Statistical Analysis Plan

Protocol: PHP-OCM-301A

Version 1.0

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Study Title: A Single-arm, Multi-center, Open-label Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients with Hepatic-Dominant Ocular Melanoma

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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LIST OF ABBREVIATIONS

AE	adverse event
ATC	anatomical class (from WHODRUG dictionary)
BAC	best alternative care
CRF	case report form
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CS	clinically significant
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
hORR	hepatic objective response rate
hPFS	hepatic progression free survival
GCP	Good Clinical Practices
ICH	International Committee for Harmonization
ITT	intent to treat
IWRS	interactive web based randomization system
KM	Kaplan-Meier
LD	longest diameter
MedDRA	Medical Dictionary for Regulatory Affairs
NCI	National Cancer Institute
NCS	not clinically significant
ND	not done
OS	overall survival
ORR	objective response rate
PD	progressive disease
PFS	progression free survival
PHP	percutaneous hepatic perfusion
PK	pharmacokinetics
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan

SAS	statistical analysis system
SD	stable disease
SDTM	Standard Data Tabulation Model
SOC	system organ class
TEAE	treatment emergent adverse event
TOR	time to objective response
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This document outlines the statistical methods and data analysis to be implemented during the analyses of data collected within the scope of Delcath Systems, Inc. Protocol PHP-OCM-301A titled "*A Single-arm, Multi-center,Open-label Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients with Hepatic-Dominant Ocular Melanoma".*

This Statistical Analysis Plan (SAP) was prepared in accordance with the protocol PHP-OCM-301A dated -22 June 2018. Please see the study protocol for additional details about the study design, procedures, and schedule of assessments.

The purpose of this SAP is to provide a framework in which answers to the protocol objectives may be achieved in a statistically rigorous fashion, without bias or analytical deficiencies, following methods identified prior to database lock. Specifically, this plan has the following purposes:

- To prospectively outline the specific types of analyses and presentations of data that will form the basis for conclusions.
- To explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry. Any deviations from these guidelines must be substantiated by sound statistical reasoning and documented in writing in the final clinical study report (CSR).

2. OVERVIEW OF STUDY DESIGN

Protocol PHP-OCM-301A is a single-arm, open-label, multi-center study to evaluate the efficacy and safety of Melphalan/HDS in patients with hepatic-dominant metastatic ocular melanoma. The study will be conducted at approximately 40 centers in the United States and the Europe.

At least 80 patients with hepatic-dominant metastatic ocular melanoma will be treated in this study. This will include at least 30 subjects randomized to Melphalan/HDS under protocol PHP-OCM-301 (subjects in this group will be referred to as PHP301 group) and an additional 50 subjects qualified to treat under protocol PHP-OCM-301A (subjects in this group will be referred to as PHP301A group).

It is anticipated that it will take approximately 12 months to enroll patients. Study closure for the purposes of analysis is planned approximately 24 months after the last patient has

received their final study treatment. Data from the long-term follow-up in patients who survived longer than 24 months after the last patient last treatment will be summarized separately to be reported in a study report addendum.

The study will consist of 3 phases, as follows:

Screening/Basline Phase: Screening assessments will be conducted within 28 days prior to the eligibility date to determine patient's overall eligibility and baseline. These assessments will include medical history, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12 lead electrocardiogram (ECG), echocardiogram (ECHO), vital signs, full hematology and biochemistry, Quality of Life questionnaire, radiologic assessments of baseline disease status, and an evaluation of the vasculature compatibility for Melphalan/HDS treatment also known as Percutaneous Hepatic Perfusion (PHP) and concomitant medications.

Re-screening will also be permitted for those patients that were consented on the PHP-OCM-301 study but were not randomized to a treatment arm.

Treatment Phase: The treatment phase of the study will be conducted as described in Section 6.1 of the protocol. Eligible patients will be treated with Melphalan/HDS 3.0 mg/kg Ideal Body Weight (IBW) and the first study treatment should occur within 14 days of the eligibility date. Melphalan/HDS treatment will be administered every 6 weeks for a total of 6 cycles with an acceptable delay of another 2 weeks (i.e., 8 weeks in total) to allow for recovery from melphalan related toxicity if needed. Tumor response will be assessed every 12 (+/- 2 weeks) until disease progression. The assessment scans will be reviewed by an Independent Central Review Commitee (IRC), but patient management will be according to the principal investigator (PI) assessment of images and clinical needs. At any time when progressive disease (PD) is observed, the patient will be removed from further study treatment and will be followed until death. Patients with progressive disease (PD) will be discontinued from study treatment, and will continue to be followed until death. Melphalan/HDS treatment will also be discontinued if recovery from treatment related toxicity requires more than 8 weeks from last treatment. An end of treatment (EOT) visit will be conducted approximately 6 to 8 weeks following the final dose of study treatment. Ongoing treatment-emergent adverse events (TEAEs) at the end of treatment visit will be followed until severity is within one of the three parameters: 1) symptoms are resolved or return to baseline, 2) CTCAE Grade $\leq$ 1 or can be explained or 3) patient death. The maximum possible duration of the study treatment phase for any patient will be 12 months.

Active Melphalan/HDS patients (currently in treatment) from the PHP-OCM-301 will continue treatment on PHP-OCM-301A following the re-consenting process.

Follow-up Phase: Once the patient has completed the end-of-treatment (EOT) visit in accordance with the schedule of events they will enter the follow-up phase. If the disease has not progressed at the EOT (Section 6.3 of the protocol), the patient will need to continue with disease assessment visits every 12 (+/- 2 weeks) until disease progression is documented. If the disease has progressed before or at the EOT their follow-up is to be by phone every 3 months for survival status until death.

