# CLINICAL STUDY PROTOCOL

## 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

**Investigational Product:** GPC-100 (Burixafor/formerly TG-0054)
**Protocol Number:** GPC-100-001

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| | |
|---|---|
| Medical Expert: | [redacted] |

# SIGNATURE PAGE

**STUDY 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**

I, the undersigned, have read this Protocol and agree that it contains all necessary information required to conduct the study.

Signature



GPCR Therapeutics, Inc.

Date

February 28, 2024

# INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this Protocol. I approve this document, and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this Protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this Protocol and access to all information furnished by GPCR Therapeutics, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to GPCR Therapeutics, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by GPCR Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regional regulations.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

# SYNOPSIS

**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

**PROTOCOL NUMBER:** GPC-100-001

**IND Number:** 077253

**INVESTIGATIONAL PRODUCT:** GPC-100 (Burixafor/formerly TG-0054)

**PHASE:** 2a

**INDICATION:** Mobilization of stem cells in patients with multiple myeloma (MM) undergoing autologous stem cell transplant (ASCT)

**OBJECTIVES:**

The primary objective of this study is 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).

The secondary objectives of this study are the following:

- To assess safety and tolerability of GPC-100 and propranolol with and without G-CSF in the mobilization of patients with MM undergoing 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 CXCL12 in peripheral blood; and
- To assess mean time to absolute neutrophil count (ANC) and platelet count recovery after ASCT.

The exploratory objectives of this study are the following:

- 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); and
- To evaluate the pharmacokinetic (PK) profile of GPC-100.

**POPULATION:**

**Inclusion Criteria**

To be eligible to participate in this study, patients must meet all the following criteria:

1. Male or female, ≥18 years of age;
2. Patients with diagnosis of MM per the International Myeloma Working Group criteria;
3. Eligible for ASCT at the Investigator's discretion;
4. >4 weeks since completion of last cycle of chemotherapy prior to the first day of leukapheresis;
5. Patient must be on first or second complete response (CR), Very Good Partial Response (VGPR) or partial response (PR);
6. Eastern Cooperative Oncology Group performance status of 0 or 1;
7. Systolic blood pressure (SBP) 100 – 160 mmHg inclusive, and diastolic blood pressure (DBP) 60 - 100 mmHg inclusive;
8. ANC $\geq 1.0 \times 10^9$/L on Screening laboratory assessments;
9. Platelet count $\geq 100 \times 10^9$/L on Screening laboratory assessments;
10. Creatinine clearance ≥30 ml/min, as calculated according to the Cockcroft-Gault formula;
11. Aspartate aminotransferase and alanine aminotransferase $\leq 2 \times$ upper limit of normal (ULN) and total bilirubin $\leq 1.5 \times$ ULN on Screening laboratory assessments;
12. White blood cell (WBC) counts of $\geq 2.5 \times 10^9$/L on Screening laboratory assessments;
13. Adequate cardiac function measured by left ventricular ejection fraction (LVEF) ≥50% on a historical imaging test (e.g. echocardiogram, cardiovascular magnetic resonance imaging, computed tomography angiography or multigated acquisition scan) within 6 months prior to screening. If no historical imaging test result is available, an imaging test is required during screening to confirm LVEF ≥50%.

14. Females of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to first dose of propranolol or be of non-childbearing potential. Non-childbearing potential is defined by one of the following criteria:
15. At least 1 year postmenopausal without an alternative medical cause. A follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient; or
16. Surgically sterile

    Females of childbearing potential must use a highly effective method of contraception for the course of the study, or agree to be abstinent, from 14 days prior to the first dose of propranolol through 3 months after the last dose of GPC-100. Highly effective methods of contraception include (1) oral, injected, or implanted hormonal methods of contraception, (2) intrauterine device, (3) intrauterine hormone releasing system, (4) bilateral tubal occlusion, (5) vasectomized partner with verified absence of sperm in ejaculate post-vasectomy. Barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception. If used, this method must be used in combination with another acceptable method listed above.
17. Males who have a female partner of childbearing potential must agree to use a highly effective method of contraception as described in inclusion criterion 14, starting with the first dose of propranolol until 28 days after the last dose of GPC-100, unless confirmed to be azoospermic (vasectomized or secondary to medical cause), or agree to be abstinent; and
18. Patients must be willing and able to provide signed informed consent.

**Exclusion Criteria**

Patients must be excluded if they meet any of the following criteria:

1. ≥25% of bone marrow irradiated within 5 years prior to Day 1;
2. No more than one year of therapy administered prior to stem cell mobilization, per institution standards;
3. Patients who have undergone previous stem cell transplant;
4. Receipt of G-CSF within 2 weeks prior to Day 1;
5. History of another malignancy except for the following:
6. Adequately treated local basal cell or squamous cell carcinoma of the skin;
7. Adequately treated carcinoma in situ of the cervix without evidence of disease;
8. Adequately treated papillary, noninvasive bladder cancer; or
9. Low-grade prostate cancer that is on active surveillance and not expected to clinically progress over 2 years.
10. Adequately treated solid tumor that has been in complete remission for at least 5 years after last receipt of chemotherapy or radiation therapy.
11. Patients who are on beta blockers (BBs) and unable to switch therapy;

Note: Patients on BBs who are able to switch therapy will undergo a gradual tapering of their current BB under the guidance of the Investigator. At the Investigator's discretion, the initial days of propranolol administration may be permitted to overlap with the final days of tapering of the previous BB.

12. Patients may not be treated with any of the following medications prior to Study Day 1 and within the below time windows
    a. non-dihydropyridine calcium channel blockers e.g., diltiazem or verapamil, within 5 half-lives of Study Day 1 (Appendix E)
    b. alpha blockers, e.g., phenoxybenzamine, phentolamine, alfuzosin, doxazosin, prazosin, silodosin, tamsulosin or terazosin, within 5 half-lives of Study Day 1 (Appendix E)
13. Patients with severe asthma who require beta agonist therapy;
14. History of poorly controlled or uncontrolled cardiovascular or pulmonary disease as assessed by the Investigator, including but not limited to the following: unstable angina, myocardial infarction within 6 months prior to screening, cardiac arrhythmias, clinically significant abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block), uncontrolled hypertension, transient ischemic attack within 6 months prior to screening, congestive heart failure (New York Heart Association heart failure class II or greater), stroke within 6 months prior to screening, unexplained syncope, or chronic obstructive pulmonary disease;
15. Pulse/heart rate < 60 beats per minute;
16. History of long QT syndrome or torsade de pointes;
17. Patients with a QTcF >470 msec or PR interval >280 msec on Screening 12-lead electrocardiogram (ECG);
18. Active infection requiring treatment in the 7 days before Day 1;
19. Positive polymerase chain reaction test from nasal specimen for severe acute respiratory syndrome coronavirus 2 within 7 days prior to Day 1—this testing only needs to occur if it is part of the institutional guidelines;
20. Pregnant or breastfeeding;
21. Any medical condition (e.g., psychiatric or substance abuse disorder) that would, in the Investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures;
22. Receipt of any other investigational drug or device within 1 month before Day 1;
23. Receipt of prior treatment with CXCR4 inhibitor for stem cell collection;
24. Radiotherapy within 14 days prior to the planned start of propranolol treatment; or
25. Major surgery within 14 days prior to the planned start of propranolol treatment;
26. Any clinically significant pulmonary disease, e.g., oxygen requirement, desaturations at rest and mild activity, moderate or severe COPD or restrictive pulmonary disease.

**STUDY DESIGN AND DURATION:**

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, the Sponsor made the decision to close the GPC-100 in combination with propranolol alone arm due to the low probability of achieving the desired efficacy outcomes. Thus, the amended study design eliminates the randomization scheme so that all patients, up to 30 total, shall be treated with GPC-100 in combination with propranolol and G-CSF. This change in study design is discussed in detail in Section 3.1. Subsequent sections and an updated diagram of the study design (Fig. S1) that follows reflect this change.

To characterize the safety and clinical activity of GPC-100, the study employs 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 (±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. 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 (±3 hr) local time on Days 3 to 7. Patients will receive G-CSF injections on Day 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.

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 min ±15 min 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 $<4 \times 10^6$ $CD34^+$ 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 posttransplant.

### Duration of the Study

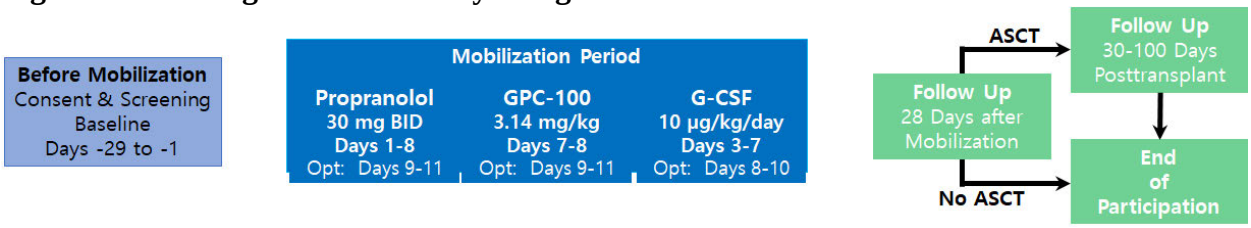
This study will consist of a Screening period (up to 28 days), a baseline visit, a mobilization period (up to 9 days), and a follow-up period (up to 100 days posttransplant).

### Duration of Follow-Up

If a patient undergoes ASCT using the stem cells collected from this study, said patient will be followed until 100 days posttransplant. If a patient does not undergo ASCT using the stem cells collected from this study, the patient will be followed until 28 days after the last dose of GPC-100.

An updated diagram of the revised study design is provided in Figure S1.

**Figure S1. 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 ug/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 $<4 \times 10^6$ $CD34^+$ 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 Day 8-10 only if they will undergo the optional days of mobilization/collection (Days 9-11) at the Investigator's discretion and with the Sponsor's approval for Days 10-11 of mobilization/collection.

ASCT = autologous stem cell transplant; BID = twice daily; CD = cluster of differentiation; D = day; EOS = end of study; G-CSF = granulocyte colony-stimulating factor; IV = intravenous(ly); Opt = optional; SC = subcutaneous(ly).

## DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

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.

**CRITERIA FOR EVALUATION:**

**EFFICACY:**

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

The secondary efficacy endpoints are the following:

- Percentage of all patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions;
- Percentage of all patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session;
- Percentage of all patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session;
- Average number of leukapheresis sessions required to collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg;
- Average number of leukapheresis sessions required to collect $\geq 4 \times 10^6$ $CD34^+$ cells/kg;
- PD profile of GPC-100 via circulating $CD34^+$ cell counts in peripheral blood and by determining circulating levels of CXCL12 in peripheral blood;
- Mean time to neutrophil engraftment defined as the first day of 3 consecutive measurements of ANC $\geq 0.5 \times 10^9$/L following the stem cell infusion; and
- Mean time to platelet engraftment defined as first day of 3 consecutive measurements of platelet count $\geq 20 \times 10^9$/L without transfusion in the previous 7 days.

The exploratory endpoints are the following:

- 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 and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire; and
- The PK profile of GPC-100.

**SAFETY:**

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

## STATISTICAL METHODS:

### Analysis Sets

The following sets will be defined during statistical analyses:

- Intent-to-Treat (ITT) Analysis Set: All randomized patients will be included in the ITT Analysis Set;
- Efficacy Analysis Set: All randomized 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;
- Safety Analysis Set: 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; and
- PD Analysis Set: 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 PD biomarkers. Analysis of PD biomarkers will be performed based on the PD Analysis Set.

### Analysis of Efficacy

Efficacy analysis will be conducted on all the patients in the Efficacy Analysis Set.

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

For the primary efficacy endpoint, each patient's $CD34^+$ cell counts will be calculated as the sum of $CD34^+$ cells collected from first 2 leukapheresis sessions by arms. Frequency and proportion will be used to evaluate the primary endpoint. Ninety-five percent and 80% 2-sided exact confidence intervals for the proportion of patients who mobilized the targeted collection goal will also be provided. Secondary efficacy endpoints including percentage of patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session and 2 leukapheresis sessions, and percentage of patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session will be analyzed in the same manner as the primary efficacy endpoint. All other efficacy endpoints will be summarized descriptively for the Efficacy Analysis Set by arms.

### Interim Analysis

The interim analysis of futility for each arm shall be performed based on availability of response data according to the BOP2 design.

## SAMPLE SIZE AND EFFICACY DETERMINATION:

A BOP2 design[32] shall be applied in this study. In the original study design, 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. Per the revised study design, the treatment arm of GPC-100 in combination with propranolol alone was closed based on Sponsor decision. As such, the randomization scheme no longer applies and all patients, up to 30 total, will be treated with GPC-100 in combination with propranolol and G-CSF.

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.[31] Treatment arms shall 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:

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

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 S1 and yields a statistical power of 84.50% under $H_1$.

**Table S1. Optimized Stopping Boundaries (GPC-100 in Combination With Propranolol Arm)**

| Patients Treated | Stop if Responses ≤# |
|---|---|
| 5 | 0 |
| 10 | 2 |
| 15 | 5 |
| 20 | 8 |

Based on Table S1, the interim analysis shall 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 shall be rejected and it shall be concluded that the treatment is acceptable if the number of responses is >8; otherwise, it shall be concluded that the treatment is not promising. The go/no-go criteria in Table S1 are nonbinding. Futility analyses shall be done based on availability of data from the first 2 leukapheresis sessions.

The 4 MM patients assigned to the GPC-100 in combination with propranolol alone arm did not achieve the primary endpoint of collecting ≥2 × $10^6$ $CD34^+$ 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 alone arm.

For the GPC-100 in combination with propranolol and G-CSF arm, the null hypothesis, $H_0: p_{eff} \leq 0.7$, and $\lambda=0.86$ and $\alpha=0.15$ 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 S2. 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 shall 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 is to be rejected and it shall be concluded that the treatment is acceptable if the number of responses is >16; otherwise, it shall be concluded that the treatment is unacceptable. The go/no-go criteria in Table S2 are nonbinding. Futility analyses are to be done based on availability of data from the first 2 leukapheresis sessions.

The 2 patients who have been 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.

**SITES:** Approximately 10 sites in the United States

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| ADRB2 | Beta-2 adrenergic receptor |
| AE | Adverse event |
| ANC | Absolute neutrophil count |
| ASCT | Autologous stem cell transplant |
| BB | Beta blocker |
| BM | Bone marrow |
| BOP2 | Bayesian Optimal Phase II |
| CD | Cluster of differentiation |
| CFU-GM | Colony-forming unit granulocyte macrophage |
| COVID-19 | Coronavirus Disease 2019 |
| CRA | Clinical Research Associate |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTRA | Conserved Transcriptional Response to Adversity |
| CXCL12 | C-X-C motif chemokine ligand 12 |
| CXCR4 | Chemokine receptor 4 |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EIU | Exposure In Utero |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire |
| EPI | Epinephrine |
| FDA | Food and Drug Administration |
| G-CSF | Granulocyte colony-stimulating factor |
| GCP | Good Clinical Practice |
| HCT | Hematopoietic cell transplant |
| HD | Hodgkin’s disease |
| HPC | Hematopoietic progenitor cell |
| HRQoL | Health-Related Quality of Life |
| HSC | Hematopoietic stem cell |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |

| Abbreviation | Definition |
|---|---|
| ITT | Intent-to-Treat |
| IV | Intravenous(ly) |
| LVEF | Left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MM | Multiple myeloma |
| MTD | Maximum tolerated dose |
| MUGA | Multigated acquisition |
| NCI | National Cancer Institute |
| NE | Norepinephrine |
| NHL | Non-Hodgkin's lymphoma |
| NRS | Numeric Rating Scale |
| PBMC | Peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| QTcF | Heart rate-corrected QT interval using Fridericia's formula |
| SAE | Serious adverse event |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SBP | Systolic blood pressure |
| SC | Subcutaneous(ly) |
| SD | Standard deviation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{1/2}$ | Terminal elimination half-life |
| TEAE | Treatment-emergent adverse event |
| ULN | Upper limit of normal |
| US | United States |
| v | Version |
| $V_{ss}$ | Apparent volume of distribution at steady state |
| WHO | World Health Organization |

# 1 INTRODUCTION AND BACKGROUND INFORMATION

## 1.1 Background

According to the National Cancer Institute (NCI), the estimated number of newly diagnosed multiple myeloma (MM) patients in the United States (US) in 2021 was 34,920 and the total estimated number of people in the US living with this diagnosis in 2018 was 146,956.[1] The Center for International Blood and Marrow Transplant Research Database reported 23,073 transplants in the US in 2019, of which 8028 were due to MM.[2]

### 1.1.1 Role of Autologous Stem Cell Transplant in MM

Large, randomized studies have demonstrated a survival benefit in MM patients undergoing autologous stem cell transplant (ASCT).[3] ASCT is a standard of care treatment indicated for MM patients after induction therapy and most often consists of a melphalan-based conditioning regimen followed by a rescue infusion of stem cells collected from the patient during mobilization.

Several new drugs to treat MM have been approved in the last 5 years, which have led to improved outcomes. However, ASCT continues to have an important role in the upfront management of newly diagnosed MM.[4]

A meta-analysis of randomized clinical studies from 2000 to 2017 showed that high-dose therapy with melphalan followed by ASCT was associated with superior progression-free survival and minimal toxic effects compared to standard-dose therapy.[5]

Therefore, all eligible patients with MM should be considered for transplant. Early transplant is preferred, especially in intermediate or high-risk patients. Standard risk patients may choose to delay transplant until first relapse. In such patients, stem cell collection and storage are recommended after a few cycles of induction therapy, as long-term lenalidomide maintenance therapy can impair future stem cell collection.[6,7]

### 1.1.2 Mobilization

Hematopoietic stem and progenitor cells constitute a very small fraction (approximately 0.1%) of circulating mononuclear cells in the peripheral blood. Therefore, collection of autologous hematopoietic stem cells (HSCs) from the peripheral blood stream requires a mobilization phase. Following mobilization, HSCs are obtained by leukapheresis, and the product may be administered fresh or may be cryopreserved for future use. In order to ensure engraftment, a minimum of $2 \times 10^6$ $CD34^+$ cells/kg are recommended to be collected. Initially, chemotherapy agents such as cyclophosphamide and etoposide were used to induce stem cell mobilization, and later granulocyte colony-stimulating factor (G-CSF) given as monotherapy following chemotherapy was used to achieve an adequate $CD34^+$ cell dose.[8]

G-CSF administered subcutaneously (SC) over multiple days results in a dose-dependent increase in circulating HSCs. Peak colony-forming unit granulocyte macrophage (CFU-GM) and $CD34^+$ cells are reached on the fifth day of G-CSF treatment at >10-fold over baseline, and a final yield of approximately $3 \times 10^6$ $CD34^+$ cells/kg. The total number of CFU-GM and $CD34^+$ cells collected correlates with the time to both platelet and absolute neutrophil count (ANC) recovery, as well as with transplant outcomes such as number of days of hospitalization and number of transfusions.[9]

Given the relationship between the $CD34^+$ cell dose and recovery from ASCT, efforts have focused on increasing the number of $CD34^+$ cells in the final product. G-CSF mobilization will fail to achieve $\geq 2 \times 10^6$ $CD34^+$ cells/kg in up to 50% of patients with either MM or non-Hodgkin's lymphoma (NHL). These patients may undergo a second collection procedure; however, this re-exposes patients to the discomforts and risks of G-CSF, which include multiple SC injections, medullary bone pain, headache, and rarely, splenic rupture. Furthermore, G-CSF is contraindicated in patients with sickle cell disease as it may potentiate a severe sickle cell crisis. For these reasons, efforts have been directed toward developing approaches that improve HSC collection in a single mobilization setting. Plerixafor, a chemokine receptor 4 (CXCR4) inhibitor, was initially studied to improve HSC collection when used in combination with a 4-day G-CSF mobilization regimen. The addition of plerixafor after 4 days of G-CSF mobilization results in approximately 2.5- to 3.5-fold increase in $CD34^+$ cells compared to G-CSF alone. The peak $CD34^+$ count occurs between 10 and 14 hours after administration of plerixafor. When used along with G-CSF, adverse reactions include gastrointestinal disturbances in addition to those reactions associated with G-CSF.[10]

### 1.1.3 CXCR4/CXCL12

CXCR4 is a member of the G protein-coupled receptor family and plays a pivotal role in many physiological processes that are critical for cancer development. CXCR4 is highly expressed in both solid and hematological malignancies and is associated with poor prognosis.[11] Activation of the CXCR4 pathway, particularly by its canonical ligand CXCL12, is shown to increase proliferation, survival, stemness, chemotaxis, and migration of cancer cells, which supports the potential of CXCR4 signaling blockade in cancer treatment.[12,13]

CXCR4/CXCL12 axis is critical for migration as well as retention of HSCs in the bone marrow (BM) microenvironment. Therefore, therapeutic utility of CXCR4 inhibitors in inducing mobilization of HSCs in circulation has been investigated. As described above, mobilization of HSCs has been shown with plerixafor, which is a small molecule CXCR4 antagonist that is clinically approved in the US and Europe for use in combination with G-CSF for HSC mobilization and subsequent ASCT in NHL and MM.[14,15] Blockade of this pathway leads to mobilization of HSCs from the BM to the peripheral blood.

