, also achieved MRD negativity, though time to MRD negativity appeared to be longer for the 2 responders in this dose group compared to responders in each of the higher dose groups (Table 9).

Potential changes to safety and efficacy at this lower dose have also been estimated based on population PK exposure-response modeling. The modeling predictions, which are based on Phase 3 Study B1931022 data, are shown in Table 10. For dose level 2, assuming the same number of treatment cycles as that for dose level 1 based on Phase 3 Study B1931022 experience, the predicted CR/CRi rate is 57% (an absolute difference of 14% lower than for dose level 1), the predicted MRD negativity rate is 43% (an absolute difference of 17% lower than for dose level 1), and the predicted rate of VOD post-HSCT is 16.6% (an absolute difference of 6.8% lower than for dose level 1). The actual efficacy and safety results observed will depend on the patients enrolled, the actual dosage of inotuzumab ozogamicin received per cycle, the number of cycles received, as well as other treatment and HSCT-related factors. The number of inotuzumab ozogamicin cycles received is expected to have an impact on CR/CRi rate as the concentrations of inotuzumab ozogamicin do not reach steady state until the beginning of Cycle 4. It is anticipated that patients who do not achieve CR/CRi in Cycle 1 and continue to receive the therapy are more likely to achieve CR/CRi at later cycles since the average serum concentration is expected to be higher at later cycles, compared to Cycle 1, until a steady state concentration is achieved at the beginning of Cycle 4. Therefore, it is likely that the extent of observed differences in CR/CRi and MRD negativity between dose levels 1 and 2 will be lower than that predicted due to more patients being able to continue to receive the therapy at dose level 2 beyond Cycles 1 or 2.

Table 10. Predicted Efficacy and Safety of Inotuzumab Ozogamicin by Dose Level Based on Previously Established Population Pharmacokinetic and Exposure-Response Models[1]

	CR/CRi	MRD negativity	Rate of Post-HSCT VOD
Dose level 1 1.8 mg/m^2/cycle followed by 1.5 mg/m^2/cycle after CR/CRi	71%	60%	23.4%
Dose level 2 1.2 mg/m^2/cycle followed by 0.9 mg/m^2/cycle after CR/CRi	57%[1]	43%[1]	16.6%[1]

Abbreviations: CR=complete response; CRi=complete response with incomplete count recovery; HSCT=hematopoietic stem cell transplant; MRD=minimal residual disease; VOD=veno-occlusive disease.

1. Model predictions based on the data from Phase 3 Study B1931022. Predictions for dose level 2 were based on the assumption that each subject would receive the same number of treatment cycles as that in dose level 1based on Study B1931022 experience.

1.2.4.2. Reference Safety Information

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the United States Package Insert (USPI).

CCI [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
To evaluate the rates of VOD and hematologic remission (CR/CRi) for 2 inotuzumab ozogamicin dose levels in adult patients with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT.	• Rate of VOD (total, during study treatment, and post-HSCT); • Rate of hematologic remission (CR/CRi).
Secondary Objective(s):	**Secondary Endpoint(s):**
Safety and efficacy of 2 inotuzumab ozogamicin dose levels:	• Adverse events and laboratory abnormalities (grade, timing, seriousness, relatedness) during study treatment and post-HSCT; • MRD negativity in patients achieving CR/CRi; • DoR in patients achieving CR/CRi; • PFS; • OS; • Rate of HSCT; • Post-HSCT relapse; • Post-HSCT mortality; • Post-HSCT non-relapse mortality; • Post-HSCT relapse-related mortality; • PK exposure-response relationships for efficacy and safety (if study enters randomized phase); • Immunogenicity testing for anti-drug antibodies, including neutralizing antibodies.
CCI [redacted]	[redacted]
[redacted]	[redacted] (Section 7.7).

3. STUDY DESIGN

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

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

Run-in phase: up to 22 patients will be enrolled to receive the starting dose of 1.2 mg/m^2/cycle (dose level 2). A Simon Two-Stage optimal design will be used. If acceptable efficacy (CR/CRi and MRD negativity) is observed in the run-in phase, the study will enter the randomized phase (see Section 9.1).

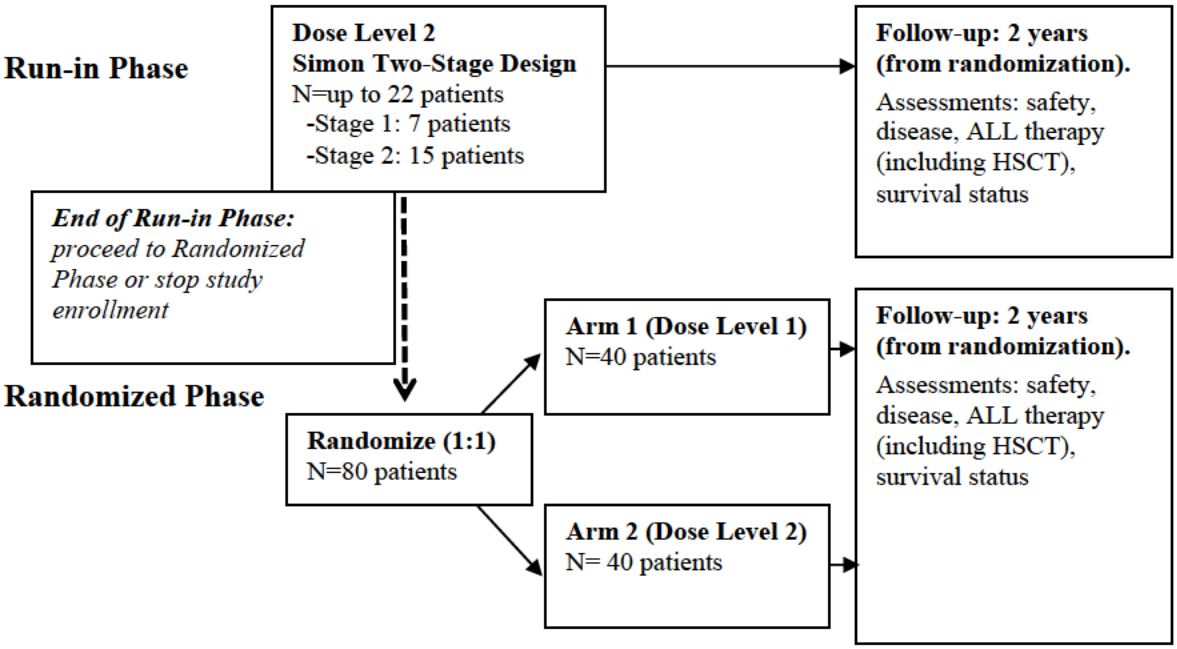
Randomized phase: if acceptable efficacy is observed in the run-in phase (see Section 9.1), the study will enter the randomized phase. A total of approximately 80 patients will be randomized (1:1) to 1 of 2 dose levels of inotuzumab ozogamicin (40 patients per dose level) (Figure 2). Patients will be stratified at randomization based on age (<55 vs ≥55 years), salvage status (Salvage 1 vs ≥2), and prior HSCT (yes vs no).