Patients from the PHP-OCM-301 trial that have completed treatment and are entering or already in the follow-up phase will be followed up for progression and survival on protocol PHP-OCM-301A.

NOTE: For the purpose of study report preparation, an interim database lock for analysis is planned approximately 24 months after the last patient last treatment. Long-term follow-up will continue in patients who survived longer than 24 months after the last patient last treatment. Data from the long-term follow-up will enventually be integrated with the interim locked database and will be summaried separately to be reported in a study report addendum.

Table 1 in the synopsis and Section 6 of the protocol have further details regarding the schedule of events.

2.1 Primary Objective

The primary objective of this study is to evaluate the objective response rate (ORR = complete + partial response) as determined by the Independent Central Review Commitee (IRC).

2.2 Secondary Objectives

- Duration of Response (DOR) as determined by IRC
- Disease control rate (DCR) as determined by the IRC
- Overall survival (OS)
- Progression-free survival (PFS) as determined by the IRC

2.3 Exploratory Objectives

- Time to Objective Response (TOR) as determined by IRC

- ORR, DOR, DCR, PFS and TOR as determined from the Investigator-assessed objective response
- Hepatic progression free survival (hPFS) as determined by IRC
- Hepatic objective response rate (hORR) as determined by IRC
- To document Quality of life (QOL)
- To evaluate the safety of treatment with Melphalan/HDS in patients with hepatic dominant metastatic ocular melanoma.
- To explore relationships between melphalan exposure and common or serious adverse reactions and clinical outcomes.
- To characterize the local and systemic exposure of melphalan administered by the HDS.

3. SAMPLE SIZE JUSTIFICATION

This is a single-arm, multi-center, open-label registration study to evaluate the efficacy and safety of treatment with Melphalan/HDS in patients with hepatic-dominant metastatic ocular melanoma. The planned sample size of approximately of 50 patients will provide a maximum width of the 95% confidence interval of ± 0.113 around the point estimate of ORR assuming the ORR is 0.210. The statistical assumption was generated based on a formal Meta-Analysis of historical data.

4. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

Data from protocol PHP-OCM-301 will be pooled with the data collected under the current protocol for the primary analysis of efficacy in the Intent-to-Treat (ITT) population and for safety analysis in the Safety population. That is, a PHP301A group will include approximately 50 patients from the PHP-OCM-301A study, and a PHP301 group will include approximately 30 patients from the randomized PHP-OCM-301 study to yield at least 80 total patients for PHP group for the ITT analysis. The BAC group from the randomized PHP-OCM-301 study will have approximately 30 subjects. Efficacy and safety data from Melphalon/HDS treatment for the PHP301A and PHP301 groups will be summarized separately, also, as a secondary analysis.

4.1 Intent-to-Treat (ITT)

The Intent-to-Treat (ITT) population will include all patients under the current protocol (PHP-OCM-301A) who have an eligibility date as well as all patients who were randomized to the Melphalan/HDS treatment arm under protocol PHP-OCM-301. The ITT population for the BAC group will include all subjects randomized to BAC in protocol PHP-OCM-301.

4.2 Safety

The Safety population will include all patients for whom a study treatment or procedure is attempted, regardless of whether they receive treatment. For Melphalan/HDS the attempted procedure is defined by the start of the "access procedures" (i.e., catheterization of femoral artery/hepatic artery, femoral vein/inferior vena cava, internal jugular venous line insertion).

All safety analyses will be based on the Safety population (unless specifically stated otherwise), and patients will be analyzed according to the study treatment which they have taken; that is, any patient that has Melphalan/HDS for any procedure/treatment will be in that arm for safety analysis.

4.3 BAC Subsets

Efficacy and safety data collected from patients randomized to the BAC treatment arm under protocol PHP-OCM-301 will be summarized separately. Patients randomized to the BAC arm may have received: dacarbazine (DTIC); transarterial chemoembolization (TACE); ipilimumab; or pembrolizumab, based on each institution's rank order of their BAC treatments based on their standard of care (SOC). Data regarding the therapy administered will be collected in the eCRF.

5. HANDLING OF DROPOUTS AND MISSING DATA

Missing or partial dates will be imputed, but no other data will be imputed. Most of the efficacy parameters are time to event variables, the analysis of which includes all ITT patients. While it is possible that some patients will have missing or partial date information for adverse events or concomitant medications, such date information should not be missing for the efficacy variables because they rely on scan dates or date of death.

Analyses that consider incidence rather than time to event will not be impacted by missing date information. Hence, the impact of missing data will primarily be observed for the analyses of the clinical laboratories and vital signs (e.g., where the parameter was not measured at a required time point). In many situations, there will often be other

measurements of the parameter within a time frame that is applicable. In such cases, the closest measurement within the appropriate time frame will be used for analysis. If such a measurement does not exist, then the patient will be excluded from the analysis of that variable at that time point.

When a patient has missing or partial date information for AEs or concomitant medications, the algorithms provided in Section 17 (Imputation of Dates) will be applied to the partial date information.

Indicator variables will be constructed to indicate which dates required such assignments.

With regard to study start and stop dates, if the study start date is missing, the date of initial treatment administration will be assumed to be the study start date. If the study end date is missing, the date when the patient completed the study (date of discontinuation or date of last visit) will be assumed to be the study end date.

6. STATISTICAL ANALYSIS CONSIDERATIONS

Unless specified otherwise, statistical testing will use a 2-sided test at the 0.05 significance level and will be considered exploratory. All nominal p-values will be reported as is without control for study-wide Type I error since all analyses are explortatry.