### 1.1.4 GPC-100

GPC-100 (Burixafor/formerly TG-0054) is a potent and selective small molecule CXCR4 antagonist. In nonclinical studies, single intravenous (IV) administration of GPC-100 resulted in a rapid increase of total white blood cell counts in peripheral blood between 1 to 3 hours post injection that returned to baseline within 6 hours. In rats given GPC-100 twice IV in combination with 8-day subcutaneous G-CSF treatment, GPC-100 did not enhance any adverse effects noted in the rats compared to G-CSF treatment alone. Nonclinical safety pharmacology and toxicology results available to date suggest no evidence to preclude the clinical development of GPC-100. Additional details for the nonclinical studies for GPC-100 can be found in the Investigator's Brochure.[16]

A US-based Phase 1 study (Study TG-0054-01) assessed the safety, tolerability, and pharmacokinetics (PK) and determined the maximum tolerated dose (MTD) of single IV dose of GPC-100 in 64 healthy volunteers. The time of the peak plasma concentration for GPC-100 was 0.26 to 0.30 hours after dosing and the mean of terminal elimination half-life ($t_{1/2}$) was approximately 2.53 to 5.17 hours. Mean apparent volume of distribution at steady state ($V_{ss}$) values

were approximately 20% of the total body weight of a 70 kg person, indicating that GPC-100 free base (active ingredient) was moderately distributed in the body. GPC-100 administered as a single IV dose in healthy patients was well-tolerated at doses up to 4.40 mg/kg. The majority of adverse events (AEs) were mild in severity and all resolved by the end of the study without medical treatment. Given that all the AEs were generally mild, per Principal Investigator's interpretation, the AEs at 4.40 mg/kg related to parasympathetic stimulation were deemed as drug-related AEs; in accordance with the dose escalation stopping rules specified in the study Protocol, these AEs precluded further dosing escalation. Therefore, the MTD was defined to be 4.40 mg/kg due to the above reasons and not because any AE observed was dose-limiting toxicity.

In an initial Phase 2 study (Study TG-0054-02) conducted in Taiwan, patients were randomized 1:1 to 2.24 mg/kg or 3.14 mg/kg GPC-100 treatment group and received 1 dose of GPC-100 by IV infusion for 15 minutes on Day 1. A total of 7 patients (3 with MM, 3 with NHL, and 1 with Hodgkin's disease [HD]) out of 19 treated patients underwent apheresis procedure. The remaining 12 out of 19 treated patients were unable to proceed with apheresis since their peak $CD34^+$ cell counts in the peripheral blood did not meet the pre-specified threshold values. Three (2 MM and 1 NHL) of the 7 patients who underwent apheresis met the target $CD34^+$ cell collection of $\geq 2 \times 10^6$ cells/kg after 2 apheresis sessions and were classified as mobilization success. Blood samples for PK assessment of GPC-100 were obtained from 6 consenting patients on study Day 1 at predose, end of infusion, and 1, 3, 6, 9, 12, 24, and 36 hours after infusion. The mean $t_{1/2}$ values ranged from 4.32 to 4.65 hours for this study. Mean $V_{ss}$ values were approximately 20% of the total body weight of a 70 kg person, indicating that GPC-100 was moderately distributed in the body. Fifteen patients (78.9% of all patients) reported a total of 53 events. All AEs were mild except for 3 events (2 hypotension and 1 dizziness) reported by the same patient, which were moderate in severity. There were 8 serious AEs (SAE) reported from 19 patients, all considered unrelated to the study drug, GPC-100. No AEs led to discontinuation of study drug treatment and there were no deaths reported in this study. Most SAEs were reported due to initiated or prolonged hospitalization for stem cell transplantation or preparation of stem cell collection procedure, which were deemed appropriate by investigators. This study was terminated as most patients (12 of 19) were unable to proceed with apheresis due to low peripheral $CD34^+$ cell counts after treatment. This could possibly be due to low baseline $CD34^+$ values, which could be associated with previous radiotherapy.

In a subsequent US-based Phase 2 study (Study TG-0054-03) of GPC-100, patients received an initial dose of GPC-100 at 3.14 mg/kg and then were assigned to receive either GPC-100 alone (Arm 1) or GPC-100 in combination with G-CSF (Arm 3) depending upon their peripheral blood $CD34^+$ cell counts between 2 to 6 hours after the initial GPC-100 injection; specifically, patients with $CD34^+$ cell counts <10 cells/μL were assigned to Arm 3 and received G-CSF in addition to GPC-100 to reach target collection goal. All 12 patients achieved the primary endpoint of collecting $\geq 2.5 \times 10^6$ $CD34^+$ cells/kg within 4 leukapheresis sessions. The average number of leukapheresis sessions required to collect $\geq 2.5 \times 10^6$ $CD34^+$ cells/kg was 2.0 for GPC-100 administration alone and 1.4 for GPC-100 in combination with G-CSF. The overall incidence of treatment-emergent adverse events (TEAEs) in this study was low, with higher frequency of TEAEs in Arm 1 than in Arm 3 (20 and 5 TEAEs, respectively). Overall, 8 (66.7%) patients reported a total of 25 TEAEs. All TEAEs, with the exception of 1 TEAE of Grade 2 diarrhea reported in Arm 1, were not considered to be drug related. The majority of TEAEs reported were

Grade 1 or 2 in severity (20 of 25). One patient in Arm 1 discontinued from the study due to a drug-unrelated SAE of pregnancy on Day 10. There were no deaths reported in this study.

GPC-100 was further evaluated in another US-based Phase 2a study (Study TG-0054-04) with 9 MM patients, 2 NHL patients, and 1 HD patient. The combination treatment with GPC-100 and G-CSF induced mobilization of $6 \times 10^6$ $CD34^+$ stem cells/kg in 89% of the patients over 2 leukapheresis sessions. All 10 subjects achieved neutrophil engraftment and platelet engraftment with a mean (standard deviation [SD]) of 11.8 (0.79) days and 24.4 (8.38) days, respectively. This effect was comparable to the current standard of care treatment with plerixafor and G-CSF.[17] From a safety perspective, 7 patients each experienced ≥1 TEAEs during the study with a total of 10 TEAEs reported. There were no SAEs reported during this study and no patient discontinued due to TEAEs. The incidence of TEAEs was higher following coadministration of GPC-100 and G-CSF, relative to incidence during the initial 4 days of treatment when G-CSF was administered alone, with 6 patients experiencing a total of 7 TEAEs following coadministration of GPC-100 and G-CSF and 2 patients reporting a total of 3 TEAEs following administration of G-CSF alone. The majority of TEAEs were Grade 1 or 2 in severity, with a single Grade 4 TEAE of decreased platelet count that was assessed by the Investigator as unrelated to the study drug. One patient experienced a single drug-related TEAE (Grade 2 bone pain) following administration of G-CSF alone and 1 additional patient experienced a single drug-related TEAE (Grade 1 diarrhea) following coadministration of GPC-100 and G-CSF.

Retrospective analysis of the changes in the presence of CD34+ stem cells in peripheral blood before and after administration of GPC-100 in Study TG-0054-04 showed peak CD34+ levels approximately an hour after GPC-100 administration. This suggests that co-administration of GPC-100 with G-CSF leads to faster mobilization of CD34+ stem cells into the periphery than previously measured based on the administration of GPC-100 alone in healthy volunteers (Study TG-0054-01). In order to better capture the optimal collection window for CD34+ stem cells, the protocol amendment Version 5.0 shortens the gap between GPC-100 administration and the start of leukapheresis to 45 minutes instead of 2 hours. Additional collection times for PK, CXCL12, and CD34+ assessments are also added to better capture the PK and PD data. Collection of samples for exploratory endpoints after GPC-100 administration are collected earlier as well (2 hr vs. 4 hr).

