Protocol B1761031

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

Statistical Analysis Plan
(SAP)

Version: 2

Date: 21-APR-2021

[redacted]

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B1761031 is based on the protocol dated 27Jun2018. The SAP was amended to clarify some analyses, to update based on changes in standards, to address COVID-19, and to document reporting strategy for reporting summaries of adult patients separately from pediatric patients.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Version Date	Change	Rationale
1	27 June 2018	Not Applicable	Not Applicable
2	21 April 2021	PK: "total calicheamicin" was corrected to "unconjugated calicheamicin"	Correction was made throughout the SAP in alignment with the protocol.
		AUC_{0-72}, AUC_{0-336} were added to PK parameters.	These parameters are estimable with the collected data.
		Definition of positive ADA & NAb was clarified.	The titer values and classification of positive were clarified based on the analytical reports.
		CR and CRi: the units for the platelet count requirement were corrected.	A PACL corrected the unit to $100x10^9/L$ (100,000/µL).
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		Clarified that Myelosuppression is also an AESI.	Myelosuppression is an AESI that had been omitted from SAP version 1.
		Reporting of laboratory parameters, particularly for urinalysis results, were clarified.	Additional clarification and details for reporting were provided to facilate organization of summaries as CTC graded or not.
		Analysis sets (PK parameter CCI [redacted] details were updated. Immunogenicity analysis set was added.	PK parameter analysis set was generalized to be consistent with other parts of the SAP. CCI [redacted] Immunogenicity analysis set was added for consistency with standards.
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		Details were added to describe that results for adult patients to	Separate CSRs are planned due to the estimated time to complete the pediatric enrollment.

SAP Version	Version Date	Change	Rationale
		reported separately from pediatric patients.	
		The last cycle defintion was updated to the min (last dose +36, start of subsequent anticancer therapy)	The change is consistent with the safety reporting period, and standard definitions that considers start of subsequent anticancer therapy.
		Additional categorizations ECG parameters were added to summaries. Clarification was added whether triplicate averages or individual replicates are included in summaries.	Given the focus on ECGs, the additional categorizations were felt to be relevant. The clarifcations about replicates was based on standards.
		Derivation of QTcS: The estimated slope was clarified to be based on individual replicates and changed to be based on only the individual replicates selected as baseline.	It was felt to be most relevant to derive QTcS based on only the individual replicates selected as baseline.
		Statistical details for LS means, SE, and CI were provided and was updated to include only data from Cycle 1.	Further details for the linear model were provided for clarity. Only data from Cycle 1 will be included because Cycle 2 was optional and at the investigator's discretion.
		Analyses for impact of COVID-19 pandemic were added.	Since study enrollment and conduct was ongoing during the COVID-19 pandemic, conventions and analyses were added per company guidance
		Missing PK data conventions were clarified.	The clarifications were made consistent with standards.
		References to listings were modified.	Consistent with standards changes, the focus is on listings required for an ICH CSR.
		Plots of PK parameters were removed.	The plots were to contain summaries for adult and pediatric patients, but pediatric enrollment has not completed
		Descriptive statistics summary of PK concentrations were added. Mean plots were removed.	The descriptive summary was indavertantly omitted from SAP version 1. Consistent with current reporting guidance some outputs were omitted to streamline reporting.
		Graphical summary of change in QTcF from baseline was added.	A graphical summary for the primary endpoint was added to streamline the presentation in the CSR.
		The descriptions of the immunogenicity summaries were modified.	Updates are consistent with current standard summaries.

SAP Version	Version Date	Change	Rationale
		Overall Survival: the probability of an event at 6 months was added.	The probability of an event at 6 months was added to provide an estimate in the event the 12 month probability is zero.
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		Summaries of height, weight, and BMI were removed from Baseline Characteristics.	The summaries were removed to facilitate production of in-text CSR tables consistent recently introduced of conventions for studies.
		Prior and Follow-Up HSCT definition has been clarified.	The definition was indavertantly not previously provided.
		Summary of protocol devations was added.	This addition is consistent with the standard process.
		Clarifications of summaries including categorization of transplant relative to GO dose which had a typographical error, and the start of Cycle 2 which needed an additional category were added.	The updates were made to correct typographical errors, and details were added consistent with the CRF.
		The high level summary of AEs was updated, and summary tables of AE that had actions taken due to the AE were added. Additional summaries were added for in-text tables.	The update is consistent with current standard tables and oncology reporting conventions. Updates to AE summaries were made to facilitate production of in-text CSR tables consistent with recently updated oncology conventions.
		A summary of AESI of INFUSION RELATED REACTIONS by ADA status was added.	The summary was added to assess the impact of ADA on safety.
		Laboratory summaries were changed from worst (maximum) grade to shift from baseline tables; similarly non-CTC graded laboratory summaries were changed to shift, and summary of liver function tests was added.	Updates to ummaries were made to facilitate production of in-text CSR tables and consistent with recently updated oncology conventions.
		ECG maximum increase from baseline as a continuous variable summarized with descriptive statistics was removed.	It was considered sufficient to summarize this categorically.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B1761031 titled: A single arm, open-label, Phase 4 study evaluating QT interval, pharmacokinetics, and safety of gemtuzumab ozogamicin (GO; MYLOTARG™) as a single-agent regimen in patients with relapsed or refractory CD33-positive acute myeloid leukemia (AML). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Any deviations from this analysis plan will be described in the Clinical Study Report.

2.1. Study Objectives

Primary Objective: To assess the effect of GO on the QTc interval

Secondary Objectives:

- To characterize the PK of single-agent GO following the fractionated regimen (i.e., 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

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2.2. Study Design

This is a single-arm, open-label, Phase 4 study evaluating the effect of gemtuzumab ozogamicin (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) patients and 6 pediatric (12 ≤ age ≤17 years) patients will be enrolled.

Treatment Plan: Three doses of GO 3 mg/m^2 (up to one vial) as a 2-hour intravenous infusion on Days 1, 4, and 7 at each cycle, up to 2 cycles. A second cycle of GO 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 where the bone marrow blasts ≥ 5% and the decrease in neutrophils and platelets is thought to be due to the underlying leukemia.

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.

Summary of Assessments: Triplicate ECGs will be performed at screening, baseline (prior to dose on Day 1) and immediately preceding serial PK draws. All triplicate ECG tracings will be sent to an independent ECG core laboratory for blinded manual interval measurements.

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}), i.e. at the end of the 2-hour infusion, in order to characterize the QTc-concentration relationship.

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. Samples that test positive for ADA will be further characterized to determine whether neutralizing antibodies (NAb) are present.

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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, whichever occurs first. 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.

After receiving the study treatment, blood cell and differential counts will be examined 3 times a week after GO dosing until having determination of remission status; 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, e.g., consolidation 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 recovery of blood counts is observed or at a maximum of 36 days after the last dose of GO treatment (EOT) using European Leukemia Net (ELN 2017) recommendations.

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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

3.1.1. QTc interval

Change from baseline in corrected QT interval (QTc) using Fridericia's heart rate correction. Refer to Section 5.2.8 for details of derivations.

3.2. Secondary Endpoints

3.2.1. PK parameters

The following PK parameters will be calculated for GO (represented by total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin) from the concentration-time values using standard noncompartmental methods: AUC_{last}, AUC_{0-72}, AUC_{0-336}, C_{max}, T_{max}, and if data permits AUC_{inf}, $t_{1/2}$, CL, V_{SS}. A tabular summary of these noncompartmental PK parameters and analyses is presented in Table 3.

3.2.2. Immunogenicity

Samples for ADA will be analyzed using a tiered approach of screening, confirmation, and titer determination. Samples that test positive for ADA to GO will be further tested for specificity (in presence of purified hP67.6 naked antibody and in the presence of calicheamicin payload) and characterized to determine whether NAb are present or absent.

ADA will be classified as negative if the titer value is less than the minimum required dilution, i.e., titer <75, and positive otherwise (titer 75 or greater).
NAb will be classified as negative if the titer value is less than the minimum required dilution, i.e., titer <20, and positive otherwise (titer 20 or greater).

