A SINGLE ARM, OPEN-LABEL, PHASE 4 STUDY EVALUATING QT INTERVAL, PHARMACOKINETICS, AND SAFETY OF GEMTUZUMAB OZOGAMICIN (MYLOTARG™) AS A SINGLE-AGENT REGIMEN IN PATIENTS WITH RELAPSED OR REFRACTORY CD33-POSITIVE ACUTE MYELOID LEUKEMIA

Investigational Product Number:	PF-05208747 (CMA-676)
Investigational Product Name:	Gemtuzumab Ozogamicin (MYLOTARG™)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2018-002619-89
Protocol Number:	B1761031
Phase:	4

Document History

Document	Version Date	Summary of Changes and Rationale
Final Protocol	27 June 2018	Not applicable (N/A)

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PROTOCOL SUMMARY

Background and Rationale:

Gemtuzumab ozogamicin (GO, MYLOTARG™) is an antibody-drug conjugate (ADC) composed of the cluster of differentiation 33 (CD33)-directed monoclonal antibody hP67.6 (recombinant humanized immunoglobulin [Ig] G4, kappa antibody produced by mammalian cell culture in NS0 cells) that is covalently linked to the cytotoxic agent N-acetyl-gamma-calicheamicin dimethylhydrazide (DMH), a semisynthetic disulfide derivative of calicheamicin. The antibody portion binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells.

On 01 September 2017, the US Food and Drug Administration (FDA) approved GO (MYLOTARG™) for the treatment of adult patients with newly diagnosed CD33-positive acute myeloid leukemia (AML) and for the treatment of adult or pediatric patients at least 2 years of age with relapsed/refractory CD33-positive AML.[1] In adults with newly diagnosed CD33-positive AML, GO can be administered as part of a combination regimen (ie, fractionated dose of 3 mg/m^2 on Days 1, 4, and 7 combined with daunorubicin [DNR] and cytarabine [Ara-C] during induction) or as a single agent (ie, 6 mg/m^2 on Day 1 and 3 mg/m^2 on Day 8 of induction). In the setting of relapsed/refractory CD33-positive AML in patients aged 2 years and older, GO is approved for use as a single agent only using the fractionated dosing regimen (ie, 3 mg/m^2 on Days 1, 4, and 7).[1]

During their review of the Biologics License Application (BLA), the FDA issued post-marketing requirements (PMRs) that requested additional assessment of the impact of the fractionated dosing regimen of GO on the risk of veno-occlusive disease or sinusoidal obstruction syndrome (VOD/SOS) in patients with previous or subsequent hematopoietic stem cell transplantation (HSCT), hemorrhage, unexpected serious risk of QT interval prolongation, and unexpected serious risk of anti-drug antibodies. Additionally, no clinical pharmacokinetics (PK) data for GO, represented by total hP67.6 antibody, have been characterized following the fractionated dosing regimen. The PK profiles included in the BLA used for exposure-response modeling of the pivotal Phase 3 trial, ie, Acute Leukemia French Association 0701 (ALFA-0701),[2] were simulated using population PK modeling based on 8 previous clinical trials. Therefore, B1761031 has been planned to address these PMRs.

On 22 February 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, and on 19 April 2018 the European Commission granted a marketing authorization for Mylotarg, indicated for combination therapy with DNR and Ara-C for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia (APL).

The CHMP identified several recommendations in the ongoing development of GO, including the addition of CCI [redacted] 6 pediatric patients into the FDA issued PMR study. Therefore, this study will include 6 pediatric patients 12-17 years of age (eg, adolescents). Patients within this defined age group are expected to have similar electrocardiogram (ECG)/PK findings, and are deemed acceptable for the schedule of assessments and blood draw requirements of this study.

Objectives and Endpoints:

Primary Objective:	**Primary Endpoint:**
• To assess the effect of GO on the QTc interval.	• Maximum change from baseline in corrected QT interval (QTc).
Secondary Objectives:	**Secondary Endpoints:**
• To characterize the PK of single-agent GO following the fractionated regimen (ie, 3 mg/m² on Days 1, 4, and 7). • To assess the safety of GO with fractionated dosing of 3 mg/m^2. • To assess the immunogenicity of GO. • To assess response and overall survival.	• PK parameters: clearance and volume of distribution. • Adverse events (AEs) and abnormal laboratory findings. • Incidence of anti-drug antibody (ADA)/neutralizing antibodies (NAb). • Response: complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) achieved after GO. • Overall Survival.
CCI [redacted]	[redacted]

Study Design:

This is a single-arm, open-label, Phase 4 study evaluating the effect of GO on the QTc, pharmacokinetics, safety, and immunogenicity of GO as a single-agent monotherapy in adult and pediatric patients with relapsed or refractory CD33-positive AML. Approximately 50 adult (age ≥18 years) and 6 pediatric (12 years ≤ age ≤17 years) patients who satisfy the study eligibility criteria will be enrolled. Enrolled patients will receive the fractionated regimen of GO 3 mg/m^2 up to 2 cycles on Days 1, 4, and 7 at each cycle. The impact of GO on VOD/SOS in the context of previous and subsequent HSCT will also be assessed.

Treatment Plan

Patients enrolled in the study will receive three doses of GO 3 mg/m^2 (up to one vial) as a 2-hour intravenous infusion on Cycle 1 Days 1, 4, and 7. A second cycle of GO 3mg/m² (up to one vial) on Cycle 2 Days 1, 4, and 7 will be allowed at the investigator's discretion for patients who meet the following criteria after Cycle 1: Bone marrow with a decrease of blast percentage to at least 25% or a decrease of pretreatment blast percentage by at least 50%; **and** Blood count with neutrophils ≥1,000/μL and platelets ≥50,000/μL, except in patients with the bone marrow blasts ≥5%, the decrease in neutrophils and platelets thought to be due to the underlying leukemia (refer to Section 7.5).

After GO treatment, subsequent anticancer therapy such as consolidation or conditioning regimen and/or HSCT could be considered at the investigator's discretion. A minimum interval of 2 months is recommended between the last dose of GO and HSCT.

Assessments:

QTc Interval

Triplicate ECGs will be performed at screening, baseline (prior to dose on Day 1) and immediately preceding serial PK draws on each day of dosing. A 12-lead tracing will be used for all ECGs, including measurements of PR interval, QT interval, RR interval, and QRS complex. All triplicate ECG tracings will be sent to an independent ECG core laboratory for blinded manual interval measurements.[3]

Pharmacokinetics (PK)

Blood samples will be collected from all participating patients for PK analysis according to the PK schedule. Samples will be collected prior to each dose and at time points around the maximum concentration (C_{max}), ie, at the end of the 2-hour infusion in order to characterize the QTc-concentration relationship.

Safety

Safety will be monitored per the protocol specified schedule. Safety assessments include adverse events (AEs) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.03), clinical examination (including blood pressure and pulse), ECGs, and laboratory tests (hematology, chemistry, coagulation and urinalysis), including hemorrhage-related laboratory data and coagulation-related assessments, such as complete blood counts and differential counts, prothrombin time (PT), activated partial thrombin time (aPTT), and fibrinogen.

Any events of veno-occlusive disease (VOD) and sinusoidal obstruction syndrome (SOS) will be reported as serious adverse event (SAE) during the study duration. Details of the HSCT will be collected in order to assess the impact of the fractionated regimen of GO on the risk of VOD/SOS with previous or subsequent HSCT.

Immunogenicity

Anti-drug antibody (ADA) samples will be collected as specified in the protocol. Samples will be analyzed for ADAs using a tiered approach of screening, confirmation, and titer determination.[4] Samples that test positive for ADA will be further characterized to determine whether neutralizing antibodies (NAb) are present.

Efficacy

Efficacy evaluation anddetermination of remission status by blood and bone marrow aspiration (and biopsy if applicable) will be conducted at the end of each cycle using European Leukemia Net (ELN 2017) recommendations (see Section 7.5).[5] Survival status for each patient will be collected for the study duration of 12 months.

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[redacted]

Statistical Methods:

The sample size is based on ensuring sufficient data to exclude a 20 milliseconds (msec) mean increase 20 msec in the QT interval using the Fridericia heart rate correction (QTcF). If the upper bounds of one-sided 95% confidence intervals of change from baseline in QT measurements using the Fridericia's heart rate correction for each of the QTc sampling time points (on Day 4, at 0 hours, and Day 7, at 0, 2, 4, and 6 hours) are below 20 msec, the post-baseline dose QTc interval will be considered to be "non-inferior" to the baseline.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES (see Section 6) and ASSESSMENTS (see Section 7) 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

	Screening	Cycle 1						Cycle 2 (if administered)						EOT	Follow-up Period[19]
		GO Treatment			Post-GO Period			GO Treatment			Post-GO Period				
Schedule Day[1]	<28 days prior to enrollment	C1 D1	C1 D4	C1 D7	C1 D10	C1 D15	C1 D21	C2 D1	C2 D4	C2 D7	C2 D10	C2 D15	C2 D21		Every 12 weeks
Visit window (Days)					±1	±1	±1				±1	±1	±1	±2	±7
Informed consent & assent[3]	X														
Immunophenotyping (including CD33)[4]	X														
CCI [redacted]		[redacted]													
ECG (in triplicate)[6]	X	X	X	X				X		X					
Pharmacokinetic samples[7]		X	X	X	X[7]	X[7]	X[7]	X[7]		X[7]		X[7]	X[7]	X	
Medical history[8]	X														
Body weight	X	X	X	X				X	X	X					
Vital signs/PE	X	X	X	X				X	X	X					
ECOG PS score[9]	X	X						X							
Imaging assessment[10]	X[10]				X[10]						X[10]				

Table 1. Schedule of Activities

	Screening	Cycle 1						Cycle 2 (if administered)						EOT	Follow-up Period[19]
		GO Treatment			Post-GO Period			GO Treatment			Post-GO Period				
Schedule Day[1]	<28 days prior to enrollment	C1 D1	C1 D4	C1 D7	C1 D10	C1 D15	C1 D21	C2 D1	C2 D4	C2 D7	C2 D10	C2 D15	C2 D21		Every 12 weeks
Visit window (Days)					±1	±1	±1				±1	±1	±1	±2	±7
Safety Laboratory[11]															
CBC and differential counts [12]	X	X	X	X	X	X[12]	X		X	X	X	X[12]		X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[17]
Urinalysis	X				X	X									
Coagulation (PT, aPTT, fibrinogen)	X	X	X	X	X	X		X	X	X	X	X			
Pregnancy test	X[13]													X[20]	
HIV, Hepatitis B, and Hepatitis C evaluation[14]	X														
Pre-medication		X	X	X				X	X	X					
BM examination and disease assessments[15]							X[15]					X[15]			
Serious and non-serious adverse event monitoring[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[17]
Concomitant medications and treatment[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival follow-up[19]															X[21]

Abbreviations: aPTT = activated partial thromboplastin time; BM = bone marrow; C = Cycle; CAT = computed axial tomography; CBC = complete blood counts; D = Day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; GO = gemtuzumab ozogamicin; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PE = physical examination; PT = prothrombin time

