MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 2, Randomized, Open-Label Study to Assess the Safety and Efficacy of GPC-100 and Propranolol With and Without G-CSF for the Mobilization of Stem Cells in Patients With Multiple Myeloma Undergoing Autologous Stem Cell Transplant
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Sponsor:	GPCR Therapeutics, Inc. 38, Nakseongdae-ro, Gwanak-gu, Seoul, Korea 08790
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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	Date
[redacted]	15-Jul-2024
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADRB2	Beta-2 adrenergic receptor
AE	Adverse event
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
ATC	Anatomical therapeutic chemical
BLQ	Below limit of quantification
BM	Bone marrow
BOP2	Bayesian Optimal Phase II
CD	Cluster of differentiation
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRF	Case report form
eCRF	Electronic case report form
CSR	Clinical study report
CTRA	Conserved Transcriptional Response to Adversity
CTCAE	Common Terminology Criteria for Adverse Events
CXCL12	C-X-C motif chemokine ligand 12
CXCR4	Chemokine receptor 4
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire
G-CSF	Granulocyte colony-stimulating factor
HRQoL	Health-Related Quality of Life
ISS	International Staging System
ITT	Intent-to-Treat
IV	Intravenous(ly)
LLOQ	Lower limit of quantitation
LVEF	Left Ventricular Ejection Fraction
MDEs	Myeloma defining events
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MUGA	Multigated Acquisition
NCI	National Cancer Institute
NRS	Numeric Rating Scale
PBMCs	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PK	Pharmacokinetics
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RS	Raw Score
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from GPCR study with protocol number GPC-100-001. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

- To determine the proportion of patients that will achieve $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions following treatment with GPC-100 and propranolol with and without granulocyte colony-stimulating factor (G-CSF).

2.1.2 Secondary Objectives

- To assess safety and tolerability of GPC-100 and propranolol with and without G-CSF in the mobilization of patients with multiple myeloma (MM) undergoing autologous stem cell transplant (ASCT).
- To determine the proportion of patients that will achieve $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions.
- To determine the proportion of patients that will achieve $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session.
- To determine the proportion of patients that will achieve $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session.
- To determine the average number of leukapheresis sessions required to collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg and $\geq 4 \times 10^6$ $CD34^+$ cells/kg.
- To evaluate the pharmacodynamics (PD) following treatment with GPC-100 and propranolol with and without G-CSF by determining circulating $CD34^+$ cell counts in peripheral blood.
- To evaluate the PD changes following treatment with GPC-100 and propranolol with and without G-CSF by determining levels of the chemokine C-X-C motif chemokine ligand 12 (CXCL12) in peripheral blood.
- To assess mean time to absolute neutrophil count (ANC) and platelet count recovery after ASCT.

2.1.3 Exploratory Objectives

- To determine the cell surface expression of beta-2 adrenergic receptor (ADRB2) and chemokine receptor 4 (CXCR4) on peripheral blood mononuclear cells (PBMCs).
- To evaluate cancer cell, stem cell, and immune cell profiles.
- To determine the protein expression of proinflammatory markers in serum.
- To determine the gene expression in PBMCs of a subset of the Conserved Transcriptional Response to Adversity (CTRA) gene program that is activated by chronic stress.
- To determine epinephrine levels in patient serum.

- To evaluate treatment impact on patient Health-Related Quality of Life (HRQoL).
- To evaluate the pharmacokinetics (PK) profile of GPC-100.

2.2 Study Design

2.2.1 Overview

The original design of this study was as a randomized, open-label study. Patients would be screened within 28 days prior to the study drug administration. Upon confirmation of eligibility, up to 40 patients were to be randomly assigned to 1 of 2 treatment arms prior to study drug administration in a 1:1 ratio to either:

- GPC-100 in combination with propranolol alone; or
- GPC-100 in combination with propranolol and G-CSF.

Based on the currently available patient data whereby 4 MM patients did not achieve the primary objective of $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions, the Sponsor made the decision to close the GPC-100 in combination with propranolol alone arm. Given that 5 patients were planned for the first interim efficacy analysis for this arm, the preliminary analysis after 4 patients does not strictly meet the patient enrollment for the interim analysis under the assumptions laid out in the protocol. However, the data suggest that there is a very low probability of achieving the desired efficacy outcomes in the GPC-100 and propranolol alone arm. In this regard, the study design is amended in the Protocol Amendment Version 5.0 to eliminate the randomization scheme so that all patients, up to 30 total, shall be treated with GPC-100 in combination with propranolol and G-CSF. Subsequent sections reflect this change to a single arm study.

To characterize the safety and clinical activity of GPC-100, the study will employ a Bayesian Optimal Phase II (BOP2) design to enroll patients.

All patients will receive 30 mg propranolol (3×10 mg tablets) twice daily at 8:30 AM ($\pm$1 hr) and 4:00 PM ($\pm$1 hr) local time from Days 1 to 8 (and on Days 9-11, if applicable). Patients will administer the first dose of propranolol onsite on Day 1. Patients will be provided with doses of propranolol for administration at time points when they are not otherwise required to be onsite. Sites should regularly contact patients via telephone to confirm propranolol administration for doses administered outside of clinic.

Patients receiving GPC-100 in combination with propranolol and G-CSF will receive subcutaneous injections of 10 μg/kg/day G-CSF at 5:00 PM ($\pm$3 hr) local time on Days 3 to 7. Patients will receive G-CSF injections on Days 8-10 at 5:00 PM ($\pm$3 hr) local time only if they will undergo the optional third day of mobilization/collection (Days 9-11) at the Investigator's discretion and Sponsor's approval for Days 10-11.

On Days 7 and 8 (and on Days 9-11, if applicable), the patient will receive a morning 30 mg propranolol dose (3×10 mg tablets) followed immediately by a 3.14 mg/kg dose of GPC-100 free base (active ingredient) and will start collection of $CD34^+$ stem cells via leukapheresis.

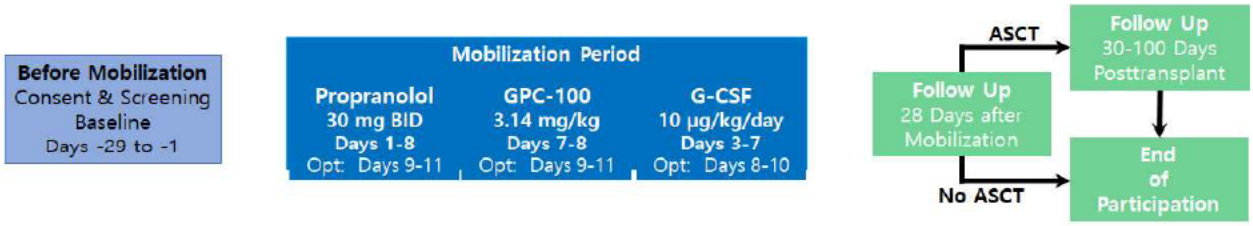
The starting time of leukapheresis is at 45 minutes $\pm$15 minutes after GPC-100 administration. The target number of $CD34^+$ cells is $\geq 2 \times 10^6$ $CD34^+$ cells/kg in the leukapheresis product obtained after 2 leukapheresis sessions.