3.2.3. Best Response

Efficacy evaluation and determination of remission status by blood and bone marrow aspiration (and biopsy if applicable) per the investigator will be classified according to European Leukemia Net (ELN 2017) recommendations according to the following categories. Thus the bone marrow will be assessed by the investigator after each cycle when 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. The date of response is also dependent on the observation of the peripheral blood recovery mentioned in the criteria below. If Cycle 2 is to be administered, note that the Cycle 1 assessment is required to be conducted prior to the start of Cycle 2.

Response will be defined as CR or CRi which are defined as follows per ELN 2017:

- 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 ≥ $100x10^9$/L (100,000/μL)

- CR with incomplete hematologic recovery (CRi): All CR criteria except for residual neutropenia; ANC < $1x10^9$/L (1000/μL); or thrombocytopenia; platelet count < $100x10^9$/L (100,000/μL)

  Best response will be derived from the CRF values for the two cycles: as CR if either Cycle 1 or Cycle 2 are CR, or if no CR then if either Cycle 1 or Cycle 2 are CRi the best response is CRi. Patients without a documented CR or CRi will be considered as non-responders.

3.2.4. **Overall Survival**

Overall survival is defined as the time from start date to the date of death due to any cause. Patients last known to be alive as censored at the date of last contact.

Refer to Section 5.2.6 for derivation of the last contact date.

The start date for a patient is date of first treatment (if treatment start date is not available, then date of enrollment will be used)

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3.4. Baseline Variables

ECG parameters: The last available planned triplicate measurements prior to first dose according to the date (selected from nominal time points of Screening and Cycle 1 Day 1 at 0 hours) will be used as baseline. Triplicate ECGs are collected; therefore the baseline for each ECG measurement is the average of the pre-dose measurements on the selected baseline day. Refer to Section 5.2.8 for further details of derivations concerning ECG parameters.

For safety (including Eastern Cooperative Oncology Group (ECOG) performance status, safety laboratory results, blasts in the bone marrow, blasts in the peripheral blood, immunogenicity) the last assessment performed on or prior to date of the first dose of study treatment will be designated as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing. For laboratory data, if there are multiple assessments that meet the baseline definition on the same day without the ability to determine which was truly last, then the worst CTC grade will be considered as the baseline grade.

CD33 expression: CCI (percent positivity CCI the baseline value will be based on the bone marrow sample that is the last available assessment on or prior to the date of first dose of study treatment. If there is no result available from bone marrow, then a result from a blood sample meeting the same criteria will be used. CCI Additionally, percent positivity will be categorized as < 30, 30 - <70, ≥ 70; CCI

The date of first dose (start date) of study treatment is the earliest date of GO dosing.

The date of last dose of study treatment is the latest date of GO dosing.

No windowing will be applied when defining baseline. Although the protocol requires screening assessments to be performed within 28 days prior to first dose; values outside this window will not be excluded when determining baseline assessments.

3.5. Safety Endpoints

Per the protocol, the active safety monitoring duration is defined as up to 36 days after the last dose of GO or start of subsequent anticancer therapy (which includes consolidation and/or conditioning regimens), whichever occurs first. Also, per protocol any event of VOD/SOS will be reported as SAE during the entire study duration. 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. Further details of the AE collection are described in the protocol Section 8.

The on-treatment period for reporting is defined as the time from the first dose of study treatment through end of study follow-up.

3.5.1. **Adverse Events**

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

An adverse event is considered treatment emergent relative to a given treatment if the event starts after the first dose of study treatment. Although time will be collected on the exposure

CRF, time will not be collected on the AE CRF. Refer to Section 5.3.1, for details, but adverse events occurring on the same day as the first dose of study treatment will be considered to have occurred during the on-treatment period.

Because the protocol requires collection of VOD/SOS for the entire duration of the study, all collected AEs that start after the first dose of study treatment will be included as treatment emergent.

3.5.1.1. **Adverse Events of Special Interest (AESI)**

Certain AEs will be grouped together to support discussion of AEs of Special Interest, these will be reported as clusters using the MedDRA coding as follows with the specific definitions provided in Appendix 2:

- MYELOSUPPRESSION
- HEAMORRHAGE
- INFECTION (Grade ≥3 and/or serious infection)
- HEPATOTOXICITY (Grade ≥3 and/or serious hepatotoxicity including all VOD/SOS)
- INFUSION RELATED REACTIONS (including Anaphylaxis): From start of infusion to within 24 hours of end of infusion
- TUMOUR LYSIS SYNDROME
- CARDIAC CONDUCTION

3.5.2. **Laboratory Data**

Laboratory data will be graded programmatically according to the NCI CTCAE v4.03 severity grade (including low and high values if both are defined for the parameter) for the following safety laboratory parameters:

- Hematology tests: hemoglobin, white blood cells, platelets, neutrophils, lymphocytes.
- Chemistry tests: sodium, potassium, magnesium, glucose, creatinine, total calcium, , albumin, total bilirubin, AST, ALT, alkaline phosphatase (ALP). For laboratory tests that can be either abnormally high or abnormally low, both directions will be computed.
- Coagulation tests: prothrombin time, international normalized ratio (INR), activated partial thromboplastin time, fibrinogen.
- Urinalaysis test: protien

The non-CTC graded laboratory tests red blood cells, hematocrit, BUN, LDH, uric acid or urate along with urinalysis tests (pH), will be categorized as below normal limit, within normal limits, and above normal limits. The remaining urinalysis tests (albumin, glucose, blood/hemoglobin, ketones/acetone) will be categorized as negative or positive.

3.5.2.1. **Time to Recovery of Neutrophils**

For patients who respond, time to recovery of neutrophils for each cycle will be defined as the date of first dose of study treatment to the date that the absolute neutrophils recover to counts of 500/μl after each cycle. During each cycle, the nadir will be calculated. Recovery is not considered to have occurred until after the date of this nadir. If the nadir equals or exceeds the target level of recovery, the date of recovery is defined as the first date after the final dose in the cycle on which the target level was reached. Patients not achieving the target levels of neutrophil recovery are censored at the last laboratory evaluation prior to the next cycle, first follow-up anti-cancer treatment, or death, whichever comes first.

3.5.2.2. **Time to Recovery of Platelets**

For patients who respond, time to recovery of platelets for each cycle will be defined as the date of first dose of study treatment to the date that the platelets recover to counts of 50,000/μl after each cycle. During each cycle, the nadir will be calculated. Recovery is not considered to have occurred until after the date of this nadir. Also, patients are required to be platelet transfusion independent on the date of recovery. Platelet transfusion independence will be defined as no platelet transfusion for at least 7 days prior to the assessment. If the nadir equals or exceeds the target level of recovery, the date of recovery is defined as the first date after the final dose in the cycle on which the target level was reached and the patient was transfusion independent. Patients not achieving the target levels of platelet recovery are censored at the last laboratory evaluation prior to the next cycle, first follow-up anti-cancer treatment, or death, whichever comes first.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

4.1. 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.

4.2. Per Protocol Analysis Set

Not applicable.

4.3. 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.

4.4. Other Analysis Sets

4.4.1. QTc Analysis Set

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

4.4.2. PK Analysis Sets

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

4.4.2.1. Concentration Analysis Set

The PK concentration analysis set is defined as all enrolled patients who received at least 1 dose of GO and have at least one PK concentration.

4.4.2.2. Parameter Analysis Set

The PK parameter analysis set is defined as all enrolled patients who received at least 1 dose of GO and who have at least one PK parameter.

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4.4.4. Immunogenecity Analysis Set

The immunogenicity analysis set include patients in the safety analysis set who have at least 1 immunogenicity sample with results.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final primary analysis will be performed at the study subject data set release after LSLV. No other reporting events are planned. If deemed agreeable to Pfizer and/or regulatory authorities, reporting for the adult cohort may be performed at study subject data set release after the LSLV for adult patients, and separately, reporting for the pediatric cohort may be performed at study subject data set release after the LSLV for pediatric patients.

5.1. Hypotheses and Decision Rules

The primary 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 adult patients for each of the QTc

sampling time points (Day 4, 0 hours, and Day 7, at 0, 2, 4 and 6 hours) from Cycle 1 are below 20 msec, the post 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 adult patients will provide 90 % power for assessing the 5 QTc sampling timepoints using paired difference in means with the t distribution. CCI [redacted]

The inclusion of 6 additional pediatric patients (12 ≤ age ≤17 years) was determined based on agreement with CHMP.