1. All assessments should be performed prior to dosing with GO on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. The exact enrollment day (Day 1) is the day when patient identifier is assigned with the first GO dose. The EOT is defined as 36 days after the last dose of GO or start of subsequent anticancer therapy, eg, consolidation and/or conditioning regimens.
2. The second cycle will be allowed at the investigator's discretion for patients who meet the following criteria after Cycle 1(see also Table 3 describing hematologic toxicities): Bone marrow with a decrease of blast percentage to at least 25% or a decrease of pretreatment blast percentage by at least 50%; **and** Blood count with neutrophils ≥1,000/μL and platelets ≥50,000/μL, except in patients with the bone marrow blasts ≥5%, the decrease in neutrophils and platelets thought to be due to the underlying leukemia. Patients who do not meet these response criteria after the first cycle of GO will not be allowed to receive a 2nd cycle see Section 7.5). Cycle 2 Day 1 must be started no later than 42 days after the last dose of GO (ie, Cycle 1 Day 7).
3. Informed Consent and assent for those patients under age 18 (or as specified per local policy/laws). Must be obtained prior to undergoing any study procedure.
4. CD33 immunophenotyping performed at screening on bone marrow (BM) or of circulating blasts in peripheral blood specimen by local laboratories. Surface CD33 expression should be measured by flow cytometry (flow-activated cell sorting, FACS); immunohistochemistry (IHC) analysis is allowed in patients with (1) dry tap; or (2) if BM specimen is inadequate and/or with insufficient circulating blasts for FACS. CCI [redacted]
6. ECGs will be in triplicate (3 consecutive ECGs approximately 2 minutes apart). All ECGs will be sent to an ECG core laboratory vendor. ECG at screening will be used to determine patient eligibility. Ideally, the patient will be supine or reclined in a semi recumbent position for the entire infusion and for both pre- and post- infusion ECGs. To minimize artifact, the patient should not change position between the pre- and post-infusion ECGs. Additional ECGs may be done if clinically required. See Table 2 for additional collection time points.
7. Pharmacokinetic samples: See Table 2 for additional time points.
8. Medical History: To be collected within 28 days prior to first dose Includes date of initial diagnosis with FAB subtype, prior AML therapies including HSCT and outcomes, and cytogenetics. Also, review study eligibility.
9. ECOG PS: Assessment is not required on Day 1 if acceptable screening assessment is done within 7 days prior to the start of investigational drug.
10. Patients with suspected extramedullary disease will have imaging assessment (eg, CAT or MRI) of all known disease sites.
11. Days 1, 4, and 7 laboratory samples should be collected prior to dosing.
12. Three times a week after GO dosing until determination of remission status (see Section 7.5); subsequently CBC and differential counts will be collected once weekly until EOT (or until start of Cycle 2 (if administered) or start of subsequent anticancer therapy).
13. Pregnancy test: Required in less than 7 days prior to Day 1.
14. Evaluations of HIV and hepatitis B serological tests and hepatitis C tests (see Section 6.1).
15. Efficacy evaluation anddetermination of remission status by blood and bone marrow aspiration (and biopsy if applicable) after recovery of blood counts is observed and/or at a maximum of 36 days after the last dose of GO treatment.
16. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03 up to 36 days after the last dose of GO or start of subsequent anticancer therapy, (eg, consolidation or conditioning regimen), whichever occurs first. Patients must be followed for AEs according to Section 8. Sites should report related SAEs including VOD/SOS as warranted. Any occurrence of VOD/SOS is to be reported as SAE to Pfizer Safety and recorded in the case report form (CRFsee Section 7.4.1).

17. Occurrence of VOD/SOS will be monitored for the study duration of 12 months for each patient (see Section 7.4.1). During Follow-up period, blood chemistry sampling should be collected only in case of occurrence of VOD/SOS.
18. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 36 days post the last dose of study treatment or starting subsequent anticancer therapy (eg, consolidation or conditioning regimen). During the follow-up period concomitant medications only related to follow-up therapy/HSCT and the management of VOD/SOS are to be collected (see Section 7.4.1). Also, the patient will be informed of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart (see Section 4.3.1).
19. Post BM assessment and determination of response: Consolidation as well as the decision of subsequent HSCT will be at physician's discretion. The study duration for each patient is 12 months. The survival data will be collected for each patient for the study duration. Patients who undergo HSCT subsequent to GO regimen will undergo relevant laboratory tests for safety monitoring per institutional standards for suspected or diagnosed VOD/SOS.
20. Pregnancy test (see Section 7.7).
21. For any patients who may not be able to visit the study site at the protocol designated time, telephone contact is acceptable method for survival follow-up plus collecting cause(s) of death.

Table 2. Schedule of Activities – ECG, Pharmacokinetics, Immunogenicity CCI Assessments

	Cycle 1															Cycle 2 (if administered)							EOT[l] (±2 days)	Follow-up Period
	D1						D4		D7				D10 (±1 day)	D15 (±1 day)	D21 (±1 day)	D1		D7			D15 (±1 day)	D21 (±1 day)		
Time (hours) relative to the start of the GO infusion	0	1	2	4	6	24	0	2	0	2	4	6	NA	NA	NA	0	2	0	2	6	NA	NA	NA	NA
Blood sample for PK[a]	X[b]	X[d]	X[c]	X[d]	X[d]	X[j]	X[b]	X[c]	X[b]	X[c]	X[d]	X[d]	X[e]	X[e]	X[e]	X[b]	X[c]	X[b]	X[c]	X[d]	X[e]	X[e]	X[e]	
[redacted]	C CI																							
Blood sample for ADA/NAb[c]	X[b]													X[e]	X[e]						X[e]	X[e]	X[e]	X[m]
Triplicate 12-lead ECG[f]	X	X	X	X			X	X	X	X	X	X				X	X	X	X	X				
[redacted]	C CI																							
[redacted]																								

ADA = anti-drug antibody; D = Day; ECG = electrocardiogram; EOT = end of treatment; GO = gemtuzumab ozogamicin; NA = not applicable; NAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics

a. PK samples collected during infusion should be taken from the arm OPPOSITE to the IV infusion site.
PK sample should ALWAYS be collected AFTER ECG.
If the dosing day is delayed, the PK and PD samples must be collected on the same day as dosing.
PK collections on Day 4 and Day 10 for all patients.

b. Pre-dose samples to be collected right before the start of GO infusion.

c. 2-hour, post-dose samples are to be drawn right before the infusion ends (maximum window of ±10 minutes allowed).

d. These post-dose samples to be drawn within ±10 minutes of the designated time.

e. Samples on Days 10, 15, 21, and EOT visit may be collected at any time during the visit.

f. Triplicate 12-lead ECG: At each time-point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart, but within 15 minutes for all ECGs, to determine the mean QTc. ECGs will be collected at Screening and on dosing Days 1, 4, and 7. It is preferable that the machine used has the capacity to calculate the standard intervals automatically. ECG interval readings by the ECG recorder's algorithm will be read and interpreted at the investigational site for eligibility determination. Additional ECGs will be performed as clinically indicated for patient safety monitoring and documentation stored in the source documents. ECG measurements will include PR interval, QT interval, RR interval and QRS complex.

[redacted]

j. 24-hour, post dose samples for PK [redacted] to be drawn from 24 to 30 hours of the designated time.
k. [redacted]
l. EOT is defined as 36 days after the last dose of GO.
m. The follow-up for patients who are ADA positive at the EOT visit (36 days after last dose) consists of visits approximately every 90 days until ADA titers are no longer detectable, return to baseline, stabilize at a level acceptable to the investigator and sponsor, or up to 1 year after their first visit in the main study, whichever comes first.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

The CD33 (cluster of differentiation) antigen is a cell surface protein expressed on the external surface of normal and leukemic myeloid cells, and leukemic blasts in more than 80-90% of patients with acute myeloid leukemia (AML). The antigen is not expressed on the pluripotent stem cells, normal precursor hematopoietic cells.[6]

Gemtuzumab ozogamicin (GO; MYLOTARG™) is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (recombinant humanized immunoglobulin [Ig] G4, kappa antibody produced by mammalian cell culture in NS0 cells) that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin dimethylhydrazide (DMH), a semisynthetic disulfide derivative of calicheamicin. The antibody portion binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells. After binding to the CD33 antigen, GO is internalized within the leukemic cell, thus delivering the calicheamicin derivative.[7] Activation of N-acetyl gamma calicheamicin DMH induces double-strand deoxyribonucleic acid (DNA) breaks, subsequently inducing cell cycle arrest and apoptotic cell death.[8] GO, the only approved AML therapy that targets CD33 antigen, is indicated for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults, and relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older.[1]

1.2. Background and Rationale

1.2.1. Incidence and Treatment of Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults and accounts for ~80% of all cases of acute leukemia. Each year there are approximately 260,000 new cases of AML worldwide with incidence 4.2 per 100,000; of these about 21,380 cases are estimated in US.[9] The average age of a patient with AML is about 68 years and it is relatively uncommon before the age of 45. Incidence increases with age and peaks in adults 65 years of age or older; slightly more than half of all patients are 60 years of age or older. Thus, AML is an orphan disease of older people.

AML is a genetically heterogeneous malignancy characterized by multiple genetic mutations at the time of diagnosis that evolve with treatment, resulting in treatment resistance, disease relapse, and reduced survival. Standard of care induction chemotherapies such as anthracycline plus cytarabine, or hypomethylating agents (eg, decitabine and azacitidine) can induce complete remissions in 5-70% of patients; however, remissions are not durable and disease relapse occurs in up to 60% of patients.[10] The most effective consolidation therapy is allogeneic stem cell transplantation, but this carries a high risk of initial mortality and a significant risk of long-term morbidity associated with chronic graft-versus-host disease, which tends to offset the therapeutic benefits of a low likelihood of relapse. But the risk of disease recurrence of chemotherapeutic-based approaches, with or without autologous stem cell rescue, still remains high. Patients with relapsed AML have a particularly poor

prognosis. A number of cytotoxic agents and combination regimens have been used for salvage chemotherapy and remission rates from 20–70% have been described. However, the period of remission typically lasts only 4-6 months.

1.2.2. Gemtuzumab Ozogamicin for Treatment of Acute Myeloid Leukemia

1.2.2.1. Regulatory History

Gemtuzumab ozogamicin originally received accelerated approval with dose of 9 mg/m² x 2 (14 days apart) given as a single-agent treatment for patients with CD33-positive AML in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy in the United States (US) on 17 May 2000 and as a monotherapy for the treatment of patients with relapsed or refractory CD33-positive AML in Japan in 2005. A Phase 3 study (Southwest Oncology Group [SWOG] S0106) evaluating GO in combination with chemotherapy in patients with previously untreated de novo AML was subsequently conducted as a post-market requirement (PMR) from 2004 to 2009 to confirm the clinical benefit of GO in order to convert the accelerated approval to full approval. S0106 was a randomized trial comparing treatment with DNR and Ara-C with or without GO 6 mg/m^2 for treatment of patients <60 years old with newly-diagnosed AML. The primary endpoint was complete remission (CR) rate post induction and disease-free survival (DFS) post consolidation. There were 637 patients randomized. The study showed no improvement in CR, DFS or overall survival (OS) with the addition of GO. In addition, there was a higher rate of fatal induction toxicities in the GO arm (5.8% versus 1.3%). FDA concluded that clinical benefit was not confirmed and that there was a potential safety issue due to the increase in early deaths. In addition, GO was associated with hepatic veno-occlusive disease (VOD), which has substantial morbidity and mortality. Therefore, Pfizer voluntarily withdrew Mylotarg from the US market in October 2010. Nevertheless, GO continued to be marketed for the treatment of patients with relapsed or refractory CD33-positive AML in Japan, hematologists requested compassionate-use GO for their AML patients, and investigators continued to evaluate GO in patients with AML.