Typically, summary statistics for continuous variables will include the mean, standard deviation, median and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized using Kaplan-Meier (KM) methods (quartitles and 95% CI, number of events, number censored). KM figures will also be prepared if data warrant. For calculation of time-to-event endpoints except DOR, the start date will be the patient eligibility date for the PHP301A group and the randomization date for PHP301 group, unless otherwise stated. Data listings will be created to support each table and to present all data.

Electronic Case Report Form (eCRF) data and other data (core laboratories, PK, etc.) for all patients will be provided in Standard Data Tabulation Model (SDTM) datasets supplied as part of the submission. Any additional data listing supplied as part of the Clinical Study Report (CSR) will be sorted by investigative site and patient identification number, and patients will be identified in the listings by the investigator number concatenated.

All data listings, summaries and statistical analyses will be generated using Statistical Analysis Software (SAS) version 9.4 or later. Table, listings, and figures will be presented in

RTF format. Upon completion, all SAS programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

7. PATIENT ACCOUNTING AND DISPOSITION

7.1 Patient Accounting

Patient enrollment overall and by site will be tabulated for all patients included in the ITT population and the safety population.

7.2 Patient Disposition

The accounting and disposition of patients will be tabulated for all patients in the ITT population. In addition, frequency counts and percentages of patients' reported reasons for study discontinuation will be summarized.

A patient listing will be presented to describe treatment group, date of first and last dose, date of last visit or contact, total number of completed cycles, and the reason for ending the study for each patient.

7.3 Major Protocol Violations

Patients who violated some portion of the protocol determined as a major violation will be identified by the medical monitors and provided to Biostatistics via Excel spreadsheet prior to database lock. The protocol deviation spreadsheet will be imported to SAS to create the protocol deviation dataset for analysis. Protocol violators will be summarized by the number and percentage of patients by treatment group having a major protocol violation based on the ITT population. A listing of all protocol violations will also be provided.

8. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Responses for the individual inclusion/exclusion criteria will not be summarized. However, it will be retained in the SDTM database. Listings of inclusion/exclusion criteria responses will be provided.

8.1 Demographics

Demographic data will be summarized using descriptive statistics, including sample size, mean, median, standard deviation, and range for continuous variables and frequency counts and percentages for categorical data. These summaries will be based on the ITT population.

Demographic variables collected during the Screening phase include date of birth, gender, race, and ethnicity. Age at study entry, age group, gender, race, and ethnicity will be summarized and reported. Age at study entry will be based on the age of the patient on the date the informed consent is signed.

Age at study entry will be summarized as a continuous variable and will also be presented using the categories: Age ≥ 65 years and Age < 65 years. Gender, ethnicity, and race will also be displayed as categorical variables.

Patient height and weight will also be collected prior to the Treatment phase. Both variables will be reported in metric units (height in cm and weight in kg) and will be summarized as continuous variables.

Those patients who are missing measurements of the baseline variable being analyzed will not be included in the summary for that variable.Baseline Disease Characteristics

8.2 Baseline Disease Characteristics

During the Screening phase, information about date of diagnosis, and the date liver metastases were diagnosed will be collected. Information about prior treatments and procedures for melanoma, both therapeutic and adjuvant, will also be collected. The screening computer tomography (CT) and/or magnetic resonance imaging (MRI) scans will provide information about baseline tumor burden and the number and location of lesions.

8.2.1 Melanoma Diagnosis History

Date variables will be converted to several time interval variables according to the following definitions. For each, the start date will be the patient eligibility date for PHP301A group and randomization date for PHP301 group:

Time since diagnosis of primary tumor = "Start Date" - Date of diagnosis of primary tumor + 1 day

Time since diagnosis of liver metastasis = "Start Date" - Date of diagnosis of liver metastasis + 1 day

Time interval between primary diagnosis and metastasis to the liver = Time since diagnosis of liver metastasis –Time since diagnosis of primary tumor

Time interval variables will be reported in months and summarized as continuous variables.

8.2.2 Baseline Tumor Burden

Baseline hepatic tumor burden will be summarized as a continuous variable and will also be classified into groups (i.e., < 25%, ≥ 25% but ≤ 50%, and Unknown) and presented as a categorical variable.

The number of hepatic lesions (classified as: 1, 2, 3, 4, and 5 or more) and number of extra-hepatic lesions (classified as 0, 1, and 2 or more) will also be displayed. The number of extra-hepatic lesions will also be summarized as a binary variable that indicates their presence or absence (i.e., hepatic lesions only vs hepatic and extra-hepatic lesions). Six binary variables will be defined with respect to the presence/absence of extra-hepatic lesions in different parts of the body: lung, lymph node, bone (includes location descriptions such as spine, lumbar spine, pelvis, ribs, sacrum and skull), soft tissue (includes location descriptions such as subcutaneous, trunk and chest wall), brain, and other visceral (e.g., collapse small intestine and spleen).

Elevations in LDH can be used to determine if melanoma has metastasized or as a surrogate for tumor burden. Baseline LDH will be classified as either Elevated or Normal.

8.2.3 Prior Therapies

During the Screening phase, all prior interventions (radiation, surgery, and chemotherapy) that were associated with treatment of a patient's melanoma will be recorded in the eCRF. For each type of therapy the number of patients who received that type of therapy will be summarized. Prior therapies of each patient will also be presented in a listing.

8.3 ECOG Performance Status

ECOG performance status will be assessed within 4 weeks prior to treatment (protocol PFP-OCM-301A) or randomization (protocol PHP-OCM-301). The ECOG scale to be used is as described below:

0 = Fully active, able to carry on all pre-disease activities without restrictions (Karnofsky 90 to 100)

1 = Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70 to 80)

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 (Karnofsky 50 to 60)

3 = Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30 to 40)

4 = Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10 to 20)

ECOG performance status will be summarized as a categorical variable using level descriptions (0 = asymptomatic; 1 = symptomatic, completely ambulatory; 2 = symptomatic, <50% bed rest; 3 = symptomatic, ≥50% bed rest; 4 = bed bound).