Patients will receive inotuzumab ozogamicin treatment, on average, for approximately three months (ie, 2-3 cycles). Safety assessments, disease assessments, and PK sample collections will be conducted throughout the treatment period.

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

This study will be conducted at approximately 50 clinical sites and is expected to be completed (last patient last visit) in approximately 6.0 years.

Figure 2. Study B1931030: Study Flow Diagram



4. SUBJECT ELIGIBILTY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the Investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Relapsed or refractory precursor CD22-positive B-cell ALL with M2 or M3 marrow (≥5% blasts) and who are eligible for HSCT.

2. Have 1 or more of the following risk factors for developing VOD:

   a. Due to receive Salvage 2 or greater;

   b. Prior HSCT;

   c. Age ≥55 years;

d. Ongoing or prior hepatic disease which may include a prior history of hepatitis or drug-induced liver injury, as well as hepatic steatosis, nonalcoholic steatohepatitis, baseline elevations of bilirubin > upper limit of normal (ULN) and ≤1.5 x ULN.

3. Ph+ ALL patients must have failed treatment with at least 1 second or third generation 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. Age 18 years to 75 years.

7. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

8. Adequate liver function, including total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome, and aspartate and alanine aminotransferase (AST and ALT) ≤2.5 x ULN.

9. Serum creatinine ≤1.5 x ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min.

10. 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.

11. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study; patients with mental capacity which requires the presence of a legally authorized representative will be excluded from the study.

12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

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

2. Burkitt's or mixed phenotype acute leukemia based on the WHO 2008 criteria.[6]

3. Active central nervous system (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. Prior chemotherapy within 2 weeks before randomization with the following exceptions:

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

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

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

5. Prior monoclonal antibodies within 6 weeks of randomization, with the exception of rituximab which must be discontinued at least 2 weeks prior to randomization.

6. Prior inotuzumab ozogamicin treatment or other anti-CD22 immunotherapy ≤6 months before randomization.

7. Prior allogeneic hematopoietic stem cell transplant (HSCT) ≤90 days before randomization. Patients must have completed immunosuppression therapy for treatment of graft versus host disease (GvHD) prior to enrollment. At randomization, patients must not have ≥ Grade 2 acute GvHD, or extensive chronic GvHD.

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

9. 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).

10. Active hepatitis B infection as evidenced by hepatitis B surface antigen, active hepatitis C infection (must be anti-hepatitis C antibody negative or hepatitis C ribonucleic acid negative), or known seropositivity for HIV. HIV testing may need to be performed in accordance with local regulations or local practice.

11. Major surgery within ≤4 weeks before randomization.

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

13. 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.

14. Patients with active heart disease or the presence of New York Heart Association (NYHA) stage III or IV congestive heart failure.

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

16. Myocardial infarction ≤6 months before randomization.

17. 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.

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

19. Prior confirmed or ongoing hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS), or other serious or current ongoing liver disease such as cirrhosis or nodular regenerative hyperplasia.

20. Administration of live vaccine ≤6 weeks before randomization.

21. 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.

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

23. 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.

24. Investigative site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

25. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation (up through the end of treatment visit).

26. 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 subject inappropriate for entry into this study.

4.3. Life Style Guidelines

All fertile male subjects and female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s), must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 8 months (females) and for at least 5 months (males) after the last dose of investigational product. The Investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below), and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the Investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the Investigator or designees will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 5 months after the last dose of the investigational product.

4.4. Sponsor Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Pfizer team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigational site and contact details for a contact center in the event that the Investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by Investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the Investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the Investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the Investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is inotuzumab ozogamicin.

All patients must be weighed within 72 hours prior to every cycle Day 1 dosing to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of inotuzumab ozogamicin required for dose preparation. A decision to recalculate the dose of inotuzumab ozogamicin based on the weight obtained at each cycle can be in accordance with institutional practice; however, if the patient has experienced either a weight loss or gain >10% (with no other evidence or clinical concern for VOD), the required amount of inotuzumab ozogamicin needed for study drug preparation and administration must be recalculated using this most recent weight/body surface area (BSA) obtained. If the dose administered is 10% greater or lower than the one prescribed, it will be reported as a dosing medication error.

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

Premedication is required for all subjects. Pre-medicate with a corticosteroid, antipyretic, and antihistamine. Premedication may also include antiemetics (see Section 5.7.3.)

See Section 5.4 for re-dosing criteria and recommended dose delays/reductions.

5.1. Dose Level 1 (Arm 1 of Randomized Phase): Inotuzumab Ozogamicin Starting Dose of 1.8 mg/m^2/cycle (administered in 3 divided doses)

The dosing schedule for dose level 1 is shown in Table 11.

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

Table 11. Dose Level 1 (Arm 1 of Randomized Phase) 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.

5.2. Dose Level 2 (Run-in Phase and Arm 2 of Randomized Phase): Inotuzumab Ozogamicin Starting Dose of 1.2 mg/m^2/cycle (administered in 3 divided doses)

The dosing schedule for dose level 2 is shown in Table 12.

For dose level 2, the starting dose of inotuzumab ozogamicin is 1.2 mg/m^2/cycle (administered in 3 divided doses). After CR/CRi is achieved, the dose is reduced to 0.9 mg/m^2/cycle (administered in 3 divided doses). The cycle length will be 21-28 days. Inotuzumab ozogamicin is administered on Day 1, 8, and 15.

For patients proceeding to HSCT, 2 cycles of inotuzumab ozogamicin are recommended. For patients who do not achieve CR/CRi with MRD negativity by 2 cycles, the minimum numbers of cycles needed to achieve CR/CRi and MRD negativity are permitted, up to a maximum of 4 cycles.

Patients who do not achieve a CR/CRi within 4 cycles should discontinue treatment.

Table 12. Dose Level 2 (Run-in Phase and Arm 2 of Randomized Phase) Dosing Schedule: Inotuzumab Ozogamicin Starting Dose of 1.2 mg/m^2/cycle (administered in 3 divided doses)

	Day 1	Day 8[a]	Day 15[a]
Dosing regimen for Cycle 1(1.2 mg/m^2/cycle)			
All patients:			
Dose[b]	0.6 mg/m^2	0.3 mg/m^2	0.3 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] (0.9 mg/m^2/cycle)			
Dose[b]	0.3 mg/m^2	0.3 mg/m^2	0.3 mg/m^2
Cycle length	28 days[f]		
Patients who have not achieved a CR[d] or CRi[e] (1.2 mg/m^2/cycle)			
Dose[b]	0.6 mg/m^2	0.3 mg/m^2	0.3 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.