On 01 September 2017 the US FDA approved Mylotarg for adults with newly diagnosed CD33-positive AML, and for adults and children 2 years and older with relapsed or refractory CD33-positive AML. Study ALFA-0701 supported use of GO in combination with chemotherapy in newly diagnosed AML, EORTC (European Organisation for Research and Treatment of Cancer) - GIMEMA (Gruppo Italiano Malattie Ematologiche dell' Adulto) AML-19 Study supported use of single-agent GO in newly diagnosed AML,[23] and Study MyloFrance-1 supported use of single-agent GO in relapsed or refractory AML. The approved dosage is as follows:[1]

- Combination regimen in newly-diagnosed AML: Induction with 3 mg/m^2 on Days 1, 4, and 7 in combination with DNR and Ara-C, followed by consolidation with 3 mg/m^2 on Day 1 in combination with DNR and Ara-C.

- Single-agent regimen in newly-diagnosed AML: Induction with 6 mg/m^2 on Day 1 and 3 mg/m^2 on Day 8, followed by continuation for patients without evidence of disease progression with a dose of 2 mg/m^2 every 4 weeks for 8 doses.

- Single-agent regimen in relapsed or refractory AML: 3 mg/m^2 on Days 1, 4, and 7.

On 22 February 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, and on 19 April 2018, The European Commission (EC) granted a marketing authorisation approval for Mylotarg, indicated for combination therapy with DNR and Ara-C for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia (APL).

1.2.2.2. Fractionated Dosing of GO

Based on in vitro studies, which showed rapid re-expression of CD33 antigenic sites on the cell surface of blasts cells after exposure to GO, it was hypothesized that fractionated doses of GO may be efficacious and better tolerated.[11] It was hypothesized that fractionated dose on Days 1, 4, and 7 may increase GO activity by binding to re-expressed CD33, thereby increasing GO uptake into leukemic blasts. In vitro data indicated that at least 90% of CD33 saturation is required for efficient killing of AML blasts.[12] The initial dose-escalation Study 101 (N=40) in relapsed AML evaluated CD33 site saturation of GO over a dose range of 0.25 to 9 mg/m^2. Based on these results, a dose of 3 mg/m^2 is estimated to produce 90% to 95% saturation of CD33.[13] Based on exposure-response modeling, lower fractionated dosing of GO was predicted to retain efficacy and improve safety. This is particularly important in patients who undergo hematopoietic stem cell transplantation (HSCT), a significant risk factor of VOD/SOS.

The safety and efficacy of the fractionated dose GO monotherapy regimen of 3 mg/m^2 on Days 1, 4, and 7, in patients with CD33-positive AML in first relapse has been demonstrated in a Phase 2 study (MyloFrance-1).[14]

1.2.2.3. CCI [redacted] Pharmacokinetics and Dosage

GO was originally approved for use in patients with CD33-positive relapsed AML. Three registrational Phase 2 studies (0903B1-201, 0903B1-202, 0903B1-203) were conducted.[15] The approved regimen was 2 doses of GO at 9 mg/m^2, administered at least 14 days apart. The 14-day interval between doses was selected on the basis of near total clearance of the antibody portion of GO, hP67.6, within this time period. Based on the non-compartmental analysis (NCA) following a 9 mg/m^2 dose on Days 1 and 14, the half-life of hP67.6 was 62 hours after the first dose and 90 hours after the second dose.

Since no clinical pharmacokinetic (PK) data are available for the fractionated dosing regimen for GO (3 mg/m^2 administered on Days 1, 4, and 7), PK profiles for this regimen were simulated, using the PK model developed based on prior clinical studies, in patients with relapsed or refractory AML or de novo AML. The model predicted that, while the total dose of the fractionated dosing regimen is half of that of the original dosing regimen (9 versus 18 mg/m^2), total area under curve (AUC) of hP67.6 over the course of treatment is 25%, and maximum concentration (C_{max}) is 24% of the original dosing regimen. Since the C_{max} has been associated with the risk of certain AEs (eg, VOD/SOS, bilirubin elevation, aspartate aminotransferase [AST] elevation), the fractionated regimen is expected to have improved safety profile than the previously used regimen.[13]

1.2.2.4. Clinical Data for GO in Patients with AML in First Relapse

Studies 201, 202, and 203 were single-arm studies in adult patients with CD33-positive AML in first relapse that supported the original accelerated approval of Mylotarg by the FDA in May 2000.[15] These studies shared a similar design and used an identical GO dosing regimen of 9 mg/m^2 on Days 1 and 15. The primary objective of these studies was to assess the efficacy (based on the number of patients achieving CR or complete remission with incomplete platelet recovery [CRp]) and safety of GO monotherapy. A pooled analysis of these 3 pivotal Phase 2 studies (N=277) reported an objective response rate of 35% (based on International Working Group [IWG] criteria).[16] The evidence from these studies indicated that patients receiving GO had a high incidence of myelosuppression, manifested by delayed recovery time for neutrophils and platelet counts, and over time, hepatic VOD (SOS) emerged.

A Phase 2 study (MyloFrance-1) used the fractionated regimen of single-agent GO (3 mg/m^2 on Days 1, 4, and 7), followed by consolidation with high-dose cytarabine in patients with AML in first relapse. Of 57 patients who received GO, 15 patients (26%) achieved CR and four patients (7%) achieved CRp. In the 19 patients who achieved a response in the MyloFrance-1 study, the median times to recovery of neutrophil count to 500/mm^3 and of platelet count to 50,000/mm^3 were 23 and 20 days, respectively, approximately half the median time to recovery observed in Studies 201/202/203 (40.5 days and 51 days, respectively). Grade 3 treatment emergent adverse events (TEAEs) reported in >1% patients in the MyloFrance-1 study included sepsis (31.5%), fever (15.8%), rash (10.5%), pneumonia (7.0%), bleeding (7.0%), mucositis (3.5%), and diarrhea, headaches, tachycardia, and edema (1.8% each). Grade 3 or 4 liver toxicity was not reported; also, there were no reports of VOD/SOS, including in 7 patients who underwent HSCT subsequent to GO treatment.[14]

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the investigator brochure (IB).

1.2.2.5. Study Rationale

Results from the studies evaluating treatment with GO in patients with CD33-positive AML in first relapse, described in Section 1.2.2.4, provide evidence that fractionated regimen of GO has enhanced safety profile than the original dosing regimen, without hampering the efficacy.

The effect of GO on the QT interval has not been evaluated clinically because the regulatory guidelines when the original studies (201, 202, and 203) were conducted did not require quantitative QT data to be collected. However, tests evaluating the effect of N-acetyl gamma calicheamicin DMH on the human ether-a-go-go-related gene (hERG) potassium channel at concentrations up to 6.77 uM resulted in <1% inhibition of the hERG current amplitude and there were no effects of GO on ECG parameters in dogs at any dose (range 4 to 40 mg/m^2) or in monkeys in the 6-week repeat-dose studies. Additionally, no PK data are available for the fractionated dosing regimen (3 mg/m^2 on Days 1, 4, and 7) of GO. Therefore, FDA has requested a PMR study to characterize the effect of the fractionated dosing regimen of GO as

a single-agent treatment in patients with relapsed or refractory CD33-positive AML on QT interval, PK, and safety. In addition, the CHMP identified several recommendations in the ongoing development of GO, including CCI [redacted] inclusion of 6 pediatric patients into the FDA issued PMR study. The 6 pediatric patients in this study will be between 12 and 17 years of age (eg, adolescents), a defined group of pediatric patients expected to have similar ECG/PK findings and for whom the schedule of assessments and blood draw requirements would be acceptable in order not to exceed 3% of total blood volume within 4 weeks.

A sample size of 50 patients 18 years or older should allow for collection of sufficient data to characterize the effect of GO on the QT interval, as well as to enhance the understanding of GO following the fractionated regimen in patients with relapsed or refractory AML.
Six (6) pediatric patients (12 years ≤ age ≤17 year) will be included based on agreement with CHMP. This study includes the collection of hemorrhage-related laboratory data and coagulation-related assessments, such as complete blood counts (CBC) and differential counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen. The impact of GO on VOD/SOS in the context of previous and subsequent HSCT, and anti-drug antibody (ADA) formation will also be assessed. CCI [redacted]

CCI [redacted]

CCI [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	Primary Endpoint:
• To assess the effect of GO on the QTc interval.	• Maximum change from baseline in corrected QT interval (QTc).
Secondary Objectives:	**Secondary Endpoints:**
• To characterize the PK of single-agent GO following the fractionated regimen (ie, 3 mg/m² on Days 1, 4, and 7). • To assess the safety of GO with fractionated dosing of 3 mg/m^2. • To assess the immunogenicity of GO. • To assess response and overall survival.	• PK parameters: clearance and volume of distribution. • Adverse events (AEs) and abnormal laboratory findings. • Incidence of anti-drug antibody (ADA)/neutralizing antibodies (NAb). • Response: complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) achieved after GO. • Overall Survival.
CCI [redacted]	[redacted]

3. STUDY DESIGN

This is a single-arm, open-label, Phase 4 study evaluating the effect of GO on the QT, pharmacokinetics, safety, and immunogenicity of GO as a single-agent monotherapy in adult and pediatric patients with relapsed or refractory CD33-positive AML. Approximately 50 adult patients (age ≥18 years) and 6 pediatric (12 years ≤ age ≤17 years) patients who satisfy the study eligibility criteria will be enrolled and treated with the fractionated regimen of GO 3 mg/m^2 on Days 1, 4, and 7 (up to 2 cycles). Triplicate ECGs will be performed at screening, baseline (prior to dose on Day 1) and right before serial PK draws on each day of dosing. All triplicate ECG tracings will be sent to an independent ECG core laboratory for blinded manual interval measurements. The active safety monitoring duration will be up to 36 days after the last dose of GO or starting of subsequent anticancer therapy, including consolidation and/or conditioning regimens. This study includes the collection of hemorrhage-related laboratory data and coagulation-related assessments, such as CBC and differential counts, PT, aPTT, and fibrinogen. Any event of VOD/SOS will continue to be reported as SAE during the entire study duration.

