16.1.9 Documentation of statistical methods

- Statistical Analysis Plan - Version 1.0

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Mundipharma-EDO GmbH
Protocol #: EDO-S101-1004

PHASE 1/2 OPEN-LABEL TRIAL OF TINOSTAMUSTINE CONDITIONING AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR SALVAGE TREATMENT IN RELAPSED / REFRACTORY MULTIPLE MYELOMA (TITANIUM 1)

Statistical Analysis Plan

Version 1.0
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I. Introduction

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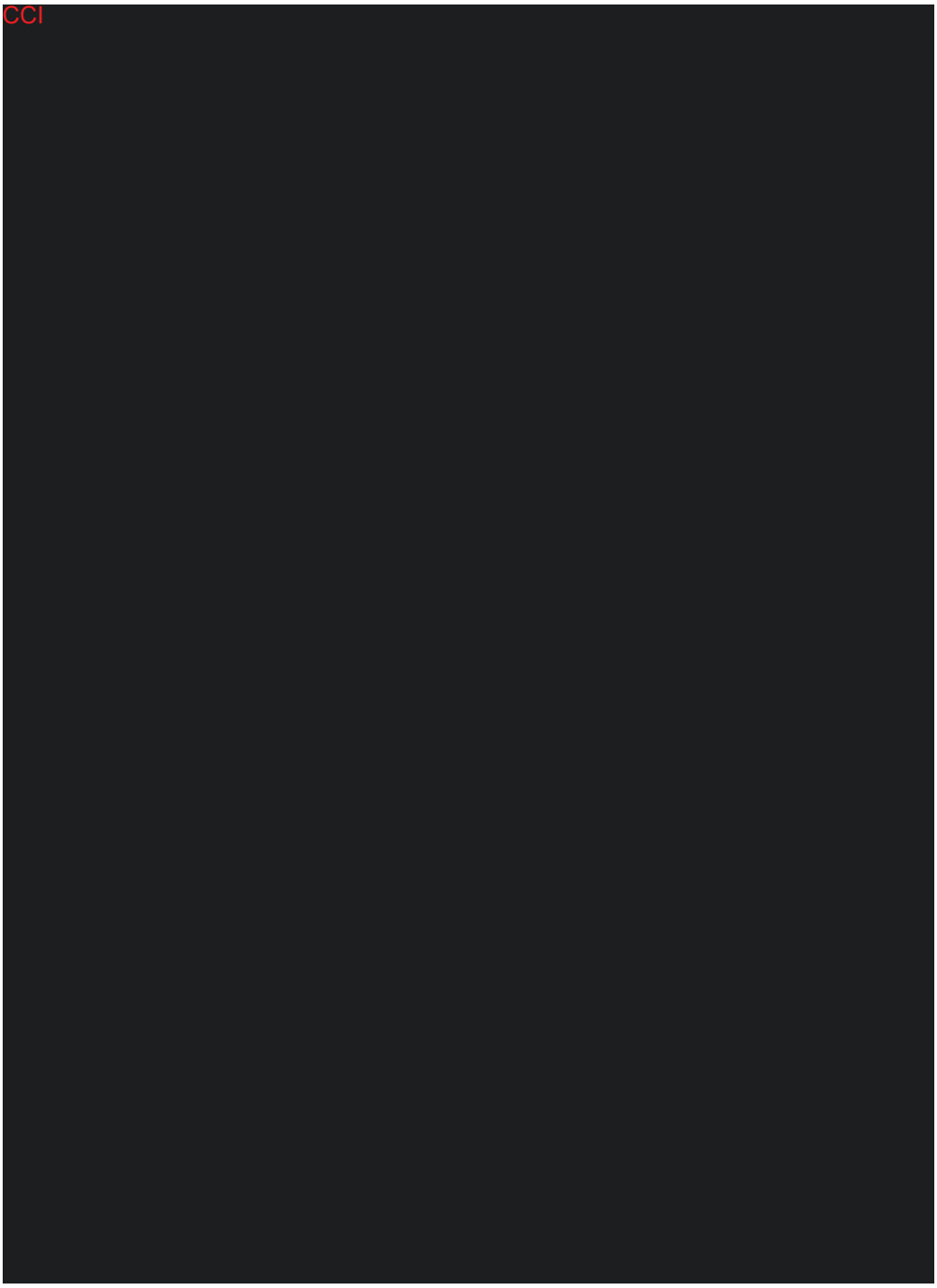

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B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on version 2 of Protocol EDO-S101-1004, which will incorporate Amendment 1.