5.3. Study Treatment for Patients Not Proceeding to HSCT (Dose Levels 1 and 2).

This study is designed to enroll patients who are eligible for HSCT. Patients must be eligible for HSCT at the time of randomization (see Section 4.1). However, in the event that a patient, who is eligible for HSCT at randomization, becomes ineligible for HSCT after randomization (eg, development of new morbidity), up to a maximum of 6 cycles of inotuzumab ozogamicin may be administered (if CR/CRi is achieved within 3 cycles [dose level 1] or 4 cycles [dose level 2]). Patients must meet all dosing criteria and follow dosing modifications as described in Section 5.4.

For dose level 1, patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment.

For dose level 2, patients who do not achieve a CR/CRi within 4 cycles should discontinue treatment.

5.4. Recommended Dose Modifications (Dose Levels 1 and 2)

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.

5.4.1. Redosing Criteria and Dose Delays (Dose Levels 1 and 2)

Unless patients meet the following criteria ***prior to the start of each cycle***, inotuzumab ozogamicin treatment will be delayed.

1. No evidence of progressive disease (PD). See Appendix 1 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 (≤50% increase in blast percentage) based on the most recent peripheral blood counts and bone marrow evaluation.
3. Recovery to Grade 1 or baseline non-hematologic investigational product-related toxicity (except alopecia) (prior to each dose of inotuzumab ozogamicin).
4. Serum bilirubin ≤1.5 x ULN, and AST, ALT ≤2.5 x ULN irrespective of the causality (prior to each dose of inotuzumab ozogamicin). Exception: Hyperbilirubinemia in the setting of documented Gilbert's disease.
5. Serum creatinine ≤2 x ULN or estimated creatinine clearance ≥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 absolute neutrophil counts (ANC) ≥1 x 10^9/L: ANC ≥1 x 10^9/L.
7. For patients with pre-treatment platelets ≥50 x 10^9/L: platelets ≥50 x 10^9/L.
8. For patients with baseline ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: ANC and platelets must recover at least to baseline values obtained for the prior cycle, or

ANC ≥1 x 10^9/L and platelets ≥50 x 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 ≤470 msec (average of 3 ECGs). Note: QTcF must be confirmed prior to Day 1 of Cycles 1, 2, 3 and 4 (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 start of subsequent cycles.

Inotuzumab ozogamicin dosing should be permanently discontinued for any patient with possible, probable or confirmed VOD or other severe liver toxicity. Dose delays due to inotuzumab ozogamicin-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 case report form (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 inotuzumab ozogamicin-related toxicity, (eg, 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 Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0).

5.4.2. Dose Reductions (Dose Levels 1 and 2)

Dose reductions may be required based on the worst toxicity experienced in the previous cycle. Patients experiencing a treatment interruption due to inotuzumab ozogamicin-related toxicity ≥14 days will resume dosing with a single 25% reduction (total dose) in inotuzumab ozogamicin for the subsequent cycle once adequate recovery is achieved. If further dose modification is indicated after a 25% dose reduction (total dose), the number of doses within the cycle should be reduced to two for subsequent cycles. Dose reduction of inotuzumab ozogamicin (total dose) by 25% are 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 patient has a dose reduction for an inotuzumab ozogamicin-related toxicity, the dose will not be re-escalated. Patients 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.

5.5. Allocation to Treatment

Once the patient has signed the informed consent, the Investigator or designee will contact the randomization system (see study manual) to obtain a patient identification number (patient ID). Following full assessment and determination that a patient meets all eligibility criteria, the Investigator or designee will enroll the patient into the study using the randomization system. Instructions on how to use the randomization system will be provided in the study manual. No patient will receive study drug therapy until the entire enrollment/randomization process has been completed.

5.6. Subject Compliance

All doses of inotuzumab ozogamicin will be administered by the appropriately designated study staff at the Investigator site.

5.7. Investigational Supplies

Study centers will receive a supply of the inotuzumab ozogamicin after site activation. Re-supplies will be made during the course of the study. The study monitor should be contacted for any issues related to inotuzumab ozogamicin supplies.

5.7.1. Dosage Form and Packaging

Inotuzumab ozogamicin is provided as a lyophilized, unpreserved white to off-white powder in a single-dose vial for reconstitution and further dilution for intravenous injection. It is light sensitive.

5.7.2. 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.

5.7.3. 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. 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.

5.7.4. Investigational Product Storage

See the Investigational Product Manual for instructions on how to store inotuzumab ozogamicin. It should be stored at 2 to 8°C (36 to 46°F).

The Investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the Investigational Product Manual for storage conditions of the product once reconstituted and/or diluted.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be

considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7.5. Investigational Product Accountability

The Investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.7.6. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). 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, and all destruction must be adequately documented.

5.8. Concomitant Medication(s)

5.8.1. Prior Medications

The start date, stop date, dose, and best response to all prior therapies/procedures for treatment of the patient's cancer will be recorded on the CRF. In addition, the start date, stop date, and indication for all treatments and/or therapies and medications received within 28 days before the first dose of investigational product (including herbal supplements or herbal teas, if applicable) will be recorded on the CRF.

5.8.2. Concomitant Medications

The start date, stop date, and indication for concomitant treatments and/or therapies and medications received from the first dose of investigational product until 4 to 6 weeks after the last dose of investigational product (ie, through end of treatment visit) will be recorded on the 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 6.3). In the Follow-up period, select concomitant medications including antifungals, prophylaxis/treatment for graft versus host disease, 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 6.4). 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.

5.8.3. Permitted Concomitant Medications

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

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 randomization 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 start of subsequent cycles.

Corticosteroids are allowed for cytoreduction, CNS prophylaxis/treatment, as premedications 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.

5.8.4. 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.

5.8.5. 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 Appendix 2 for a list of medications.

At clinically relevant concentrations, N-acetyl-gamma-calicheamicin (which is released from inotuzumab ozogamicin followng 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. STUDY PROCEDURES

The same study procedures are conducted for both arms. Please refer to the SCHEDULE OF ACTIVITIES (Table 1) and additional tables provided within the protocol.

SAE/AE will be reported throughout the study, as described in the specific section of the protocol (see Section 8).

6.1. Screening

Screening procedures will occur within 28 days before randomization unless otherwise noted. Informed consent document (ICD): an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved ICD must be signed and dated before any study-specific procedures are done. Results from laboratory tests or assessments, performed as a standard of care, prior to the date of informed consent but within the allowed timeframe for screening procedures, can be used for determining the patient's eligibility and will be entered in the CRF. Use of pre-consent results to support inclusion/exclusion criteria must be clearly documented in the patient's source documents.