5.2. General Methods

Summary tables will have separate tabulations (columns) for adult and pediatric patients, and also a total column combining adult and pediatric patients. If adult and pediatric patients are to be reported at different times, for example if adult LPLV is reached while pediatric enrollment is still ongoing, with pediatric patients to be reported at a later database release then summary tables may not contain a total column. Data will be pooled across sites and countries.

5.2.1. Nominal Timepoints

For data where visit labels are specified on the CRF, then these labels will be used for all algorithms and analyses as the nominal timepoint. Where visit labels are not specified on the CRF such as data captured on log pages, data will be assigned to cycles; refer to Section 5.2.5 for further detail. Unplanned records may also be assigned to visits according to dates.

ECG parameters: Only the scheduled ECGs will be used in the primary analysis, and only the specific Cycle 1 timepoints of Day 4, 0 hours, and Day 7, at 0, 2, 4 and 6 hours for adult patients will be assessed for interpretation of study results. The nominal timepoints are Screening, Cycle 1 Day 1 at 0, 1, 2, 4 hours; Day 4 at 0, 2 hours; Day 7 at 0, 2, 4, 6; and Cycle 2 Day 1 at 0, 2 hours; Day 7 at 0, 2, 6. As noted in Section 3.4, the Screening and Cycle 1 Day 1 at 0 hours timepoints will be considered in the determination of the baseline value based on the dates.

Response: Response by investigator is assessed after each cycle. These nominal timepoints (Cycle 1 and Cycle 2) will be used in reporting.

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5.2.2. **Unscheduled Assessments**

ECG parameters: Only the scheduled ECGs will be used in the primary analyses. Interval measurements from unscheduled ECGs will be included in some of the categorical analyses, refer to Section 5.2.8.4 for further details.

5.2.3. **Definition of Study Day**

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

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

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

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

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

5.2.4. **Definition of Cycle and Cycle Day**

For Cycle 1 and Cycle 2 the actual start date for each patient will be determined from the first start date of dosing from the respective CRF exposure page with a dose recorded.

If Cycle 2 is administered, then the actual stop date for Cycle 1 will be calculated as the start date of Cycle 2 minus one day.

For the last Cycle, actual stop date will be calculated as the minimum of the last dose + 36 and the start date of subsequent anticancer therapy.

The cycle day will be calculated as Cycle day = Date of the assessment/event – cycle start date + 1.

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

5.2.5. **Assignment to Cycles**

Data collected in log pages, such as adverse events, and laboratory results, will be assigned to cycles. Cycles are defined in Section 5.2.4. For adverse events, the assignment will be based on the start date. Adverse events that start after the end of the last cycle will be assigned to a cycle called Follow-up.

5.2.6. **Date of Last Contact**

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

- All patient assessment dates including local laboratory assessment dates, vital signs, performance status, ECG, bone marrow assessments, extramedullary disease assessment),
- Start and stop dates of concomitant therapies including non-drug treatments or procedures, including transfusions,
- Start and end dates of anti-cancer treatments administered after study treatment discontinuation including systemic therapy, radiation, and HSCT,
- AE start and end dates,
- Last date of contact collected on the 'Survival Follow-up' CRF (do not use date of survival follow-up assessment unless status is 'alive'),
- Study treatment start and end dates,
- Enrollment date, and
- Date of discontinuation on disposition CRF pages (do not use if reason for discontinuation is lost to follow-up or death).

5.2.7. **Standard Derivations and Reporting Conventions**

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

Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. E.g., 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

Duration calculations such as Overall Survival (defined in Section 3.2.4) will be reported in months will use +1 thus OS = ((death date or censoring date) – start date +1)/ 30.4375.

5.2.8. **ECG Derivation Details**

5.2.8.1. **Corrected QT interval derivation**

Fridericia's heart rate correction: $\frac{QT}{\sqrt[3]{60/HeartRate}}$

Bazzett's heart rate correction: $\frac{QT}{\sqrt{60/HeartRate}}$

The ECG core laboratory (vendor) will provide the corrected QT intervals according to the Fridericia's and Bazzett's corrections.

A study specific correction for adult patients will be derived as $QT/(RR)^S$ where S is determined as follows:

The study specific QT correction factor (ICH E14 Step 4, May 12, 2005) will be derived for adult patients in the QTc analysis set using the individual replicates from the selected baseline (baseline is defined in Section 3.4) QT and RR.

No study specific QT correction factor will be assessed for the 6 pediatric patients.

Prior to estimating the regression, QT and RR will be transformed by the natural logarithm to Ln(QT) and Ln(RR), respectively. Ln (RR) will be treated in the regression as the explanatory variable with Ln (QT) as the response variable. The regression equation will be as follows:

$$Ln(QT) = Intercept + S \times Ln(RR) + Error$$

Where S = slope of the regression line.

Once (S) is estimated, it will be used to derive the study specific QT correction, QTcS, for adult patients in the QTc analysis set.

5.2.8.2. **Averaging of triplicate ECG parameter measurements**

After the above variables have been derived within each patient and scheduled timepoint, each ECG parameter (including QTcF, QTcB, QTcS, QT, HR, PR, RR, QRS) should each be averaged as follows: (1^{st} measurement + 2^{nd} measurement + 3^{rd} measurement) / 3. All summary statistics, analyses and figures will be based on the triplicate averaged data from the ECG core laboratory.

5.2.8.3. **Change from baseline**

The change from baseline calculations for ECG parameter measurements is derived from the triplicate averaged measurements. Change from baseline is defined as a patient's parameter value at a particular timepoint minus baseline value (value - baseline value). Change from baseline calculations should only use post-dose ECG measurements at the scheduled nominal timepoints (Day 1 at 1, 2, 4 hours; Day 4 at 0, 2 hours; Day 7 at 0, 2, 4, 6 for Cycle 1; and in Cycle 2 Day 1 at 0, 2 hours; Day 7 at 0, 2 6 hours). Baseline is defined in Section 3.4.

5.2.8.4. **Categorization of ECG parameters**

The categorization of QTc will be per ICH E14 guidance:

The absolute QTc interval (QTcF and QTcS) value for each patient will be categorized as <=450; >450 - <=480, >480 - <=500; >500 msec, using the maximum value post baseline (considering both cycles) based on the averaged triplicate values. Similarly, the absolute values of HR, PR and QRS will be categorized as follows: HR <= 50 bpm, HR >= 120 bpm, PR >= 220 msec and QRS >= 120 msec.

The maximum increase from baseline QTc will be categorized as: <=30 msec, >30 - <=60 msec and >60 msec based on the averaged triplicate values. Similarly, the maximum increase from baseline for HR will be categorized as >= 20 bpm and maximum increase from baseline for PR will be categorized as >=20 msec.

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5.2.10. **Analyses for Binary Data**

Binary variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

If the analysis refers only to certain cycle or timepoints, then percentages will be based on the number of patients with an assessment at that cycle or timepoint, unless otherwise specified.

Best response will be summarized as a binary variable using frequency counts, percentages, and will additionally include a 95% Clopper-Pearson CI for the rate.

5.2.11. **Analyses for Continuous Data**

Most continuous variables will be summarized using descriptive statistics i.e., number of non-missing values and number of missing values [i.e., n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3). Some summaries will also include the coefficient of variation (cv). The values for some continuous variables will be categorized, and will be analyzed as described in Section 5.2.12.

If the analysis refers only to certain cycle or timepoints, then percentages will be based on the number of patients with an assessment at that cycle or timepoints, unless otherwise specified.

For the change from baseline in ECG parameters, including the primary endpoint (the change from baseline in corrected QT interval) will be summarized with descriptive statistics, as above. Additionally, a linear model with the Cycle 1 nominal timepoints as a fixed effect and unstructured variance/covariance to account for the repeated measurements from patients will be used for the primary analysis to estimate the mean change in QTc at the post baseline Cycle 1 nominal timepoints (using least squares mean) along with 2-sided 90% confidence interval for the least squares mean. Confidence intervals will use the approximate t distribution with degrees of freedom by Kenward Rogers method.

ECG parameter results (absolutes) will be summarized with descriptive statistics and a 90% CI for the mean will be calculated using the t-distribution and the observed standard deviation from the particular timepoint.

5.2.12. **Analyses for Categorical Data**

Qualitative variables (including some continuous variables where categories are defined) will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

If the analysis refers only to certain cycle or timepoints, then percentages will be based on the number of patients with an assessment at that cycle or timepoint, unless otherwise specified.