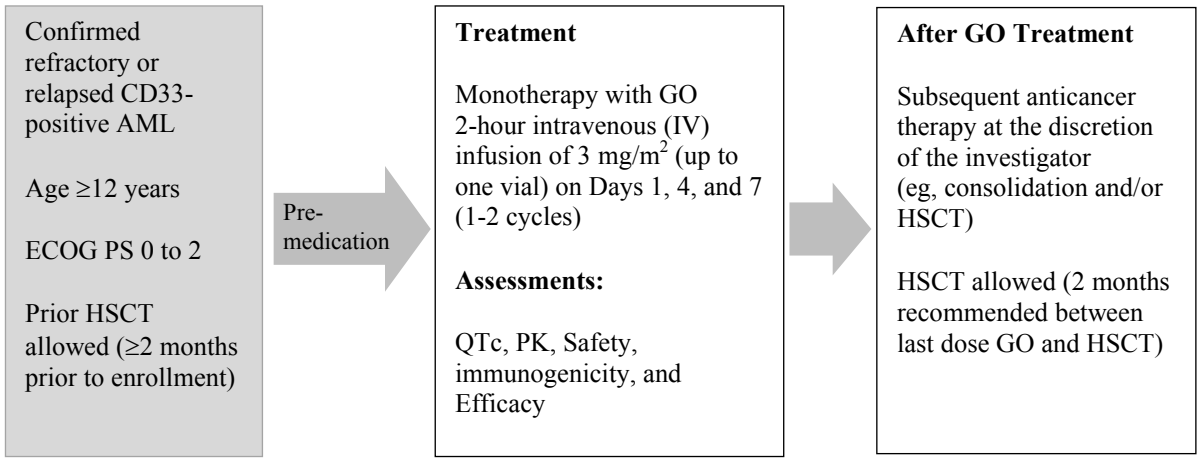
After receiving the study treatment (Cycle 1 and Cycle 2, if administered), blood cell and differential counts will be examined 3 times a week after GO dosing until having determination of remission status (see Section 7.5); subsequently CBC and differential counts will be collected once weekly until 36 days after the last dose of GO or until start of subsequent anticancer therapy, eg, consolidation or conditioning regimen. Efficacy evaluation and final determination of remission status by blood and bone marrow aspiration (and biopsy if applicable) will be conducted after recovery of blood counts is observed or at a maximum of 36 days after the last dose of GO treatment (EOT). Study duration for each patient is a total of 12 months from enrollment, survival data will be collected for the study duration of 12 months.

Treatment Plan

Patients enrolled in the study will be receive three doses of GO 3 mg/m^2 (up to one vial) as a 2-hour intravenous infusion on Cycle 1 Days 1, 4, and 7. A second cycle 3mg/m² (up to one vial) on Cycle 2 Days 1, 4, and 7 will be allowed at the investigator's discretion for patients who meet the following criteria after Cycle 1: Bone marrow with a decrease of blast percentage to at least 25% or a decrease of pretreatment blast percentage by at least 50%; **and** Blood count with neutrophils ≥1,000/µL and platelets ≥50,000/µL, except in patients with the bone marrow blasts ≥5%, the decrease in neutrophils and platelets thought to be due to the underlying leukemia (see Section 7.5).

After GO treatment, subsequent anticancer therapy such as consolidation or conditioning regimen and/or HSCT could be considered at the investigator's discretion. A minimum interval of 2 months is recommended between the last dose of GO and HSCT.

Figure 1. B1761031 Study Schematic



4. PATIENT ELIGIBILITY CRITERIA

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

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

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

1. Refractory or relapsed (ie, bone marrow blasts ≥5%) CD33-positive AML.

2. Age ≥12 years.

3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 2.

4. Initial peripheral white blood cells (WBC) counts <30,000/μL; patients with a higher WBC count should undergo cytoreduction.

5. Adequate renal/hepatic functions, ie:

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

    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2.5×ULN; total bilirubin <2×ULN.

6. Negative serum or urine pregnancy (human chorionic gonadotropin [hCG]) test within 1 week before treatment for women of child bearing potential.

7. Evidence of a personally signed and dated informed consent document and obtaining proper pediatric assent in addition to consent according to local regulations (by the caregivers or legally acceptable representative [eg, parents] in the pediatric patients) indicating that the patient [or a legally acceptable representative/parent(s)/legal guardian] has been informed of all pertinent aspects of the study.

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

9. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure.

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

4.2. Exclusion Criteria

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

1. Patients with prior treatment with GO.
2. Patients with prior history of VOD/SOS.
3. Prior HSCT is not allowed, if it was conducted within 2 months prior to study enrollment.
4. Patients with known active central nervous system (CNS) leukemia.
5. Uncontrolled or active infectious status.
6. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.
7. Uncontrolled cardiac dysrhythmias of NCI CTCAE Grade 2, uncontrolled atrial fibrillation of any grade.
8. Sero-positivity to human immunodeficieny virus (HIV).
9. Active hepatitis B or hepatitis C infection (see Appendix 2).
10. Chemotherapy, radiotherapy, or other anti-cancer therapy (except hydroxyurea as cytoreduction) within 2 weeks prior to enrollment in the study.
11. Major surgery within 4 weeks prior to enrollment.
12. Diagnosis of any other malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

13. QTc interval >470 milliseconds (msec) using the Fridericia (QTcF) (based on the mean value of the triplicate electrocardiograms [ECGs]), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP).

14. The use of medications known to predispose to Torsades de Pointes within 2 weeks prior to enrollment (see Appendix 4).

15. History of allergic reactions attributed to compounds of similar chemical or biologic composition to GO.

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

17. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.

18. 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 patient inappropriate for entry into this study.

19. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for 7 months after the last dose of investigational product.

4.3. Lifestyle Requirements

4.3.1. Contraception

In this study, fertile male patients and female patients who are of childbearing potential as applicable to the study will receive GO, which has been associated with demonstrated teratogenicity/fetotoxicity. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 7 months after the last dose of GO in female patients of reproductive potential, and for at least 4 months after the last dose of GO in male patients with female partners of reproductive potential. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation,

and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or 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 the following:

- Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient'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.

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

- 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.

- Male sterilization with absence of sperm in the postvasectomy ejaculate.

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

- 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 36 days after the last dose of GO.

4.4. Sponsor's 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 investigator file.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator 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 patient'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 patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENT

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 gemtuzumab ozogamicin (GO).

5.1. Allocation to Treatment

Once the patient has signed the informed consent (and assent for pediatric patients), the investigator or designee will contact the interactive response technology (IRT) system 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 IRT system. Instructions on how to use the IRT system will be provided in the study manual. No patient will receive study drug therapy until the entire enrollment process has been completed.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Patient Compliance

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

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

5.3. Investigational Product Supplies

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

5.3.1. Dosage Form(s) and Packaging

GO for injection is supplied as a white to off-white, unpreserved, lyophilized cake or powder in a single-dose 20-mL Type I amber glass vial with rubber closure and flip-off cap. Vials will be labeled in accordance with local requirements.

Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system on Days 1, 4, and 7 per cycle. 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 including GO.

See the Investigational Product Manual (IP manual), for instructions on how to prepare the investigational product for administration. Investigational product 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.

5.4. Administration

5.4.1. Administration of the Premedication

Premedication is required for all patients.

Patients will be pre-medicated with acetaminophen 650 mg orally and diphenhydramine 50 mg orally or intravenously 1 hour prior to GO dosing and 1 mg/kg methylprednisolone or an equivalent dose of an alternative corticosteroid within 30 minutes prior to infusion of GO (given prior to GO infusion may ameliorate infusion-related symptoms).

Follow standard practice of the institution to prevent tumor lysis syndrome.

Vital signs should be monitored during infusion and for 2 hours following infusion.

5.4.2. Administration of GO

Three doses of GO 3 mg/m^2 (up to one vial per dose) will be administered at investigational site as a 2-hour intravenous infusion after premedication on Days 1, 4, and 7 at each cycle. Patients will receive 1 or 2 cycles of GO. The second cycle of GO will be allowed at the investigator's discretion for patients who meet selected dosing criteria after the first cycle. (see Section 7.5).

Use appropriate aseptic technique for the reconstitution and dilution procedures. Protect the reconstituted and diluted GO solution from light. See the IP manual for instructions on how to administer GO.

5.4.3. Dosage Modification for Toxicities

- Every effort should be made to administer study medication on the planned dose and schedule. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed.

- Full recovery from hematologic toxicities is not a requirement for administration of the second or third dose on Day 4 or 7, respectively.

- In the event of non-hematologic toxicities, dosing may be delayed, omitted or discontinued as described below (Table 3) by monitoring chemistries especially total bilirubin, AST, ALT, and other severe or life-threatening non-hematologic toxicities through recovery from treatment-related toxicities.

- In the event of persistent hematologic toxicities after Cycle 1, conditional Cycle 2 dosing may be delayed or discontinued as described below (Table 3) by monitoring blood counts through recovery from treatment-related toxicities.

Table 3. Dosage Modifications for Non hematologic and Hematologic Toxicities

Non-hematologic Toxicities	**Recommended Actions**
VOD/SOS	• Discontinue GO.
Total bilirubin greater than 2×ULN, or AST and/or ALT greater than 2.5×ULN	• Delay treatment with GO until recovery of total bilirubin to less than or equal to 2 × upper normal limit (ULN) and AST and ALT to less than or equal to 2.5 × ULN prior to each dose. • Omit scheduled dose if delayed more than 2 days between sequential infusions.
Infusion-related reactions	• Interrupt the infusion and institute appropriate medical management. • Administer acetaminophen, diphenhydramine and/or methylprednisolone, if needed. • Provide supportive care measures as needed. • For mild, moderate or severe infusion related reactions, once symptoms resolve, consider resuming the infusion at no more than half the rate at which the reaction occurred. Repeat the procedure above in the event of recurrence of symptoms. • Permanently discontinue GO upon occurrence of a severe infusion reaction or for any life-threatening infusion reaction.
Other severe or life-threatening non-hematologic toxicities	• Delay treatment with GO until recovery to a severity of no more than mild (Grade ≤1). • Omit scheduled dose if delayed more than 2 days between sequential infusions.
Hematologic Toxicities	**Recommended Actions**
Persistent thrombocytopenia	• If platelet count does not recover to greater than or equal to 50,000 /μL within 42 days after the last dose of GO in the first cycle, DO NOT administer the 2nd cycle.*
Persistent neutropenia	• If neutrophil count does not recover to greater than or equal to 1,000/μL within 42 days after the last dose of GO in the first cycle, DO NOT administer the 2nd cycle.*

* except in patients with the bone marrow blasts ≥5%, the decrease in neutrophils and platelets thought to be due to the underlying leukemia.

5.5. Investigational Product Storage

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 investigator 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.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.6. 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.

5.6.1. 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.

5.7. Concomitant Treatment(s)

All concomitant medications required to clinically manage patients while they are receiving GO therapy are permitted, including any palliative and supportive care for cancer related symptoms. Investigational drugs, anti-cancer therapy (except hydroxyurea as cytoreduction), and radiation (eg, cranial irradiation for CNS leukemia) are prohibited 2 weeks prior to study entry, during the GO treatment period, and before the determination of remission status by bone marrow (BM) assessment.

The patients treated with medications that are known to predispose to Torsades de Pointes should discontinue the drugs at least 2 weeks prior to enrollment. Medications that are known to cause QT prolongation should be avoided whenever possible during the GO treatment period and the post-GO period, but allowed after EOT visit. Refer to Appendix 4 for assessing drugs known to predispose to Torsades de Pointes.