The following will be collected at screening:

- Sign informed consent form.
- Review study eligibility (inclusion and exclusion criteria).
- Locally obtained characterization of leukemia, including CD22 immunophenotyping (flow cytometry) from peripheral blood or bone marrow aspirate obtained within 28 days of randomization. However, local results will be reported in the CRF. IHC is allowed in patients with a dry tap or otherwise inadequate bone marrow aspirate in the absence of circulating blasts.
- Medical history. Presence of chronic conditions and/or medical history of significance including relevant surgical procedures. A prior history of confirmed VOD must be excluded. Investigators must be rigorous in evaluation to rule out presence of any potential of VOD at baseline.
- Cancer history and treatment. Current and initial cancer diagnosis, prior cancer therapies and treatments.
- Prior treatments and/or therapies and medications (including herbal supplements or herbal teas, if applicable) as described in the Prior Medications section.
- Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 3).

- Focused physical examination performed with clinical judgment evaluating potential areas of ALL relapse and any clinically significant abnormalities which may include the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, testes, abdomen, extremities, neurological, back/spinal, and lymph nodes; including worsening of medical history conditions.

- Vital signs including height, weight, blood pressure, pulse and temperature.

- Laboratory evaluations as described in Safety Laboratory Requirements (Table 4).

- For women of childbearing potential, a beta-human chorionic gonadotropin (β-HCG) serum or urine pregnancy test must be done up to 72 hours prior to dosing.

- Confirm appropriate contraception usage (see Section 4.3).

- Hepatitis B (HbsAg) and C (anti-HCV antibody, HCV ribonucleic acid) tests.

- Bone marrow aspirate (including bone marrow biopsy if available) and clinical disease assessments. Disease assessments to include liver and spleen assessments. The value for blast percentage in the bone marrow and blood (see Safety Laboratory Requirements, Table 4) must be confirmed prior to the patient's first dose. Karyotyping to be performed locally.

- Bone marrow aspirate (peripheral blood sample if BM aspirate is inadequate) will be sent to a central laboratory for immunophenotyping and MRD assessment. The leukemic phenotype and/or genotype may also be evaluated by other test methods at the discretion of the Sponsor.

- Patients with suspected extramedullary disease will have radiographic assessment (ie, computerized tomography [CT] or magnetic resonance imaging [MRI]) of all known disease sites, as clinically indicated. Liver, spleen and testes can be assessed by palpation; assessment of CNS disease (eg, lumbar puncture) will be done in patients with signs or symptoms suggestive of CNS disease or if any prior history of CNS leukemia.

- Electrocardiogram (ECG). ECGs will be collected to determine patient eligibility.

- Following successful completion of the pre-study assessment and screening procedures and confirmation of eligibility, patients may be randomized.

- Collection of adverse events.

6.2. Study Period

The 'study treatment period' is defined as the period starting with the first dose of investigational product up to and including the end-of-treatment visit.

Unplanned laboratory assessments will be recorded in the CRF only if clinically significant (eg, associated with an AE).

6.2.1. Day 1

- Laboratory evaluations will be conducted as described in Table 1 and Table 4. Laboratory tests can be done up to 72 hours prior to dosing. Results of complete blood counts, serum chemistry, coagulation tests, and pregnancy tests must be available before dosing;

- Blood sample collected prior to inotuzumab ozogamicin administration for the measurement of antibodies to inotuzumab ozogamicin;

- Patients will be weighed up to 72 hours prior to the beginning of a new cycle and if needed the BSA should be recalculated (see Section 5);

- Urine or serum pregnancy test in all females of childbearing potential at every cycle prior to dosing; a pregnancy test is required up to 72 hours prior to Cycle 1 Day 1;

- Confirm appropriate contraception usage (see Section 4.3);

- Focused physical examination performed with clinical judgment evaluating potential areas of ALL relapse and any clinically significant abnormalities which may include the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, testes, abdomen, extremities, neurological, back/spinal, liver, spleen, and lymph nodes; including worsening of medical history conditions;

- Vital signs including blood pressure, pulse and temperature. Performed on all days that inotuzumab ozogamicin is administered for all cycles (predose and 1 hour after the end of each inotuzumab ozogamicin infusion; also performed 2 hours after the end of inotuzumab ozogamicin infusion for Cycle 1 Day 1 dose);

- Bone marrow aspirate and clinical disease assessments will be conducted as described in Table 1;

- MRD assessment and karyotyping for patients with CR/CRi; MRD samples will be sent to central vendor while karyotyping will be performed locally;

- Bone marrow biopsy collected at least once in patients with CRi (ANC $<1 \times 10^9$/L and/or platelets $<100 \times 10^9$/L) to assess cellularity at the study site as described in Table 1;

- Patients with extramedullary disease at screening will have radiographic assessment (ie, CT or MRI) to confirm CR or CRi, and as medically indicated. Use the same method of assessment for each evaluation (eg, CT scan);

- Pharmacokinetic evaluations will be conducted as described in Table 3;

- Electrocardiograms (ECGs) will be collected prior to the start of each cycle as described in Table 1;

- [redacted]

- Administration of premedications and inotuzumab ozogamicin per randomized assignment; Cycle 1 Day 1 dosing must be taking place within 3 days from randomization, unless otherwise agreed with the Sponsor (see Section 5);

- Collection of adverse events.

6.2.2. Day 4

- Pharmacokinetic evaluations will be conducted as described in Table 3;

- Collection of adverse events.

6.2.3. Days 8 and 15

- Laboratory evaluations will be conducted as described in Table 1 and Table 4. Day 8 and Day 15 laboratory assessments must be performed within 2 days prior to dosing;

- Focused physical examination performed with clinical judgment evaluating potential areas of ALL relapse and any clinically significant abnormalities which may include the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, testes, abdomen, extremities, neurological, back/spinal, liver, spleen and lymph nodes; including worsening of medical history conditions;

- Vital signs including blood pressure, pulse and temperature (predose and 1 hour after the end of each inotuzumab ozogamicin infusion;

- Pharmacokinetic evaluations will be conducted as described in Table 3;

- Administration of premedications;

- Administration of inotuzumab ozogamicin will be conducted as described in Section 5;

- Collection of adverse events.

6.3. End of Treatment

An end-of-treatment (EOT) visit is required for all patients. It occurs approximately 4 to 6 weeks after the last dose of inotuzumab ozogamicin. However, in the event that a patient requires initiation of a new anti-cancer therapy, the end-of-treatment visit, including procedures, should be performed before the initiation of the new anti-cancer therapy as close as possible to 4 to 6 weeks after the last dose of inotuzumab ozogamicin. Safety laboratory

tests continue to be collected in the CRF through at least 9 weeks after the last dose of study inotuzumab ozogamicin unless a new anti-cancer therapy is given. Adverse events and associated concomitant medications must continue to be collected in the CRF through at least 9 weeks after the last dose of study inotuzumab ozogamicin unless a new anti-cancer therapy is given; thereafter, serious adverse events (SAEs) are reported as described in Section 8.1.4. VOD cases will be reported as SAEs (Section 8.4.3) and recorded in the CRF for the entire duration of study participation, including the Follow-up period, regardless if new anti-cancer therapy is given. The end-of-treatment visit procedures and tests include the following:

- Blood sample collected for the measurement of antibodies to inotuzumab ozogamicin;
- ECOG performance status;
- Focused physical examination performed with clinical judgment evaluating potential areas of ALL relapse and any clinically significant abnormalities which may include the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, testes, abdomen, extremities, neurological, back/spinal, and lymph nodes; including worsening of medical history conditions;
- Vital signs including blood pressure, pulse, temperature and weight;
- Laboratory evaluations will be conducted as described in Table 1 and Table 4;
- For women of childbearing potential, a beta-human chorionic gonadotropin (β-HCG) pregnancy test must be done;
- Confirm appropriate contraception usage (see Section 4.3);
- Disease assessment (see Section 7.1), including bone marrow aspirate, which should be done prior to the start of new anti-cancer treatment;
- Electrocardiogram (ECG).