An optional third day of mobilization/collection (Day 9) will be allowed per the Investigator's discretion for patients who have achieved <4 × 10^6 $CD34^+$ cells/kg after 2 leukapheresis sessions. Sites that have institutional goals to collect a specific number of $CD34^+$ cells/kg may perform optional fourth and fifth days of mobilization/collection (Days 10 and 11, respectively) if a written request is received and approved by the Sponsor.

All patients will attend a safety follow-up visit at 28 days after receiving the last dose of GPC-100. This safety follow-up visit will be the last visit for patients that have not undergone ASCT using the stem cells collected from this study. Patients who have undergone ASCT using the stem cells collected from this study by the 28-day safety follow-up visit will be followed up until 100 days posttransplant. Patients who have undergone ASCT will be assessed during follow-up visits at 30 and 100 days post-transplant.

A diagram of the study design is provided in Figure 1.

Figure 1. Diagram of the Study Design



	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Propranolol 30 mg BID oral	+	+	+	+	+	+	+	+	Opt*	Opt*	Opt*
GPC-100 3.14 mg/kg IV							+	+	Opt*	Opt*	Opt*
G-CSF 10 µg/kg/day SC			+	+	+	+	+	Opt*	Opt*	Opt*	
Apheresis							+	+	Opt*	Opt*	Opt*

*Optional

1. An optional third day of mobilization/collection (Day 9) will be allowed per the Investigator's discretion for patients who have achieved <4 × 10^6 $CD34^+$ cells/kg after 2 leukapheresis sessions.
2. Sites that have institutional goals to collect a specific number of $CD34^+$ cells/kg may perform optional fourth and fifth days of mobilization/collection (Days 10 and 11, respectively) if a written request is received and approved by the Sponsor.
3. Patients will receive G-CSF injections on Days 8-10 only if they will undergo the optional third day of mobilization/collection (Days 9-11) at the Investigator's discretion and with the Sponsor's approval for Days 10-11 of mobilization/collection.

BID = twice daily; D = day; EOS = end of study; IV = intravenous(ly); Opt = optional; SC = subcutaneous(ly).

2.2.2 Randomization and Blinding

The original study design was a randomized, open-label study The revised study design is a single arm study and eliminates the randomization.

This is an open-label study and no blinding is required.

2.2.3 Study Drug

GPC-100 is supplied as a sterile lyophilized powder containing 53 mg of GPC-100 free base (active ingredient) in a 30 mL clear glass vial with rubber stopper. The label amount is 50 mg/vial GPC-100 free base and the product has a 6% overfill to account for vial needle and syringe losses. The inert ingredient is D-mannitol. The contents of the GPC-100 vial should be reconstituted with 26.5 mL of 0.9% sterile saline prior to injection. Each vial should be gently swirled and inspected for complete dissolution of the drug. The final concentration is equivalent to 2.0 mg GPC-100 free base/mL. The calculated volume of reconstituted solution will then be transferred from the vials to the administration container (e.g., an empty intravenous [IV] bag) using aseptic technique.

GPC-100 is to be administered at a dose of 3.14 mg/kg GPC-100 free base via IV infusion. The corresponding volume of the reconstituted GPC-100 solution calculated based on the patient weight will be administered via IV infusion over 15 min. GPC-100 is not to be administered as an IV push or bolus.

2.2.4 Sample Size Determination

A BOP2 design shall be applied in this study. In the original study design, a total of approximately 40 evaluable patients were to be randomized in a 1:1 ratio to either the GPC-100 in combination with propranolol arm or the GPC-100 in combination with propranolol and G-CSF arm. Patients who were randomized but did not receive the study drug (GPC-100) or did not have at least 1 $CD34^+$ stem cell collection via leukapheresis shall be considered not evaluable for efficacy.

According to the BOP2 design, in order to stop arms for futility and limit exposure of additional patients in a given arm in case of lack of sufficient clinical activity is observed, an interim futility analysis shall be conducted for the GPC-100 in combination with propranolol arm after every 5 patients have response data in leukapheresis sessions. For the GPC-100 in combination with propranolol and G-CSF arm, an interim futility analysis shall be conducted after 10 patients have response data in leukapheresis sessions.

The response rates for futility for this study are based on previous data with G-CSF with and without plerixafor in 302 patients with MM.[1] Treatment arms will be considered promising in the population if response rate =0.55 and 0.89, respectively.

For the GPC-100 in combination with propranolol arm, let p_{eff} denote the probability of clinical activity (response rate) and define the null hypothesis H_0: $p_{eff} \leq 0.3$, representing that the treatment is inefficacious. The patient enrollment is to be stopped and it shall be claimed that the treatment is not promising if:

$$\Pr\left(p_{eff} > 0.3 | data\right) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

where n and N denote the interim sample size and maximum sample size, respectively, and λ=0.82 and α=0.86 are design parameters optimized to maximize power under the alternative hypothesis, H_1: p_{eff}=0.55, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a Beta (0.3, 0.7) prior distribution for p_{eff}, the above decision rule corresponds to the stopping boundaries shown in Table 1 and yields a statistical power of 84.50% under H_1.

Table 1. Optimized Stopping Boundaries (GPC-100 in Combination with Propranolol Alone Arm)

Patients Treated	Stop if Responses ≤ #
5	0
10	2

15	5
20	8

Based on Table 1, the interim analysis is to be performed when the number of evaluable patients reaches 5, 10, and 15. When the total number of evaluable patients reaches the maximum sample size of 20, then the null hypothesis will be rejected and it will be concluded that the treatment is acceptable if the number of responses is >8; otherwise, it will be concluded that the treatment is not promising. The go/no-go criteria in Table 1 are nonbinding. Futility analyses are to be done based on availability of data from the first 2 leukapheresis sessions.

The operating characteristics of the design based on 10,000 simulations using shiny app "BOP2" published by MD Anderson Software are presented in Table 2.