8.3.1 Other Medical History

The other medical history of each patient will be presented in a listing.

9. EFFICACY ANALYSIS

The primary efficacy measurement is the Objective Response Rate (ORR). Secondary efficacy measurements include duration of response (DOR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS). The outcome related parameters (ORR, DCR and PFS) will have 2 sets of results: one set will be determined by an IRC and a second set will be determined by the Investigator). The results determinded by the IRC will be the primary and secondary efficacy endpoints whereas the results determined by the investigator will be evaluated as the exploratory endpoints.

The primary population for efficacy analyses and summaries will be the ITT population. A sensitivity analysis on the efficacy endpoints will also be conducted based on other subsets if data warrants.

A listing of all efficacy data, including tumor measurements, will be provided sorted by study center and patient number.

9.1 Primary Efficacy Analysis (ORR)

The primary efficacy endpoint, Objective Response Rate (ORR), will be determined by an Independent Central Review Commitee, and may be evaluated after all subjects have completed protocol therapy and all objective responses have been confirmed.

ORR is defined as the proportion of patients with a best overall response (BOR) of a confirmed complete response or partial response (CR+PR) determined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) based on IRC. Per RECIST:

CR: disappearance of all target lesions, any pathological lymph nodes (target or non-target) must be < 10 mm in short axis diameter;

PR: ≥ 30% decrease in the sum of the long axis diameters of the target lesions, using the baseline sum as reference.

For CR or PR, tumor measurements must be confirmed by repeat assessments ≥ 4 weeks after initial documentation.

The summary table for ORR will include the number of patients for each best response category CR, PR, SD, PD, and Not Evaluable/Not Assessed for the ITT population. The number of patients with a best response of PR or CR (i.e. ORR) for each treatment group will be summarized using frequency counts, percentages, and exact 95% confidence intervals.

An exploratory analysis will compare the ORR between the PHP group and the BAC group using Fishers Exact Test. The difference between the groups (PHP vs BAC) in observed ORR along with 95% CI (using the exact method) will also be provided.

9.2 Secondary Efficacy Analysis

9.2.1 Duration of Response (DOR)

Duration of Response (DOR) is defined as the time from first documented confirmed response of CR or PR based on RECIST v1.1 determined by the IRC to the first documented progression or death due to any cause. DOR is only evaluated for subjects with a confirmed response of CR or PR. Censoring criteria will be the same as for PFS (see Section 9.2.4).

The summary table for DOR will include estimates based on the Kaplan-Meier methods (number of events, number censored, median, 25%tile, and 75%tile estimates and 95% confidence limits, Kaplan-Meier figures) for each treatment group.

9.2.2 Disease Control Rate (DCR)

Disease Control Rate (DCR) will be determined from BOR as assessed by IRC. DCR is defined as the proportion of patients with a best overall response of CR of any duration, PR of any duration, or stable disease (SD) for a minimum of 12 weeks from the eligibility date for PHP301A patients (and randomization date for PHP301 patients).

The summary table for DCR will include the number of patients for each best response category CR, PR, SD, PD, and Not Evaluable/Not Assessed for the ITT population. The number of patients with a best overall response of PR or CR or SD (i.e., DOR) for each treatment group will be summarized using frequency counts, percentages, and exact 95% confidence intervals.

9.2.3 Overall Survival (OS)

Overall Survival will be measured from the eligibility date for PHP301A patients (and randomization date for PHP301 patients) to the date of death (included all-cause mortality). When analysis for the study report is conducted (24 months after last patient last treatment), all patients will have been monitored for either their death date or will be censored on the date the patient was last known to be alive.

Kaplan-Meier methods (number of events, number censored, median and 95% confidence limits, Kaplan-Meier figures) will be utilized to summarize overall survival for each treatment group.

An exploratory analysis will compare the PHP group and the BAC group using a 2-sided log-rank test at the 0.05 significance level. A second exploratory analysis utilizing Cox proportional hazards models will be performed with main effect of treatment and covariates of investigative site (US vs EU) and extent of liver involvement (1-25% vs 26-50%).

In addition, a forest plot of the confidence intervals for the overall and by potential prognostic factors will be presented as a check for internal consistency of overall survival.

Overall survival will be updated when the study long term follow-up is completed. The final OS results will be reported in a study report addendum.

9.2.4 Progression Free Survival (PFS)

PFS is defined as the time from the eligibility date for PHP301A patients (and randomization date for PHP301 patients) to the first occurrence of disease progression (either hepatic or extra-hepatic), as determined by the IRC using RECIST (version 1.1), or death from any cause. Patients without a documented disease progression or death will be censored according to the following rules:

(1) If patients are removed from the treatment because of the progression of existing lesions or the development of new lesions which requires initiation of new or different systemic treatment regimens, then they will be censored at the time of their removal from the treatment;

(2) If patients do not have post-baseline tumor assessment or clinically determined progression and have not died, then PFS will be censored at Day 1;

(3) If patients do not have documented disease progression and have not died at the time of analysis, the PFS will be censored at last tumor assessment date;

(4) If patients are lost-to-follow up without documented progression or death, the PFS will be censored at last tumor assessment date;

(5) If a patient has two or more consecutive missing visits, the PFS will be censored at the time of last complete tumor assessment no matter whether the patient has a PFS event or not after the missing visit.

The analyses for PFS will follow the same approaches as described for the OS

For sensitivity analysis on PFS, Cox proportional hazards models will also be employed as described for OS.