All concomitant medications, including prescription and nonprescription drugs, nondrug treatment, and dietary supplements and herbal preparations, will be entered on the case report form (CRF). Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 36 days post the last dose of study treatment or starting subsequent anticancer therapy (eg, consolidation or conditioning regimen).

6. STUDY PROCEDURES

The enrollment (study entry) day is defined as Day 1, when patient identifier is assigned with the first GO dosed.

6.1. Screening

Informed consent document (ICD) approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be signed and dated before any study-specific procedures are conducted. Screening procedures for evaluating eligibility and baseline data will be completed within 28 days prior to dosing on Day 1 unless otherwise noted.

The following will be collected at screening:

- Sign informed consent form and obtain documentation of assent at screening for those patients under age 18 (or as specified per local policy/laws).
- Review study eligibility (inclusion and exclusion criteria).

- Evidence of CD33 positivity for eligibility at screening, eg, by immunophenotyping of bone marrow or leukemia blasts in the peripheral bloodperformed by local laboratory using a validated assay and obtained within 28 days of enrollment will be collected and recorded in the CRF. Surface CD33 expression should be measured by flow cytometry (flow-activated cell sorting, FACS); immunohistochemistry (IHC) analysis is allowed in patients with (1) dry tap; or (2) if BM specimen is inadequate and/or with insufficient circulating blasts for FACS. CCI [redacted]

- Medical history: To be collected within 28 days prior to first dose.

  - Chronic conditions and/or medical history of significance including alcohol use and relevant radiation and surgical procedures;

  - Any other previous cancer diagnosis;

  - Patients with prior HSCT are allowed in the study but those with history of VOD/SOS are not allowed. Medical history must be reviewed for evidence of VOD/SOS (eg, weight gain, elevated bilirubin, tender hepatomegaly, and ascites may indicate underlying VOD/SOS), especially if a patient received high-dose chemotherapy followed by HSCT;

  - Current disease: Initial AML diagnosis, relevant information for conclusive morphologically documented, refractory or relapsed CD33-positive AML, Eastern Cooperative Oncology Group performance status (ECOG PS) will be assessed. (Definition of refractory and relapsed AML as per ELN 2017 recommendation,[5] see Appendix 5).

- Focused physical examination performed with clinical judgment evaluating potential areas of AML 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.

- Imaging Assessment: Patients with suspected extramedullary disease will have imaging assessment (eg, computed axial tomography [CAT] or magnetic resonance imaging [MRI]) of relevant sites.

- Vital signs including height, weight, blood pressure, pulse, and temperature. ECOG PS will also be assessed.

- Laboratory evaluations as described in Section 7.4, Appendix 3, and Schedule of Activities (Table 1).

- For women of childbearing potential, a beta-human chorionic gonadotropin (β-hCG) urine or serum pregnancy test must be conducted as specified in Section 7.7.

- ECG at screening will be collected in triplicate within 28 days prior to enrollment. The results will be read and interpreted at the investigational site for eligibility determination; results of QTcF assessment are to be available prior to enrollment.

- Patients may be enrolled following successful completion of the pre-study assessments, screening procedures, and confirmation of eligibility.

- Evaluations of HIV and hepatitis B serological tests and hepatitis C tests will be conducted (see Appendix 2).

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

6.2. Study Period

The total study period at each cycle is comprised of following periods:

- GO Treatment: Starts with the first dose of GO (Day 1) and ends with the last dose of GO (usually Day 7).

- Post-GO Period: Starts on the day after the last dose of GO and ends on 36 days after the last dose of GO or start of subsequent anticancer therapy, including consolidation and/or conditioning regimen. This period ends with End-of-Treatment (EOT) visit.

- If the optional second cycle of GO is administered, the same GO Treatment and Post-GO Periods are repeated starting once when Cycle 1 remission status is determined. The second cycle must be started no later than 42 days after the last dose of GO. This period ends with End-of-Treatment (EOT) visit.

- Follow-up Period: Starts on the day after EOT visit and ends when a patient completes 12 months on the study or death, whichever occurs first. This is end of study for each patient.

6.2.1. GO Treatment

Each cycle includes an active GO treatment phase (Days 1, 4, and 7) and a post GO treatment phase (Day 10 to 21).

The second cycle is allowed at the investigator's discretion for patients who meet the following dosing criteria after Cycle 1(refer also to Table 3 describing hematologic toxicities): Bone marrow with a decrease of blast percentage to at least 25%, or a decrease of pretreatment blast percentage by at least 50%; **and** blood count with neutrophils ≥1,000/μL and platelets ≥50,000/μL, except in patients with the bone marrow blasts ≥5%, the decrease in neutrophils and platelets thought to be due to the underlying leukemia.

Patients who don't meet these criteria after the first cycle of GO are not allowed to receive the 2nd cycle. Cycle 2 Day 1 must be started no later than 42 days after the last dose of GO (ie, Cycle 1 Day 7).

6.2.2. Cycle 1

6.2.2.1. Cycle 1 Day 1 (GO Treatment)

- On Day 1 patients may be admitted at the site for 24 hours for pharmacokinetic/pharmacodynamic (PK/PD) sampling at investigator's discretion. Hospitalization beyond Day 1 is per standard of practice and investigator judgment. If there is prolongation of hospitalization, consider if SAE criteria are met (see Section 8.2.4).

- Laboratory specimen will be collected per the Schedule of Activities (and assessed per Section 7. Results of complete blood counts, and serum chemistry tests must be checked before dosing. Patients will have a blood sample collected prior to GO administration for the measurement of immunogenicity (antibodies to GO [ADA] and neutralizing antibody [NAb]).

[redacted]

- Patients will be weighed for body surface area (BSA) calculation.

- Physical examination (PE) performed with clinical judgment evaluating potential areas of AML 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, and body temperature will be performed prior to GO infusion and 2 hours after the infusion is complete (see Table 1). ECOG PS assessment will be conducted if acceptable screening assessment is not done within 7 days prior to the start of investigational drug.

- Pre-medication should be given before GO infusion. See Section 5.4.1 and Section 5.4.2 for administration of premedication and GO, respectively.

- Electrocardiograms (ECGs) will be collected in all patients according to Schedule of Activities (Table 2) and as described in Section 7.1. The ECGs will be collected in triplicate (3 consecutive ECGs approximately 2 minutes apart). Predose ECGs will be performed prior to GO dosing, after administration of premedications. Triplicate ECGs will also be performed prior to selected serial PK draws, around the time when the C_{max} is expected and immediately before the end of the infusion, ie, prior to the Hour 2 PK sample collection (within 15 minutes).[3]

[redacted]

- Pharmacokinetic (all patients) [redacted] PK collections will include predose (Hour 0), Hour 1, 2, 4, 6, and 24 as described in Schedule of Activities (Table 2). [redacted] Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.2.2. Cycle 1 Day 4 and Day 7 (GO Treatment)

- Laboratory tests, PE, and vital signs will be conducted as described in Schedule of Activities (Table 1). Vital signs will also be performed 2 hours after the infusion is complete.

- For the dose calculation and adjustment of GO, if the patient experiences a weight loss or gain >10% from the prior record of weight, the body surface area (BSA) and the amount of GO required for dose preparation must be re-calculated (maximum dosage up to one vial).

- Full recovery from hematologic toxicities is not a requirement for administration of the second or third dose on Days 4 and 7, respectively.

- Pre-medication should be given before dosing. See Section 5.4.1 and Section 5.4.2 for administration of premedication and GO, respectively.

- Pharmacokinetic (all patients [redacted] and triplicate ECGs will be collected according to Schedule of Activities (Table 2). If the dosing day is delayed beyond Day 4, these samples are to be collected on the day of dosing.

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.2.3. Cycle 1 Day 10 (Post-GO Period)

- Laboratory tests, PE, body weight, and vital signs will be conducted according to Schedule of Activities (Table 1).

- Pharmacokinetic (all patients), pharmacodynamic (only for patients 18 years or older), and metabolic profiling (only for patients 18 years or older) samples will be collected according to Schedule of Activities (Table 2).

- Patients with suspected extramedullary disease will have imaging assessment (eg, CAT or MRI) of all known disease sites.

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.2.4. Cycle 1 Days 15 and 21 (Post-GO Period)

- Laboratory tests (except CBC and differential counts) will be conducted according to Schedule of Activities (Table 1).

- Starting with Day 15, CBC and differential counts will be examined 3 times a week until having determination of remission status (see Section 7.5); subsequently CBC and differential counts will be collected once weekly until EOT visit (ie, 36 days after the last dose of GO) or until start of subsequent anticancer therapy, eg, Cycle 2, consolidation and/or conditioning regimen (see Schedule of Activities Table 1).

- Pharmacokinetic (all patients) CCI [redacted] according to Schedule of Activities (Table 2).

- Blood sample will be collected for the measurement of antibodies to GO (ADA) and neutralizing antibody (NAb) on Days 15 and 21.

- Patients with extramedullary disease during screening or clinically suspicious after GO near the scheduled day for bone marrow aspiration (and biopsy if applicable) will have imaging assessment (eg, CAT or MRI). (Day 21)

- Efficacy evaluation and determination of remission status will be assessed by peripheral blood andbone marrow aspiration (and biopsy if applicable) after recovery of blood counts is observed, typically between Day 21 and Day 28. This evaluation should be conducted prior to Cycle 2 (if administered) or EOT (ie, 36 days after last the dose of GO).

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.3. Cycle 2

The second cycle will be allowed at the investigator's discretion for patients who meet selected dosing criteria after Cycle 1 (see Section 7.5). Cycle 2 Day 1 must be started no later than 42 days after the last dose of GO (ie, Cycle 1 Day 7).

6.2.3.1. Cycle 2 Day 1

- On Day 1 patients may be admitted at the site for 24 hours as per investigator's discretion. Hospitalization beyond Day 1 will be per standard practice and investigator judgment. If there is prolongation of hospitalization, consider if SAE criteria are met (see Section 8.2.4).

- Laboratory specimen will be collected per the Schedule of Activities (Table 1) and assessed per Section 7. Results of complete blood counts, and serum chemistry tests must be checked before dosing. Patients will be weighed for BSA calculation. Physical examination (PE) performed with clinical judgment evaluating potential areas of AML 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 and temperature will be performed prior to GO infusion and 2 hours after the infusion is complete (see Table 1).

- Pre-medication should be given before GO infusion. Section 5.4.1 and Section 5.4.2 for administration of premedication and GO, respectively.

- Electrocardiograms (ECGs) will be collected in all patients according to Schedule of Activities (Table 2) and as described in Section 7.1. The ECGs will be collected in triplicate (3 consecutive ECGs approximately 2 minutes apart). Predose ECGs will be performed prior to GO dosing, after administration of premedications. Triplicate ECGs will also be performed prior to selected serial PK draws, around the time when the C_{max} is expected and immediately before the end of the infusion, ie, prior to the Hour 2 PK sample collection (within 15 minutes).[3]

- PK collections (all patients) will include predose (Hour 0) and Hour 2 as described in Schedule of Activities (Table 2).

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.3.2. Cycle 2 Day 4 and Day 7 (GO Treatment)

- Laboratory tests, PE, and vital signs will be conducted as described in Schedule of Activities (Table 1). Vital signs will also be performed 2 hours after the infusion is complete.