5.2.13. **Analyses for Time to Event Data**

Time to event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically. Graphs will describe the number of patients at risk over time. The quartiles and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. Confidence intervals for quartiles will be based on the Brookmeyer-Crowley method. Confidence intervals for the estimated probability of event at a particular timepoint will be generated using the log(-log) method with back transformation to a confidence interval on the untransformed scale. Summaries of the number and percentages of patients with an event will also be provided on summary tables.

5.2.14. **Impact of COVID-19 Pandemic**

The study enrollment was ongoing during the COVID-19 pandemic period. Data summaries and analyses will be performed to assess the impact of COVID-19 on the trial population and study data.

An anchor date will be used as a start date for COVID-19 pandemic related periods [redacted]

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

For China reference date: the date COVID-19 was identified as the causative agent of outbreak in Wuhan by the China Center for Disease Control and Prevention - January 9, 2020. (This study has no sites in China).

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

A different anchor date may be used for purposes of regulatory submission if requested by a regulatory authority.

5.3. Methods to Manage Missing Data

5.3.1. **Missing Dates**

In data listings, dates will reflect the information provided by the investigator on the CRF, if any imputation was applied to data presented in listings, such data will be clearly marked as imputed.

5.3.1.1. **Missing or Partial Adverse Event dates/times**

Complete adverse event dates are needed to determine treatment emergence, and to assign adverse events to cycles, therefore missing or partial dates will be imputed. Completely missing AE dates will be imputed as follows with the end result that the events will be considered treatment emergent.

AE Start Date: If the AE start date is missing, and if the date of first dose is less than AE end date, then the start date will be assigned as the date of first dose. Otherwise if the date of first dose is after the AE end date then the AE start date will be imputed as the earliest of non-missing AE end date or informed consent date.

AE Stop Date: If the AE end date is missing then the end date will be imputed as the latest of the Subject Withdrawal/Completion date, death date, last dose of study treatment, or AE start date.

5.3.1.2. **Missing or Partial Death Dates:**

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

- If the entire date is missing it will be imputed as the day after the date of last contact (see derivation of date of last contact in Section 5.2.6); or
- If the day or month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death, or
  - Missing day and month: January 1st of the year of death.

5.3.1.3. **Missing or Partial Anti-cancer Treatment dates**

Incomplete dates for new (follow-up) anti-cancer treatment will be imputed as follows:

- The end date of new anti-cancer therapy will be included in the imputation for start date of new anti-cancer therapy. If the end data of new anti-cancer therapy is:
    - completely missing then it will be ignored in the imputations below,
    - partially missing with only year available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy, or
    - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy.
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy will be:

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

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

    Year = Year of min (last dose of study treatment + 1, end date of new anti-cancer therapy)

    Month < Month of min (last dose of study treatment + 1 day, end date of new anti-cancer therapy)

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

5.3.1.4. **General concomitant medications and concomitant non-drug procedures**

If start dates of concomitant medications or concomitant non-drug treatments are completely missing, the medications and non-drug treatments/procedures will be considered concomitant unless the medication stop date is prior to first study treatment. If only partial information are available, (e.g. only a month and year or only a year) dates will be imputed (see Section 5.3.1.5) and thus if the imputed dates based on the partial information provides sufficient information to indicate the dates are prior to the start of study treatment (e.g. month/year less than month/year of first dose) then these will be considered to have started prior to treatment; otherwise these will be considered to have started after treatment.

5.3.1.5. **Other Missing or Partial Dates**

Imputation methods for other missing or partial dates which will be used in computations of durations will be as follows (e.g. date of diagnoses):

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

- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.
- If the date is completely missing, no imputation will be performed (other than as explicitly described in this section).

5.3.2. **Missing Toxicity Grades of Adverse Events**

In summaries which present maximum toxicity grade, the maximum of non-missing grades will be displayed. A patient will be counted as a missing grade only when all occurrences for a particular event are reported as missing.

5.3.3. **Missing absolute WBC differential counts and Normal Ranges**

For WBC differential counts (total neutrophil [including bands], lymphocyte counts), the absolute value will be used when the results are reported in this manner. When only percentages are available the absolute value will be derived as follows:

Derived differential absolute count = (WBC count) × (Differential % value / 100)

If both the absolute and % value for Neutrophils or Lymphocytes are reported from the same laboratory sample date and patient, only the absolute value will be graded. The % value will not be graded in this scenario.

If the % value is converted to the differential absolute count for grading and the LLN for the differential absolute count is not available (only LLN for % is available) then Grade 1 will be assigned if the following conditions are met:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq 800/mm^3$
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq 1500/mm^3$

5.3.4. **Missing Pharmacokinetic (PK) Data**

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ

will be replaced with the value for the lower limit of quantification.) If a summary statistic is a BLQ value, it will also be reported as zero.

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

- A concentration has been reported as ND (i.e., not done) or NS (i.e., no sample);
- A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular timepoint if more than 50% of the data are missing. Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from the concentration data, the parameter will be coded as NC (i.e. not calculated). NC values will not be generated beyond the day that a patient discontinues.

In summary tables of PK parameters, statistics will be calculated by setting NC values to missing; and statistics will not be presented if more than 50% of the data are NC and statistics will be presented for ≥3 evaluable measurements .

If an individual patient has a known biased estimate of a PK parameter, this will be footnoted in summary tables and will not be included in the calculation of summary statistics.

5.3.5. **Missing ECG Data**

For ECG parameters, no values will be imputed for missing replicates within a scheduled assessment. Thus if the three triplicate measurements for an ECG parameter are not available, then the average will not be computed.

6. ANALYSES AND SUMMARIES

If both adult and pediatric patients enrollment are completed and respective LPLV are included in the same same database release, all summary tables will have separate tabulations (columns) for adult and pediatric patients, and also a total column combining adult and pediatric patients, unless noted otherwise. If adult and pediatric patients are to be reported at different times, for example if adult LPLV is reached while pediatric enrollment is still ongoing, with pediatric patients summary to be reported at a later database release then summary tables may not contain a total column.

Listings will be provided as required for an ICH CSR. Additional details for some data listings are described for some data types in the following sections. As relevant, listings or summary tables focused on COVID-19 will be provided such as participants affected by COVID-19 related study disruption, protocol deviations, COVID-19 related deaths, COVID-19 related discontinuations.

6.1. Primary Endpoint

6.1.1. **Change in QTcF from baseline**

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 from adult patients in Cycle 1 and the particular timepoints of Day 4, 0 hours, and Day 7 at 0, 2, 4, and 6 hours will be interpreted for 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) according to Fridericia's (QTcF) method.

A linear model (for adult patients and pediatric patients separately) with the Cycle 1 nominal timepoints as a fixed effect and unstructured variance/covariance to account for the repeated measurements from patients will be used for the primary analysis to estimate the mean change in QTcF (primary endpoint) at the post baseline nominal timepoints for Cycle 1 along with the estimated least squares means and 2-sided 90% confidence interval for the mean. Confidence intervals will use the approximate t distribution with degrees of freedom by Kenward Rogers method. Refer to Section 5.2.8 for further details of derivations. Although the 90% CI for the mean change in QTcF from the Cycle 1 Day 4, 0 hours, and Cycle 1 Day 7, at 0, 2, 4 and 6 hours summarized for adult patients will be interpreted (see Section 5.1), all Cycle 1 timepoints will be included in the estimation.

Summary will be for the QTc analysis set. The least squares mean and its 90 % confidence interval will be displayed graphically.

Additional summaries of QT interval data are described in Section 6.6.5 along with the summary of other ECG data.

6.2. Secondary Endpoints

6.2.1. **Pharmacokinetc Endpoints**

6.2.1.1. **Non-Compartmental Analysis**

To assess the pharmacokinetics of GO (represented by total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin if possible), the PK parameters detailed in Section 3.2.1 will be summarized for subjects in the PK analysis set (as defined in Section 4.4.2). Missing values will be handled as detailed in Section 5.3.4.

Each PK parameter for each analyte (total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin) will be summarized using the set of descriptive statistics as specified in the table below:

Table 2. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{0-72}, AUC_{0-336}, AUC_{inf}[a], C_{max}, CL[*,a] and V_{ss}[*,a]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$[a]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

[*] for total hP67.6 antibody only
[a] if data permit

Supporting data from the estimation of t½ and AUCinf will be listed by analyte or provided in data sets where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); the first, last, and number of time points used in the estimation of k_{el}.