9.3 Exploratory Endpoints

9.3.1 Time to Objective Response (TOR)

TOR will be summaries for each treatment group with descriptive statistics (number with events, number censored25%tiles, 50%tiles, and 75%tiles and 95% confidence intervals using Kaplan-Meier time-to-event analysis techniques. Kaplan-Meier figures will also be presented.

9.3.2 Investigator-assessed Outcomes of ORR, DOR, DCR, PFS and TOR

Investigator-assessed outcomes will be summarized descriptively following the same approach as those determined by the IRC (see Sections 9.1 and 9.2).

9.3.3 Hepatic Progression Free Survival (hPFS)

Hepatic PFS (hPFS) is defined as the time from randomization or from confirmed eligibility to the first occurrence of intra-hepatic disease progression, as determined by the IRC on imaging studies using RECIST 1.1 or death from any cause.

hPFS on the ITT population will be summarized for each treatment group with descriptive statistics (number with events, number censored, 25%tiles, median, 75%tiles, and 95% confidence intervals) using Kaplan-Meier time-to-event analysis techniques. Kaplan-Meier figures will also be presented.

9.3.4 Hepatic Objective Response Rate (hORR)

Hepatic Objective Response Rate (hORR), is defined as the proportion of patients with tumor size reduction when evaluating hepatic lesions after study treatment as determined by the IRC using RECIST version 1.1.

The summary table for hORR will include the number of patients for each best response category CR, PR, SD, PD, and Not Evaluable/Not Assessed for the ITT population. The number of patients with a best response of PR or CR for each treatment group (i.e., hORR) will be summarized using frequency counts, percentages, and exact 95% confidence intervals.

9.3.5 Quality of Life

The FHSI-8 quality of life instrument will be scored per standard methodology developed for the questionnaire. Results will be compared using descriptive statistics between treatment groups; changes from baseline will also be calculated. Analyses of individual questions relevant to side effects from each treatment may also be performed.

9.4 Exploratory Subgroup Analysis

If data warrants, subgroup analyses will be performed by forming subsets of patients from the ITT population in order to evaluate the robustness of the results based on the primary efficacy analysis. These univariate analyses may include, but are not limited to, comparisons between treatment groups based on several baseline characteristics such as:

- Age (<65 years vs ≥65 years),
- ECOG performance status (0,1 vs other),
- Gender (Female vs Male),
- Patients region where they live (US vs Europe),
- Extent of liver involvement (1-25% / 26-50%),
- Race (American Indian or Alaska Native, Asian , Black or African American, Native Hawaiian or Other Pacific Islander, White),
- Ethnicity (Hispanic or Latino vs. Not Hispanic or Latino),
- Additional efficacy subgroup analyses for exploratory purposes will be identified at the time of statistical analyses and fully described in the clinical study report.

A forest plot of the OS treatment group hazard ratios for each subgroup will be presented if data warrant.

10. SAFETY ANALYSIS

To evaluate the safety of treatment with Melphalan/HDS in patients with hepatic-dominant metastatic ocular melanoma, all patients in the Safety Population will be included in the safety summaries.

All AEs will be coded by system organ class and by preferred terms using MedDRA dictionary (version 15.0 or later). The National Cancer Institutes Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 4.0.3) will be used to classify the severity of AEs. Relationship of AE to study therapy will be classified by the investigator as: 1) to study drug, 2) to study procedure, 3) to study device, 4) to study disease, 5) other causes, 6) unrelated.

Only descriptive statistics will be utilized for safety analysis.

Additional safety assessments may include:

- To explore relationships between melphalan exposure and common or serious adverse reactions and clinical outcomes; and
- to characterize the local and systemic exposure of melphalan administered by the HDS.

10.1 Study Medication Administration

10.1.1 Melphalan/HDS

The melphalan infusion time, dose administered, and if full dose not administered the reason why; will be reported by cycle along with the reason why patients did not receive further cycles (i.e., discontinued melphalan). The cumulative dose administered across all cycles for each patient will also be reported.

The reasons for discontinuation will include: death, disease progression (overall and for hepatic and extra-hepatic separately), adverse event, patient decision, investigator's decision, lost to follow-up and completed Melphalan/HDS therapy.

10.1.2 Best Alternative Care (BAC)

Patients randomized to BAC could receive any treatment as noted in Section 5.3 based on each institution's rank order of their BAC treatments based on their standard of care. The BAC therapy will be listed only.

10.2 Extent of Study Drug Exposure

Study treatment exposure will be summarized in the Safety Population.

Analyses for the extent of exposure will focus on the duration of the safety surveillance period which will be broken into cycles. As mentioned in Section 17.3, the cycle start date will either be the date the Melphalan/HDS treatment procedure begins, or the date treatment was administered for BAC, while the cycle end date will be either the day prior to the next cycle or the date the patient withdrew from treatment.

Cycle Length will be defined as:

Cycle Length = Date of Cycle End – Date of Cycle Start +1.

Extent of Exposure will be defined as the cumulative cycle length which is the sum of the cycle lengths across cycles. Cycle length (in days) will be descriptively presented by cycle along with the number of patients who were delayed from starting the cycle (Cycle 2 and beyond). Since the planned cycle length for Melphalan/HDS treatment is 6 weeks with an acceptable delay for an additional 2 weeks (i.e., 8 weeks in total), the cycle will be considered delayed if the previous cycle was 9 weeks or greater.

This report will be generated using the first 6 cycles (the maximum number of Melphalan/HDS treatment cycles allowed) for Melphalan/HDS versus BAC.