Additional details for the clinical studies for GPC-100 can be found in the Investigator's Brochure.[16]

## 1.2 Rationale

### 1.2.1 Rationale for Improvement of ASCT in MM

ASCT is being increasingly used to treat hematological malignancies. However, successful ASCT in lymphoma and MM patients is often hindered by poor mobilization with at least 15% of patients failing to produce the target cell dose of $>2 \times 10^6$ $CD34^+$ cells/kg required to proceed with ASCT.[17] Newer therapies for MM patients approved in recent years may also have a negative impact on mobilization. For example, recent studies have shown that MM patients receiving daratumumab induction before ASCT have poorer mobilization.[18] Daratumumab use is also associated with an increased rate of neutropenic fever, leading to increased antibiotic usage and prolonged hospitalization.[19] This further increases the patient burden, another factor to consider in the treatment of MM patients. Compared to patients with other hematological malignancies, MM

patients have been found to have a higher symptom burden and worse Health-Related Quality of Life (HRQoL).[20]

### 1.2.2 Rationale for Addition of a Non-Selective Beta Blocker in Stem Cell Mobilization

The development and progression of cancer is driven in part by the components of the tumor microenvironment, where innervation by the sympathetic nervous system modulates neoplastic changes via neural and humoral pathways. Recent data have shown that the effects of the nervous system on cancer progression are mediated by the sympathoadrenal system mainly via β-adrenergic receptor signaling through the release of the neurotransmitters norepinephrine (NE) and epinephrine (EPI). Both NE and EPI exert stimulatory effects on cancer development and progression by modulating tumorigenesis, proliferation of cancer cells, and metastasis via multiple downstream signaling pathways, which are mediated predominantly by β2-adrenergic receptor signaling.[21,22,23,24]

Further support for the involvement of β-adrenergic signaling in the context of hematologic cancers is observed in patients who are receiving non-selective BBs, which target β1-, β2-, and β3-adrenergic receptors. Several clinical and epidemiological studies have noted the link between BB usage and positive survival outcome in multiple cancer types, including MM.[25] In a recent pomalidomide study conducted in 208 MM patients, positive impact of BB on survival outcome was documented. Overall survival in the 77 (37%) patients who reported BB usage for ≥3 months at any time after diagnosis was significantly longer than those without BB usage (107 versus 86 months).[26] Consistent with these observations, a biomarkers retrospective epidemiologic study showed that BB usage was associated with better prognosis in MM patients, including progression-free and overall survival.[25]

Hematopoietic cell transplant (HCT) recipients exposed to conditions of chronic stress show activation of a Conserved Transcriptional Response to Adversity (CTRA) gene expression profile, which in turn is associated with increased relapse and decreased disease-free survival. Furthermore, a Phase 2 biomarker-driven randomized study was conducted in MM patients that were treated with a non-selective BB, propranolol. This study demonstrated the capacity of propranolol to inhibit the sympathetic nervous system BM-derived adverse gene expression profile that has been shown to be associated with poor outcomes in HCT. Additionally, propranolol shifted cell differentiation away from a myeloid bias to an upregulation of $CD34^{+}$ stem cells and genes associated with this phenotype, as well as promoted enhanced engraftment.[27] Further support that β-adrenergic stimulation impacts the BM was reported in a study of severely injured patients with persistent anemia in which treatment with propranolol was shown to reduce BM dysfunction.[28]

In summary, multiple clinical studies have now reported the protective role of non-selective BB, like propranolol, in maintaining the BM cellularity. Collectively, these data suggest that inhibiting the β-adrenergic signaling systemically, and particularly in the BM environment, could potentially improve treatment outcomes in the context of HCT. Our in vivo mouse data show that the combination of BB and GPC-100 improves stem cell mobilization similar to the standard of care, plerixafor and G-CSF.

### 1.2.3 Rationale for the Study

The aim for this clinical study is to evaluate the efficacy of GPC-100 and propranolol with and without G-CSF. Elimination of G-CSF will improve patient experience and reduce the potential side effects, such as bone pain, which have been reported with G-CSF. With the inclusion of a triple combination arm, this study will allow for investigation of whether maximal stem cell mobilization can be achieved. In summary, the combination of BB, together with GPC-100, which mobilizes stem cells, supports clinical efforts to improve mobilization in hematological disorders. Pilot studies of GPC-100 in combination with G-CSF have shown the potential for collection of an adequate number of $CD34^+$ cells within a shorter time frame compared to historical results with either G-CSF alone or in combination with plerixafor, another hematopoietic stem cell mobilizer.[30] Administration of G-CSF can be burdensome with a 4-day schedule of subcutaneous treatment regimen and it is associated with side effects bone pain. In addition, G-CSF is contraindicated in patients with autoimmune diseases, such as sickle cell anemia. Thus, the goal of this study is to determine if G-CSF can be eliminated or reduced by providing an alternative oral approach with the use of propranolol as a non-selective beta blocker. In a Phase 2 study, stem cell mobilization with GPC-100 was increased when administered in the presence of G-CSF compared with GPC-100 administration alone. In this Phase 2 study, average number of leukapheresis sessions required to collect $\geq 2.5 \times 10^6$ $CD34^+$ cells/kg was 2.0 for GPC-100 administration alone and 1.4 for GPC-100 in combination with G-CSF.

Preclinical in vivo studies in mice indicated that GPC-100 in combination with propranolol was a potent mobilizer of white blood cells, which was further augmented with the addition of G-CSF. This effect was also recapitulated in the mobilization of mouse stem cells, as measured by analysis of the Lineage negative Sca1 positive and c-kit positive stem cell population and with the colony forming unit assay. Similarly, the goal of this clinical study is to evaluate the efficacy of GPC-100 and propranolol in the presence and absence of G-CSF. The use of the triple combination of GPC-100, propranolol, and G-CSF is predicted to be best in class and can target patient populations where other treatment regimens have failed. However, mobilization with a double combination of GPC-100 and propranolol will allow for an option when G-CSF is not tolerated.

Furthermore, this study has the potential to address the variable needs of the MM patient population in terms of improved stem cell mobilization for poor mobilizers and reduced patient burden, especially for newly diagnosed patients who are dealing with the psychological impact of a cancer diagnosis and complex treatment regimen.[30]

Based on the current data, wherein 4 MM patients did not achieve the primary objective of $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions, the GPC-100 in combination with propranolol alone arm has been closed. The 2 MM patients in the GPC-100 in combination with propranolol and G-CSF arm have reached the primary endpoint. Therefore, all subsequent enrolled patients in the study shall receive GPC-100 in combination with propranolol and G-CSF. The study design has been revised accordingly to reflect these changes as detailed in Section 3.1.

The results of this study will help in the decision for approaches to be used in the follow-on Phase 3 studies.

## 1.3 Coronavirus Disease 2019 Impacts

In March 2020, Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was characterized as a pandemic by the

World Health Organization (WHO). The COVID-19 pandemic has impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures.

This study Protocol includes contingency measures to manage disruptions due to COVID-19 illness and COVID-19 control measures; see Section 3.1.3. The impacts of the implemented contingency measures on the outcomes of this study, including any Protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the Clinical Study Report (CSR).

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is 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 G-CSF.

## 2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess safety and tolerability of GPC-100 and propranolol with and without G-CSF in the mobilization of patients with MM undergoing 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 CXCL12 in peripheral blood; and
- To assess the mean time to ANC and platelet count recovery after ASCT.

## 2.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To determine the cell surface expression of beta-2 adrenergic receptor (ADRB2) and 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 CTRA gene program that is activated by chronic stress;
- To determine epinephrine levels in patient serum;
- To evaluate treatment impact on patient HRQoL; and
- To evaluate the PK profile of GPC-100.

# 3 STUDY DESCRIPTION

## 3.1 Summary of Study Design

The original design of this study was 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 receive GPC-100 in combination either with or without G-CSF. The study design included an interim analyses of futility for each arm of the study that is to be performed after the pre-specified number of evaluable patients have been reached (see Section 9.2.5).

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 this 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 (±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. 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 SC injections of 10 μg/kg/day G-CSF at 5:00 PM (±3 hr) local time on Days 3 to 7. Patients 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.

On Days 7 and 8 (and on Days 9-11, if applicable), the patients 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 min ±15 min 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 $< 4 \times 10^6$ $CD34^+$ 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 posttransplant.

### 3.1.1 Duration of the Study

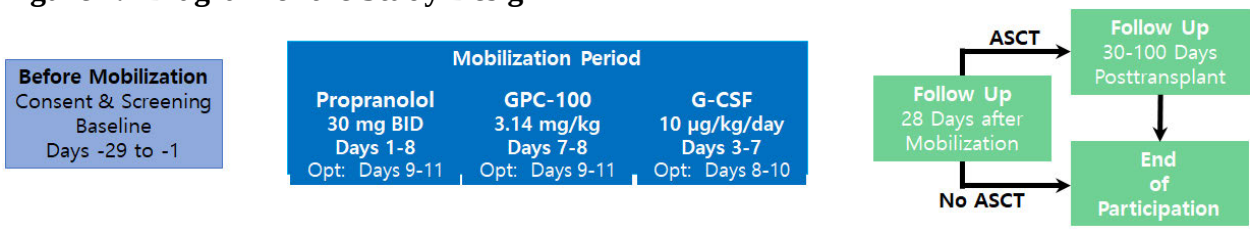
This study will consist of a Screening period (up to 28 days), a baseline visit, a mobilization period (up to 9 days), and a follow-up period (up to 100 days posttransplant).

### 3.1.2 Duration of Follow-Up

If a patient undergoes ASCT using the stem cells collected from this study, said patient will be followed until 30 and 100 days posttransplant. If a patient does not undergo ASCT using the stem cells collected from this study, they will be followed until 28 days after the last dose of GPC-100.

A diagram of the revised 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 ug/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 $<4 \times 10^6$ $CD34^+$ 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 Day 8-10 only if they will undergo the optional days of mobilization/collection (Days 9-11) at the Investigator's discretion and with the Sponsor's approval for Days 10-11 of mobilization/collection.

ASCT = autologous stem cell transplant; BID = twice daily; CD = cluster of differentiation; D = day; EOS = end of study; G-CSF = granulocyte colony-stimulating factor; IV = intravenous(ly); Opt = optional; SC = subcutaneous(ly).

### 3.1.3 Coronavirus Disease 2019 Contingency Measures

This study Protocol includes contingency measures to manage disruptions due to COVID-19 control measures.

In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of the patients. If necessary, the Sponsor will implement and document mitigation strategies. It may be necessary to conduct some study visits virtually. At the Investigator's discretion, the study visit(s) can be conducted in-clinic or virtually. If conducted virtually, the visit will include alternative methods for safety assessments, efficacy assessments, and distribution/collection of study drug, including, but not limited to, the following: phone/video contact, alternative location for biologic sample collection, alternative secure delivery of study drug, home health care (if available), and a secured way of transferring patient data from and to home health services and the site.

If these contingency measures occur, the Sponsor will document the changes made, communicate recommendations about such changes in a timely fashion to minimize or prevent disruptions to the study, and support sites in implementing these changes. Documentation of these cases and the site's management of patients should be recorded in the Investigator's study files. The impacts of the implemented contingency measures on the outcomes of this study, including any Protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the CSR. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the Protocol requirements as set forth.