Presentations for plasma concentrations of GO (total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin) will include:

- Listings will be consistent with ICH CSR requirements and may include: A listing of all concentrations sorted by participant ID, cycle, day and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by nominal time postdose, where the set of descriptive statistics will include n, mean, median, standard deviation, coefficient of variation(cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose for Cycle 1 Day 1 and Cycle 1 Day 7 .

For summary statistics, median plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

6.2.1.2. **Population Pharmacokinetics/Pharmacodynamics**

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.

6.2.2. **Immunogenicity**

Immunogenicity will be summarized for the immunogenicity analysis set (as defined in Section 4.4.4).

The percentage of patients with positive ADA and NAb will be summarized (eg. at baseline, treatment-induced (positive for the first time after dosing), and treatment-boosted (pre-existing positive titers that were at a higher level post-baseline), and overall (treatment-induced + treatment-boosted). The overall percentage will be computed excluding baseline positive patients without any post-dose assessment. The other percentages will be based on the number of patients in the immunogenecity analysis set.

For patients with positive ADA/NAb, the magnitude of the titer will be described with summary statistics (median, Q1, Q3) for positive baseline titers, peak titer for treatment-induced and treatment-boosted, and titer fold increase for treatment-boosted (calculated as the ratio of peak post-dose titer to baseline titer), if data permit.

For patients with treatment induced ADA/NAb, time of onset, and duration will also be described with summary statistics (median, Q1, Q3), if data permit. Onset of ADA/NAb will be calculated as date of date of first positive result – date of first dose +1. Duration of ADA/NAb will be calculated as date of last positive result – date of first positive result +1. The number and percent of transient and persistent positive ADA/NAb will be summarized out of the number of patients with treatment-induced ADA/NAb.

Transient ADA/NAb will be defined as treatment-induced ADA/NAb meeting the following conditions:

- detected only at one sampling time point during the treatment or follow-up (excluding the last sampling time point which will be considered persistent unless shown to be undetectable at a later time) or
- detected at two or more sampling time points during the treatment (including follow-up), where the first and last positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the last sampling time point is negative

Persistent ADA/Nab will be defined as treatment-induced ADA/NAb meeting the following conditions:

- detected at two or more sampling time points during the treatment (including follow-up), where the first and last positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
- detected only in the last treatment sampling time point or at a sampling time point with less than 16 weeks before a negative last sample.

Analyses to assess the impact of ADA on safety are described in Section 6.6.1. The impact of ADA on PK will be assessed in population PK analysis and will be reported separately.

6.2.3. **Best Response**

Best response will be summarized for the full analysis set.

Best response is derived from the cycle 1 and cycle 2 disease assessments according to the investigator (Section 3.2.3). The summary will include response (CR+CRi), along with the subcategories CR, CRi, and no response.

Best response will be summarized as a binary variable using frequency counts, percentages, and will additionally include a 95% Clopper-Pearson CI for the rate.

Additionally, summaries of the disease assessment for each cycle (Cycle 1 and Cycle 2) summarizing the categories as collected on the CRF with the exception that CR will be used (combining any CRF category with CR in the label). The denominator will include only patients who received that cycle.

6.2.4. **Overall Survival**

Overall Survival will be summarized for the full analysis set.

Overall survival is defined as the time from the start date to the date of death due to any cause. Patients last known to be alive as censored at the date of last contact (Section 5.2.6).

Overall survival will be reported in months and derived as ((death date or censoring date) – start date +1)/ 30.4375.

The summary will include the number of deaths as well the cause of death, the number of censored patients as well as the reason for censoring (Withdrawal of consent, Lost to Follow-up, Alive).

Overall survival will be summarized using the Kaplan-Meier method. The quartiles and probabilities of an event at 6 months and 12 months will be estimated by the Kaplan-Meier method. Confidence intervals (95 %) for quartiles will be based on the Brookmeyer-Crowley method. Confidence intervals (95%) for the estimated probability of event at 12 months will be generated using the log(-log) method with back transformation to a confidence interval on the untransformed scale.

The estimated overall survival curves will be displayed graphically, with one graph including estimates for the adult and pediatric patients separately,. Graphs will describe the number of patients at risk over time.

Deaths related to COVID-19 will be presented in listings, if there are < 5 COVID-19 related deaths.

CCI [redacted]

6.4. Subset Analyses

CCI [redacted]

Time to Recovery as described in Sections 3.5.2.1, 3.5.2.2 and 6.6.3.1 is defined only for responding patients.

Description of HSCT characteristics is provided only for patients with HSCT; refer to Sections 6.5.1.4 and 6.5.5.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Refer to Section 3.4 for the definition of baseline.

6.5.1.1. Demographic and Physical Characteristics

The following demographic and baseline characteristics will be summarized by number and percentage: (full analysis set)

- Sex (male, female)
- Age according to the categories: (< 12, 12- <18 years, 18-<45; 45- <65; ≥65). Age will be derived based on the collected year of birth.
- Race (according to the categories collected on the CRF, if multiple categories were indicated, then the patient will be reported as "Other")

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Region (US, Canada, and Europe including also the countries within Europe)
- Eastern Cooperative Oncology Group (ECOG) Performance status (by values 0, 1, 2, etc.).

Age (years, as continuous variable), and Body Surface Area (BSA) (m^2) will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

Body Surface Area (BSA) (m^2) will be computed using Du Bois Formula: $0.007184 \times \text{Weight(kg)}^{0.425} \times \text{Height(cm)}^{0.725}$

6.5.1.2. **Disease Characteristics**

The following disease and baseline characteristics will be summarized by number and percentage: (full analysis set)

- CCI [redacted]
- Percent CD33 positivity based on local laboratory (0, >0 - <30, 30 - <70, ≥70)
- FAB Subtype (according to values collected on the CRF)
- Risk according to the ELN 2017 guidelines (favorable, intermediate, adverse) per the investigator as collected on the CRF.
- Patients with extramedullary disease (EMD) (yes, no derived from baseline assessment of EMD).

Additionally the following variables will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum) (full analysis set)

- Absolute blasts in the peripheral blood (10^9/L)
- Percentage of blasts in the bone marrow
- The CCI measures of CD33 expression (percent CD33 positivity CCI [redacted]
- Baseline White Blood Cell Count (10^9/L)

Time since initial diagnosis (months), defined as (first dose date – date of initial diagnosis)/30.4375, will be summarized by descriptive statistics (mean, median, standard deviation, minimum, and maximum).

Time since onset of current episode (days), defined as (first dose date – date of current diagnosis), will be summarized by descriptive statistics (mean, median, standard deviation, minimum, and maximum).

CCI [redacted]

6.5.1.3. **Medical History**

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's System Organ Class (SOC) and PT. Each patient will be counted only once within each PT or SOC. Summaries will be ordered by primary SOC and PT in alphabetical order. The summary will include conditions that were recorded as either past or present. (safety analysis set)

6.5.1.4. **Prior Anti-Cancer Treatments**

Summaries will be for the full analysis set.

Prior anti-cancer systemic therapies will be identified as therapies with start date prior to the first dose of study treatment.

A summary of the number of prior regimens according to the number and percentage of patients with 1, 2, 3, or >3 induction regimens will be provided.

A summary of the number and percentage of patients with at least one prior regimen, and the number of patients with at least one induction regimen, at least one conditioning regimen, at least one consolidation or intensification regimen, and at least one maintenance regimen).

Prior radiation treatments will be identified by start date prior to the first dose of study treatment. A summary of the number and percentage of patients with at least one prior radiation treatment given for conditioning, and the number and percentage of patients with at least one prior radiation treatment for other reasons will be provided.

Prior HSCT will be identified by start date prior to the first dose of study treatment. The number and percentage of patients with at least one prior HSCT and a summary of patients according to the number of prior HSCT (1, >1) (number and percentage) will be provided. Prior HSCT will be identified by HSCT date prior to the first dose of study treatment. If a patient has more than one prior HSCT, then the last HSCT prior to study treatment will be included in the summary.

For the patients with a prior HSCT, a summary of the following characteristics (number and percentage) using patients with a prior HSCT as the denominator will be provided. Each of the following aspects will be summarized according to the categories collected on the CRF.