Extent of exposure (in days) will be compared between the randomized groups using the Wilcoxon Rank Sum test. In addition, the numbers of patients treated for $\geq 1, \geq 2, \ldots \geq 6$ cycles will be presented by treatment group, along with the median cycle length for cycles 1 through 6.

All dose modifications and treatment delays and associated AEs will be summarized in a listing.

Study treatment exposure will be summarized in the Safety Population.

10.3 Adverse Events

Adverse Events (AEs) will be collected from the day the patient gives informed consent until 30 days after the final dose of study drug or until resolution of all serious adverse events (SAEs). Adverse events will be reported as:

- Pre-Treatment AEs

- All Treatment-Emergent AEs (TEAE)
- Adverse events of special interest
- TEAEs by time periods for PHP group only based on time of occurrence in relation to the Melphalan/HDS procedures:
    - Peri-Procedure TEAEs: includes the events occurred on the day of procedure to 3 days post-procedure or hospital discharge, whichever occurs earlier
    - Post-Procedure TEAEs: includes events occurred 3 days post-procedure / discharge to the day prior to the date of the next treatment cycle
    - Post-Treatment TEAEs: include events that the patient's personal physician believes could be related to prior study drug treatment or procedures with an onset date more than 30 days after the last administration of melphalan.

lost to follow-up and completed Melphalan/HDS therapy.

10.3.1 All Treatment-Emergent Adverse Events (TEAEs)

All AEs with an onset date of the planned procedure date and through the end of the study will be considered treatment-emergent adverse events (TEAEs). Adverse events with a missing start date will be classified as TEAE.

All summaries of TEAE will be summarized for each treatment group, presenting the number of patients with at least one TEAE, for each system organ class (SOC), and for each preferred term (PT). SOCs will be presented in alphabetical order; PTs will be presented in order of overall decreasing frequency. A patient with multiple TEAEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

The incidence of TEAEs by CTCAE severity and by relationship to study therapy (i.e., to study drug, to study procedure, to study device, to study disease, other cause, or unrelated) will be tabulated similarly. Each patient will be counted only once within a system organ class or a preferred term by using the TEAEs with the highest severity grade.

All information pertaining to TEAEs noted during the study will be listed per patient, detailing verbatim, preferred term, system organ class, start date, stop date, severity and relationship to study therapy. TEAE onset will be shown relative (in number of days) to the day of the first study treatment.

No statistical testing will be performed for comparisons of TEAEs.

10.3.1.1 Peri-Procedure TEAEs

A Peri-Procedure Period is defined as the period from the date of the planned procedure until patient discharge from the hospital or 3 days, whichever is earlier.

10.3.1.2 Post-Procedure TEAEs

A Post-Procedure Period is defined as the time from the end of the peri-procedure period (Section 10.3.1.3., below) until the day prior to the date of the next treatment cycle. For the last treatment cycle, the end of the post-procedure period will be 30 days after date of the final study dose or the date of death, whichever is earlier. Any adverse event with an onset date more than 30 days after the last administration of Melphalan, which is determined by the investigator as either study drug or procedure-related will be defined as Post-Treatment TEAEs (Section 10.3.1.3).

10.3.1.3 Post-Treatment TEAEs

At the study **drug treatment** completion/early termination visit, each patient should report any subsequent AEs that the patient's personal physician believes could be related to prior study drug treatment or study procedures. This will include any adverse event with an onset date more than 30 days after the last administration of melphalan. These post-**treatment** AEs will be summarized and reported through patient listings.TEAEs Leading to Discontinuation from Study

10.3.2 TEAEs Leading to Discontinuation from Study

All adverse events leading to discontinuation from study will be summarized using the same reports used for TEAEs and by period in which the TEAE occurred (peri-procedure, post-procedure, or post treatment).

10.3.3 Serious TEAEs

An SAE is an AE that met one or more of the following criteria:

- Is fatal
- Is life-threatening
- Requires or prolongs hospitalization
- Is significantly or permanently disabling or incapacitating
- Constitutes a congenital anomaly or a birth defect or

- Jeopardizes the patient and may require medical or surgical intervention to prevent one of the above outcomes

Serious TEAEs will be summarized using the same reports used for TEAEs and by period in which the TEAE occurred (peri-procedure, post-procedure, or post treatment).

10.3.3.1 TEAEs Resulting in Death

All deaths will be summarized using the same reports used for TEAEs and by period in which the TEAE occurred (peri-procedure, post-procedure, or post treatment).

10.3.3.2 Hospitalizations

The number and percent of patients plus the total number of hospitalizations will be reported for each of the following type of hospitalizations: total, hospitalizations for study treatment, treatment hospitalizations prolonged due to an AE, hospitalizations due to an AE, and other hospitalizations. In addition, descriptive statistics will be presented by cycle for duration of the procedure-related hospitalizations and TEAEs requiring or prolonging hospitalization.

10.4 Clinical Laboratory Tests

Due to the discrepant nature of the lab collection between the treatment groups, analyses of clinical laboratories will focus less on comparisons and more on extreme laboratory values on the Melphalan/HDS group.

Analyses of clinical laboratories will focus on blood chemistry and hematology, specifically, sodium, potassium, total bicarbonate, creatinine, non-fasting glucose, albumin, total calcium, total magnesium phosphate, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, total bilirubin, uric acid, creatine phosphokinase (CPK), white blood cells (WBC), hemoglobin, hematocrit, platelets, MCV, MCHC, RDW, MPV, and absolute neutrophils (ANC). Other labs and urinalysis results will be provided in patient listings.