Version	Approval Date	Salient Changes, if any*
Original	22 March 2018	
2	18 June 2018	

* Changes expected to require accommodation in analysis plan.

This SAP will govern the analysis of data from this study. The plan may be modified until database lock. Any deviations from the analysis plan, including any after the time of database lock, will be documented as such in the study report.

C. Study Conduct Changes

Based on safety signals this study was halted, and later discontinued, to enhance the protection of subjects and to allow for further evaluation of the investigational product. As a result, the following analyses described in the protocol are no longer appropriate or applicable:
Phase 1 – number and frequency of DLTs, neutrophil and platelet engraftment failure, treatment-related mortality (TRM) and transplant-related non-hematologic Grade 3 toxicity over time through Day 30, results and duration of cytopenia, change from baseline in standard hematology and coagulation laboratory test
Phase 2 – neither the primary nor secondary objectives/endpoints will be explored.

II. Protocol Objectives and Analysis Endpoints

Objective	Endpoint (Assessment)
Phase 1	
Primary: • Establish the safety, toxicity, and maximum tolerated dose (MTD) of the tinostamustine conditioning regimen. • Identify the recommended Phase 2 dose (RP2D) of tinostamustine for use in the	• The number and frequency of DLTs, adverse events (AEs), serious adverse events (SAEs), neutrophil and platelet engraftment failure, treatment-related mortality (TRM) and transplant-related

Objective	Endpoint (Assessment)
Phase 2 portion of the study.	non-hematologic Grade 3 toxicity over time through Day 30; as well as change from baseline in standard laboratory test, results and duration of cytopenia.
Secondary: • Investigate the pharmacokinetics (PK) of tinostamustine.	• Assessment of PK parameters.
Phase 2	
Primary: • Investigate the efficacy of the tinostamustine conditioning regimen at the RP2D dose.	• Objective response rate (ORR), and in patients treated at the RP2D (in Phases 1 and 2) who achieve CR, minimal residual disease-negativity (MRD-N) at Day 100 (± 7 days) post-ASCT.
• Investigate the safety of the tinostamustine conditioning regimen.	• The number and frequency of adverse events (AEs), serious adverse events (SAEs), neutrophil and platelet engraftment failure, treatment-related mortality (TRM) and transplant-related non-hematologic Grade 3 toxicity over time through Day 30; as well as change from baseline in standard laboratory test results and duration of cytopenia.
Secondary: • Evaluate the PK of tinostamustine.	• Assessment of PK parameters.

III. Study Design

A. Design Overview

This is a 2-part, international, multi-center, open-label study of salvage treatment with tinostamustine conditioning followed by ASCT in patients with relapsed/refractory MM.

Phase 1 of the study employs a standard 3+3 dose escalation design with the objective of defining the DLTs of the tinostamustine conditioning regimen and defining the MTD and RP2D for use in the Phase 2 portion of the study. The initial dose of tinostamustine in the Phase 1 portion of the study is 180 mg/m^2, with escalation to 220, 260, and then 300 mg/m^2 or higher planned. If the 180 mg/m^2 dose level is not tolerable, then a lower tinostamustine dose of 160 mg/m^2 will be explored. Furthermore, if the 300 mg/m^2 is tolerable, with <33% of patients experiencing a DLT at this dose level, a dose higher than 300 mg/m^2 may be explored. The Safety Review Committee can make a decision to stop dose escalation or explore intermediary doses at any time.

Phase 2 of the study employs a 2-step sequential design. In Stage 1 of Phase 2, up to 31 patients initially will be enrolled. Recruitment will continue during the evaluation period needed for Stage 1 of Phase 2. If ≤25 patients of these initial 31 patients experience a response, then no additional patients will be enrolled. However, if >25 patients in Stage 1 of Phase 2 experience a response, then enrollment in this cohort will continue (Stage 2), with up to 71 patients enrolled. In Phase 2 of the study, all patients will receive tinostamustine at the RP2D administered in Phase 1 according to the same schedule.