6.4. Follow-up Visits

Disease assessments will be conducted for all patients whose disease has not progressed (including patients undergoing stem-cell transplant or other subsequent anti-leukemic therapy) until disease progression for up to at least 2 years after randomization (every 12 weeks up to 1 year from randomization and every 24 weeks between year 1 and 2). Visits for disease assessment are planned starting approximately 12 weeks after the last disease assessment then continuing until the patient completes at least 2 years (relative to the day of randomization) or has documented disease progression, whichever occurs first (see Table 2). Visits for disease assessment will include the following evaluations:

- Laboratory evaluations which include complete blood count (CBC) with differential, total bilirubin, alkaline phosphatase, ALT, AST, gamma-glutamyl transpeptidase (GGT), and albumin, hematology. Evaluations will be done up to a year from randomization or until a new cancer treatment has started. For patients in disease follow up beyond a year from randomization, CBC with differential and platelets are required until disease progression;

- Bone marrow aspirate (and biopsy if indicated per standard of care) and extramedullary disease assessments. Disease assessments to include testicular, liver and spleen assessments. No bone marrow aspirate is necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation; required every 12 weeks (±1 week) for one year from randomization, then every 24 weeks (±2 weeks) for the second year; all disease assessments should be recorded on CRF until relapse/disease progression unless consent is withdrawn;

- Reporting of follow-up anticancer therapy. Medication name, surgical or radiotherapy procedure, start/stop dates will be collected for 2 years (total, relative to the day of randomization). 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 randomization. Follow-up anticancer therapy and response will be recorded for all randomized patients (even if the patient was never treated on study);

- Select concomitant medications including antifungals, prophylaxis/treatment for graft versus host disease, 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.

All randomized patients (including patients undergoing stem-cell transplant) will be followed for survival for at least 2 years. Follow-up limited to survival status will start approximately 12 weeks after the completion of the disease follow-up period. Follow-up for survival can be conducted every 12 weeks either by telephone interview or email. Also, information about other anticancer therapy will be collected.

All known cases of VOD must be reported in the CRF for the entire duration of study participation, including the Follow-up period, irrespective of causality. Also, cases of VOD will be reported as SAEs as detailed in Section 8.4.3.

6.5. Subject Withdrawal

Prior to randomization, Investigators should ensure the consent process includes full disclosure of the risks and procedures.

The patient should not be randomized unless they understand and accept the chance of being randomized to either arm (dose level).

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section) section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. Every effort should be made to schedule an end of treatment visit and to complete all the assessments required. This visit should take place 4 to 6 weeks after the last dose of study treatment. If a patient does not return for a scheduled visit, every effort should be made to contact the patient for 1 year before declaring a patient lost to follow-up. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs), disease progression and survival.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

The same assessments are conducted for both arms. Please refer to the Schedule of Activities (Table 1) and additional tables provided within the protocol.

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

7.1. Efficacy Assessments

Assessment of response and progression status will be evaluated according to a modified Cheson Criteria described in Appendix 1. 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

randomization will have radiographic assessment (CT or MRI) to confirm a CR or CRi using the same method of assessment, unless contraindicated.

Bone marrow aspirate (or biopsies if clinically indicated) and disease assessments (see Appendix 1) will be performed at screening, once at day 16-28 of Cycles 1 and 2, or until CR/CRi and MRD negativity are achieved, then after every 1-2 cycles as clinically indicated, at the end-of-treatment visit (unless previously done within 28 days), and during follow-up visits (see Section 6.4).

Bone marrow aspirates will be analyzed at the study site. A BM biopsy is recommended at the time of bone marrow aspirates and will be done during treatment at least to evaluate cellularity in patients achieving CRi.

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 randomization;
- 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 randomization;
- G-CSF should be discontinued at least 72 hours prior to every bone marrow assessments;

Karyotyping will be performed locally 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.

For determination of MRD, bone marrow aspirate will be sent to a central laboratory and analyzed by flow cytometry for cell surface markers associated with B-ALL. The leukemia phenotype and/or genotype may also be evaluated by other test methods at the discretion of the Sponsor.

7.2. Safety Assessments

Safety endpoints include adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 3.0), clinical examination (including blood pressure and pulse), laboratory tests (hematology, chemistry, and coagulation) and 12-lead electrocardiograms (ECGs).

Additional procedures or samples may be undertaken as medically required at the discretion of the Investigator.

7.3. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, 72 hours prior to every cycle Day 1, and at the end of treatment visit (to confirm the patient has not become pregnant during the study) (Table 1). A negative pregnancy result is required before the patient may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

7.4. Pharmacokinetic Measures

In order to correctly utilize the PK data, it is critical that the actual time and date of inotuzumab ozogamicin administration and PK sample collection is recorded on the CRF. Concentrations of inotuzumab ozogamicin and free calicheamicin in serum will be determined by validated bioanalytical assays. These analyses will be performed at a central laboratory designated by the Sponsor. Sample collection, labeling, storage and shipping information for central laboratory analyses can be found in the Study Manual.

7.5. Pharmacodynamic Evaluations

Bone marrow aspirate, collected at screening and for remission status, will be sent to the central vendor, for immunophenotyping and assessment of MRD. MRD will be assessed by flow cytometry for CD22 and other cell surface markers associated with B-cell ALL. The leukemia phenotype and/or genotype may also be evaluated by other test methods at the discretion of the sponsor. MRD analysis will be done at least once in patients with prior assessment of CR or CRi. A peripheral blood sample must be provided to the central vendor if a patient has an inadequate aspirate at screening.

7.6. Immunogenicity Testing

To assess the immunogenicity of inotuzumab ozogamicin, blood sample will be collected at Day 1 of every cycle prior to the inotuzumab ozogamicin infusion and at the End-of-Treatment visit (Table 1, Schedule of Activities).

The immunogenicity of inotuzumab ozogamicin will be evaluated using a validated electrochemiluminescence (ECL)-based immunoassay. For patients whose sera tests positive for anti-inotuzumab ozogamicin antibodies, a validated cell-based luminescence assay will be performed to test for neutralizing antibodies.