## 3.2 Study Stopping Rules

Enrollment will be stopped should any of the following stopping rules occur:

1. Any Grade ≥4 AE related to GPC-100; or
2. Failure of neutrophil engraftment, defined as failure to achieve ANC >500 cells/mL by Day 30 after ASCT.

All safety data will be reviewed by the Sponsor and the Investigator to confirm study stopping criteria.

## 3.3 Study Indication

GPC-100 is indicated for the mobilization of stem cells in patients with MM undergoing ASCT.

# 4 SELECTION AND WITHDRAWAL OF PATIENTS

## 4.1 Inclusion Criteria

To be eligible to participate in this study, patients must meet all the following criteria:

1. Male or female, ≥18 years of age;
2. Patients with diagnosis of MM per the International Myeloma Working Group criteria[29];
3. Eligible for ASCT at the Investigator's discretion;
4. >4 weeks since completion of last cycle of chemotherapy prior to the first day of leukapheresis;
5. Patient must be on first or second complete response (CR), Very Good Partial Response (VGPR) or partial response (PR);
6. Eastern Cooperative Oncology Group performance status of 0 or 1 (see Appendix C);
7. Systolic blood pressure (SBP) 100 – 160 mmHg inclusive, and diastolic blood pressure (DBP) 60 - 100 mmHg inclusive;
8. ANC ≥1.0 × $10^9$/L on Screening laboratory assessments;
9. Platelet count ≥100 × $10^9$/L on Screening laboratory assessments;
10. Creatinine clearance ≥30 ml/min, as calculated according to the Cockcroft-Gault formula;
11. Aspartate aminotransferase and alanine aminotransferase ≤2 × upper limit of normal (ULN) and total bilirubin ≤1.5 × ULN on Screening laboratory assessments;
12. White blood cell (WBC) counts of ≥2.5 x $10^9$/L on Screening laboratory assessments;
13. Adequate cardiac function measured by left ventricular ejection fraction (LVEF) ≥50% on a historical imaging test (e.g. echocardiogram, cardiovascular magnetic resonance imaging, computed tomography angiography or multigated acquisition scan) within 6 months prior to screening. If no historical imaging test result is available, an imaging test is required during screening to confirm LVEF ≥50%.
14. Females of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to first dose of propranolol or be of non-childbearing potential. Non childbearing potential is defined by one of the following criteria:
    a. At least 1 year postmenopausal without an alternative medical cause. A follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient; or
    b. Surgically sterile

Females of childbearing potential must use a highly effective method of contraception for the course of the study, or agree to be abstinent, from 14 days prior to the first dose of propranolol through 3 months after the last dose of GPC-100. Highly effective methods of contraception include (1) oral, injected, or implanted hormonal methods of contraception, (2) intrauterine device, (3) intrauterine hormone releasing system, (4) bilateral tubal occlusion, (5) vasectomized partner

with verified absence of sperm in ejaculate post-vasectomy. Barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception. If used, this method must be used in combination with another acceptable method listed above.

15. Males who have a female partner of childbearing potential must agree to use a highly effective method of contraception as described in inclusion criterion 14, starting with the first dose of propranolol until 28 days after the last dose of GPC-100, unless confirmed to be azoospermic (vasectomized or secondary to medical cause), or agree to be abstinent; and
16. Patients must be willing and able to provide signed informed consent.

### 4.2 Exclusion Criteria

Patients must be excluded if they meet any of the following criteria:

1. ≥25% of BM irradiated within 5 years prior to Day 1 (see Appendix D);
2. No more than one year of therapy administered prior to stem cell mobilization, per institution standards;
3. Patients who have undergone previous stem cell transplant;
4. Receipt of G-CSF within 2 weeks prior to Day 1;
5. History of another malignancy except for the following:
   a. Adequately treated local basal cell or squamous cell carcinoma of the skin;
   b. Adequately treated carcinoma in situ of the cervix without evidence of disease;
   c. Adequately treated papillary, noninvasive bladder cancer; or
   d. Low-grade prostate cancer that is on active surveillance and not expected to clinically progress over 2 years.
   e. Adequately treated solid tumor that has been in complete remission for at least 5 years after last receipt of chemotherapy or radiation therapy.
6. Patients who are on BBs and unable to switch therapy;

   Note: Patients on BBs who are able to switch therapy will undergo a gradual tapering of their current BB under the guidance of the Investigator. At the Investigator's discretion, the initial days of propranolol administration may be permitted to overlap with the final days of tapering of the previous BB.
7. Patients may not be treated with any of the following medications prior to Study Day 1 and within the below time windows
   a. non-dihydropyridine calcium channel blockers e.g., diltiazem or verapamil, within 5 half-lives of Study Day 1 (Appendix E)
   b. alpha blockers, e.g., phenoxybenzamine, phentolamine, alfuzosin, doxazosin, prazosin, silodosin, tamsulosin or terazosin, within 5 half-lives of Study Day 1 (Appendix E)
8. Patients with severe asthma who require beta agonist therapy;

9. History of poorly controlled or uncontrolled cardiovascular or pulmonary disease as assessed by the Investigator, including but not limited to the following: unstable angina, myocardial infarction within 6 months prior to screening, cardiac arrhythmias, clinically significant abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block), uncontrolled hypertension, transient ischemic attack within 6 months prior to screening, congestive heart failure (New York Heart Association heart failure class II or greater), stroke within 6 months prior to screening, unexplained syncope, or chronic obstructive pulmonary disease;
10. Pulse/heart rate < 60 beats per minute;
11. History of long QT syndrome or torsade de pointes;
12. Patients with a QTcF >470 msec or PR interval >280 msec on Screening 12-lead electrocardiogram (ECG);
13. Active infection requiring treatment in the 7 days before Day 1;
14. Positive polymerase chain reaction test from nasal specimen for severe acute respiratory syndrome coronavirus 2 within 7 days prior to Day 1—this testing only needs to occur if it is part of the institutional guidelines;
15. Pregnant or breastfeeding;
16. Any medical condition (e.g., psychiatric or substance abuse disorder) that would, in the Investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures;
17. Receipt of any other investigational drug or device within 1 month before Day 1;
18. Receipt of prior treatment with CXCR4 inhibitor for stem cell collection;
19. Radiotherapy within 14 days prior to the planned start of propranolol treatment; or
20. Major surgery within 14 days prior to the planned start of propranolol treatment;
21. Any clinically significant pulmonary disease, e.g., oxygen requirement, desaturations at rest and mild activity, moderate or severe COPD or restrictive pulmonary disease.

### 4.3 Withdrawal Criteria

A patient may prematurely discontinue study drug and/or withdraw from the study at any time. A distinction must be made between premature discontinuation of study drug and withdrawal from the study. A patient may prematurely discontinue study drug and still continue his/her participation in the study. Patients who prematurely discontinue study drug dosing will be encouraged to continue in the study and complete visits and procedures as per Protocol.

The reasons for premature discontinuation of study drug and for withdrawal from the study must be documented in the electronic case report form (eCRF). Reasons include, but are not limited to, the following:

- Withdrawal of consent;
- Any event, laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient;

- Pregnancy;
- Patient failure to comply with Protocol requirements or study-related procedures;
- Termination of the study by the Sponsor or regulatory authority;
- Initiation of any of the excluded medications described in Section 5.6.1;
- Severe allergic reactions to the study drug; or
- Any stopping rule as described in Section 3.2.

If a patient withdraws prematurely from the study for any reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit (see Appendix A). The reason for patient withdrawal must be documented in the eCRF.

In the case of a patient lost to follow-up, attempts to contact the patient must be made and documented in the patient's records.

Withdrawn patients will be replaced.

# 5 STUDY TREATMENTS

## 5.1 Treatment Groups

In the original study design, approximately 40 patients were to be randomized and assigned in a 1:1 ratio to the following treatment arms:

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

Based on the currently available patient data, the Sponsor made the decision to close the treatment arm of GPC-100 in combination with propranolol alone. Thus, the revised study design eliminates the randomization scheme so that all patients, up to 30 total, shall be treated with GPC-100 in combination with propranolol and G-CSF.

GPC-100 is to be administered at a dose of 3.14 mg/kg GPC-100 free base via IV infusion.

## 5.2 Rationale for Dosing

The dose of 3.14 mg/kg GPC-100 free base was selected as previous Phases 1 and 2 clinical studies conducted in healthy volunteers and patients with MM, NHL, or HD indicated that it is an effective dose and is expected to be well tolerated within the patient population.

## 5.3 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.

## 5.4 Breaking the Blind

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

## 5.5 Drug Supplies

### 5.5.1 Formulation and Packaging

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.

### 5.5.2 Study Drug Preparation and Dispensing

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 IV bag) using aseptic technique.

### 5.5.3 Study Drug Administration

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.

#### 5.5.3.1 Overall Schema

The drug administration schedule is outlined in Table 1.

**Table 1. GPC-100 in Combination with Propranolol and G-CSF Group**

| Procedure | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9-10[a] | D11[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Propranolol 30 mg BID oral | X | X | X | X | X | X | X | X | Opt | Opt |
| G-CSF 10 µg/kg/day SC | | | X | X | X | X | X | Opt | Opt | |
| GPC-100 3.14 mg/kg IV | | | | | | | X | X | Opt | Opt |
| Leukapheresis | | | | | | | X | X | Opt | Opt |

a. Optional days of mobilization and apheresis.
BID = twice daily; D= day; G CSF = granulocyte colony-stimulating factor; IV = intravenous(ly); Opt = optional; SC = subcutaneous(ly).

An optional third day of mobilization/collection (Day 9) will be allowed per the Investigator's discretion for patients who have achieved $<4 \times 10^6$ $CD34^+$ cells/kg after 2 leukapheresis sessions.

Sites that have an institutional goal 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.

#### 5.5.3.2 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. Sites should regularly contact patients via telephone to confirm propranolol administration for doses administered outside of clinic. Patients are to indicate propranolol doses administered in the dosing diary and blood pressure (BP) log provided to them.

On the days of collection, the patient should not take the morning dose of propranolol unit instructed by the apheresis unit. The propranolol dose should be given in the apheresis unit 2 hours (±20 minutes) prior to start of leukapheresis. On the last day of collection, the 4:00 PM dose of propranolol may be held provided the stem cell collection has been completed.

Blood pressure should be measured within 30 minutes prior to the first dose of propranolol on Day 1 and on the days of collection (on Day 7 and 8, and if applicable on Days 9-11). Propranolol should not be administered unless the systolic blood pressure (SBP) is ≥100 mm Hg and the diastolic blood pressure (DBP) is ≥60 mm Hg. Patients will also be provided with a blood pressure monitoring kit to measure their blood pressure at home. Instructions for use will be provided during the onsite administration of the first dose of propranolol on Day 1. Patients should measure blood pressure within 30 minute prior to taking any dose of propranolol, as well as at any time that they feel symptoms of light-headedness, fatigue, or increase in heart rate. The patients should record their blood pressure in a patient log to record their blood pressure measurements. Patients should

be instructed to contact the site if symptomatic or if SBP <100 mm Hg or DBP <60 mm Hg. Sites should regularly contact patients via telephone to confirm propranolol administration for doses administered outside of clinic.

Management of propranolol before leukapheresis (Days 1-6)

Blood pressure should be taken within 30 minutes of each morning and afternoon dose. Measurements should be recorded on the patient dosing diary and BP log that is provided. If SBP <100 or DBP <60, the dose should not be taken. Patients should be instructed to contact the site if a dose is skipped or missed for any reason, including low blood pressure.

If one dose is skipped due to low blood pressure, the subsequent dose should be reduced to 15 mg (50% dose), provided SBP>100 mm Hg and DBP>60 mm Hg. If the patient tolerates the dose of 15 mg for at least two sequential administrations, the subsequent dose may be increased to 30 mg per Investigator's discretion or can continue at 15 mg per dose.

If two sequential doses of propranolol are skipped due to low blood pressure, the propranolol should be discontinued. If two non-sequential doses are skipped due to low blood pressure, then subsequent doses should not exceed 15 mg (50% dose) each, and propranolol may be held per Investigator's discretion.

If the SBP is ≥100 mm Hg and DBP is ≥60 mm Hg but the patient has symptoms suggestive of low blood pressure, such as light-headedness, increase in fatigue, or increase in heart rate, the patient should contact the site. The site may ask the patient to hold the propranolol dose if clinically indicated based on symptoms.

Management of propranolol on days of leukapheresis.

On days of leukapheresis, the patient's blood pressure will first be measured before administration of any drug. If SBP ≥100 mm Hg and DBP ≥60 mm Hg, study drugs can be administered.

During the apheresis, the patient should be treated for symptoms or signs of low blood pressure per institutional standard practices, including modification of the apheresis settings, infusion of fluids, or other supportive measures. If in the opinion of the investigator the blood pressure does not improve within 30 minutes despite usual supportive measures, then the subsequent doses of propranolol should be discontinued. If the low blood pressure resolves within 30 minutes with standard supportive measures, then subsequent propranolol dose should be modified as follows: the afternoon (4:30 pm) dose following the leukapheresis procedure should be skipped. The subsequent morning dose (8:30 am) should be reduced to 15 mg (50% dose).

Patients on beta blocker (BB) medication

Patients on beta blockers who are able to switch therapy will undergo a gradual tapering of their current BB under the guidance of the Investigator. At the Investigator's discretion, the initial days of propranolol administration may be permitted to overlap with the final days of tapering of the previous BB. If necessary, additional non-BB blood pressure medication can be added to manage hypertension during the BB taper. After completion of protocol-prescribed propranolol, the original beta blocker therapy may be resumed according to standard practice.

#### 5.5.3.3 GPC-100 Administration

GPC-100 is to be administered at a dose of 3.14 mg/kg GPC-100 free base via IV infusion on Day 7 and Day 8 for all patients, and on the days of optional mobilization/collection. The infusion of

GPC-100 should be started immediately following the propranolol dose. 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.

Clinical sites should follow their institutional guidelines for rounding up or down doses of G-CSF to the closest vial dose, as long as the final G-CSF dose is within 10% of the 10 µg/kg/day dose. This dose adjustment is only permitted when using vials or pre-filled syringes of 300 µg and 480 µg.

#### 5.5.3.4 G-CSF Administration

Patients will receive G-CSF as SC injections of 10 µg/kg/day G-CSF 5:00 PM (±3 hr) local time on Days 3 to 7. Patients will receive G-CSF injections on Days 8, 9, or 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. Patients are to indicate G-CSF doses administered in the dosing diary and BP log provided to them.

#### 5.5.3.5 Supportive Care

All standard supportive care will be allowed. Patients may be given loperamide (Imodium®) or other agents for the prevention or management of diarrhea per standard institutional practice to mitigate potential effect of anti-CXCR4 therapy as had been observed with Plerixafor and, rarely, with GPC-100.

### 5.5.4 Treatment Compliance

Study drug will be administered at clinical sites as described in Section 5.5.3. Clinical site personnel will verify that the treatment was administered correctly, and this information will be recorded in the source documentation for each patient.

### 5.5.5 Storage and Accountability

Prior to reconstitution, GPC-100 should be stored at room temperature (20 to 25°C [68 to 77°F]), with excursions permitted to 15 to 30°C (59 to 86°F). Study drug solution is stable for 8 hours following reconstitution in 0.9% saline. Reconstituted study drug solution should be discarded after 8 hours.

All study drugs must be stored in a secure facility with access limited to site staff involved in the study. Instructions for destruction or return of used study drug to the Sponsor will be provided in a Pharmacy Manual.

## 5.6 Prior and Concomitant Medications and/or Procedures

### 5.6.1 Excluded Medications and/or Procedures

The following medications and/or procedures are excluded during the study and during the time period prior to the study, as indicated:

- Last cycle of chemotherapy ≤4 weeks prior to the first day of leukapheresis;
- Irradiation of ≥25% of BM within 5 years prior to Day 1 (see Appendix D);

- No more than one year of therapy administered prior to stem cell mobilization, per institution standards;
- Previous stem cell transplant;
- G-CSF within 2 weeks prior to Day 1;
- Patients may not be treated with cardiovascular drugs that would interact with propranolol including non-dihydropyridine calcium channel blockers, and alpha blockers at study enrollment and while on propranolol during the study (Appendix E);
- BBs that cannot be tapered during this study;
- Beta agonist therapy;
- Any other investigational drug or device within 1 month before Day 1; or
- Prior treatment with CXCR4 inhibitor for stem cell collection.

### 5.6.2 Restricted Medications and/or Procedures

Patients on BBs who are able to switch therapy will undergo a gradual tapering of their current BB under the guidance of the Investigator. At the Investigator's discretion, the initial days of propranolol administration may be permitted to overlap with the final days of tapering of the previous BB.

### 5.6.3 Documentation of Prior and Concomitant Medication Use

The use of prior or concomitant medications will be recorded from Screening to the final study visit or the follow-up visit at 30 days posttransplant, whichever comes first.

## 6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures (Appendix A).

# 7 EFFICACY ASSESSMENTS

## 7.1 Efficacy Endpoints

### 7.1.1 Primary Efficacy Endpoint

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

### 7.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the following:

- Percentage of all patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions;
- Percentage of all patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session;
- Percentage of all patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session;
- Average number of leukapheresis sessions required to collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg;
- Average number of leukapheresis sessions required to collect $\geq 4 \times 10^6$ $CD34^+$ cells/kg;
- PD profile of GPC-100 via circulating $CD34^+$ cell counts in peripheral blood and by determining circulating levels of CXCL12 in peripheral blood;
- Mean time to neutrophil engraftment defined as the first day of 3 consecutive measurements of ANC $\geq 0.5 \times 10^9$/L following the stem cell infusion; and
- Mean time to platelet engraftment defined as first day of 3 consecutive measurements of platelet count $\geq 20 \times 10^9$/L without transfusion in the previous 7 days.

### 7.1.3 Exploratory Endpoints

The exploratory endpoints include the following:

- 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 Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30); and
- The PK profile of GPC-100.

### 7.2 Hematopoietic Stem Cell Collection

The total number of HSCs collected in leukapheresis product will be assessed following treatment with GPC-100 and propranolol with and without G-CSF. A continuous flow centrifugation device will be used for peripheral blood stem cell collections according to institutional standard procedures for leukapheresis. During each leukapheresis procedure, the volume of whole blood processed will be approximately 18 to 24 L. The starting time of leukapheresis will occur 45 min ±15 min after GPC-100 administration. The leukapheresis products will be processed at the study sites for $CD34^+$ cell enumeration and then stored under standardized liquid nitrogen conditions.

### 7.3 Health-Related Quality of Life

HRQoL will be assessed using the NRS and EORTC QLQ-C30 assessments at the visits indicated in the Schedule of Procedures (Appendix A). Only non-hematologic AEs, graded according to the NCI Common Terminology Criteria for AEs (CTCAE) version (v)5.0, should be collected as part of HRQoL assessments.

## 8 SAFETY ASSESSMENTS

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

### 8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF. The Investigator should update the appropriate eCRF if additional follow-up information becomes available (e.g., the AE has subsided, stabilizes, or the condition becomes chronic in nature).

AEs, which include clinical laboratory test results, will be monitored and documented from the time of informed consent until the final study visit or the follow-up visit at 30 days posttransplant, whichever comes first. Patients should be instructed to report any event that they experience to the Investigator, whether or not they think the event is due to study drug. From the time of informed consent until the final study visit or the follow-up visit at 30 days posttransplant, whichever comes first, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at informed consent should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at informed consent and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Thus, abnormal test results that are determined to be an error should not be reported as an AE, while laboratory abnormalities or other abnormal clinical findings (e.g., ECG abnormalities) should usually be reported as an AE if any of the following are applicable:

- An intervention is required as a result of the abnormality;
- Action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

### 8.1.1 Adverse Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse reaction. "Responses" to a medicinal product mean that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

### 8.1.2 Unexpected Adverse Reaction

An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

### 8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and will also categorize each AE as to its potential relationship to study drug.

#### 8.1.3.1 Assessment of severity

The severity of all AEs should be graded according to the NCI CTCAE v5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;

- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; or
- CTCAE Grade 5: Death related to the AE.

#### 8.1.3.2 Causality assessment

The relationship of an AE to the administration of study drug is to be assessed according to the following definitions:

- **No (not related or unlikely related):** The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and/or another cause (concomitant drugs, therapies, complications, etc.) is suspected; or
- **Yes (possibly, probably, or definitely related):** The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

  Note: The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- **The temporal sequence from study drug administration:** The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event;
- **Underlying, concomitant, intercurrent diseases:** Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have;
- **Concomitant drug:** The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question;
- **Known response pattern for this class of study drug:** Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect;
- **Exposure to physical and/or mental stresses:** The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event; and
- **The pharmacology and PK of the study drug:** The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

### 8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalization;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect; or

- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

  Note: Events of progression of a patient's underlying cancer, as well as events clearly related to the progression of a patient's cancer (signs/symptoms of progression), should not be reported as an SAE, including events where the outcome is fatal during the study or within the safety reporting period. Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as an SAE.

## 8.3 Serious Adverse Event Reporting − Procedures for Investigators

### 8.3.1 Initial Reports

All SAEs occurring from the time of informed consent until the final study visit or the follow-up visit at 30 days posttransplant, whichever comes first, must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the final study visit or the follow-up visit at 30 days posttransplant, whichever comes first, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the AE form with the SAE information electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Clinical Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Clinical Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line, and fax/email the completed paper SAE form to Medpace (contact information listed in

Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered as soon as possible.

### 8.3.2 Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

## 8.4 Pregnancy Reporting

If a patient becomes pregnant during the study, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring during the study and up to 6 months after the last dose of study drug must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

## 8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), other regulatory authorities, as applicable, and to applicable Institutional Review Boards (IRBs), and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported, as applicable, to the FDA, other regulatory authorities, as applicable, and to applicable IRB(s) as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also submit any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to IMPs.

## 8.6 Special Situation Reports

Special Situation Reports include reports of IMP overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the Protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the Protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of patients missing doses of investigational product are not considered reportable as medication errors.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situation Report form will only be completed if a complaint is associated with an adverse reaction.

All special situation events as described above must be reported on the Special Situation Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation Reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – US:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

## 8.7 Clinical Laboratory Evaluations

Clinical laboratory assessments will include chemistry, hematology, and coagulation. See Appendix B for a complete list of laboratory analytes. Clinical laboratory samples will be collected at visits specified in Appendix A. Clinical laboratory samples will be sent to a local laboratory for analysis.

## 8.8 Vital Signs

Vital signs will be measured as indicated in Appendix A. Vital signs will include temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure. Peripheral oxygen saturation will be measured at Screening only.

## 8.9 Electrocardiograms

12-lead ECGs will be performed in triplicate as indicated in Appendix A. Data obtained directly from 12-lead ECG traces will include heart rate, QRS duration, and PR and QT intervals.

## 8.10 Physical Examinations

A complete physical examination will be performed at Screening. Directed physical examinations will be performed at the other visits as indicated in Appendix A.

## 8.11 Imaging Tests

If there is no historical imaging test (e.g. echocardiogram, cardiovascular magnetic resonance imaging, computed tomography angiography or multigated acquisition scan) within 6 months prior to screening, LVEF will be measured by an imaging test at Screening.

# 9 STATISTICS

Changes in study visit schedules, missed or delayed visits, or patient discontinuations and the relationship to COVID-19 will be captured in the eCRFs. Modifications for collection of efficacy endpoints (e.g., virtual assessments, delays in assessments, and alternate collection methods) will also be documented in the eCRFs. Protocol deviations in study procedures due to COVID-19 will be reported in the CSR.

All continuous data will be summarized descriptively at scheduled time points using descriptive summary statistics (number of non-missing observations, mean, SD, minimum, and maximum). Categorical data will be summarized as frequency counts and percentages.

Baseline will be defined as the last available, non-missing observation prior to first study drug administration. Only data from nominal Protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the data listings.

Details of the statistical analyses will be provided in a separate Statistical Analysis Plan.

## 9.1 Analysis Sets

The following sets will be defined during statistical analyses:

- Intent-to-Treat (ITT) Analysis Set: All randomized patients will be included in the ITT Analysis Set;
- Efficacy Analysis Set: All randomized 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;
- Safety Analysis Set: 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; and
- PD Analysis Set: 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 PD biomarkers. Analysis of PD biomarkers will be performed based on the PD Analysis Set.

## 9.2 Statistical Methods

### 9.2.1 Analysis of Demographics and Other Baseline Characteristics

Patient disposition will be tabulated by arm and overall using ITT Analysis Set. Demographic and baseline data (ie, age, gender, race, ethnicity, height, and weight) and disease history and characteristics will be summarized using descriptive statistics for the ITT Analysis Set.

### 9.2.2 Primary Estimand

The estimand for the primary endpoint 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 with $\geq 2 \times 10^6$ $CD34^+$ cells/kg in first 2 leukapheresis sessions.
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 with $\geq 2 \times 10^6$ $CD34^+$ cells/kg in first 2 leukapheresis sessions

### 9.2.3 Analysis of Efficacy

Efficacy analysis will be conducted on all the patients in the Efficacy Analysis Set.

The primary efficacy endpoint will be the percentage of patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 2 leukapheresis sessions. 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 using multiple imputation (MI) method under the assumption of missing at random (MAR). The specification of the multiple imputation method will be provided in the SAP.

For the primary efficacy endpoint, each patient's $CD34^+$ cell counts will be calculated as the sum of $CD34^+$ cells collected from first 2 leukapheresis sessions by arms. Frequency and proportion will be used to evaluate the primary endpoint. Ninety-five percent and 80% 2-sided exact confidence intervals for the proportion of patients who mobilized the targeted collection goal will also be provided. Secondary efficacy endpoints including percentage of patients who collected $\geq 4 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session and 2 leukapheresis sessions, and percentage of patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 1 leukapheresis session will be analyzed in the same manner as the primary efficacy endpoint. All other efficacy endpoints will be summarized descriptively for the Efficacy Analysis Set by arms.

### 9.2.4 Analysis of Safety

Safety analysis will be conducted using the Safety Analysis Set. The safety analysis will include the assessment of the incidence and severity of AEs, and assessment of changes in safety parameters from baseline (e.g., clinical laboratory parameters, vital signs, and physical examination and 12-lead ECG findings).

TEAEs are AEs with an onset on or after the initiation of study drug. TEAEs will be graded according to NCI CTCAE v5.0, coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term. In addition, summaries of SAEs, TEAEs leading to study drug discontinuation, TEAEs by maximum NCI CTCAE grade, and TEAEs related to study treatment will also be presented.

Other safety endpoints including laboratory results, vital signs, and ECG findings will be summarized for all patients in the Safety Analysis Set.

Concomitant medications will be coded using the most current version WHO Drug Dictionary and will be listed and summarized.

### 9.2.5 Interim Analysis

The interim analysis of futility shall be performed based on availability of response data according to the BOP2 design (see Section 9.2.6).

### 9.2.6 Sample Size and Efficacy Determination

A BOP2 design[32] 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.[31] 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:

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

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 2 and yields a statistical power of 84.50% under $H_1$.

**Table 2. 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 2, 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 is to be rejected and it shall be concluded that the treatment is acceptable if the number of responses is >8; otherwise, it shall be concluded that the treatment is not promising. The go/no-go criteria in Table 2 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 3.

**Table 3. 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 | 3.7 | 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 | 84.5 | 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 $\lambda=0.86$ and $\alpha=0.15$ 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 4. 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 shall 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 is to be rejected and it shall be concluded that the treatment is acceptable if the number of responses are >16; otherwise, it shall be concluded that the treatment is unacceptable. The go/no-go criteria in Table 4 are nonbinding. Futility analyses shall 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 5.

**Table 5. 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 |
| 0.60 | 83.27 | 1.47 | 11.7 |
| 0.65 | 73.84 | 4.1 | 12.6 |
| 0.70 | 61.72 | 9.95 | 13.8 |

| Response Rate | Early Stopping (%) | Claim Promising (%) | Average Sample Size |
|---|---|---|---|
| 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 | 84.7 | 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.

# 10 DATA MANAGEMENT AND RECORD KEEPING

## 10.1 Data Management

### 10.1.1 Data Handling

Data will be entered into eCRFs in the EDC system by personnel allocated to this task, as documented on the site delegation log, and will be reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data will be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

### 10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

### 10.1.3 Data Entry

Data will be recorded using the EDC system as the study is in progress. All delegated site personnel will log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

### 10.1.4 Medical Information Coding

The following dictionaries will be used for coding medical information:

- MedDRA for AEs and medical history; and
- WHO Drug dictionary for prior and concomitant medications.

### 10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to ensure accurate, consistent, and reliable data. Data identified as erroneous or missing will be referred to the investigative site for resolution through data queries.

The eCRFs will be reviewed and electronically signed by the Investigator.

## 10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

## 10.3 End of Study

The end of the study (study completion) is defined as the date of the last Protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

# 11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

## 11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible. This study will be conducted in compliance with the Protocol and with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) guidelines for GCP, and applicable regional regulations.

## 11.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (i.e., Medpace) to ensure the IRB/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where written IRB/IEC approval has been obtained. The Protocol, Investigator's Brochure, Informed Consent Form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the Protocol, any Protocol Amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

## 11.3 Informed Consent Procedures

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor/designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation, and that patients have sufficient opportunity to have all questions answered in a suitable facility. The Investigator must ensure that the patient has been informed of his/her rights to privacy and his/her rights and guarantees regarding his/her protection, in particular the right to refuse to participate and the right to withdraw from the clinical study at any time without any resulting detriment and without having to provide any justification. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed, unless the activity is part of standard-of-care for the patient and/or indication and should document in the source that consent was obtained prior to enrollment in the study. A patient is considered enrolled once consent is signed, all Screening procedures are completed, and the Investigator has documented that the patient meets all inclusion and exclusion criteria.

The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies.

A copy of the signed ICF will be given to the patient.

## 11.4 Subject Card

On enrollment in the study, the patient will receive a subject card to be carried at all times. The subject card will state that the patient is participating in a clinical research study, and will specify the type of treatment, number of treatment packs received, and contact details in case of an SAE.

## 11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the Protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well-organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor/designee will review with the Investigator and site personnel the following documents: Protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor/designee to monitor the study as frequently as deemed necessary to determine that data recording and Protocol adherence are satisfactory. Study monitoring may include onsite, remote, or a combination of both onsite and remote monitoring. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site designee, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived.

## 11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor/designee, applicable foreign health authorities, and the IRB/IEC, as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

## 11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, such as eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE

forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator or institution, or to the Sponsor.

## 11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

# 12 STUDY ADMINISTRATIVE INFORMATION

## 12.1 Protocol Amendments

Any Amendments to the study Protocol will be communicated to the Investigators by Medpace or the Sponsor. All Protocol Amendments will undergo the same review and approval process as the original Protocol. A Protocol Amendment may be implemented after it has been approved by the IRB/IEC and applicable competent authorities, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC and applicable competent authorities within 5 working days.

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# APPENDIX A: SCHEDULE OF PROCEDURES

## Table 6. Schedule of Procedures

| | Before Mobilization | | Mobilization [x] | | | | | | | | | | | Safety Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening* | Baseline[w] | | | | | | | | | Optional[0] | | | | ASCT | | |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | |
| Day | -29 to -2 | -1[b] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 28 Days After Final Day of Mobilization | 30 Days PT | 100 Days PT | ET |
| Window (±Days) [y] | | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±7 | ±7 | ±7 | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X[c] | | | | | | | | | | | | | | | | |
| Demographic information | X | | | | | | | | | | | | | | | | |
| Medical/surgical history[d] | X | | | | | | | | | | | | | | | | |
| Prior/concomitant medications[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Weight and height[f] | X | X | | | | | | | | | | | | | | X | |
| Physical examination[g] | X | X | X | | | | | | X | X | X | | | X | X | X | X |
| Vital signs[h] | X | X | X | | | | | | X | X | X | | | X | X | X | X |
| ECOG performance status | X | X | X | | | | | | X | X | X | | | X | X | X | X |
| Pregnancy test[i] | | X | | | | | | | | | | | | X | X | | X |
| Triplicate 12-lead ECG [u] | X | | X | | | | | | X | X | X | | | X | X | | X |
| Clinical laboratory assessments[j] | X | X | | | | | | X | X | X | X | | | X | X | X | X |
| Urinalysis | | X | | | | | | X | X | X | X | | | X | X | | X |
| LVEF[k] | X | | | | | | | | | | | | | | | | |
| Randomization[t] | | X | | | | | | | | | | | | | | | |
| Propranolol administration[l] | | | X | X | X | X | X | X | X | X | X | X | X | | | | |
| GPC-100 administration[m] | | | | | | | | | X | X | X | X | X | | | | |

**Table 6. Schedule of Procedures (Continued)**

| | Before Mobilization | | Mobilization [x] | | | | | | | | Safety Follow-Up | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening* | Baseline[w] | | | | | | | | Optional[0] | | | | ASCT | | |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| Day | -29 to -2 | -1[b] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 28 Days After Final Day of Mobilization | 30 Days PT | 100 Days PT | ET |
| Window (±Days)[y] | | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±7 | ±7 | ±7 | |
| G-CSF administration[n] | | | | | X | X | X | X | X | X | X | X | | | | | |
| Leukapheresis[o] | | | | | | | | | X | X | X | X | X | | | | |
| Assessment of $CD34^+$ cells in peripheral blood[p] | | X | | | | | | | X[q] | X[q] | X[q] | | | | | | |
| Total CD34+ cells collected per apheresis session | | | | | | | | | X | X | X | X | X | | | | |
| PK[r] | | | | | | | | | X[q] | X[q] | | | | | | | |
| CXCL12 | | X | | | | | | | X[q] | X[q] | X[q] | | | | | | |
| Exploratory biomarkers | | X | | | | | | | X[s] | | | | | | | | |
| NRS [v] | | X | X | X | X | X | X | X | X | | | | | X | X | X | X |
| EORTC QLQ-C30 | | X | | | | | | | X | | | | | X | X | X | X |
| Adverse events[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |

* The screening period is from Day -29 to Day -2. If a subject is deemed eligible, they are scheduled for the Visit 2 / Baseline Day -1 Visit, which can be combined with Visit 3 / Day 1. If the subject is not deemed eligible during the screening period, they are considered a screen failure.

a. Day 9 is optional at the Investigator's discretion. 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.
b. Day -1 is the calendar day immediately preceding Day 1. A patient must be considered enrolled prior to Visit 2 (Day -1) to continue in the study.
c. Scheduling of Visit 2 should accommodate the timeframe requirements for eligibility according to the inclusion and exclusion criteria, whenever possible and within reason.
d. Medical/surgical history will include prior antineoplastic therapy.
e. This assessment can be performed remotely via telephone without requiring patient to visit the site for patients in the treatment arm receiving GPC-100 in combination with propranolol on Days 2 through 5 and for patients in the treatment arm receiving GPC-100 in combination with propranolol and G-CSF treatment arm on Day 2.
f. Height will be collected at Screening only.
g. A complete physical examination will be performed at Screening. Directed physical examinations will be performed at the other visits.
h. Vital signs will include temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure. Peripheral oxygen saturation will be measured at Screening only.
i. 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.

j. Clinical laboratory assessments include chemistry, hematology, and coagulation. Clinical laboratory samples will be sent to a local laboratory for analysis.
k. LVEF will be measured by an imaging test at Screening if there is no historical imaging test taken within 6 months prior to Screening.
l. 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 Day 9, 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 contact patients via telephone to confirm propranolol administration for doses administered outside of clinic.
m. On Days 7 and 8 (and on Day 9, 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).
n. Patients receiving GPC-100 in combination with propranolol and G-CSF will receive SC 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 Day 8 at 5:00 PM (±3 hr) local time only if they will undergo the optional third day of mobilization/collection (Day 9) at the Investigator's discretion.
o. Leukapheresis will be performed over the course of 1, 2, or 3 days, depending on the following parameters: $CD34^+$ cell counts, procedure start/end time, volume of blood processed, volume of product collected, and the occurrence of procedure-related adverse events. The starting time of leukapheresis will occur at 45 min ±15 min after GPC-100 administration.
p. CD34+ cell count in peripheral blood will be recorded as cells/uL.
q. Samples will be collected predose and at 1, 2, 3, 4 , 5, and 6 hours following GPC-100 dosing. Collection of the 6-hour postdose timepoint will be optional and should be performed if the patient is available onsite for the collection of this timepoint. Sampling timepoints are shown in Table 7
r. PK sampling timepoints are shown in Table 7. Patients will need to come into the clinic for collection of the PK sample at 23 hr (±15 min) and 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.
s. Exploratory endpoints will be collected at predose and 2 hr after GPC-100 administration on Visit 9. See Section 7.1.3 for a list of endpoints.
t. Randomization would occur as soon as the patient is deemed eligible. This can be done during the 28-day Screening period, prior to Day -1.
u. A triplicate ECG on Visit 11, Visit 12, and Visit 13 (optional collection days) is only required if leukapheresis is performed
v. The NRS can be performed either in person or over the phone if the subject does not come into the clinic for a study visit.
w. Visit 2 / Baseline (Day-1) and Visit 3 / Day 1 may be combined or conducted as separate visits.
x. Visit 8 / Day 6 and Visit 9 / Day 7 may be combined or conducted as separate visits.
y. Window (±Days) do not apply to administration of the study drugs GPC-100, propranolol, and G-CSF

ASCT = autologous stem cell transplant; CD = cluster of differentiation; CXCL12 = C-X-C motif chemokine ligand 12; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire; ET = early termination; G-CSF = granulocyte colony-stimulating factor; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; NRS = Numeric Rating Scale; PK = pharmacokinetic(s); PT = posttransplant; SC = subcutaneous(ly).

## Table 7. Pharmacokinetic, CD34+, and CXCL12 Sampling Timepoints after GPC-100 Administration

| 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).

# APPENDIX B: CLINICAL LABORATORY ANALYTES

**Standard Safety Chemistry 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: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

**Table 8. ECOG Performance Status**

| Grade | Descriptions |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light sedentary nature (eg, light housework, office work). |
| 2 | Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

ECOG = Eastern Cooperative Oncology Group.
Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655

# APPENDIX D: DISTRIBUTION OF BONE MARROW FOR CALCULATION OF RADIATION EXPOSURE

**Table 9. Distribution of Bone Marrow for Calculation of Radiation Exposure**

| Anatomical Site | Mean Percentage of Proliferating Bone Marrow |
|---|---|
| Cervical spine | 4.3% |
| Lumbar spine | 16.6% |
| Pelvis | 25.3% |
| Proximal femurs | 4.5% |
| Proximal humeri | 1.9% |
| Ribs and clavicles | 8.8% |
| Sacrum | 9.2% |
| Scapulas | 3.8% |
| Skull | 2.9% |
| Sternum | 2.9% |
| Thoracic spine | 19.9% |
| Source: Hayman JA, Callahan JW, Herschtal A, et al. Distribution of proliferating bone marrow in adult cancer patients determined using FLT-PET imaging. *Int J Radiat Oncol Biol Phys.* 2011;79(3):847-852 | |

# APPENDIX E: EXCLUDED CARDIOVASCULAR DRUGS

**Table 10 List of excluded cardiovascular drugs (alpha blockers and non-dihydropyridine calcium channel blockers)**

| Alpha blockers | Non-dihydrophyridine Calcium Channel Blockers |
|---|---|
| Alfuzosin | Diltiazem (benzothiazepine) |
| Doxazosin | Verapamil (phenylalkamine) |
| Prazosin | |
| Silodosin | |
| Tamsulosin | |
| Terazosin | |
| Phenoxybenzamine | |
| Phentolamine | |