Table 2. Operating Characteristics (GPC-100 in Combination with Propranolol Arm)

Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
0.20	94.27	0.89	10.2
0.25	85.98	3.70	11.8
0.30	73.53	10.34	13.4
0.35	58.29	21.94	15.1
0.40	42.45	37.81	16.5
0.45	28.19	55.48	17.7
0.50	16.92	71.83	18.6
0.55	9.09	84.50	19.3
0.60	4.32	92.71	19.6
0.65	1.78	97.13	19.8

The 4 patients assigned to the GPC-100 in combination with propranolol arm did not achieve the primary endpoint of collecting $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions. Outside of the Bayesian framework for this study, if the true probability of response was 0.55, then the probability of observing 0 responses out of 4 patients is 0.041. This indicates a low probability that the observed response rate would occur randomly. Thus, the Sponsor has decided to close this GPC-100 in combination with propranolol arm.

For the GPC-100 in combination with propranolol and G-CSF arm, the null hypothesis, H_0: $p_{eff} \leq 0.7$, and λ=0.86 and α=0.15 are optimized to maximize power under the alternative hypothesis H_1: p_{eff} = 0.89. Assuming a Beta (0.7, 0.3) for p_{eff} and type I error rate at 0.1, the statistical power is 80.70% under H_1.

Table 3. Optimized Stopping Boundaries (GPC-100 in Combination with Propranolol and G-CSF Arm)

Patients Treated	Stop if Responses ≤#
10	7
20	16
G-CSF = granulocyte colony-stimulating factor.	

The interim analysis of futility will be performed when the number of evaluable patients reaches 10. When the total number of evaluable patients reaches the maximum sample size of 20, then the null hypothesis will be rejected and it will be concluded that the treatment is acceptable if the number of responses is >16; otherwise, it will be concluded that the treatment is unacceptable. The go/no-go criteria in Table 3 are nonbinding. Futility analyses will be done based on availability of data from the first 2 leukapheresis sessions.

The operating characteristics of the design based on 10,000 simulations are represented in Table 4.

Table 4. Operating Characteristics (GPC-100 in Combination with Propranolol and G-CSF Arm)

Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
0.50	94.53	0.12	10.5
0.55	90.04	0.45	11.0
0.60	83.27	1.47	11.7
0.65	73.84	4.10	12.6
0.70	61.72	9.95	13.8
0.75	47.44	21.11	15.3
0.80	32.22	38.98	16.8
0.85	17.98	62.22	18.2
0.90	7.02	84.70	19.3

G-CSF = granulocyte colony-stimulating factor.

The 2 patients assigned to the GPC-100 in combination with propranolol and G-CSF arm have achieved the primary endpoint of collecting $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions. Therefore, all subsequent patients are to be enrolled in this arm and futility analysis is to be performed as scheduled.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in the first 2 leukapheresis sessions.

2.3.2 Secondary Efficacy Endpoints

- Percentage of all patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in the first 2 leukapheresis sessions
- Percentage of all patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session out of the first 2 leukapheresis sessions
- Percentage of all patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session out of the first 2 leukapheresis sessions
- Number of leukapheresis sessions required to collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg within all leukapheresis sessions
- Number of leukapheresis sessions required to collect $\geq 4 \times 10^6$ $CD34^+$ cells/kg within all leukapheresis sessions
- Time to neutrophil engraftment defined as the number of days from ASCT to the first day of 3 consecutive measurements of ANC $\geq 0.5 \times 10^9$/L following the stem cell infusion for patients who received ASCT
- Time to platelet engraftment defined as the number of days from ASCT to the first day of 3 consecutive measurements of platelet count $\geq 20 \times 10^9$/L without transfusion in the previous 7 days for patients who received ASCT.

2.3.3 Exploratory Efficacy Endpoints

- Biomarkers:
    - ADRB2 and CXCR4 cell surface expression levels on PBMCs measured by flow cytometry

- Cancer cell, stem cell, and immune cell profiles determined by using flow cytometry
- Protein expression in serum of proinflammatory markers
- Gene expression levels in PBMCs in a subset of the 55 genes of the CTRA gene program
- Epinephrine levels in patient serum.

- HRQoL as measured by the Numeric Rating Scale (NRS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30).

2.3.4 Pharmacokinetic Endpoints

- The PK profile of GPC-100 (PK concentrations and PK parameters as described in Section 3.5.4).

2.3.5 Pharmacodynamic Endpoints

- PD profile of GPC-100 via circulating $CD34^+$ cell counts in peripheral blood and by determining circulating levels of CXCL12 in peripheral blood.

2.3.6 Safety Endpoints

The safety endpoints include the assessment of the incidence and severity of adverse events (AEs), and assessment of changes in safety parameters from baseline (e.g., clinical laboratory parameters, vital signs, and physical examination and 12-lead Electrocardiogram (ECG) findings).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0, in alignment with international data standards for clinical trials. Analysis day will be calculated as (date of clinical event – date of first dose of study drug) + 1 if the date of the event is on or after the date of first dose and as (date of clinical event – date of first dose of study drug) if the date of event is before the date of first dose.

3.1.2 Analysis Visits

All scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). Visit windowing will not be used for handling unscheduled visits. Instead, all unscheduled visits will be assigned a visit name of “Unscheduled”. Such visits will be included in data listings and will contribute to the derivation of baseline or best- or worst-case value where applicable.

Changes in study visit schedules, missed or delayed visits, or patient discontinuations and the relationship to Coronavirus Disease 2019 (COVID-19) will be captured in the electronic case report form (eCRF).

3.1.3 Definition of Baseline

For all variables, the last available, non-missing measurement prior to the first dose of study drug (propranolol, GPC-100, or G-CSF) will be used as the baseline value.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

All individual patient data will be listed as measured.

3.1.5 Hypothesis Testing

The primary efficacy endpoint is the percentage of patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in first 2 leukapheresis sessions. For the GPC-100 in combination with propranolol and G-CSF arm, the null and alternative hypotheses are formulated as:

$$H_0: p_{eff} \leq 0.7$$

$$H_1: p_{eff} > 0.7,$$

where p_{eff} denotes the probability of clinical activity (response rate).

The treatment will be claimed as unacceptable if:

$$\Pr\left(p_{eff} > 0.7 | data\right) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

where n and N denote the interim sample size and maximum sample size; $\lambda = 0.86$ and $\alpha = 0.15$ are design parameters as detailed in section 2.2.4.

3.1.6 Handling of Dropouts and Missing Data

Missing data can have an impact on the interpretation of the trial data. Missing data for the first 2 leukapheresis sessions may be the result of intercurrent event. The handling of these cases for analyses of the primary endpoint and all secondary histological endpoints is discussed in Section 3.4 with Estimand framework. With these exceptions, values for missing data will not be imputed unless specified.