The intracycle change for a laboratory parameter will be defined as the difference between the last measurement during the cycle and the cycle baseline value. Descriptive statistics for the cycle baseline value, the last measurement in the cycle, and the intracycle change will be provided by cycle. Additionally, for each laboratory analyte, a CTCAE shift table of worst post-baseline grade versus baseline grade will be provided. The rows and columns of the shift table will be 0, 1, 2, 3, 4, Missing, and Total.

Additionally for each laboratory analyte, a CTCAE shift table of worst post-baseline grade versus baseline grade will be provided. The rows and columns of the shift table will be 0, 1, 2, 3, 4, Missing, and Total.

All laboratory data, values, units, normal reference range, and out-of-range flags collected in the clinical database will be included in by-patient listings for further medical review.

10.5 Vital Signs and Physical Examination

Like clinical labs, the collection of vital signs differed between the treatment groups. Thus, analyses of vital signs will focus primarily on the Melphalan/HDS group.

The pre- and post-procedure measurements include; temperature, pulse, respiration rate, and blood pressure,. They will be used to analyze the intracycle change. Descriptive statistics for the cycle baseline value, the last measurement in the cycle, and the intracycle change will be provided by cycle.

For weight, descriptive statistics of the last measurement during the treatment period and the change will be provided.

Clinically significant abnormalities on physical examination noted at baseline will be presented as pre-existing conditions. New clinically significant abnormalities (≥ Grade 3) reported during the study will be presented as AEs.

All vital sign parameters will be included in by-patient listings for further medical review.

10.6 ECGs

ECGs are logged in a separate eCRF module. Only the date of the procedure, a finding of Normal or Abnormal, and the abnormality are recorded. To help assess safety, a listing of the abnormalities observed in patients who had a normal ECG prior to initiating treatment/procedure will be provided.

10.7 ECOG

For ECOG performance status, shift tables of the worst post-baseline score versus the baseline score and the best post-baseline score versus the baseline score will be provided. The rows and columns of the shift table will be 0, 1, 2, 3, 4, Missing, and Total.

10.8 Concomitant Medications

Concomitant medications will be defined as medications taken on or after the date and time of the initial attempt to administer study drug or a study procedure and on or before 30 days after the date of the last treatment.

The reporting of concomitant medications will be by WHODD ATC (anatomical class) and preferred drug name (often the generic drug name).

A report of all concomitant medications taken during the study will be prepared by treatment using the Safety Population, but special attention will be given to the administration of concomitant medications during the Peri-Procedure and the Post-Procedure Periods. The period specific reports will use the BAC Subset in place of All BAC, since the drug classes of special interest are related to chemotherapeutic or procedural intervention.

During the Peri-Procedure Period, all classes of drugs, except the anti-tumor agents, will be examined. The incidence of each drug will be presented within the Peri-procedure period. During the Post-Procedure Period, the following drug classes will be examined: blood products, growth factors, antibiotics/anti-infectives, and anti-tumor agents.

All reports in this section will provide the number of patients who received a concomitant medication by preferred drug name, drug class, and overall. A patient who received multiple agents within a drug class will only be counted once for that class. Similarly, a patient who received drug multiple times will only be counted once for that drug.

11. PHARMACOKINETIC (PK) ANALYSIS

A separate analysis plan will detail the pharmacokinetic analyses to be performed. The PK analysis plan is included as Appendix E to the study protocol.

12. SAFETY MONITORING

The DSMB will meet approximately every 3 months (quarterly) to review adverse events, serious adverse events, laboratory values, vital signs, and other safety-related data. In the intervals between planned meetings, any serious adverse event that is considered by the investigator to be unexpected and related to the study agent will be reported to the DSMB within 24 hours of receipt. The DSMB will be provided with summaries of adverse events, serious adverse events, laboratory measurements, deaths and IND safety reports. The DSMB will make recommendations to stop, continue, or modify the trial based on these safety

reviews. Section 9.2 of the DSMB charter provides additional details regarding specific safety rules for interrupting or terminating the study.

Unplanned meetings may be called at any time by the DSMB Chairperson or Sponsor should questions of patient safety arise.

In addition to the safety monitoring described above, the DSMB will evaluate the safety data after the first 20 patients have been treated. A report describing in detail any significant findings in the safety profile, discontinuations due to adverse events, serious adverse events, and common adverse events will be reported to FDA.

To summarize the planned DSMB meetings:

SAFETY REVIEW TIMELINE	DATA REVIEW BY	TYPE OF DATA
• Review of unexpected and related SAEs in real time and cumulative monthly reports of SAEs, AEs and safety lab listings • Review of safety data summary and convene scheduled DSMB Meeting quarterly • Review of safety summary report of first 20 patients treated • Review of safety and efficacy data and convene scheduled DSMB Meeting at interim analysis at approximately 50% total events (96/192) • Scheduled DSMB Meeting once Melphalan/HDS treatment for all patients enrolled has been completed (30 days after the last Melphalan/HDS administration)	Entire DSMB	• Procedure-specific safety monitoring • Common and serious AE listing • Protocol deviations listing • Enrollment summary • Dose modifications • Holds and discontinuations

13. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

Statistical analysis section in the protocol was amended accordingly to support the protocol amendment. This document is prepared according to the updated statistical analysis section of the amended protocol.

14. CONVENTIONS

Unless otherwise noted, data will be summarized in tabular format by treatment groups. Baseline summaries will also include a total summary column.

The precision of original measurements will be maintained in summaries, when possible. Means, medians and standard deviations will be presented with an increased level of precision; means and medians will be presented to one more decimal place than the raw data, and the standard deviations will be presented to two more decimal places than the raw data.

Summaries of continuous variables that have some values recorded using approximate values (e.g., < or ≥) will use imputed values. The approximate values will be imputed using the closest exact value for that measurement. For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, if the round-off unit is the ones place (i.e., integers), values ≥ XX.5 will be rounded up to XX+1 while values < XX.5 will be rounded down to XX.