- Time of transplant relative to first GO dose (<2 mos or ≥2 mos before the first dose of GO)
- Type of transplant
- Donor relatedness
- HLA compatibility
- Stem Cell Source
- Type of conditioning
- Disease Risk at Transplant

6.5.2. **Study Conduct and Subject Disposition**

Evaluation Groups: A summary of the number of patients screened, the number of screen failures, the number of patients enrolled, and the number treated and not treated with percentages for the last two items based on the number of patients enrolled. Additionally, the number of patients in each analysis set will be summarized.

Protocol Devations: Protocol deviations will be compiled prior to database closure and categories will be assigned by the study clinician. Potentially important protocol deviations will be summarized by category (number and percent) (full analysis set). As relevant, important protocol deviations due to COVID-19 will be included. Protocol deviations related to COVID-19 will be presented in listings.

Disposition: Disposition events will be summarized for each phase (screening, treatment, and follow-up (representing end of study)) with number and percentage. Within a phase, a summary of the reason for discontinuation as collected on the CRF, and the number completed that phase. (full analysis set) Discontinuations related to COVID-19 will be presented in a separate summary table.

Inclusion and Exclusion Criteria: The number and percentage of patients who did not meet at least one of these criteria will be summarized. Additionally, the number and percentage of patients who did not meet each criterion will be summarized. (full analysis set and screen failure patients)

Impact of COVID-19 on Missed ECG Assessments: Impact to Cycle 1 ECG assessments will be assessed by showing assessments completed before and after the anchor date (Section 5.2.14) and planned assessments (relative to the first dose date).

6.5.3. **Study Treatment Exposure**

Study treatment exposure (GO dosing) will be summarized for the safety analysis set.

The following will be summarized with frequencies and percentages for each cycle:

- Patients receiving each dose (GO on Day 1, Day 4, Day 7) according to nominal timepoint.
- Patients receiving all doses in the cycle.
- Duration of treatment of GO computed from the first dose to the last dose within the cycle and categorized as <7 days, 7 days, >7 days.

For patients receiving Cycle 2, the study day for the start (first GO dose) in Cycle 2 categorized as Before Day 28, Day 28 to Day 34, Day 35 to Day 42, Day 43 to Day 49, After Day 50 will be summarized with number and percentage.

Exposure including all cycles received in terms of total number GO doses categorized as <3, 3, 4, 5, 6 doses which will be summarized with number and percentage.

6.5.4. **Concomitant Medications and Non-Drug Treatments**

Per protocol, 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 start of subsequent anticancer therapy (e.g., consolidation or conditioning regimen). Medications and treatments for the managements of VOD/SOS during the follow-up period are also to be collected.

Concomitant medications and non-drug treatments received by patients during the study will be summarized for the safety analysis set.

Concomitant medications refer to all medications which started prior to first dose of study treatment but continued during the on-treatment period (see Section 3.5) as well as those started during the on-treatment period (including starting on the date of the first dose of study drug). Concomitant medications will be coded in the WHO Drug coding dictionary and will be tabulated by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term in alphabetical order. A patient will be counted only once within a given drug class and within a given drug name, even if the same medication was received at different times. Preferred Terms will be reported under each ATC class that it is included under within WHO Drug (since no primary path is available in WHO Drug).

Concomitant non-drug treatments refer to all non-drug treatments administered during the on-treatment period (including on the date of the first dose of study drug). Non-drug treatments will be MedDRA coded and will be summarized by MedDRA SOC and PT alphabetical order. Patients will be counted only once per PT even if the same treatment was received multiple times.

Any medications which were only administered prior to treatment start will be summarized for the safety analysis set by WHO Drug coding dictionary preferred term in alphabetical order.

Any non-drug treatments, aside from anti-cancer treatments described in Section 6.5.1.4, which were only administered prior to treatment start will be listed as needed to be compliant with ICH required listings but not summarized.

Transfusions: for each of the two transfusion types (Packed RBC and Platelets) the number of days with a transfusion during the on-treatment period for each cycle will be computed for each patient. For each cycle, each transfusion type will be summarized with summary statistics (n, mean, median, standard deviation, minimum, and maximum) of the number of days with transfusion. Additionally, the number of days will be categorized as (<=7 days, 8-14, 15-21, 22-28, 29-36, >36) and the number and percent of patients in each category will be summarized.

6.5.5. **Follow-up Anti-cancer Treatments**

Summaries will be for the full analysis set.

Follow-up anti-cancer systemic therapies will be identified as therapies with start date after the last dose of study treatment.

A summary of number of follow-up regimens according to the number and percentage of patients with 1, 2, 3, or >3 induction regimens will be provided.

A summary of the number and percentage of patients with at least one follow-up regimen, and the number of patients with at least one induction regimen, at least one conditioning regimen, at least one consolidation or intensification regimen, and at least one maintenance regimen will be provided.

Follow-up radiation treatments will be identified by start date after the last dose of study treatment. A summary of the number and percentage of patients with at least one follow-up radiation treatment given for conditioning, and the number and percentage of patients with at least one follow-up radiation treatment for other reasons will be provided.

Follow-up HSCT will be identified by start date after to the last dose of study treatment. The number and percentage of patients with at least one follow-up HSCT and a summary of patients according to the number of follow-up HSCT (1, >1) (number and percentage) will be provided. Follow-up HSCT will be identified by HSCT date after the last dose of study treatment. If a patient has more than one follow-up HSCT, then the first HSCT after to study treatment will be included in the summary.

For the patients with a follow-up HSCT a summary of the following characteristics (number and percentage) using patients with a follow-up HSCT as the denominator will be provided.

Each of the following aspects will be summarized according to the categories collected on the CRF.

- Time of transplant relative to last GO dose (< 2 mos or ≥ 2 mos after the last dose of GO)
- Type of transplant
- Donor relatedness
- HLA compatibility
- Stem Cell Source
- Type of conditioning
- Disease Risk at Transplant

6.6. Safety Summaries and Analyses

Safety (AE and other parameters) summaries will be provided for the safety analysis set unless otherwise specified.

6.6.1. **Adverse Events**

The following general considerations will be applied to AE summaries:

All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in Section 3.5.1. AEs not considered treatment emergent will be flagged in data listings (as applicable to listings needed to be compliant with ICH required listings).

- For summaries including CTCAE grade, patients will be counted according to the worst grade for the particular PT or SOC and will also include a total across grades.
- For summaries including toxicity grade, as described in Section 5.3.2, in the case that a patient has events with missing and non-missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed in the event that only one event has been reported for a patient and the grade is missing.
- There will also be a row for the number and percentage of patients reporting at least 1 AE.
- For summaries including SOC, the number and percentage of patients with at least 1 AE in that SOC will be reported.
- The denominator for percentages will be the number of patients treated in the group being summarized.
- Each patient will be counted only once within each SOC and PT.
- In summaries of treatment related AEs, if the relationship to study treatment is missing on the CRF, it will be assumed to be related to treatment.

A high level summary of adverse events (all causality and also for treatment related events) will include the number and percentage of patients with:

- Any Adverse Event
- Serious AE

- Adverse Events with CTCAE Grade 3-4
- Grade 5 events
- AEs that caused the subject to be discontinued from the study
- AEs with Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from the study

- AEs leading to dose reductions or temporary discontinuations (note that no dose reductions are specified per protocol and the CRF used the term interruptions rather than temporary discontinuations)
- Additionally, the number of events will be provided. Each unique adverse event at the PT level for a patient is included in the count.

Seriousness, toxicity grade, action taken will be as reported by the investigator on the adverse event CRF.

Summaries by SOC and PT in decreasing frequency within SOC based on frequencies observed for adult patients will be provided for:

- Treatment Emergent Adverse Events by Maximum CTCAE Grade (All Causality); (which will have a column for each of the grades)

- Treatment Emergent Adverse Events by Maximum CTCAE Grade (Treatment Related);

- Serious Treatment Emergent Adverse Events (All Causality);

- Serious Treatment Emergent Adverse Events (Treatment Related);

The summary of Treatment Emergent Adverse Events by SOC, PT, and Maximum CTCAE Grade (All Causality); will also be provided by Cycle (1, 2, and Follow-up) CCI [redacted]

Each AESI defined in Section 3.5.1.1 will be summarized by PT and Maximum CTCAE Grade (All Causality) (which will have a column for each of the grades)

The AESI of INFUSION RELATED REACTIONS (including Anaphylaxis) will also be summarized for by ADA status (patients overall ADA positive and patients ADA negative).