Where appropriate, safety data for patients that did not complete the study will be included in summary statistics. For example, if a patient received study drug, but does not return for follow-up, the patient will be included in a summary of AEs according to the treatment received; otherwise, if the patient is not dosed then they will be excluded from the summary. If safety laboratory results for a patient are missing for any reason at a time point, the patient will be excluded from the calculation of summary statistics for that time point. If the patient is missing a baseline value, then the patient will be excluded from the calculation of summary statistics for the baseline value and the change from baseline values.

Values for missing safety laboratory data or vital signs data will not be imputed.

Missing or partially missing start or end dates for AEs and medications will be imputed based on the conventions described in Appendix C. The purpose of the imputation for AEs is to determine if an AE with an incomplete date is treatment-emergent, as defined in Section 3.7.1. Similarly, the purpose of the imputation for medications is to determine if a medication with an incomplete date was given concomitantly with study drug, as defined in Section 3.3.8.

Missing or partially missing dates for initial disease diagnosis will be imputed. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 01. If only

the year is provided, then the missing month and day are imputed as January 01 for the calculation. If the date is completely missing, no imputation will be performed.

Listings of the AEs, prior medications, concomitant medications and medical history will present the actual partial dates and the imputed dates will not be shown.

3.2 Analysis Sets

3.2.1 Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set is defined as all randomized/enrolled patients.

3.2.2 Efficacy Analysis Set

Efficacy Analysis Set is defined as randomized/enrolled patients who received at least 1 dose of GPC-100 and had at least 1 $CD34^+$ stem cell collection via leukapheresis.

The Efficacy Analysis Set will be used for efficacy analyses.

3.2.3 Safety Analysis Set

Safety Analysis Set is defined as all enrolled patients who received at least 1 dose of propranolol, G-CSF, or GPC-100.

All safety analyses will be based on the Safety Analysis Set and actual treatment received if it differs from the randomized treatment.

3.2.4 PD Analysis Set

PD Analysis Set is defined as all enrolled patients who received at least 1 dose of GPC-100 and had the baseline assessment and, where applicable, at least 1 postbaseline assessment for at least one PD biomarker.

Analysis of PD biomarkers will be performed based on the PD Analysis Set.

3.2.5 PK Analysis Set

The PK Analysis Set is defined as all enrolled patients included in the Safety Analysis Set who received at least 1 dose of GPC-100 and have at least 1 PK measure of GPC-100.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized/enrolled will be summarized in total based on all screened patients. Reasons for screen failure will also be summarized.

Patient disposition information will be summarized by arm and in total based on ITT Analysis Set. The following disposition categories will be included:

- Patients who were treated
- Patients who received ASCT
- Patients who completed the study
- Patients who discontinued from the study.

For patients who discontinued from the study after randomization/enrollment, a summary will be provided by reason of discontinuation. The number and percentage of patients who discontinued early from the study due to COVID-19 impact will be summarized.

A listing will be provided that indicates each patient's inclusion/exclusion reason(s) from the specified analysis set.

All disposition data will be listed by patient.

3.3.2 Protocol Deviations

Protocol deviations will be defined in the Protocol Deviation Plan. Protocol deviations in study procedures due to COVID-19 will be reported in CSR. Counts and percentages of patients with CSR reportable protocol deviations by deviation category and by COVID-19 relationship will be summarized by treatment arm and in total based on ITT Analysis Set.

All protocol deviations will be listed by patient.

3.3.3 Analysis Sets

Counts and percentages of patients in each analysis set will be summarized by treatment arm and in total based on all randomized/enrolled patients.

3.3.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment arm and in total for ITT Analysis Set, Efficacy Analysis Set, and Safety Analysis Set. If two analyses sets are identical, the table will be presented only once.

The following baseline variables will be summarized:

- Age (years) and Age Categories (<65, ≥65)
- Sex (Male, Female)
- Race
- Ethnicity
- Height (cm)
- Baseline weight (kg)
- Body Surface Area (BSA) (m^2)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Systolic Blood Pressure (mmHg) at Baseline
- Diastolic Blood Pressure (mmHg) at Baseline
- Heart rate at Baseline

All demographic and baseline characteristics data will be listed by patient.

3.3.5 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment arm and in total for the ITT Analysis Set, Efficacy Analysis Set, and Safety Analysis Set. If two analyses sets are identical, the table will be presented only once.

- Time from initial multiple myeloma diagnosis to randomization/enrollment (months)

- Time from most recent relapse or refractory diagnosis to randomization/enrollment (months)
- International Staging System (ISS) stage at diagnosis (I, II, III, Unknown)
- Light chain myeloma (Yes, No)
- Plasmacytoma (Yes, No)
- Cytogenetic risk category (High, Standard, Unknown)
- Percent of Bone Marrow (BM) irradiated within 5 years prior to Day 1 (<25%, >=25%)
- Any evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder (Yes, No)
    - Type of evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder (Hypercalcemia, Renal insufficiency, Anemia, Bone lesions).
- Any biomarkers of malignancy (myeloma defining events (MDEs)) (Yes, No)
    - Type of Biomarkers of malignancy (60% or greater clonal plasma cells on bone marrow examination, serum involved / uninvolved free light chain ratio of 100 or greater, more than one focal lesion on MRI that is at least 5mm or greater in size)
- Mutation test
    - del (17p) (Present, Absent, Unknown)
    - TP53 status (Mutated, Unmutated, Unknown)
    - t(4;14) (Present, Absent, Unknown)
    - t(14;16) (Present, Absent, Unknown)
    - t(11;14) (Present, Absent, Unknown)
    - t(14;20) (Present, Absent, Unknown)
    - Gain 1q (+1q) (Present, Absent, Unknown)
    - Other relevant test result (Yes, No)

All primary cancer history will be listed by patient.

3.3.6 Prior Cancer Treatment

The following variables will be summarized for the ITT Analysis Set, Efficacy Analysis Set, and Safety Analysis Set by treatment arm and in total. If two analyses sets are identical, the table will be presented only once.

- Line of the last prior cancer therapy, best response of the last prior cancer therapy
- Prior Cancer Radiation Therapy (yes or no)
- Prior Cancer Surgery (yes or no)
- Prior Cell Transplant/Therapy (yes or no) and type of prior cell transplant/therapy.

All prior cancer treatment will be listed by patient.

3.3.7 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) v25.1.

Counts and percentages of patients with medical history by system organ class and preferred term will be summarized by treatment arm and in total based on ITT Analysis Set.

Counts and percentages of patients with cardiovascular disease history will be summarized by treatment arm and in total based on ITT Analysis Set. The events of cardiovascular disease will be identified by cardiac arrhythmias, cardiac failure, cardiomyopathy, ischeamic heart disease, hypertension and shock-associated circulatory or cardiac conditions (excl torsade de pointes) SMQs (Standardized MedDRA Queries).