- For the dose calculation and adjustment of GO, if the patient experiences a weight loss or gain >10% from the prior record of weight, the body surface area (BSA) and the amount of GO required for dose preparation must be re-calculated (Maximum dosage will be up to one vial).

- Full recovery from hematologic toxicities is not a requirement for administration of the second or third dose on Day 4 or 7, respectively.

- Pre-medication should be given before dosing. See Section 5.4.1 and Section 5.4.2 for administration of premedication and GO, respectively.

- Pharmacokinetic (all patients) and triplicate ECGs will be collected on Day 7 according to Schedule of Activities (Table 2). If the dosing day is delayed beyond Day 4, these samples are to be collected on the day of dosing.

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.3.3. Cycle 2 Day 10 (Post-GO Period)

- Laboratory tests will be conducted according to Schedule of Activities (Table 1).

- Patients with suspected extramedullary disease will have imaging assessment (eg, CAT or MRI) of all known disease sites.

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.3.4. Cycle 2 Days 15 and 21 (Post-GO Period)

- Laboratory tests (except CBC and differential counts) will be conducted according to Schedule of Activities (Table 1).

- Starting with Day 15, blood cell and differential counts will be examined 3 times a week until having determination of remission status (see Section 7.5); subsequently CBC and differential counts will be collected once weekly until EOT visit (ie, 36 days after the last dose of GO) or until start of subsequent anticancer therapy, eg, consolidation and/or conditioning regimen (see Schedule of Activities Table 1).

- Blood sample will be collected for PK assessment and the measurement of antibodies to GO (ADA) and neutralizing antibody (NAb) on Days 15 and 21.

- Patients with extramedullary disease during screening or clinically suspicious after GO near the scheduled day for bone marrow aspiration (and biopsy if applicable) will have imaging assessment (eg, CAT or MRI).

- Determination of remission status will be assessed by peripheral blood and the bone marrow aspiration (and biopsy if applicable) after recovery of blood counts is observed, , typically between Day 21 and Day 28. This evaluation should be conducted prior to EOT (ie, 36 days after the last dose of GO).

- Adverse events should be documented and recorded using NCI CTCAE version 4.03 (see Section 8).

- Concomitant medications and treatments will be recorded.

6.2.4. The End-of-Treatment (EOT) Visit (36 Days after the Last Dose of GO)

- This visit is required for all patients. It occurs 36 days after the last dose of GO. However, in the event that a patient requires initiation of a consolidation treatment or another anti-cancer therapy, the end-of-treatment visit, including procedures (laboratory tests, PE, sampling for PK and ADA/NAb assays), should be performed before the initiation of a consolidation treatment or subsequent anti-cancer therapy. Adverse events, safety laboratory tests, and associated concomitant medications must continue to be collected in the CRF through at least 36 days after the last dose of GO or start of subsequent therapy, eg, consolidation and/or conditioning regimen, whichever occurs first.

- Adverse Event (AE) Assessments should be documented and recorded at each visit using NCI CTCAE version 4.03 up to EOT visit, or start of subsequent anticancer therapy, eg, consolidation and/or conditioning regimen, whichever occurs first.

- Concomitant medications and treatments will be recorded up to 36 days after the last dose of study treatment or starting subsequent anticancer therapy (eg, consolidation or conditioning regimen).

- EOT visit procedures and tests include the following:

  - Blood sample collection for PK assessment and ADA/NAb measurement;

  - Limited physical examination, with clinical judgment to evaluate potential areas of AML 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;

- Laboratory evaluations, including pregnancy test, according to the Schedule of Activities (Table 1).

- Disease assessment for final determination of remission status should be conducted no later than 36 days after last dose of GO (EOT) or/and prior to the start of subsequent anticancer therapy (eg, consolidation and/or conditioning regimen).

6.2.5. Follow-up Period

Each patient will visit the study site every 12 weeks during study duration of 12 months after enrollment; for procedures to be followed during these visits see Schedule of Activities (Table 1). For any patients who may not be able to visit the study site at the protocol designated time, telephone contact is acceptable method for survival follow-up for study duration of 12 months. Any occurrences of VOD/SOS will be recorded in the CRF for entire study duration of 12 months regardless of causality, subsequent anticancer therapy or HSCT.

Following information will be collected during the follow-up period:

- Blood sample collection for ADA/NAb measurement for patients known to be ADA positive at the EOT visit: Samples will be collected every 12 weeks until ADA titers that are no longer detectable, return to baseline, or stabilize at a level acceptable to the investigator and sponsor; or up to 1 year after their enrollment in the study, whichever comes first.

- Subsequent anticancer therapy information (eg, consolidation and/or conditioning regimens, type of HSCT).

- Concomitant medication for graft-versus-host disease (GVHD) prophylaxis and VOD/SOS prophylaxis.

- Survival including causes of death.

6.3. Patient Withdrawal

Reasons for discontinuation of study treatment may include:

- Withdrawal of consent and/or assent;

- Adverse events of unacceptable toxicity as determined by the investigator, or need for treatment delay or continuous interruption of the second study dose beyond 2 days after the scheduled day of dosing due to study treatment related non-hematologic toxicity;

- Global deterioration of health status requiring discontinuation;

- Lost to follow-up;

- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

Withdrawal of consent:

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

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients 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 Section 8.1.3) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. 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 patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved adverse events.

If the patient 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.

Patients who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

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 patient. 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. Electrocardiogram Assessment

7.1.1. QT Interval Prolongation

As indicated in the Schedule of Activities (Table 2), triplicate ECGs will be performed at screening, baseline (prior to dose on Day 1) and on each day of dosing (Days 1, 4, and 7 of at cycle). ECGs will be paired with PK blood sampling and collected immediately prior to the PK blood sample collection, such that the blood sample is collected at the nominal planned time. Ideally, the patient will be supine or reclined in a semi recumbent position for the entire infusion and for both pre and post infusion ECGs. To minimize artifact, the patient should not change position between the pre and post infusion ECGs. If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at the time of the event. Additional ECGs will be performed as clinically indicated for patient safety monitoring and documentation stored in the source documents.

A 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. For triplicate measures, at each time point, three consecutive ECGs will be performed approximately 2 minutes apart, but within 15 minutes for all 3 ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

All ECGs will be sent to the ECG core laboratory for independent reading and interpretation.

7.1.2. Core Laboratory Manual Measurement for ECGs/QTc

Core ECG laboratory, which acts like a central laboratory (vendor) for reading ECGs, performing manual interval measurement will carry out independent reading and interpretation of QTc interval.[3]

The ECG core laboratory will follow the below directions for the ECGs assessments:

- Blinding of ECG reader to time, and day identifiers.
- Review of ECGs from a particular patient should be performed by a single reader.
- Pre-specification of the lead for interval measurements.
- Baseline and on-treatment ECGs should be based on the same lead.

7.2. Pharmacokinetics Assessment

7.2.1. Pharmacokinetic Samples

Blood samples for pharmacokinetic analysis will be collected from all participating patients at the times indicated in Schedule of Activities (Table 2), during infusion and from the arm opposite to the infusion site, according to the procedures in the lab manual.

Later samples (Days 10 to EOT visit) are collected primarily to assess immunogenicity (with a companion PK sample).

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, some flexibility in sampling times has been provided to allow for variation in assessment schedules. Samples obtained within the specified time windows will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). During the trial, actual collection times may change but the number of samples will remain the same.[18]

PK samples will be assayed for total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin, using validated analytical methods in compliance with Pfizer standard operating procedures. Details regarding the storage and shipping of plasma samples will be provided in the Study Manual.

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7.3. Immunogenicity

Anti-drug antibody (ADA) samples will be collected according to Schedule of Activities (Table 2). Procedures related to the handling, storage and shipments will be described in the laboratory manual.

Samples will be analyzed for anti-drug antibodies using an electrochemiluminescent method, with a tiered approach of screening, confirmation, titer determination and additional specificity (characterization in the presence of purified hP67.6 (naked antibody) and Calicheamicin (Payload). Samples that test positive for ADA may be further characterized for specificity to the unconjugated naked antibody and Payload and to determine whether neutralizing antibodies (NAb) are present.

Samples collected for detecting ADA and NAb will be retained in accordance with local regulations and, if not used in the timeframe, will be destroyed. Additional exploratory testing of samples may be performed to further characterize the ADA response.

7.4. Safety Assessments

Safety assessments include adverse events (AEs) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.03), clinical examination (including blood pressure and pulse), ECGs, and laboratory tests (hematology, chemistry, coagulation and urinalysis).

Additional (unscheduled) assessments should be conducted if laboratory values are abnormal (or if clinically indicated) and repeated until resolution, until return to baseline, or until NCI CTCAE Grade ≤1.

Safety assessments will be conducted until patient discontinues from the study or as protocol specified for 36 days after the last dose of GO or start of subsequent anticancer therapy such as consolidation and/or conditioning regimen (Schedule of Activities Table 1). Survival status will be collected for the study duration of 12 months for each patient.

The laboratory tests specified in Appendix 3 will be conducted.

7.4.1. Veno-occlusive Disease Assessments and Sinusoidal Obstruction Syndrome

Patients with prior history of VOD/SOS will be excluded from enrollment. Investigators must be vigilant when reviewing medical history for any evidence of VOD/SOS that might not have been formally evaluated for diagnosis, and must be rigorous in evaluation to rule out presence of any potential of VOD/SOS at baseline. VOD/SOS may present as a constellation of signs and symptoms such as weight gain, elevated bilirubin, tender hepatomegaly, and ascites. As it is sometimes a complication of high-dose chemotherapy (conditioning therapy) given before HSCT, careful evaluation in the context of previous and subsequent HSCT is essential. Table 4 provides European Group for Blood and Marrow Transplantation (EBMT) criteria of VOD/SOS for recommended reference.[21,21] In the event of serious or severe hepatic adverse events, patients should have a hepatology consultation and work-up including (but not limited to) hepatic function test monitoring (eg, AST, ALT, and total bilirubin), ultrasound evaluation, weight gain monitoring, and active hepatitis evaluation, eg, viral autoimmune, etc.

All cases of VOD/SOS, regardless of causality or severity, must be reported as a SAE within the entire study duration of 12 months (see Section 8.1.4).

Table 4. EBMT Criteria for VOD/SOS Diagnosis

EBMT Criteria for VOD/SOS Diagnosis in Adults[21]	
Classical VOD/SOS In the first 21 days after HSCT (Baltimore Criteria)	**Late onset VOD/SOS** >21 Days after HSCT

• Bilirubin ≥2 mg/dL and two of the following criteria must be present:
  • Hepatomegaly (painful hepatomegaly);
  • Ascites;
  • Weight gain >5% from baseline.
	• Classical VOD/SOS beyond Day 21,
	OR
	• Histologically proven VOD/SOS,
	OR
	• Presence of two or more of the following criteria AND hemodynamic or/and ultrasound evidence of SOS/VOD:
	  • Bilirubin ≥2 mg/dL (or 34 μmol/L) Painful hepatomegaly;
	  • Weight gain >5%;
	  • Ascites.