Percentages will be based on available data and denominators will generally exclude missing values. For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the patients discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.

Unless otherwise specified, percentages will be calculated based on the number of patients specified by the appropriate population definition.

For adverse event incidence tables:

- The order of SOCs presented in tables will be according to the internationally agreed order of SOCs according to MedDRA. Within each SOC, the preferred terms will be shown in alphabetic order.
- Patients who have multiple events in the same SOC and/or preferred term will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of AEs by severity, only the highest severity of AE will be counted at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of related AEs, patients with more than one related AE will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables.

15. DEFINITION OF STUDY TIME POINTS

15.1 Definition of Baseline

For the efficacy parameters based on imaging data, study baseline for a patient will be the last evaluable scan collected either within the patient eligibility date for PHP301A group and the randomization date for PHP301 group, or on or before the first dose of study medication.

For the safety parameters study baseline for a patient will be the last evaluation of the parameter before the first attempt to administer a study treatment or procedure. This final value should be the most representative of the patient's condition before dosing.

A baseline value will also be defined for each cycle. The cycle baseline value will be the last evaluation of the safety parameter before the attempt to administer a study treatment or procedure for that cycle. To avoid having the cycle baseline be too influenced by treatment from the previous cycle, the evaluation must be collected within the 7 days prior to the cycle treatment.

15.2 Definition of Post baseline Time Windows

The post baseline time period is divided into a sequence of treatment cycles (the On-Study Period) and a follow-up period. Each treatment cycle will be further divided into the following

- A Peri-Procedure Period is defined as the period from the date of the planned procedure until patient discharge from the hospital or 3 days, whichever is earlier.
- A Post-Procedure Period is defined as the time from the end of the peri-procedure period until the day prior to the date of the next treatment cycle. For the last treatment cycle, the end of the post-procedure period will be 30 days after date of the final study dose or the date of death, whichever is earlier.

These subdivisions are related to the administration of Melphalan via the Hepatic Delivery System (HDS).

- The Follow-up Period commences once the patient has completed or been withdrawn from treatment. During the follow-up period, patients will be periodically evaluated for disease progression (if not already present) and survival.

15.3 Definition of Study Day and Cycle Day

To align all patients' progress during the study with a single point of reference, each date collected during the study will be converted to Study Day, defined as follows. The start date will be the patient eligibility date for PHP301A group and randomization date for PHP301 group:

Study Day = Date – "Start Date" +1.

Similarly, for each cycle Cycle Day will be defined as:

*Cycle Day = Date – Date of Cycle Start +1*if (Date/Time >= Date/Time of Cycle Start).*

The cycle start date will either be the date the Melphalan/HDS procedure is started, or the date treatment was administered for BAC.

16. STANDARD CALCULATIONS

Variables requiring calculation will be derived using the following formulas:

Study day – For a given date (date), study day is calculated as days since the date of first dose of study drug (firstdose):

Study day = date – firstdose + 1, where date ≥ firstdose

Study day = date – firstdose, where date < firstdose

Days – Durations, expressed in days between one date (date1) and another later date (date2), are calculated using the following formula: *duration in days = (date2-date1).*

Weeks – Durations, expressed in weeks between one date (date1) and another later date (date2), are calculated using the following formula: *duration in weeks = (date2-date1)/7*.

Months – Durations, expressed in months between one date (date1) and another later date (date2), are calculated using the following formula: *duration in months = (date2-date1)/30.4.*

Years – Durations, expressed in years between one date (date1) and another later date (date2), are calculated using the following formula: *duration in years = (date2-date1)/365.25*.

Minutes – Durations, expressed in minutes between one time point (time1) and another later time point (time2), are calculated using the following formula: *duration in minutes = (time2-time1)/60.*

1 pound = 0.454 kg.

1 inch = 2.54 cm.

Age – The patient's age is calculated as the number of years from the patient's date of birth to the date of randomization into the study:

Age = ([Randomization Date - Date of Birth] / 365.25).

Time-to-Event endpoints – will be reported in months, where the number of months is derived from days to event by dividing by 30.4 (e.g. 365.25/12).

17. IMPUTATION OF DATES

Incomplete Cancer Diagnosis

If day is missing, day will be set to 15th of the month, or date of first dose, whichever is earlier. If month and day are missing, month and day will be set to July 1st, or date of first dose, whichever is earlier.

Adverse Event

If onset date is completely missing, onset date is set to date of first dose unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.

If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dose, then set month and day to month and day of first dose unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.
- If year < year of first dose, then set month and day to December 31st.
- If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing:

- If year=year of first dose and if month = month of first dose then set day to day of first dose date unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.
- if month < month of first dose then set day to last day of month
- if month > month of first dose then set day to 1st day of month
- if year < year of first dose then set day to last day of month
- if year > year of first dose then set day to 1st day of month

For all other cases, set onset date to date of first dose unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.

Concomitant Medications

If start date is completely missing: start date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to January 1.

If year and month are present and day is missing: set day to 1st day of month.

If end date is completely missing: end date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to December 31.

If year and month are present and day is missing: set day to last day of the month.

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009). No other imputation of missing data will be performed.

18. REFERENCES

1. Protocol No. PHP-OCM-301 dated 8 June 2015.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
4. International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 14.0 Reston, Virginia, USA; 2008.
5. WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. June 2012 B Format edition. Uppsala, Sweden; 2008.
6. SAS Institute Inc. SAS Version 9.1. Cary, NC, USA; 2002-2003.

19. SCHEDULE OF EVENTS

Please see the Schedule of Events in Section 6 of the Protocol.