B. Study Population

Individuals eligible to participate in this study must meet the criteria listed in Sections 5.1 and 5.2 of the protocol.

C. Sample Size Predictions

Across both Phases 1 and 2 of the study, a total of up to ~86 patients may be enrolled.

A formal sample size determination/power calculation was not performed for the first phase of the study. Based on experience from previously published similar studies, a total number of 9 (minimum) to 12 (maximum) patients in the dose escalation stage of the study are foreseen.

For Phase 2 of the study, superiority testing will be performed to investigate the null hypothesis that the primary endpoint of responder rate is below or equal to the gold standard against the alternative hypothesis that it is higher than the gold standard. The gold standard is assumed to be 77.5% and a one-sided chi-square test will be performed at the 2.5% level of significance. For power considerations, the alternative working hypothesis is that the responder rate for the study treatment is at least 90%.

Using the methodology proposed by Simon and per the minimax design, 31 patients are to be enrolled in Stage 1. If >25 of 31 patients (in the Full Analysis Set [FAS]) in Stage 1 experience a response to treatment, then enrollment will continue into Stage 2, with up to 40 patients planned to be enrolled. However, if ≤25 patients in Stage 1 experience a response to treatment, no further patients will be enrolled (in the ongoing Stage 2 recruitment). Thus, a total of up to 71 patients will be enrolled in Phase 2.

If the total number of patients who experience a response is ≥ 62 of 71, then the study is considered a success.

D. Treatment Randomization

This is a non-randomized study. A patient will be considered enrolled when the patient has been consented and screened and when all eligibility criteria have been confirmed in the eCRF (electronic case report form).

E. Assessment Schedule

Please refer to Table 1 of the protocol for the schedule of assessments.

Visits that subjects make to the clinic outside the assessment schedule are recorded as unscheduled visits.

IV. Interventions

A. Conditioning

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CCI The drug substance is a class 4 cytotoxic agent and should be handled with care by experienced health care professionals. For administration, tinostamustine powder will be reconstituted with 20 mL saline (0.95) and the solution will be further diluted with saline to a final volume of 50 mL. Tinostamustine is to be administered IV through a Peripheral vein over 1 hour on Day -1.

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B. ASCT Infusion

Patients will receive ASCs on Day 1. The ASCs will be infused via a central venous catheter using standard blood infusion tubing, per standard institutional practice.

V. General Analytical Considerations

A. Data Sources

All data in the clinical database of this study will be collected via electronic case report forms (eCRFs) through remote data entry into InForm.

ECG data will be received via electronic data transfers from ERT.

In addition, PK serum data will be received via electronic data transfers from CSM for the analysis of PK parameters.

Sections 10.2.1 and 12 of the protocol provide additional details regarding study management.

B. Definition of Baseline

Tinostamustine is given 24 hours pre-ASCT on Day -1 (conditioning). Screening or last available observation prior to the tinostamustine dose will be considered as baseline. Where assessments are made the day of treatment that are scheduled per protocol to take place prior to treatment, it will be assumed that these pre-dose assessments will be baseline assessments.

The 'study day' variable in SDTM and ADaM is intended to capture the number of days since first exposure to the study treatment. Therefore, to comply with FDA guidelines, there will be no 'study day' value of 0. The conditioning dose of tinostamustine will start with 'study day' 1, and the ASCT will start with 'study day' 2. This 'study day' variable is separate from the time and events schedule specified in the protocol, where conditioning and ASCT would have taken place on Day -1 and Day 0, respectively. Therefore, any events after the tinostamustine dose, will be calculated as event date plus (+) number of days since the date of tinostamustine dose ('study day' 1). For any events prior to the tinostamustine dose date, the study date will be calculated as event date minus (-) the date of the tinostamustine dose date.

The data will be analyzed according to the visits recorded in the eCRF; no analysis windows will be applied.

C. Missing Data

Unless stated otherwise, missing data will not be replaced with imputed values. When relevant, sections below will address how missing data will be handled for the particular analyses.

D. Covariate Adjustment in Primary Analysis

No adjustments for covariates are planned for the analysis of primary or secondary endpoints.

E. Sample Size Reassessment

Not applicable.

F. Interim Analyses or Timing of Analyses

There will be no interim analyses for this study.

G. Test Sizes

Not applicable.