EBMT Criteria for VOD/SOS Diagnosis in Pediatrics[21]	

• No limitation for time of onset of SOS/VOD.
• The presence of two or more of the following:[a]
  • Unexplained consumptive and transfusion-refractory thrombocytopenia;[b]
  • Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain >5% above baseline value;
  • Hepatomegaly (best if confirmed by imaging) above baseline value;[c]
  • Ascites (best if confirmed by imaging) above baseline value;[c]
  • Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥2 mg/dL within 72 hours.	

a. With the exclusion of other potential differential diagnoses.
b. ≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.
c. Suggested: imaging (ultrasonography, CAT, or MRI) immediately before HSCT to determine baseline value for both hepatomegaly and ascites.

Doppler Ultrasonography for Clinical Suspicion for VOD/SOS

When VOD/SOS 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).

Assessments and Laboratory Tests

Any of the following assessments, used to diagnose VOD/SOS, should be reported.

- Biopsy;

- Doppler ultrasonography;
- Measurement of venous pressures;
- Laboratory tests must include liver function tests (LFTs), eg, total bilirubin, AST/ALT, ALK-P (alkaline phosphatase), PT/INR (prothrombin ratio/international normalized ratio), aPTT, fibrinogen, and creatinine level.

Risk factors for VOD/SOS or other factors affecting liver function such as GVHD prophylaxis and/or treatment, and anti-infectives used as treatment or prophylaxis should be reported. The information on HSCT (eg, allogeneic, matched, or related/unrelated) with conditioning regimens will be collected.

Management of VOD/SOS

The diagnosis of VOD/SOS, interpretation of severity, and appropriate management of the event will be medically determined by investigator per institutional standard(s).

Treatment of VOD/SOS must be described and entered into the CRF (eg, defibrotide).

7.5. Response Assessments

Response assessment will be determined as follows:

- Starting with Day 15, blood cell and differential counts will be examined 3 times a week after GO dosing until determination of remission status; subsequently CBC and differential counts will be collected once weekly until EOT visit (ie, 36 days after the last dose of GO), or until start of Cycle 2 (if administered), or until start of subsequent therapy (eg, consolidation and/or conditioning regimen).
- Efficacy evaluation and determination of remission status by blood and bone marrow aspiration (and biopsy if applicable) will be conducted at the end of each cycle after blood count recovery (neutrophils ≥500/μL and platelet ≥50,000/μL) is observed or at a maximum of 36 days after the last dose of GO regimen.
- A bone marrow aspirate is required to assess response to treatment, and a bone marrow biopsy is also recommended to confirm response and to assess cellularity and is required in case of a dry tap.

The second cycle will be allowed at the investigator's discretion for patients who meet the following dosing criteria after Cycle 1(refer also to Table 3 describing hematologic toxicities):

- Bone marrow with a decrease of blast percentage to at least 25% or a decrease of pretreatment blast percentage by at least 50%; **and**

- Blood count with neutrophils ≥1,000/μL and platelets ≥50,000/μL, except in patients with the bone marrow blasts ≥5%, the decrease in neutrophils and platelets thought to be due to the underlying leukemia.

Patients who don't meet these criteria after the first cycle of GO will not be allowed to receive the 2nd cycle.

Response will be assessed using European Leukemia Net (ELN 2017) recommendations (Table 5).[5]

Table 5. European Leukemia Net (ELN 2017) Recommendations[5]

Complete Remission (CR)	• Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; • ANC ≥1x10^9/L (1000/μL); platelet count ≥1x10^9/L (100,000/mL).
CR with incomplete hematologic recovery (CRi)	• All CR criteria except for residual neutropenia; ANC <1x10^9/L (1000/μL); or thrombocytopenia; platelet count <1x10^9/L (100,000/mL).

7.6. Survival

Survival status will be followed for all patients for the study duration. For any enrolled patient who may not be able to visit the study site at the protocol designated time, telephone contact is acceptable method for survival follow-up, plus collecting cause(s) of death.

7.7. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting administration of study medication —once at the start of screening and once at the baseline visit, immediately before starting the study treatment. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit before the patient may receive the study medication. Pregnancy tests will be repeated at at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study.

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7.9. Imaging Assessments

- Patients with suspected extramedullary disease will have imaging assessment (eg, CAT or MRI) of relevant disease sites during screening. Imaging assessment will be repeated during the post-GO period (Schedule of Activities Table 1).

- For imaging assessment using Doppler sonography in patients with suspected VOD/SOS, please see Section 7.4.1.

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 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 patient 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 (Section 8.4.1), 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 patient/legally acceptable representative. In addition, each study patient/legally acceptable representative 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 Patient Withdrawal Section 6.3)

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 patient 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 patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product) through and including a minimum of 36 calendar days after the last administration of the investigational product.

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

Any patient with VOD/SOS will be monitored for the study duration of 12 months from enrollment as described in Section 7.4.1.

8.1.4.1. Reporting SAEs to Pfizer Safety

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

SAEs occurring in a patient 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 starts a subsequent anticancer therapy (eg, consolidation, and/or conditioning regimen, or HSCT), SAEs occurring during the above-indicated active collection period (ie, within 36 days of last dose of GO) must still be reported to Pfizer Safety irrespective of any intervening treatment and causality.

Incidence of VOD/SOS will be reported for the entire study duration of 12 months, regardless of causality, or start of subsequent anticancer therapy (eg, consolidation and/or conditioning regimen, or HSCT). All cases of VOD/SOS must be reported as SAEs (recorded on the CRF and CT SAE Report Form).

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 patient 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 patient 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, patient 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 patient;
- 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

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

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.

Investigators should report AEs using concise medical terminology (verbatim) as well as collect on the CRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03, Publish Date: 14 June 2010, NCI CTCAE) listed in the Cancer Therapy Evaluation Program. New protocols of projects that have been utilizing a previous version may continue to use that version.

If required on the AE page of the CRF, the investigator will use the following definitions of severity in accordance with the current CTCAE version to describe the maximum intensity of the adverse event.

Grade	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between 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 AML. However, these events should still be recorded as adverse events on the case report Form (CRF).

Protocol-specified SAEs that will not normally be reported to Pfizer Safety in an expedited manner:

- Febrile neutropenia (unless Grade 5).
- Neutropenic sepsis (unless Grade 5).

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 patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug induced liver injury (DILI). Patients 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 patient's individual baseline values and underlying conditions. Patients 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:

- Patients 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 patients 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 patient 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/SOS Cases

All cases of VOD/SOS with or without previous HSCT, regardless of causality and severity must be reported as an SAE for entire study duration of 12 months from enrollment, regardless of subsequent anticancer therapy (eg, consolidation and/or conditioning regimen, or HSCT).

The assessment and management of VOD/SOS will be up to physician's discretion and per institutional standards of practice. All the assessments and management (eg, prophylaxis and/or treatment) should be recorded in the CRF. In this study, the diagnosis of VOD/SOS is as described in Section 7.4.1.

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 patient or patient's partner becomes or is found to be pregnant during the patient'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 patient 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]), then 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 patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient 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 patient 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 patient, or at the wrong time, or at the wrong dosage strength.

- Medication errors include:
  - Medication errors involving patient 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 patient.

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 is outlined here and further detailed 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 QTc analysis will be based on a non-inferiority hypothesis testing framework.

If the upper bounds of one-sided 95% confidence intervals of change from baseline in QT measurements using Fridericia's heart rate correction for each of the QTc sampling time points (Day 4, 0 hours, and Day 7, at 0, 2, 4 and 6 hours) are below 20 msec, the post-baseline dose QTc interval will be considered to be "non-inferior" to the baseline; the QTc effect of GO will be concluded to be not unacceptable.

Thus with an overall 1-sided significance level of 0.05 and a non-inferiority margin of 20 msec, assuming a standard deviation of 18.8 msec and a mean change from baseline for QTcF up to 10 msec, 50 patients will provide 90 % power for assessing the 5 QTc sampling timepoints using paired difference in means with the t distribution. CCI

If the upper bounds of one-sided 95% confidence intervals of change from baseline in QT measurements using Fridericia's heart rate correction for each of the QTc sampling time points (on Day 4, at 0 hours, and Day 7, at 0, 2, 4, and 6 hours) are below 20 msec, the post-baseline dose QTc interval will be considered to be "non-inferior" to the baseline.

The inclusion of 6 pediatric patients was determined based on agreement with CHMP.

9.2. Analysis Sets

9.2.1. Full Analysis Set

The full analysis set will include all enrolled patients, and will be the primary analysis set for evaluating all efficacy endpoints and patient characteristics.

9.2.2. Safety Analysis Set

The safety analysis set will include all enrolled patients who receive at least 1 dose of study medication. The safety analysis set will be the primary analysis set for evaluating treatment administration/compliance and safety.

9.2.3. QTc Analysis Set

The QTc analysis set will include all patients in the safety analysis set who have a baseline ECG and at least one post-dose ECG.

9.2.4. PK Analysis Set

All patients who are treated with GO and contribute at least one PK sample will be included in the PK analysis set.

9.2.5. PK/PD Analysis Set

QTc PKPD analysis set: All patients who are treated with GO and contribute at least one PK sample who have a baseline ECG and at least one post-dose ECG.

Safety and Efficacy PKPD analysis set: All patients who are treated with GO and contribute at least one PK sample.

9.3. Planned Analyses

Separate summaries for adult and pediatric patients will be presented. Combined summaries of adult and pediatric patients will also be presented.

9.3.1. Analysis of Primary Endpoint

ECG measurements from the ECG core laboratory (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Only the scheduled ECGs will be used in the primary analysis. The last available planned triplicate measurements prior to first dose will be used as baseline.

QT measurements will be corrected by heart rate (QTc) including Bazzett's (QTcB) and Fridericia's (QTcF) methods, and a study-specific correction method (QTcS) will be evaluated according to the observed data. QTcF will be used for the primary analysis.

The absolute corrected QT interval and changes in QTc (QTcB, QTcF, and/or QTcS) from baseline will be summarized using descriptive statistics by nominal time point.

A random effect model with the nominal timepoints as a fixed effect and patients as a random effect will be used for the primary analysis to estimate the mean change in QTcF (primary endpoint) at the post baseline nominal timepoints (Day 4, 0 hours, and Day 7, at 0, 2, 4 and 6 hours) along with 2-sided 90% confidence interval for the mean. The maximum increase in QTc from baseline will be computed over all time points. The maximum increase from baseline will be summarized with descriptive statistics.

Categorical analysis of changes in QTc (QTcB, QTcF, and/or QTcS) from baseline including absolute QTc interval prolongation and maximum increase will be provided. Interval measurements from unscheduled ECGs will be included in the categorical analyses.

Baseline versus worst on treatment QTc according to maximum CTCAE grade will be summarized using a shift table.

9.3.2. Analysis of Secondary Endpoints

9.3.2.1. Safety Analysis

9.3.2.1.1. Adverse Events

AEs will graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. CCI [redacted]

9.3.2.1.2. Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be graded according to CTCAE version 4.03 and summarized according to worst toxicity grade observed for each laboratory test.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

For patients who respond, time to neutrophil recovery (>500/μl) and time to platelet recovery (>50,000/μl) will be summarized using Kaplan-Meier methods.