Listing will present system organ class, preferred term, and verbatim text by patient.

3.3.8 Prior and Concomitant Medications

All medications taken by patients will be recorded in the patient's electronic case report form (eCRF).

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using World Health Organization (WHO) Drug Global B3 Sep 2022. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started after the first dose of study drug). Medications with missing or partially missing start or end dates will be handled according to the conventions described in Appendix C.

Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment arm and in total based on the Safety Analysis Set.

The use of any prior medication or concomitant medication will be listed for all randomized/enrolled patients.

3.3.9 Concomitant Medical Procedures

All concomitant medical procedures data will be listed by patient.

3.3.10 Prior and Concomitant Transfusions

Prior transfusions are transfusions used and stopped before the first dose of study drug. Concomitant transfusions are transfusions taken any time from the start of the first dose of study drug.

The type and reason of prior and concomitant transfusions will be summarized by treatment arm and in total based on Safety Analysis Set.

Listing will be provided for all randomized/enrolled patients.

3.3.11 Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized and listed for the Safety Analysis Set.

Days of exposure to all study drug (propranolol, GPC-100, or G-CSF) will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a patient was exposed to study drug and therefore does not take study drug interruptions into account.

3.3.11.1 GPC-100

GPC-100 is to be administered at a dose of 3.14 mg/kg GPC-100 free base via IV infusion. The corresponding volume of the reconstituted GPC-100 solution calculated based on the patient weight will be administered via IV infusion over 15 min.

The following summaries of study drug exposure to GPC-100 will be presented for patients who received GPC-100:

- Number of doses administered
- Percentage of dose administered (total actual dose (mg)/total planned dose (mg))
- Frequency and percentage of patients with infusion interruptions and type of reasons (AE, Other)
- Planned dose intensity (mg/kg) per day that is defined as the cumulative of planned dose of GPC-100 (mg/kg) divided by the number of days with GPC-100 administered
- Actual dose intensity (mg/kg) per day that is defined as the cumulative dose of GPC-100 (mg/kg) administered divided by the number of days with GPC-100 administered
- Relative dose intensity (%) is defined as actual dose intensity divided by planned dose intensity and multiplied by 100.

Note that for patients who discontinued treatment, the total/cumulative planned dose should be based on the number of doses expected until discontinuation.

3.3.11.2 Propranolol

All patients will receive 30 mg propranolol (3 × 10 mg tablets) twice daily at 8:30 AM (±1 hr) and 4:00 PM (±1 hr) local time from Days 1 to 8 (and on Days 9-11, if applicable). Patients will administer the first dose of propranolol onsite on Day 1. Patients will be provided with doses of propranolol for administration at time points when they are not otherwise required to be onsite.

The following summaries of study drug exposure to Propranolol will be presented for patients who received Propranolol:

- Duration of treatment (days)
- Duration of treatment categories (≤ 6, >6 and ≤8, >8 and ≤11 (Days))
- Compliance rate and compliance categories (<80%, 80%-100%, >100%)

$$\text{Compliance rate (\%)} = \frac{\text{Total number of tablets administered}}{6 \times (\text{Total number of medication days in the treatment period})} \times 100$$

Note that for patients who discontinued treatment, the total number of medication days in the treatment period should be the total number of medication days from the first dose to treatment discontinuation.

3.3.11.3 G-CSF

Only patients randomized/enrolled to the treatment arm receiving GPC-100 in combination with propranolol and G-CSF will receive subcutaneous injections of 10 µg/kg/day G-CSF at 5:00 PM (±3 hr) local time on Days 3 to 7. Patients in this arm will receive G-CSF injections on Days 8-10 at 5:00 PM (±3 hr) local time only if they will undergo the optional days of mobilization/collection (Days 9-11) at the Investigator's discretion and Sponsor's approval for Days 10-11.

The following summaries of study drug exposure to G-CSF will be presented for patients who received G-CSF:

- Number of doses administered
- Percentage of dose administered (total actual dose (mg)/total planned dose (mg))
- Frequency and percentage of patients with total dose not administered and type of reasons (AE, Other)
- Planned dose intensity (μg/kg) per day that is defined as the cumulative of planned dose of G-CSF (μg/kg) divided by the number of days with G-CSF administered
- Actual dose intensity (μg/kg) per day that is defined as the cumulative dose of G-CSF (μg/kg) administered divided by the number of days with G-CSF administered
- Relative dose intensity (%) is defined as actual dose intensity divided by planned dose intensity and multiplied by 100.

Note that for patients who discontinued treatment, the total/cumulative planned dose should be based on the number of doses expected until discontinuation.

All study drug administration data will be listed by patient.

3.4 Efficacy Assessment

Efficacy data will be summarized by randomized/enrolled arms based on the Efficacy Analysis Set. Additionally, supportive analyses will be performed based on the ITT Set for the primary and key secondary efficacy endpoints.

3.4.1 Primary Efficacy Endpoints

The primary efficacy endpoint will be the percentage of patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in the first 2 leukapheresis sessions. Each patient's $CD34^+$ cell counts will be calculated as the sum of $CD34^+$ cells collected from the first 2 leukapheresis sessions by treatment arm.

3.4.1.1 Primary Endpoints in Estimand Framework

The primary endpoints in Estimand framework of this study is defined as follows:

1. Treatment: GPC-100 in combination with propranolol and G-CSF
2. Population: patients with multiple myeloma undergoing autologous stem cell transplant as defined by the inclusion/exclusion criteria
3. Endpoint: the percentage of patients who collected a total of $\geq 2 \times 10^6$ $CD34^+$ cells/kg in first 2 leukapheresis sessions combined.
4. Inter-current events and their corresponding approaches:

Intercurrent Event	**Status**
Early discontinuation after first leukapheresis session	Patient's $CD34^+$ cell counts will be calculated based on the first leukapheresis only.

5. Population level summary: the proportion of patients who collected a total of $\geq 2 \times 10^6$ $CD34^+$ cells/kg in first 2 leukapheresis sessions.

3.4.1.2 Primary Analysis

Counts and percentages of patients who collected a total of $\geq 2 \times 10^6$ $CD34^+$ cells/kg in the first 2 leukapheresis sessions will be provided. The 95% and 80% 2-sided exact binomial confidence intervals (CIs) for the proportion of patients who mobilized the targeted collection goal will be calculated using the Clopper-Pearson Exact method.

The analysis will be performed using Efficacy Analysis Set. No Imputation will be performed.