H. Multiple Comparisons

Aside from the control of Type I error in the primary analysis of the primary endpoint, no control for the effect of multiple comparisons is planned.

I. Analysis Populations

Four analysis populations will be defined for use with various analyses. The following table illustrates the relationship between each population and the analyses for which the data from the population will be used.

Analysis	Analysis Population			
	Safety	Full Analysis Set	Per-Protocol	Pharmacokinetic
Baseline	X			
Subject Disposition	X			
Efficacy		X	X	
Immunogenicity	X			
Safety	X			

1. Safety Population

The Safety Population includes all patients who receive tinostamustine.

2. Full Analysis Set

The Full Analysis Set (FAS) includes all patients in the Safety Population who had at least one post-ASCT response evaluation.

3. Per-Protocol Population

The Per-Protocol Population includes all patients in the Full Analysis Set with no major protocol deviations.

4. Pharmacokinetic (PK) Population

The PK Population includes all patients in the Safety Population with at least one quantifiable pre-dose and one quantifiable post-dose PK plasma concentration.

J. Subgroups of Analysis Populations

Not applicable.

K. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Additional data listings may be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Summary tables will be produced as specified in following sections. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF or derived for each subject. They will be ordered by treatment, site, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject. Data listings will not display subject initials.

Summary tables will display summary statistics calculated for each of the dose groups and all subjects combined, unless described otherwise in the following sections. For most summary tables, the dose group will be presented in a column and the summary statistics of interest will be presented in rows.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum). Categorical variables will be summarized showing the number and percentage of patients within each classification.

VI. Subject Accountability

A. Subject Characteristics

The subject characteristics defined below will be presented in summary tables and data listings using data collected at the screening visit for subjects in the Safety Population. No formal statistical comparisons will be performed.

Demographics.

- *Age*. Age will be calculated as the number of years elapsed between birth date and the date of the screening visit, adjusted for whether the birthday has passed as of the day of the screening visit. (This corresponds to the typical calculation of age a person would use in conversation.)
- *Sex*. If Female, reproductive status will be summarized as well.
- *Race*. White or Caucasian, Black or African American, Asian, Other, Not Reported.
- *Ethnicity*. Hispanic, Not Hispanic, Unknown, Not Reported.

Baseline Characteristics.

- *Height*.
- *Weight*.
- *Body Mass Index (BMI).* BMI will be calculated as the individual's body mass divided by the square of their height – with the value universally being given in units of kg/m2.
- *Baseline ECOG Performance Status.*
- *Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) Total Score at Screening.* The HCT-CI provides information with regard to the overall as well as non-relapse mortality risk a patient is likely to experience after SCT.
- *Baseline Left Ventricular Ejection Fraction (LVEF).*

Multiple Myeloma-Specific Diagnostic and Historical Information.

- *Disease Stage at Initial Diagnosis.*
- *Disease Stage at Current Diagnosis.*
- *Time Since Initial Diagnosis.* The number of months from date of original diagnosis to the date of informed consent.
- *Prior ASCT and all Other Previous Anti-Cancer Treatment*. Yes, No.
- *Best Response to Previous Anti-Cancer Treatment.*

Prior Cancer Treatment History.

- *Prior Cancer Treatment History*. The medically relevant prior cancer treatments reported by the patient will be coded using World Health Organization Drug Dictionary (WHO-DD) and raw and coded data will be summarized.

In addition, data listings will be provided for all the above baseline data.

B. Disposition

A summary table of patient disposition as recorded during the End of Study visit will summarize the numbers for enrolled patients. Counts and percentages of patients who completed or withdrew for each of the reasons on the End of Study form will be calculated using the number of enrolled patients in the relevant cohort as the denominator. The reasons for end of study include:

- *Completed*
- *Adverse Event*
- *Death*
- *Engraftment Failure*

- *Lost to Follow-Up*
- *Physician Decision*
- *Pregnancy*
- *Progressive Disease*
- *Screen Failure*
- *Study Terminated by Sponsor*
- *Subject Non-Compliance / Protocol Violations*
- *Withdrawal of Consent*

A listing of study exit data will also be generated for all enrolled patients in the Safety Population.