Summaries by PT only (i.e. summaries will not include SOC) in decreasing frequency based on the frequencies observed for adult patients for the following: Cutoffs in terms of percentage of events such as ≥10% in any patient group or number of patients (SAE tables such as 2 adult patients) may be applied.

- Treatment Emergent Adverse Events Leading to Study Drug Withdrawal (ie based on last action taken for study drug; not study discontinuation) (All causality) by Maximum CTCAE grade showing at least Grade 5.

- Treatment Emergent Adverse Events Leading to Study Drug Withdrawal (ie based on last action taken for study drug; not study discontinuation) (Treatment Related) by Maximum CTCAE grade showing at least Grade 5.

- Treatment Emergent Adverse Events Leading to Study Drug Interruption (All causality)

- Treatment Emergent Adverse Events Leading to Study Drug Interruption (Treatment Related)

- Treatment Emergent Adverse Events by Maximum CTCAE Grade (All Causality) with grouped grades such as Grade 1-2; Grade 3-4; Grade 5; Grade ≥3 with a cutoff such as ≥10% of any patient group

- Treatment Emergent Adverse Events by Maximum CTCAE Grade (Treatment Related) with grouped grades such as Grade 1-2; Grade 3-4; Grade 5; Grade ≥3 with a cutoff such as ≥10% of any patient group

- Serious Treatment Emergent Events (All Causality) with a cutoff such as ≥ 2 adult patients

- Serious Treatment Emergent Events (Treatment Related) with a cutoff such as ≥ 2 adult patients

6.6.1.1. **VOD**

Summaries focused on VOD/SOS (The MedDRA PTs of Venoocclusive liver disease and Venoocclusive disease) will include the following number and percentage of patients out of the following groups (denominator):

- Any VOD with denominator of safety analysis set
- VOD before (first) follow-up HSCT with denominator of safety analysis set
- VOD before (first) follow-up HSCT with denominator of safety analysis set with a prior HSCT
- VOD after follow-up HSCT with denominator of safety analysis set with a follow-up HSCT
- VOD after follow-up HSCT with denominator of safety analysis set with both a prior and a follow-up HSCT.

Timing relative to study treatment and HSCT (days): The timing of the first VOD relative to the nearest prior GO dose will be summarized with descriptive statistics (VOD start date – nearest GO dose date +1). The timing of the first HSCT relative to the nearest VOD after the

HSCT date (days) will be summarized with descriptive statistics (VOD start date – first HSCT date +1).

6.6.1.2. **Basic Results**

The following additional summaries required for basic results disclosures in the US and EU will be provided:

- Treatment Emergent Non Serious Adverse Events by SOC and PT (All Causality) in >5% of patients in either group;
- Treatment Emergent Non Serious Adverse Events by SOC and PT (All Causality);
- Treatment Emergent Serious Adverse Events by SOC and PT; and
- Fatal Adverse Events by SOC and PT (based on safety database).

Each of the above summaries for EU will include a count of the number of occurrences of all causality events and the number of occurrences of treatment related events.

6.6.2. **Deaths**

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 36 days after last dose of study treatment as well as the cause of death, will be tabulated based on information from the 'Notice of Death' CRFs.

The frequency (number and percentage) of patients in the safety analysis set who died within 30 days of first dose of study treatment will also be provided.

Date and cause of death will be provided in individual patient data listing (as needed to be compliant with ICH required listings) together with selected GO dosing information (date of first / last administration).

Refer to Section 6.2.4 for the description of the summaries of all deaths observed in the study.

6.6.3. **Laboratory Data**

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

Laboratory data will be graded programmatically according to the NCI CTCAE v4.03 severity grade (including low and high values if both are defined for the parameter). Non-numeric qualifiers will not be taken into consideration in the derivation of grade (e.g. hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summaries the number and percentage of patients corresponding to grades that only include non-quantitative criteria will be displayed as a

blank or NA (not assessed). If there is any overlap between grade criteria (e.g. CTCAE grading criteria for Creatinine Increased – a value can fall into one range based on comparison to ULN and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data.

Grade 0 or Outside Toxicity Reference (OTR) is not defined specifically by in the CTCAE guidance. However, programmatically this is used as a category to represent those patients who did not meet any of the Grades 1 to 4 criteria. If the laboratory value is evaluable for CTCAE criteria grading (numeric value is present, valid units and ranges are present as required to allow conversion to standard units and grading), and does not qualify for any of the Grade 1-4 criteria for a given laboratory test, then the value is assigned as Grade 0 or OTR.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte counts), the absolute value will be used when the results are reported in this manner. When only percentages are available the absolute value will be derived as follows:

Derived differential absolute count = (WBC count) × (Differential %value / 100)

If both the absolute and % value for Neutrophils or Lymphocytes are reported from the same laboratory sample date and patient, ONLY the absolute value will be graded. The % value will not be graded in this scenario. Further details of the grading of the computed absolute values are provided in Section 5.3.3.

Several laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high (hyper) values will be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 Hypercalcemia will be classified as a Grade 0 Hypocalcemia.

The following summaries will be provided for the safety analysis set.

The denominator for percentages will be the number of patients treated in the group being summarized with at least 1 post baseline assessment of the laboratory parameter.

Displays will be organized by laboratory category: Hematology parameters including coagulation parameters will be summarized together, chemistry parameters will be summarized together, and urinalysis parameters will be summarized together. Laboratory parameters with CTCAE grades will be summarized separately from laboratory parameters with no CTCAE grades.

For each CTCAE term, patients will be counted according to the worst (maximum) CTCAE grade on treatment (excluding baseline values). Baseline is defined in Section 3.4. If there are multiple assessments that meet the baseline definition on the same day without the ability

to determine which was truly last, then the worst CTC grade will be assigned as the baseline CTC grade.

The following summary tables will be created:

- Shift summary of laboratory parameters of baseline CTCAE grade by maximum post baseline CTCAE grade.
- Shift summary of laboratory parameters from ≤ Grade 2 at baseline to ≥ Grade 3 post-baseline.

The non-CTC graded laboratory tests (red blood cells, hematocrit, BUN, LDH) along with urinalysis test (pH) will be presented according to the following categories overall: below normal limit, within normal limits, and above normal limits. In the unlikely event that for a given participant, clinically significant abnormalities are noted in both directions (eg, > ULN and < LLN), then both abnormalities are counted. The remaining urinalysis tests (albumin, glucose, blood/hemoglobin, ketones/acetone) will be categorized as negative or positive.

A shift summary of laboratory test results with no CTCAE criteria of baseline assessment by worst on-treatment assessment will be created. .

6.6.3.1. **Time To Recovery**

The analysis of Time to Recovery of Neutrophils and the analysis of Time to Recovery of Platelets will be similar, therefore this section is written generically as “Time to Recovery”.

Time to Recovery for responders will be reported in days and derived as ((recovery date or censoring date) – date of first dose +1) for each cycle (for responders in that cycle).

The summary will include the number of patients recovered to the level of interest and the number of patients not recovered and reported for the safety analysis set.

Time to Recovery will be summarized using the Kaplan-Meier method. The quartiles will be estimated by the Kaplan-Meier method. Confidence intervals (95%) for quartiles will be based on the Brookmeyer-Crowley method.

The estimated survival curves will be displayed graphically (unless there are < 5 responders) with one graph including estimates for the adult and pediatric patients separately. Graphs will describe the number of patients at risk over time.

Prolonged Cytopenias (Neutrophils and Platelets): For each cycle, patients with Time to Recovery longer than 42 days will be considered prolonged and summarized for the safety analysis set. The percentage will be based on a denominator that will exclude patients without data to determine the status at Day 42 relative to the cycle start. Thus prolonged cyotopenias applies only to patient who are responders in the respective cycle.

6.6.3.2. **Hy's Law Assessment**

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity.

An evaluation of drug-induced serious hepatotoxicity (eDISH) by scatterplots of using all data from the on treatment period will be produced to assess hepatotoxicity and to identify any potential Hy's Law cases. This summary does NOT indicate actual Hy's law cases.