3.4.1.3 Sensitivity Analysis

The primary endpoint will be repeated in the ITT analysis set where the first 2 missing leukapheresis sessions will be imputed as non-responders and by using multiple imputation (MI) method via logistic regression under the assumption of missing at random (MAR).

Multiple Imputation Method:

The multiple imputation procedure will be conducted by two parts, PROC MI and PROC MIANALYZE:

- Multiple imputation (using SAS® PROC MI). Missing leukapheresis sessions are imputed 100 times to generate 100 complete data sets. The imputed values will be obtained using a logistic model including the patient demographics and baseline disease characteristics (age (<median, ≥median), baseline weight (<median, ≥median) and time (months) from initial MM diagnosis to randomization/enrollment).

  Sample SAS code is provided below:

```
**********************************************************************
 TREATMENT: Keep only (GPC-100 + propranolol + G-CSF) treatment arm
 Age: 1 (<median), 2(≥median)
 Weight: 1 (<median), 2 (≥median)
 Time: months from initial MM diagnosis to randomization/enrollment
 Response: Y (collected 2 × 10⁶ CD34⁺ cells/kg in first 2 leukapheresis
           sessions), N (not collected 2 × 10⁶ CD34⁺ cells/kg in first 2
           leukapheresis sessions)
**********************************************************************
proc mi data= data seed= 1234  nimpute=100 out=outmi1 noprint;
  class Age Weight Response;
  monotone logistic(Response = Age Weight Time /likelihood=augment);
  var Age Weight Time Response;
run;
```

- Analysis of imputed datasets. Imputed datasets will be analyzed separately using the PROC FREQ to calculate the proportion estimates and their asymptotic standard errors.

  Sample SAS code is provided below:

```
********* Estimate proportions of responders in treatment arm*****

proc freq data = out_mi;
  by _Imputation_;
  tables Response / binomial alpha = 0.05 ;
  ods output BINOMIAL = prop;
run ;

*******Combine estimated proportion of responders standard errors******
data prop_trt;
```

```
  merge
    prop(where = (Label1="Proportion")
    keep = _Imputation_ nValue1 Label1
    rename = (nValue1=prop))
    prop(where = (Label1="ASE")
    keep = _Imputation_ nValue1 Label1
    rename = (nValue1= prop_se));
    by _Imputation_;
run;
```

- Combination estimated across imputed datasets (using SAS PROC MINANLYZE). The results from the 100 completed data sets obtained in the analysis step are combined for the inference. The pooled estimate of the response rate along with 2-sided 95% CI and 80% CI will be obtained using the method developed by Rubin.[2]

  Sample SAS code is provided below:

```
proc mianalyze data = prop_trt;
  modeleffects prop;
  stderr prop_se;
  ods output parameterestimates = out_est;
run;
```

3.4.2 Secondary Efficacy Endpoints

The Estimand attributes for the following secondary efficacy endpoints are defined in the same manner as that for the primary endpoint in Section 13.4.1.1.

- Percentage of all patients who collected a total of $\geq 4 \times 10^6$ CD34$^+$ cells/kg in the first 2 leukapheresis sessions
- Percentage of all patients who collected $\geq 2 \times 10^6$ CD34$^+$ cells/kg in a single leukapheresis session within the first 2 leukapheresis sessions
- Percentage of all patients who collected $\geq 4 \times 10^6$ CD34$^+$ cells/kg in a single leukapheresis session within the first 2 leukapheresis sessions

Counts and percentage of patients will be provided. The 95% and 80% 2-sided CIs for the proportion of patients who mobilized the targeted collection goal will be calculated using the Clopper-Pearson Exact method. The analysis will be performed using Efficacy Analysis Set. No Imputation will be performed. Analyses of the secondary endpoints above will be repeated in the ITT analysis set where patients with no leukapheresis session will be excluded from analysis.

Other secondary efficacy endpoints as follows will be summarized descriptively in Efficacy Analysis Set for GPC-100 in combination with propranolol and G-CSF arm :

- Number of leukapheresis sessions required to collect 2×10^6 CD34$^+$ cells/kg
- Number of leukapheresis sessions required to collect 4×10^6 CD34$^+$ cells/kg
- Time to neutrophil engraftment defined as the number of days from ASCT to the first day of 3 consecutive measurements of ANC $\geq 0.5 \times 10^9$/L following the stem cell infusion for patients who received ASCT. This summary will be presented for only those patients who achieve engraftment.

- Time to platelet engraftment defined as the number of days from ASCT to the first day of 3 consecutive measurements of platelet count $\geq 20 \times 10^9$/L without transfusion in the previous 7 days for patients who received ASCT. This summary will be presented for only those patients who achieve engraftment.

3.4.3 Exploratory Efficacy Endpoints

The change from baseline for the following exploratory efficacy endpoints will be summarized descriptively in Efficacy Analysis Set for GPC-100 in combination with propranolol and G-CSF arm. The exploratory biomarker assessment will be performed at Baseline and Days 7, 8, and optional Day 9. If the quantitative data were reported as "< X", i.e., below the lower limit of quantification, or "> X", i.e., above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries.

- ADRB2 and CXCR4 cell surface expression levels on PBMCs measured by flow cytometry
- Cancer cell, stem cell, and immune cell profiles determined by using flow cytometry
- Protein expression in serum of proinflammatory markers
- Gene expression levels in PBMCs in a subset of the 55 genes of the CTRA gene program
- Epinephrine levels in patient serum.

3.4.4 Health-Related Quality of Life

The endpoint is as follows:

- HRQoL as measured by the NRS and the EORTC QLQ-C30.

The NRS includes a ten-level score, from 0 indicating no pain to 10 indicating worst possible pain.

The EORTC QLQ-C30 includes five functional scales, three symptom scales, a global health status and six single items. All the scales and single-item measures range in score from 0 to 100.

	Number of Items	Item Range	Version 3.0 Item Numbers
Global health status/ QoL			
Global health status	2	6	29, 30
Functional scales			
Physical functioning	5	3	1 to 5
Role functioning	2	3	6, 7
Emotional functioning	4	3	21 to 24
Cognitive functioning	2	3	20, 25
Social functioning	2	3	26, 27
Symptom scales / items			
Fatigue	3	3	10, 12, 18
Nausea and vomiting	2	3	14, 15
Pain	2	3	9, 19
Dyspnoea	1	3	8
Insomnia	1	3	11
Appetite loss	1	3	13
Constipation	1	3	16
Diarrhoea	1	3	17
Financial difficulties	1	3	28

The principle for scoring these scales:

1. Estimate the average of the items that contribute to the scale; this is the Raw Score (RS).

Raw scores for the symptom, functional, and global health status/QoL scales are calculated by taking the mean score of the items composing the scale. Raw scale scores are computed for a patient at time points for which at least half of the items composing the scale are non-missing. If less than half of the items are non-missing, the scale is considered to be missing at that time point for the patient.