In patients who test positive for anti-inotuzumab ozogamicin antibodies, the impact of anti-inotuzumab ozogamicin antibodies on clearance, safety, and efficacy will be assessed.

CCI

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8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the Investigator **are to be reported regardless of whether the event is determined by the Investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the Investigator does not become immediately aware of the occurrence of an event, the Investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the Investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the Investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious 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.

As noted in the Protocol-Specified Serious Adverse Events section, should an Investigator judge one of the identified protocol-specified SAEs to have a causal relationship with the investigational product, the Investigator must report the SAE to Pfizer Safety within 24 hours of Investigator awareness.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are 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.

8.1.2. Eliciting Adverse Event Information

The Investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 9 weeks after the last administration of the investigational product.

The "active collection period" for VOD is the entire duration of study participation, including the Follow-up period, regardless of whether new anti-cancer treatment is initiated. All cases of VOD must be reported as SAEs (recorded on the CRF and CT SAE Report Form).

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the Investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

If a patient 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.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious 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.

8.1.5. Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. 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. If the Investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;

- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

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.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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 or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;

- Respite care (eg, caregiver relief);

- Skilled nursing facilities;

- Nursing homes;

- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 3.0 CTCAE document but may be used in certain circumstances.)
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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

Unless the Investigator believes that there is a causal relationship between the investigational product and an event specified below, these events should not be reported to Pfizer Safety by the Investigator as SAEs. These events are anticipated to occur commonly in a population with ALL. However, these events should still be recorded as AEs on the CRF.

Protocol-specified SAEs that will not normally be reported to Pfizer Safety in an expedited manner, **unless Grade 5 (or with an outcome of fatal) or if a causal relationship with the investigational product is considered at least reasonable**:

- Febrile neutropenia;
- Neutropenic sepsis;
- The following occurring post-HSCT and after discontinuation of inotuzumab ozogamicin:
    - Acute graft versus host disease (GvHD);
    - Infection requiring IV antibiotics;
    - Hemorrhage/bleeding;
    - Weight loss/anorexia;
    - Acute kidney injury;
    - Nausea/vomiting/diarrhea;
    - Thrombocytopenia/anemia.

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 standard operating procedures.

8.4.2. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (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 lab 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 subject’s individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 at least 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 subject 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, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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) 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 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.

8.4.3. Potential VOD Cases

All cases of veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), regardless of causality, severity and treatment arm must also be reported as an SAE for the entire duration of study participation, including the Follow-up period (Table 2). 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 work-up 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 non-infectious, including non-alcoholic steatohepatitis [NASH, also known as non-alcoholic 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, non-study medications [including herbal supplements and herbal teas, if applicable], sites of disease other adverse events particularly recent and/or concurrent infections, and other non-study 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 sinusoidal obstruction syndrome [SOS]) is defined as:[7]

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 13).[7]

Table 13. 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 X ULN	>2 and ≤5 x ULN	>5 and ≤8 x ULN	>8 x ULN
Weight increase	<5%	≥5% and <10%	≥5% and <10%	>10%
Renal Function	<1.2 x baseline at HSCT	≥1.2 and <1.5 x baseline at HSCT	≥1.2 and <1.5 x baseline at HSCT	≥2 x 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).

e. and the date when the symptoms fulfilled VOD diagnostic criteria.

See also Appendix 4 for guidance about recommendation for patients proceeding to HSCT and potential VOD cases.

8.4.4. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of Investigator awareness.

8.4.4.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products);

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, 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. In addition, the Investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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 includes miscarriage and missed abortion;

- 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 investigational product.

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.4.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the Investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.4.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported 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 does not pertain to a subject 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.

8.4.5. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.5.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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.

In the event of a medication dosing error, the Sponsor should be notified immediately.

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 non-serious, are recorded on an AE page of the CRF.

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (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. Sample Size Determination

The objective of this study is to evaluate safety and efficacy of two inotuzumab ozogamicin dose levels through descriptive analyses. A total of up to approximately 102 patients will be enrolled in the study: up to 22 patients in the run-in phase (dose level 2) and 80 patients (40 patients per dose level arm) in the randomized phase if acceptable efficacy is observed for dose level 2 in the run-in phase.

The observed CR/CRi rate for the subgroup of patients with factors for higher risk of VOD post-HSCT in Phase 3 Study B1931022 was 70.5% for the inotuzumab ozogamin arm and 31.2% for the control arm. However, the true response rates for this subgroup could be lower, depending on the prognostic factors of the patients in this group; the response rate for inotuzumab ozogamin could be as low as 57% in this patient population based on the exposure response model. Based on these results, the run-in phase will test the null hypothesis (H_0) that the CR/CRi rate is ≤31.2% versus the alternative hypothesis (Ha) that the CR/CRi rate is ≥57% . In order to minimize the expected number of patients enrolled in the event that the lower dose level (1.2 mg/m^2/cycle of inotuzumab ozogamicin, dose level 2) proves to be of minimal efficacy benefit, a Simon Two-Stage optimal design will be used for the run-in phase. A total of up to 22 patients will be enrolled in the run-in phase. This sample size will provide 80% power to reject the null hypothesis with significance level of 0.10 if the true CR/CRi rate is 57%.

Seven (7) patients will be enrolled in Stage 1. If ≤2 CR/CRi responders are observed in Stage 1, accrual will be stopped for further evaluation. Once at least 3 (ie, 42.9%) CR/CRi responders are documented, an additional 15 enrolled patients will be evaluated in Stage 2. If ≥10 CR/CRi responders are observed in the total of 22 patients from both stages, it will be concluded that the true CR/CRi rate for the lower dose is higher than the historical control (31.2% for Study B1931022 control arm subgroup of patients with risk factors for VOD post-HSCT).

The expected MRD negativity rate among the patients who achieve CR/CRi is ≥70%. With ≥10 CR/CRi responders expected at the end of Stage 2, the expected number of patients with MRD negativity among the 22 patients in the run-in phase is ≥7. Given a CR/CRi rate of 57%, predicted by the exposure response model, and an expected MRD negativity rate of ≥70% among CR/CRi responders, 40% is the expected MRD negativity rate among all the patients enrolled in the run-in phase. Twenty-two (22) patients will also provide 80% power to reject the null hypothesis of the MRD negativity rate ≤20% when the alternative hypothesis of the true MRD negativity rate is ≥40% with significance level of 0.10. There will be 84% probability to observe a minimum of 7 patients who have achieved MRD negativity if the true MRD negativity rate is at least 40%.

To review the totality of the efficacy data, DoR will also be analyzed for the run-in phase. Safety data will also be reviewed for the run-in phase.