9.3.2.1.3. Deaths

The number of deaths (and the cause of death) during the study periods will be summarized.

9.3.2.1.4. VOD/SOS

Incidence and timing of VOD/SOS and HSCT will be summarized.

9.3.2.2. Pharmacokinetic Analysis

These analyses will be conducted in the PK analysis set.

The pharmacokinetics of three analytes will be measured in patient samples in this study: total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin. The primary analyte representing GO PK is the total hP67.6 antibody. Noncompartmental analysis (NCA) will be performed to characterize the clearance and volume of distribution of total hP67.6 antibody following the fractionated regimen (secondary endpoint).

Population PK analysis, using nonlinear mixed effects modeling methodology as implemented in NONMEM® Version 7.3.0 (ICON Development Solutions, Ellicott City, MD), will also be conducted and reported separately. A population modeling approach will be used to further characterize the PK of total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin, as well as to assess intrinsic and extrinsic covariates that may account for some of the interindividual variability of population PK parameters.

9.3.2.3. Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis

Population PK/PD modeling analyses will be explored, as necessary, based on emerging safety/clinical response data. The results of these population modeling analyses will be reported separately from the clinical study report.

CCI [redacted]

9.3.2.4. QTc-Concentration Analysis

Concentration data of total hP67.6 antibody and unconjugated calicheamicin (if feasible) will be listed by patient and by actual collection time and day.

The relationship between observed drug concentration (total hP67.6 antibody and unconjugated calicheamicin) to changes in QT/QTc will be evaluated to further characterize the effect on QT interval. QTc- concentration- analysis will be conducted using linear regression, ie, a linear mixed effects model. If appropriate, other models may also be examined. Exploratory analyses (via graphical displays and/or model fitting) may include accounting for a delayed effect and the justification for the choice of pharmacodynamics model. Diagnostic evaluation will be included to explore the adequacy of the model. The results of these modeling analyses may be reported separately from the clinical study report.[3]

9.3.2.5. Immunogenicity

The percentage of patients with positive ADA and neutralizing antibodies will be summarized. For patients with positive ADA and neutralizing antibodies, the magnitude (titer), time of onset, and duration of ADA response will also be described, as data permit. In addition, potential effects of ADA formation on the PK profile of GO will be examined individually, and evaluated between the groups with and without positive ADA.

Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection and immune status of the patients, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

These analyses will be conducted in the Safety Analysis Set.

Samples will be analyzed for ADAs using a tiered approach of screening, confirmation, and titer determination. Samples that test positive for ADA will be further characterized to determine whether neutralizing antibodies (NAb) are present.

9.3.2.6. Efficacy Analyses

Efficacy evaluation anddetermination of remission status by blood and bone marrow aspiration (and biopsy if applicable) will be conducted at the end of each cycle using European Leukemia Net (ELN 2017) recommendations (see Section 7.5). Survival status for each patient will be collected for the study duration of 12 months.

9.3.2.6.1. Response

The proportion of the patients who respond (CR + CRi [CR with incomplete hematologic recovery] according to best response) and a 95% confidence interval will be reported.

9.3.2.6.2. Overall Survival

Overall survival rate at 12 months with a 95% confidence interval will be estimated using Kaplan Meier methods and presented graphically.

9.4. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.5. Data Monitoring Committee

This study will not use a data monitoring committee.

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 patient 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 patient'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 patient. 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 form and will be password protected 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 patient 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 patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent 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/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent 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 patients. 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. In addition, the study will be conducted in accordance with applicable local regulatory requirements and laws.

12.3. Patient 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 patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable law.

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, patient 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 patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

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

The informed consent/assent documents used during the informed consent process and any patient 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 patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study, the sharing of data relating to 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 patient's personal data. The investigator further must ensure that each study patient, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, 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.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor patients who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative and the patient's assent, when applicable, before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent/assent document.

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 patients 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 patients 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 Other Participating Countries

End of trial in all other participating countries is defined as last patient last visit (LPLV).

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 GO at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 4 weeks. 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 patient 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, patient 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 in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings assigned to them in the CSA.

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

16. REFERENCES

1. MYLOTARG™ (gemtuzumab ozogamicin) for injection, for intravenous use [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.; 2017.

2. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012; 379(9825):1508-16.

3. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf.

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5. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017; 129(4):424-47.

6. Peiper SC, Ashmun RA, Look AT. Molecular cloning, expression, and chromosomal localization of a human gene encoding the CD33 myeloid differentiation antigen. Blood 1988; 72(1):314-21.

7. Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol 2001; 19(13):3244-54.

8. Hamann PR, Hinman LM, Hollander I, et al. Gemtuzumab ozogamicin, a potent and selective anti-CD33 antibody-calicheamicin conjugate for treatment of acute myeloid leukemia. Bioconjug Chem 2002; 13(1, Jan-Feb):47-58.

9. Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia (AML), SEER Cancer Statistics Review, the National Cancer Institute of the National Institutes of Health 2017. https://seer.cancer.gov/statfacts/html/leuks.html.

10. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015; 126(3):291-9.

11. an der Velden VHJ, te Mervelde JG, Hoogeveen PG, et al. Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. Blood 2001; 97(10):3197-204.

12. van der Velden VHJ, van Dongen JJM. Effectiveness of gemtuzumab ozogamicin (Mylotarg) treatment: cellular and systemic determinants. EJHP Science 2006; 12(6):118-122.

13. U.S. Department of Health and Human Services, Food and Drug Administration, Oncologic Drugs Advisory Committee Briefing Document, Mylotarg, 11 July 2017. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566015.pdf.

14. Taksin AL, Legrand O, Raffoux E, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia 2007; 21(1):66-71.

15. Bross PF, Beitz J, Chen G, et al. Approval summary: Gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res 2001; 7(6):1490-1496.

16. Larson RA, Sievers EL, Stadtmauer EA, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer 2005; 104(7 Oct 1):1442-52.

17. Cheson BD, Bennett JM, Kopecky KJ, 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; 21(24):4642-9.

18. Guidance for Industry: Population pharmacokinetics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Feb 1999: 34 pages. https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf.

19. Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP); Part 1: immunization of infants, children, and adolescents. MMWR 2005; 54(RR-16):1-34.

20. Getchell JP, Wroblewski KE, DeMaria A Jr, et al. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal. Wkly Rep 2013; 62(18):362-5.

21. 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. Bone Marrow Transplant 2016; 51(7):906-12.

22. Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. Bone Marrow Transplant. 2018 Feb;53(2):138-145.

23. Amadori S, Suciu S, Selleslag D, et al. Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. J Clin Oncol. 2016 Mar 20; 34(9):972-9.

Appendix 1. Abbreviations

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

Abbreviation	Term
ADA	anti drug antibody
ADC	antibody drug conjugate
AE	adverse event
ALFA	Acute Leukemia French Association
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
Ara-C	cytarabine
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under curve
BSA	body surface area
CCI	[redacted]
BLA	Biologics License Application
BM	bone marrow
BUN	blood urea nitrogen
CAT	computed axial tomography
CBC	complete blood counts
CD33	cluster of differentiation 33
CERT	Center for Education and Research on Therapeutics
CHMP	Committee for Medicinal Products for Human Use
CK	creatine kinase
C_{max}	maximum concentration
CNS	central nervous system
CR	complete remission
CRF	case report form
CRi	complete remission with incomplete hematologic recovery
CR_{MDR}	complete remission without minimal residual disease
CRp	complete remission with incomplete platelet recovery
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease free survival
DILI	drug-induced liver injury
DMH	dimethylhydrazide

Abbreviation	Term
DNA	deoxyribonucleic acid
DNR	daunorubicin
DU	dispensable unit
EBMT	European Group for Blood and Marrow Transplantation
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EOT	end of treatment
ELN	European Leukemia Net
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
EudraCT	European Clinical Trials Database
FACS	flow activated cell sorting
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto
GO	gemtuzumab ozogamicin
GVHD	graft-versus-host disease
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCV RNA	Quantitative hepatitis C virus RNA measurement
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HRQL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
IB	investigator’s brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous

Abbreviation	Term
IWG	International Working Group
IWR	interactive web response
CCI [redacted]	[redacted]
LDH	Lactate dehydrogenase
LFT	liver function test
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
msec	millisecond
N/A	not applicable
NAb	neutralizing antibodies
NCA	non compartmental analysis
NCI	National Cancer Institute
OS	overall survival
PCD	primary completion date
PD	Pharmacodynamics(s)
PE	physical examination
PI	principal investigator
PK	Pharmacokinetic
PMR	post marketing requirements
PS	performance status
PT	prothrombin time
QTc	corrected QT interval
QTcF	QT interval using the Fridericia heart rate correction
QTcS	QT interval using a study-specific heart rate correction method
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SOS	sinusoidal obstruction syndrome
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group
TBili	total bilirubin
TdP	Torsades de Pointes
TEAEs	treatment emergent adverse event
ULN	upper limit of normal
US	United States
VOD	veno-occlusive disease
WBC	white blood cells

Appendix 2. Definition of Active Hepatitis Infection

- Hepatitis B serological tests and definition of active infection.[19]

Serological Test	Test outcomes	Interpretation
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	**Acutely infected**
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	**Chronically infected**

HBsAg: Hepatitis B surface antigen
anti-HBs: Hepatitis B surface antibody
anti-HBc: Total hepatitis B core antibody

- IgM anti-HBc: IgM antibody to hepatitis B core antigen.
  Hepatitis C tests and Definition of active hepatitis C.[20]

Test	Test outcomes	Interpretation
HCV antibody HCV RNA	Reactive Detected	**Current HCV infection**

HCV antibody: antibody to hepatitis C virus
HCV RNA: Quantitative hepatitis C virus RNA measurement

Appendix 3. Laboratory Tests

Hematology Panel	Chemistry Panel	Coagulation Panel	Urinalysis
WBC/differential counts including blast RBC count Hemoglobin Hematocrit Platelet count	Sodium Potassium Magnesium Total calcium Creatinine Albumin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Glucose Total Bilirubin Blood urea nitrogen (BUN) Uric acid or urate Alkaline phosphatase (ALK-P) Lactate dehydrogenase (LDH)	international normalized ratio/prothrombin time (INR/PT) Activated Partial thromboplastin time (aPTT) Fibrinogen	pH Protein/albumin Glucose Blood/hemoglobin Ketones/acetone

Appendix 4. List of Drugs Known to Predispose to Torsades de Pointes

The medications which are known to be associated with a risk of TdP and known to prolong the QTc interval are listed in the CredibleMeds® TdP risk category (https://www.crediblemeds.org).

(CredibleMeds® is associated with University of Arizona Cancer Center for Education and Research on Therapeutics [CERT]: "Torsades List: Drugs with a Risk of Torsades de Pointes," Advisory Board).

Appendix 5. Definition of Refractory and Relapsed AML (ELN 2017 Recommendation)[5]

Refractory Disease:

- No complete remission (CR) or CR with incomplete hematologic recovery (CRi) after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause.

Relapsed Disease:

- After CR without minimal residual disease (CR_{MDR-}), CR, or CRi, bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease.