# STATISTICAL ANALYSIS PLAN

A Phase II, Open-Label, Pharmacokinetic Study of Propylene Glycol-Free Melphalan HCl for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation (IIS-MEL-MCW-001)

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## STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (*n*), mean, median, standard deviation, minimum and maximum for continuous data, and frequencies and percentages for categorical data.

All statistical analysis will be conducted with the SAS® System, Version 9.1.3 or higher.

### 10.1 Data Collection Methods

The data will be recorded on the Oncore-CRF. The Investigator must submit a completed CRF for each subject who signs an informed consent form (ICF), regardless of duration. All documentation supporting the CRF data, such as laboratory or hospital records, must be readily available to verify entries in the CRF.

Documents (including laboratory reports, hospital records subsequent to SAEs, CT scan results, etc.) should not carry the subject's name. This will help to ensure subject confidentiality.

### 10.2 Statistical Analysis Plan

A statistical analysis plan (SAP) will be created prior to the review of any data. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

### 10.3 Sample Size Estimates

A sample size of 24 patients is planned for this study. The mean±SD results of $AUC_{0-t}$ and $C_{max}$ of 100 mg/m$^2$ melphalan dose from a previously conducted study were 376,577±93,401 min·ng/mL and 4374 ± 1050 ng/mL respectively. Twenty-four patients will provide ±10% width for the 90% CI around the point estimates of $AUC_{0-t}$ and $C_{max}$ in this study. A study size of 24 patients would also provide for a 95% confidence interval having a width of ±20% to estimate an AE incidence rate for common AEs occurring at a frequency of 25 -30%.

### 10.4 Analysis Populations

The PK evaluable population is defined as all patients, who completed dosing and adequate subsequent PK blood draws for the calculation of AUC and $C_{max}$ for melphalan HCl for injection (propylene glycol free). PK analysis will be performed on the evaluable population.

All enrolled patients receiving melphalan HCl for injection (propylene glycol free) will be defined as the population for analysis. All safety and efficacy analysis will be performed on all patients who received study medication.

## 10.5 Interim and End-of-Study Analysis

**Interim Analysis**

An independent DSMB at the Medical College of Wisconsin will review safety data on an ongoing basis (see Section 11.6.1). Safety analysis will be presented in a manner consistent with the presentations intended for the final analysis according to CTCAE v 4.0 criteria

**End-of-Study Analysis**

A final analysis is planned after the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

## 10.6 Pharmacokinetic Analysis

PK parameters will be determined by nonparametric PK data analysis techniques. PK parameters computed from plasma drug concentration time data will include, but not necessarily be limited to the following parameters:

- $C_{max}$ derived from the individual raw data.
- $T_{max}$ derived from the individual raw data.
- Apparent terminal first-order elimination rate constant ($k_{el}$).
- Apparent elimination $t_{1\backslash 2}$.
- Area under the plasma concentration-time curve to the last measurable time point ($AUC_{0-t}$) calculated by the trapezoidal rule.
- Area under the plasma concentration-time curve to infinity ($AUC_{0-\infty}$): $AUC_{0-t}$ + area under the plasma concentration-time curve from the last measurable time point extrapolated to infinity determined from the concentration at the last measurable time point divided by the $k_{el}$.

The plasma concentrations and pharmacokinetic parameters for melphalan HCl for injection (propylene glycol free) will be summarized in the following manner:

Descriptive Statistics

Arithmetic means, standard deviations and coefficients of variation will be calculated for the parameters listed above. Additionally, geometric means will be calculated for $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$.

## 10.7 Efficacy Analysis

### *10.7.1 Efficacy Endpoints*

The rates of myeloablation and engraftment will be determined based on the following definitions:

Myeloablation is defined as any one of the following:

- ANC $<0.5 \times 10^9$/L.
- Platelet count $<20{,}000/mm^3$ or bleeding requiring transfusion.

The first of two consecutive days for which cell counts drop below these cut-off levels will be recorded as the date of myeloablation.

Engraftment is defined as per Section 8.3.2.1 as:

ANC recovery is defined as an absolute neutrophil count (ANC) of ≥ 0.5 x 10^9 /L (500/mm3) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where the ANC is ≥ 0.5 x 10^9 /L. Platelet recovery is reported when the recipient's platelet count is ≥ 20 x 10^9 /L seven days after platelet transfusion and is maintained for three consecutive lab values obtained on different days. Time to myeloablation will be calculated as the time from receiving melphalan for injection (propylene glycol free) to the date of myeloablation.

Time to engraftment will be calculated as the time from transplant to the date of engraftment.

### *10.7.2 Analysis of Efficacy Endpoints*

Efficacy analysis will be performed on all patients who received study medication.

The rates of myeloablation and engraftment during the study will be calculated and will be summarized descriptively.

Time to myeloablation and time to engraftment will be calculated for each patient and summarized, using Kaplan-Meier / cumulative incidence.

Myeloma responses will be calculated for each patient and summarized.

## 10.8 Safety Analysis

Safety analysis will be performed on all patients who received study medication. The following safety analysis will be performed for this study and will include all collected data through the final study visit:

- Incidence of all treatment-emergent AEs and drug-related treatment-emergent AEs by system organ class and preferred term.
- Incidence of all treatment-emergent AEs by system organ class, preferred term, and severity.
- Incidence of all treatment-emergent AEs and treatment-emergent drug-related AEs by CTCAE v4.0 grade.
- Incidence of treatment-emergent AEs, treatment-emergent drug-related AEs, and treatment-emergent CTCAE v4.0 Grade 3 or 4 AEs by preferred term in descending frequency.

- Incidence of all AEs that led to discontinuation of study medication.
- Incidence of all SAEs and drug-related SAEs, including deaths.
- Summary of changes in laboratory parameters from baseline to post-dose time points.
- Laboratory parameters summarized by CTCAE v4.0 Grade (frequency and shifts).
- Summary of changes in vital signs from baseline to post-dose time points.