Once at least 10 CR/CRi responders and at least 7 patients achieving MRD negativity are documented among the 22 patients in the run-in phase, patients enrolled in the randomized phase will then be evaluated, with approximately 80 patients randomized (1:1) to the approved dose level of 1.8 mg/m^2/cycle (dose level 1, Arm 1) or the lower dose level of 1.2 mg/m^2/cycle (dose level 2, Arm 2).

Until analyses for decision-making are completed, enrollment will continue between Stage 1 and Stage 2 of the run-in phase and between the run-in and randomized phases of the study.

At the end of the study, descriptive analyses will be conducted by dose level. For the randomized phase, a sample size of 40 patients per arm will provide the estimated VOD rate in each dose level with a maximum standard error (SE) of 0.08. The maximum SE estimated for other binary endpoints in each dose level (eg, CR/CRi rate) will also be 0.08. In addition, for summary of dose level 2, patients in the run-in phase will be combined with Arm 2 of the randomized phase, for a sample size of approximately 62 patients (ie, 22 patients enrolled in the run-in phase and 40 patients enrolled in Arm 2 in the randomized phase) to provide the above-mentioned estimated rates with a maximum SE of 0.06.

Table 14 shows the possible estimated VOD rate and CR/CRi rate with 95% CI with a sample size of 40 patients and 62 patients, respectively.

Table 14. Estimated VOD Rate and CR/CRi Rate with 95% Confidence Interval

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

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

9.2. Analysis Populations

This study is designed to enroll patients who are eligible for HSCT. Patients must be eligible for HSCT at the time of enrollment (see Section 4.1). Patients who are eligible for HSCT at enrollment but who subsequently are not able to proceed to HSCT will not be replaced. Analyses will be performed for the Intent-to-Treat, Safety Population, and Per Protocol Populations as described below.

9.2.1. Intent-to-Treat (ITT)

The ITT population will include all patients who are enrolled into the study, with study drug assignment designated according to initial randomization.

9.2.2. Safety Population

The safety population includes all enrolled patients who receive at least 1 dose of investigational product (inotuzumab ozogamicin), with treatment assignments designated according to actual treatment received.

Safety post-HSCT will also be evaluated. The HSCT safety population includes all enrolled patients who receive at least 1 dose of investigational product (inotuzumab ozogamicin), with treatment assignments designated according to actual treatment received, and who undergo HSCT after inotuzumab ozogamicin treatment.

9.2.3. Per Protocol (PP) Population

All patients who meet all of the following criteria:

1. Randomized and receive at least one dose of investigational product (inotuzumab ozogamicin), with treatment assignments designated according to actual treatment received.

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.

4. Proceeds to follow-up HSCT.

9.3. Efficacy Analysis

All analyses will be done by dose level and by study phase (ie, run-in phase, Arm 1 of randomization phase , and Arm 2 of the randomization phase will be summarized separately). In addition, for the summary of dose level 2, patients enrolled in the run-in phase will be combined with Arm 2 of the randomization phase.

9.3.1. Analysis of the Primary Endpoint

Hematologic response, defined as complete remission (CR) + complete remission with incomplete hematologic recovery (CRi), will be summarized in the ITT population. Descriptive analyses (ie, the number, percent of patients achieving CR/CRi along with 2-sided 95% confidence interval [CI]) without formal hypothesis testing will be provided. A sensitivity analysis will also be conducted for CR/CRi in the PP population.

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 absolute neutrophil count (ANC) ≥1000/µl and platelets ≥100,000/µl. Absence of extramedullary disease status is required. CRi is defined as CR except with absolute neutrophil count (ANC) <1000/µl and/or platelets <100,000/µl (see Appendix 1).

9.3.2. Analysis of Secondary Endpoints

MRD negativity (in patients who achieved CR/CRi) will be defined as the minimum MRD percentage between the date of CR/CRi and end of treatment test is <0.01%. Descriptive analyses (ie, the number, percent of patients achieving MRD negativity along with 2-sided 95% CI) will be provided for both ITT and PP populations.

DoR will be defined as time from date of first response in responders (CR/CRi) to the date of disease progression or death due to any cause, whichever occurs first. DoR will be summarized descriptively using Kaplan-Meier methods and displayed graphically where appropriate in both ITT and PP populations.

PFS will be defined as time from date of randomization to the date of disease progression or death due to any cause, whichever occurs first. PFS will be summarized descriptively using Kaplan-Meier methods and displayed graphically where appropriate in both ITT and PP populations.

OS will be defined as the time from date of randomization to the date of death due to any cause. OS will be summarized descriptively using Kaplan-Meier methods and displayed graphically where appropriate in both ITT and PP populations.

Rate of HSCT will be summarized by descriptive analyses (ie, the number, percent of patients underwent HSCT along with 2-sided 95% CI) in ITT population and PP population.

Post-HSCT relapse will be defined as the time from date of HSCT to the date of first relapse post-HSCT. Post-HSCT relapse will be summarized descriptively using competing-risks analyses and displayed graphically where appropriate in both ITT and PP populations.

Post-HSCT mortality will be defined as the time from date of HSCT to the date of death due to any cause. Post-HSCT mortality will be summarized descriptively using Kaplan-Meier methods and displayed graphically where appropriate in both ITT and PP populations.

Post-HSCT non-relapse mortality (NRM) will be defined as time from date of HSCT to the date of death due to any cause without prior relapse/progression post-HSCT. Post-HSCT NRM will be summarized descriptively using competing-risks analyses and displayed graphically where appropriate in both ITT and PP populations.

Post-HSCT relapse-related mortality (RRM) will be defined as time from date of HSCT to the date of death due to any cause with prior relapse/progression post-HSCT. Post-HSCT RRM will be summarized descriptively using competing-risks analyses and displayed graphically where appropriate in both ITT and PP populations.

The immunogenicity of inotuzumab ozogamicin will be summarized descriptively.

9.4. Analysis of Other Endpoints

9.4.1. Population Pharmacokinetic Analysis

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

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

The results of population PK analysis and exposure response analyses with respect to safety and efficacy endpoints of interest (if applicable) will be provided separately as part of a population modeling analysis report.

9.5. Safety Analysis

Similar to efficacy analyses, safety analyses will be done by dose level and by study phase (ie, run-in phase, Arm 1 of randomization phase , and Arm 2 of the randomization phase will be summarized separately). In addition, for the summary of dose level 2, patients enrolled in the run-in phase will be combined with Arm 2 of the randomization phase.

9.5.1. Analysis of the Primary Endpoint

Rate of VOD (total, on-study treatment, and post-HSCT) will be summarized for each arm in the safety population and PP population. Descriptive analyses (ie, the number, percent of patients with VOD along with 2-sided 95% CI) without formal hypothesis testing will be performed. A subgroup analysis will also be conducted for VOD in the HSCT 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 (recorded on the CRF and the CT SAE Report Form, see Table 2 and Section 8.1.4).