2. Use a linear transformation to standardize the RS, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms

   Function scales: $S = 100 \times \left\{1 - \frac{(RS-1)}{Range}\right\}$

   Symptom scale/ items/ Global health status: $S = 100 \times \left\{\frac{(RS-1)}{Range}\right\}$

The change from baseline for NRS and all the scales for EORTC QLQ-C30 will be summarized descriptively in Efficacy Analysis Set for GPC-100 in combination with propranolol and G-CSF arm. NRS will be measured at Baseline, Day 1, 2, 3, 4, 5, 6 and 7, and safety follow up duration. EORTC QLQ-C30 will be collected at Baseline, Day 7 and safety follow up duration.

3.5 Pharmacokinetic Assessment

3.5.1 Sample Collections for Pharmacokinetic Analysis

The PK sampling for Day 7 and Day 8 is detailed in Table 5:

Table 5. Pharmacokinetic Sampling Timepoints

Timepoint	Predose	First GPC-100 Dose	1 hr Postdose	2 hr Postdose	3 hr Postdose	4 hr Postdose	5 hr Postdose	6 hr Postdose	23 hr Postdose	24 hr Postdose
Collection Window (±min)			±15	±15	±15	±15	±15	±15	±15	±15
GPC-100 administration		X								
PK	X[a]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]	X[b,c]	X[d]
CD34+ assessment in peripheral blood	X[a]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]		
CXCL12	X[a]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]		

a. The predose sample will be collected up to 2 hr before administration of the first dose of GPC-100.
b. In the instance where collection would significantly interfere with ongoing leukapheresis procedure for the 1, 2, 3, 4, and 6 hr postdose timepoints, the sample should be obtained as close to the timepoint as feasible.
c. Collection of the 6 hr and 23 hr postdose timepoint will be optional and should be performed if the patient is available onsite during the collection window for this timepoint.
d. Patients will need to come into the clinic for collection of the PK sample at 24 hr (±15 min) postdose following receipt of the first dose of GPC-100. Timing of PK sample collection should precede the administration of the second dose of GPC-100.

PK = pharmacokinetic(s).

3.5.2 Handling Missing or Below the Lower Limit of Quantification Data

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the scheduled time point may be used for the calculation of PK parameters.

In cases of missing pre-dose concentrations for each treatment on Day 7, the missing components may be assumed as zero.

For the individual concentration and PK parameter calculation of each treatment, the following rules will be applied:

- If one or more Below Limit of Quantification (BLQ) values occur before the first measurable concentration, they will be assigned a value of zero.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be omitted (set to missing).
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).

For the concentration summary and mean concentration plot preparation of each treatment, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the patients have valid values (i.e., quantifiable and not missing) at this time point for each treatment.
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to missing.
- BLQ values will be set to zero.

3.5.3 Pharmacokinetic Concentration

Individual plasma concentrations of GPC-100 will be summarized by treatment arm at each nominal time point for the PK Analysis Set descriptively. Individual plasma concentrations will also be listed for the PK Population.

Individual plasma concentration will be plotted by treatment arm on a linear and semi-log scale against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by treatment arm, when available. LLOQ will be plotted as a reference line in both instances.

Actual sampling times that are outside the sampling time windows may be excluded from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting.

3.5.4 Pharmacokinetic Parameters

The following plasma PK parameters of GPC-100 will be determined if feasible for Day 7 and Day 8 using non-compartmental methods as appropriate:

Parameters	**Description**
C_{max}	Maximum plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than one time point, C_{max} is defined as the first maximum value
T_{max}	Time to C_{max}; If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.

λz	First-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using points in the terminal log-linear phase.
$t_{½}$	First-order terminal elimination half-life; calculated as ln(2)/λz
AUC_{0-t}	Area under the plasma concentration vs time curve (AUC) from pre-dose (time 0) to the last quantifiable plasma concentration (C_{last})
AUC_{0-4}	Area under the plasma concentration vs time curve (AUC) from pre-dose (time 0) to the 4-hour post-dose concentration
AUC_{0-24}	Area under the plasma concentration vs time curve (AUC) from pre-dose (time 0) to the 24-hour post-dose concentration
AUC_{0-inf}	AUC from time 0 to infinity; calculated as (AUC_{0-t} + C_{last}/λz)
$AUC_{\%extrap}$	Percent of AUC_{0-inf} extrapolated, represented as (1 - AUC_{0-t}/AUC_{0-inf})×100
CL	Total plasma clearance after IV administration; calculated as Dose/AUC_{0-inf}
Vz	Volume of distribution during terminal elimination phase after IV administration; calculated as Dose/(λz×AUC_{0-inf})

Actual collection times will be used in PK parameter calculations. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in Pheonix WinNonlin) will be used in the computation of all AUC values. In order to estimate the apparent first-order terminal elimination constant, λz, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate λz. The constant λz will not be assigned if one of the following occurs:

1. The terminal elimination phase is not linear (as it appears on a semi-logarithmic scale).
2. The terminal elimination rate constant indicates a positive slope (λz > 0).
3. T_{max} is one of the three last data points.

The constant λz and its derived parameters will be listed but excluded from statistical analysis if one of the following occurs:

1. The adjusted regression coefficient (R^2) is less than 0.8.
2. The $AUC_{\%extrap}$ exceeds 20%.

No value for λz, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL, Vz, or $t_{½}$ will be reported for cases that do not exhibit an acceptable terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for patients with 2 or fewer detectable concentrations in their PK profile (Cmax and Tmax may be reported based on two quantifiable concentrations if all other samples in a profile are BLQ. A minimum of 3 quantifiable concentrations is recommended to report AUCs.).

3.6 Pharmacodynamic Assessment

The circulating $CD34^+$ cell counts in peripheral blood and the levels of the chemokine CXCL12 in peripheral blood following treatment for the PD Analysis Set will be summarized by treatment arm as data is available. Individual PD data will be presented in a data listing.

3.7 Safety Assessment

All safety data will be listed and summarized by treatment arm based on Safety Analysis Set. No statistical hypothesis testing will be performed.