- Maximum serum ALT vs maximum total bilirubin including reference lines at ALT=3×ULN and total bilirubin=2×ULN.
- Maximum serum AST) vs maximum total bilirubin including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, a listing of all total bilirubin, ALT, AST and alkaline phosphatase values for patients with a post-baseline total bilirubin ≥ 2×ULN, ALT ≥ 3×ULN or AST ≥ 3×ULN will be provided.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized:

- ALT ≥ 3×ULN, ALT ≥ 5xULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

Summary of liver function tests will also be provided by Cycle (1, 2, Follow-up).

6.6.4. **Vital Signs**

Vital sign data will be listed as needed to be compliant with ICH required listings and not summarized.

6.6.5. **Electrocardiogram**

This section describes all ECG parameter summaries including secondary analyses of changed from baseline in QTc. Refer to Section 6.1.1 for the primary endpoint analysis. As noted in Section 5.2, separate summaries for adult and pediatric patients will be presented. As noted in Section 5.2.8.1, a study specific QT interval correction will be evaluated only for adult patients. All analyses will be provided for the QTc analysis set. All summaries will be based on the ECG core laboratory (vendor) results for ECG parameters.

6.6.5.1. **Assessment of Correction Factors**

Scatterplots of QTc (QTcB, QTcF, QTcS) versus RR interval (msec) using individual replicates (non-averaged) from the timepoint selected as baseline including the linear regression line with description including slope and its 95% CI, intercept, and coefficient of determination (R^2) will be presented.

6.6.5.2. **ECG Parameter Results**

The absolute corrected QT interval (QTcB, QTcF, and/or QTcS) will be summarized using descriptive statistics (n, mean, median, standard deviation (SD), minimum, maximum and a 90% confidence interval for the mean) by cycle and nominal time point within cycle (Screening, Cycle 1: Day 1 at 0, 1, 2, 4 hours; Day 4 at 0, 2 hours; Day 7 at 0, 2, 4, 6, and Cycle 2 Day 1 at 0, 2 hours; Day 7 at 0, 2, 6. The 90% CI for the mean will be calculated using the t-distribution and the observed standard deviation from the particular timepoint.

In addition to QTc, the ECG parameters of HR, PR interval, QRS interval, QT interval will be summarized similarly with descriptive statistics (n, mean, median, standard deviation (SD), minimum, maximum).

6.6.5.3. **Change from baseline**

The change in QTc (QTcF, QTcB and/or QTcS) from baseline will be summarized using descriptive statistics (n, mean, median, standard deviation (SD), minimum, maximum for each cycle and nominal time point within cycle.

A linear model (for adult patients and pediatric patients separately) with the Cycle 1 nominal timepoints as a fixed effect and unstructured variance/covariance to account for the repeated measurements from patients will be used to estimate the mean change from baseline (in QTcB and/or QTcS) at the post baseline nominal timepoints for Cycle 1 along with the estimated least squares means and 2-sided 90% confidence interval for the mean. Confidence intervals will use the approximate t distribution with degrees of freedom by Kenward Rogers method.

In addition to QTc, the change from baseline in ECG parameters of HR, PR interval, QRS interval, QT interval will be summarized similarly with descriptive statistics (n, mean, median, standard deviation (SD), minimum, maximum).

6.6.5.4. **Absolute QTc interval prolongation**

Categorical analysis of absolute QTc interval prolongation for QTc (QTcF and/or QTcS) according the maximum post-baseline value per patient will be summarized. . As described in Section 5.2.8.4, the categories of <=450; >450 - <=480, >480 - <=500; >500 msec will be used to classify post baseline values and the number and percentage of patients in each category will be summarized. A similar categorical analysis of HR, PR and QRS will be provided (HR <= 50 bpm, HR >= 120 bpm, PR >= 220 msec and QRS >= 120 msec).

Additionally a shift summary will be presented using CTCAE grade, where the baseline value will also be classified into the same categories and cross classified with the post baseline values. Baseline is based on the triplicate average, but worst post baseline interval measurements will based based on individual repliates including values from unscheduled ECGs. The baseline versus the worst on treatment QTc will be summarized.

6.6.5.5. **Maximum increase from baseline QTc**

Categorical analysis of maximum increase from baseline in QTc (QTcF and/or QTcS) and will be summarized. . As described in Section 5.2.8.4, the categories of <=30 msec, >30 - <=60 msec and >60 msec will be used and the number and percentage of patients in each category will be summarized. A similar categorical analysis of HR and PR will be provided (HR increase from baseline >= 20 bpm and PR increase from baseline >=20 msec).

6.6.6. **Physical Examination**

Physical examination data will be be listed as needed to be compliant with ICH required listings and not summarized.

7. INTERIM ANALYSES

Not applicable.

8. APPENDICES

Appendix 1. SUMMARY OF PK ANALYSES

The following PK parameters will be calculated for GO (represented by total hP67.6 antibody, conjugated calicheamicin, and unconjugated calicheamicin) (if possible) from the concentration-time values using standard noncompartmental methods (Table 3).

Appendix 1. Table 3. Noncompartmental PK Parameters

Parameter	Analysis Scale	Total hP67.6 antibody	Conjugated calicheamicin	Unconjugated calicheamicin
AUC_{inf}*	Ln	D	D	D
AUC_{last}	Ln	D	D	D
AUC_{0-72}	Ln	D	D	D
AUC_{0-336}	Ln	D	D	D
C_{max}	Ln	D	D	D
T_{max}	R	D	D	D
$t_{1/2}$*	R	D	D	D
CL*	Ln	D	D	D
V_{ss}*	Ln	D	D	D

Key: D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits.

Appendix 2. AESI Definitions

HEPATOTOXICITY: **(Severe (Grade ≥3) and/or serious hepatotoxicity including all VOD/SOS)** encoded to MedDRA preferred terms (PTs) within the following Standardised MedDRA Query SMQ and PTs**:**

SMQs:
- Cholestasis and jaundice of hepatic origin (SMQ narrow)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ narrow)
- Hepatitis, noninfectious (SMQ narrow)
- Liver related investigations, signs and symptoms (SMQ narrow and broad)

PTs:
Hepatic vein occlusion
Hepatic vein thrombosis
Portal vein thrombosis
Portal vein occlusion
Budd-Chiari syndrome

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

HEAMORRHAGE:
SMQ:
Haemorrhage terms (excluding laboratory terms) (SMQ narrow)

MYELOSUPPRESSION: AEs encoded to MedDRA preferred terms (PTs) within the following SMQ:

- Haematopoietic thrombocytopenia (SMQ narrow and broad)
- Haematopoietic leukopenia (SMQ narrow)
- Haematopoietic erythropenia (SMQ narrow and broad)
- Haematopoietic cytopenias affecting more than one type of blood cell (SMQ narrow)

INFECTIONS: Grade ≥3 AEs and/or serious AEs encoded to MedDRA preferred terms (PTs) within the following SOC and HLT

SOC (General infections):
- Infections and Infestations SOC

HLTs (Lung infections):
- Bacterial lower respiratory tract infections
- Fungal lower respiratory tract infections
- Lower respiratory tract infections NEC

- Respiratory tract infections NEC
- Viral lower respiratory tract infections

INFUSION RELATED REACTIONS (including Anaphylaxis): From start of infusion to within 24 hours of end of infusion:
Include events that occurred from start of infusion to within 24 hours of end of infusion:
SMQ:
- Anaphylactic reaction (SMQ narrow)
- Angioedema (SMQ narrow)
- Hypersensitivity (SMQ narrow)

PT:
- Cytokine release syndrome
- Infusion related reaction
- Chills
- Pyrexia
- Hot flush
- Flushing
- Feeling hot
- Hyperhidrosis
- Dizziness
- Dyspnoea
- Wheezing
- Tachycardia
- Hypotension

Thus only AEs that start within a window according to the treatment exposure records of the start of the GO infusion in terms of date and time to 24 hours after the date and time of the stop of the infusion. Since the AE CRF collects only AE start date and not start time, the AE start date will be compared to the date part only of the exposure window (rather than using imputed time of AE start.

TUMOUR LYSIS SYNDROME:

SMQ:
Tumour lysis syndrome (SMQ narrow)

CARDIAC CONDUCTION:

SMQ Cardiac arrhythmias; Torsade de pointes/QT prolongation (SMQ narrow and broad)