9.5.2. Analysis of Secondary Endpoints

The safety analysis will be conducted on the safety population, the HSCT safety population, and the PP 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.

9.6. Interim Analysis

This study is designed to have one interim analysis for Stage 1 of the run-in phase and one interim analysis at the end of the run-in phase to allow early stopping due to insufficient efficacy for dose level 2. See Section 9.1 for details.

9.7. Data Monitoring Committee

This study will use an internal review committee (IRC). The IRC will review run-in phase results and provide recommendations about the conduct of the study (see Section 9.1). During the randomization phase, the IRC will review safety data for both arms at regular intervals during the study. The IRC will be comprised of 3 members who are not directly involved in the study, including a statistician and two medically qualified individuals.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The Investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the Investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The Investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with Pfizer or its agents to prepare the Investigator site for the inspection and will allow Pfizer 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 subject's medical records. The Investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the Investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The Investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the Investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the Investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The Investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another Investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The Investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The 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, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The Investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The Investigator further must ensure that each study subject 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 Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The Investigator will retain the original of each subject's signed consentdocument.

12.4. 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of trial in all participating countries is defined as last patient last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of inotuzumab ozogamicin at any time.

If a study is prematurely terminated, Pfizer will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a timeframe agreed at the time with the Sponsor and in accordance with local and regulations and/or IEC/IRBs. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial 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 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 Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are 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 subject 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 (clinical study report synopses in which any data that could be used to identify individual patients has 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.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the Principal Investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the Investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The Investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the Investigator agrees that the first publication is to be a joint publication covering all Investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Dijoseph JF, Dougher MM, Armellino DC, et al. Therapeutic potential of CD22-specific antibody-targeted chemotherapy using inotuzumab ozogamicin (CMC-544) for the treatment of acute lymphoblastic leukemia. Leukemia 2007;21(11):2240-5.

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3. United States package insert, BESPONSA™ (inotuzumab ozogamicin) for injection, for intravenous use. Initial U.S. Approval: 2017.

4. Carreras E, Bertz H, Arcese W, Vernant J-P, Tomas J-F, et al, Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for blood and marrow transplantation. Blood. 1998; 92: 3599-3604.

5. DeAngelo DJ, Stock W, Stein AS, et al. Inotuzumab ozogamicin in adults with relapsed or refractory CD22-positive acute lymphoblastic leukemia: a phase 1/2 study. Blood Advances 2017; 1(15):1167-1180.

6. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.

7. Mohty M, Malard F, Abecassis M, et al, Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation Blood Marrow Transplantation. 2016; 51: 906-912.

APPENDICES

Appendix 1. Outcome Definitions

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

- 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 absolute neutrophil count (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 absolute neutrophil count (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 (PD) is defined as a doubling of peripheral blasts with an absolute increase of >5 x 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 of 1 cm or greater; or palpable lesions with both diameters ≥2 cm. Note: although CT 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 greatest transverse diameter (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 disease must be assessed using the same technique as at baseline.

- C2: Patient does not qualify for C1 status

Modified from: Cheson et. al., Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003 Dec 15;21(24):4642-9.

Appendix 2. 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: intraveneous (IV) dose >16 mg (reference, 29Jun2012 FDA Drug Safety Communication; FDA website http://www fda.gov/Drugs/DrugSafety/ucm310190.htm)

Appendix 3. 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 house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix 4. 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 or the fewest number of cycles required to achieve a CR/CRi (if CR/CRi not achieved after 2 cycles). See Section 5.1 and Section 5.2 for recommendations for dose level 1 and dose level 2, respectively.

- 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 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.[1,2]

- 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 TBI (defined as >12 Gy).

- If using a busulfan-containing conditioning regimen, please consider using pharmacokinetically-dosed busulfan.[3]

- 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.[4] 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, these recommendation should be reviewed with the new treating physicians.

*Ursodeoxycholic acid is not authorised for use by regulatory authorities in this setting.
** Defibrotide is not authorized for use by all regulatory authorities in this setting.

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Appendix 5. Abbreviations

Abbreviation	Term
ADC	Antibody-drug conjugate
AE	Adverse event
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASH	Alcoholic steatohepatitis
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AV block	Atrioventricular block
β-HCG	Beta-human chorionic gonadotropin
CCI	[redacted]
BSA	Body surface area
BM	Bone marrow
BMA	Bone marrow aspirate
CalichDHE	N-acetyl γ-calicheamicin dimethyl hydrazide
CBC	Complete blood count
CI	Confidence interval
CK	Creatine kinase
CMC-544	Inotuzumab ozogamicin; investigational product composed of a conjugate of a humanized IgG4 anti-CD22 antibody.
CNS	Central nervous system
CR	Complete response
CRi	Complete response with incomplete count recovery
CRF	Case report form (including electronic case report forms)
CSA	Clinical study agreement
CSF	Cerebrospinal fluid
CSXRT	Craniospinal radiation
CT	Computed tomography
CTA	Clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DoR	Duration of remission
EAC	Endpoint Adjudication Committee
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EOT	End of treatment
EU	European Union

Abbreviation	Term
EudraCT	European Clinical Trials Database
FACS	Fluorescence activated cell sorting
FDA	Food and Drug Administration
FLAG	Fludarabine, cytarabine, G-CSF
FSH	Follicle-stimulating hormone
G544	A humanized IgG4 anti-human CD22 monoclonal antibody
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transpeptidase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVHD	Graft versus host disease
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIDAC	high-dose cytarabine
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplant
hyper-CVAD	Cyclophosphamide, vincristine, doxorubicin, dexamethasone
ICD	Informed consent document
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent ethics committee
IHC	Immunohistochemistry
IND	Investigational new drug application
INR	International normalization rate
IRB	Institutional review board
IRC	Internal review committee
ITT	Intent to treat
IUD	Intrauterine device
IV	Intravenous, intravenously
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LDH	Lactate dehydrogenase
LFT	Liver function test
mAb	Monoclonal antibody
MOF	Multiorgan failure
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MXN/AraC	Mitoxantrone + cytarabine
NASH	Non-alcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall survival

Abbreviation	Term
PCD	Primary completion date
PD	Progressive disease
PE	Physical exam
PFS	Progression-free survival
Ph+	Philadelphia chromosome positive
PI	Principal investigator
PK	Pharmacokinetics
PMR	Post-marketing requirement
PP	Per protocol
PT	Prothrombin time
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcS	QT interval corrected for heart rate using a population-specific method
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
SE	Standard error
SOS	Sinusoidal obstruction syndrome
SRSD	Single reference safety document
SUSAR	Suspected unexpected serious adverse drug reaction
TKI	Tyrosine kinase inhibitor
TBili	Total bilirubin
ULN	Upper limit of normal
US	United States
USPI	United States package insert
VOD	Veno-occlusive disease
VS	Vital signs
WBC	White blood cell
WHO	World Health Organization