3.7.1 Adverse Events

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA v25.1. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug (propranolol, GPC-100 or G-CSF). Missing or partially missing start and end dates for AEs will be handled according to the conventions described in Appendix C. AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- Any TEAEs (overall and by maximum severity). AEs with missing severity will be excluded from the presentation by maximum severity.
- Any study drug (propranolol, GPC-100 or G-CSF) related TEAEs (overall and by maximum severity). Missing relationship to study drug will be considered as related.
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of propranolol
- Any TEAEs leading to discontinuation of GPC-100
- Any TEAEs leading to discontinuation of G-CSF

TEAEs by system organ class and preferred term will be also presented by mobilization period (Day 1 to the last day of mobilization [inclusive]) and safety follow up period for patients who

received ASCT and safety follow up period for patients who did not receive ASCT, respectively. Safety follow up period is defined as the period from the last day of mobilization (exclusive) to the end of study.

Counts and percentages of patients (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings including verbatim term, preferred term, system organ class and NCI CTCAE grade will be provided by patient for all AEs. All deaths will be listed.

3.7.2 Clinical Laboratory Tests

Biochemistry, hematology, coagulation and other samples that will be collected for clinical laboratory tests are outlined in Appendix B and measured at Baseline, Days 6, 7 and 8 and safety follow up duration.

All laboratory parameters will be summarized descriptively by value at Baseline, Days 6, 7 and 8 and safety follow up duration. The incidence of abnormalities (as defined by normal ranges) at baseline, at each scheduled time-point of post-baseline and any post-baseline will be summarized with counts and percentages of patients.

The incidence of worst post-baseline lab abnormalities may be summarized with frequencies and percentages of patients for selected parameters (Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine, and total bilirubin) using the grading scheme in the NCI CTCAE Version 5.0. detailed in Appendix D.

All clinical safety laboratory data will be listed.

3.7.3 Vital Signs

Height, body surface area and peripheral oxygen saturation will be measured at Screening.

Values and change from baseline will be summarized for the vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate), which will be measured at Baseline, Day 7 and Day 8, and safety follow up duration.

The vital sign assessment will be listed.

3.7.4 Electrocardiograms

Triplicate 12-lead ECGs measurements including heart rate, QRS duration, and PR, RR, QT and QTcF intervals will be performed at Baseline, Day 7 and Day 8, and safety follow up duration. If QTcF is not reported, Frederica's correction to the reported QT interval will be derived for all patients and timepoints as follows:

$$QTcF = QT / (RR)^{1/3}, \text{ where } RR = 60 / VR.$$

All of the last three 12-lead ECGs measurements prior to the first dose of study drug are defined as Baseline measurement, and the mean of the three measurements is defined as the Baseline value. If only one or two measurements of triplicate are available, the single measurement or average of the two measurements will be used for analysis. Value and change from Baseline to each visit for ECGs will be summarized descriptively for each arm. Triplicate measurements will be averaged prior to summary. Additionally, overall ECG interpretation will be summarized with count and percentage by visit.

QTcF will be summarized with count and percentage by visit for the following categories:

- ≤450 msec
- >450 and ≤480 msec
- >480 and ≤500 msec
- >500 msec
- QTcF change from baseline >30 msec
- QTcF change from baseline >60 msec

Listing for ECGs data will be provided.

3.7.5 ECOG Performance Status

ECOG performance status will be collected at Baseline, Days 7, and 8 and safety follow up duration.

ECOG data will be summarized with counts and percentages of patients by visit for each treatment arm. ECOG data will be listed by patient.

3.7.6 Left Ventricular Ejection Fraction (LVEF) Assessment

Echocardiogram or multigated acquisition (MUGA) will be performed at Screening and will be listed.

4 INTERIM ANALYSIS

The interim analysis of futility will be performed based on availability of response data according to the BOP2 design detailed in Section 2.2.4.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Per the section 9.2.3 of protocol amendment version 5.0, the efficacy analysis should be conducted on all the patients in the Efficacy Analysis Set. However, the estimand framework in section 9.2.2 requires only the GPC-100 in combination with propranolol and G-CSF treatment arm. Therefore, the closed arm of GPC-100 in combination with propranolol alone is excluded in the efficacy analysis but will be included in the listings. In the event of minor changes or inconsistencies between the planned statistical analyses in the SAP and the protocol, the SAP should take precedence.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient identification and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

PK parameters will be calculated via SAS® and confirmed with the results of Phoenix WinNonlin™ (version 8.3 or higher).

APPENDIX A: REFERENCES

1. DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood 2009 (113:5720-5726).

2. Rubin, D.B. Multiple Imputation for Nonresponse in Surveys 1987. John Wiley & Sons Inc., New York.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Biochemistry Panel

Alanine aminotransferase
Albumin
Alkaline phosphatase
Amylase
Aspartate aminotransferase
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatine kinase
Creatinine
Creatinine clearance [1]
Estimated glomerular filtration rate
Gamma-glutamyl transferase
Glucose
Inorganic phosphorus
Lactate dehydrogenase
Lipase
Potassium
Sodium
Total bilirubin
Total protein
Uric acid

1. Creatinine clearance will be calculated using the Cockcroft-Gault formula.

Endocrinology

Human chorionic gonadotropin [1]

1. For female patients that are <1 year postmenopausal and not surgically sterile, a serum pregnancy test will be conducted during Visit 2 that will be analyzed locally. A urine pregnancy test will be conducted and analyzed locally at the other visits. If any urine pregnancy test result is positive, a serum pregnancy test should be completed.

Hematology

Hematocrit
Hemoglobin
Platelets
Red blood cell count
White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

International normalized ratio
Partial thromboplastin time
Prothrombin time

Urinalysis

Bilirubin
Blood
Glucose
Ketones
Leukocyte esterase
Microscopy [1]
Nitrite
pH
Protein
Specific gravity
Urobilinogen

1. Microscopy is performed only as needed based on positive dipstick test results.

APPENDIX C: ALGORITHMS FOR HANDLING PARTIAL DATES

- **Treatment-Emergent Adverse Events**

AE Start Date	AE Stop Date	Action
Known	Known	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
	Missing or Unknown	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
Partial, but the known date components show that it cannot be on or after study drug start date	Known	Not TEAE
	Partial	Not TEAE
	Missing or Unknown	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day is unknown or 31 Dec if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing or Unknown	Assumed TEAE
Missing or Unknown	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day is unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing or Unknown	Assumed TEAE

- **Concomitant Medications (CM)**

CM Stop Date	Action
Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date assign as CONCOMITANT
Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31 Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date assign as CONCOMITANT
Missing or Unknown	If stop date is missing, then assign as CONCOMITANT

APPENDIX D: CTCAE V5.0

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Biochemistry	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
	Total bilirubin increased	Total Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	Total Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	Total Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	Total Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal

Note: The grading criterion for baseline will be applied to post-baseline assessments only. A value is considered abnormal at baseline if it is abnormal in the direction of the toxicity (i.e., a high creatinine at baseline would be considered abnormal; a low value would not.).