C. Population Inclusions and Protocol Deviations

A summary of the numbers and percentages of patients in each of the analysis sets (Safety Population, Full Analysis Set, Per-Protocol Population, Pharmacokinetic Population) for each dose cohort and overall will be prepared.

Protocol deviations are recorded in the Clinical Trial Management System, InfoLink2, and will be included in a data listing of deviations.

VII. Efficacy Analyses

The Investigator's assessment of disease response will be used for patient management during the study. An Independent Review Committee (IRC) will provide an objective, unbiased, independent review of objective response, using the IMWG criteria (see Table 6 in the protocol), as demonstrated based on the pertinent clinical data from the study. Response assessments as determined by the Investigator and IRC will be displayed.

Disease response assessment variables will be listed as reported on the eCRFs.

VIII. Safety Analyses

Safety data, including changes from baseline, if applicable, will be summarized at each dose level for the Safety Population.

Additional safety analyses may be determined at any time without prejudice, in order to enumerate rates of toxicities most clearly, and to define further the safety profile of tinostamustine.

A. Adverse Events

Per the protocol, Adverse Events will be collected from the time written informed consent is obtained through Day 100 (±7 days), or after the end of the study, if thought to be related to study drug, and will be defined as Treatment-Emergent Adverse Events (TEAE). Any events occurring prior to the tinostamustine dose are part of the subject's baseline status and will be recorded on the Medical History form.

If the start date of an adverse event is missing, the site will be queried to obtain the missing date. If that attempt is unsuccessful, the following rules will be applied to impute the start date of an adverse event:

- If the day (or the day and the month) are missing, but all other date components match with the first dose date of study drug, use the first dose date of study drug.
- If the day (or the day and the month) are missing, but some of the other date components do not match with the first dose date of study drug, use the earliest possible date. For example, use Jan 1 if the day and the month are missing; use the first day of the actual month if only the day is missing.
- If the day, month, and year are missing, use the first dose date of study drug, as long as the adverse event end date is not prior to the first dose date of study drug. Otherwise, do not impute.

AEs will be coded using MedDRA, associating lower-level terms with preferred terms and system organ classes by the primary hierarchy. The tables will display counts and percentages of patients who reported at least one AE in each system organ class represented in the AE data. Within each system organ class, the tables will display the counts and percentages of patients reporting at least one AE, as designated by the preferred terms. AE summaries will include treatment-emergent AEs (TEAEs).

Summary tables of TEAEs by default MedDRA System Organ Class (SOC) and Preferred Term (PT) will be sorted by decreasing order of frequency of SOC, and then, within that, by decreasing order of frequency of PT in the All Subjects group.

The following AE summary tables displaying counts and percentages of patients with adverse events will be produced:

- All TEAEs by Preferred Term.
- TEAEs by SOC, PT and Severity. On this table, treatment groups will be subdivided into five potential grades of AE severity, based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version v4.03). An AE reported by a patient more than once will be represented in the most severe category.

The AE listings shown here will be produced, sorted chronologically within patient. Each listing will include system organ class, preferred term, onset and end time, CTCAE grade, relation to each study drug, action taken with each study drug, outcome, type (DLT) and SAE status:

- All AEs.

B. Exposure

Descriptive statistics for the percent of expected tinostamustine dose received and the actual dose received will be summarized. A tabular summary and listing of tinostamustine administration and dose level, and a by-patient listing of the date and time of each study drug dose and the dose administered also will be presented.

Data listings will be provided for the ASC infusion and engraftment data as reported on the eCRFs.

C. Clinical Laboratory Results

For each clinical chemistry (including kidney function tests) laboratory parameter, summary tables displaying the number of non-missing values, mean, standard deviation, median, and range (minimum and maximum) for actual values and changes from baseline for each assessment time point will be prepared. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

All laboratory test results (including serum chemistry and kidney function tests) will also be presented in data listings for the Safety Population. Any out of range values will be flagged in the data listings.

D. Concomitant Medications

Concomitant medication is defined as any medication with a start date within 28 days prior to the first dose of tinostamustine through Day 100 (± 7 days). These medications will be documented as administered pre-conditioning (i.e., pre-tinostamustine); during conditioning (i.e., after the start of the first tinostamustine infusion through immediately before the start of autologous stem cell infusion); or after ASCT (i.e., after the start of ASC infusion). Any medication with a stop date prior to the first dose of study treatment is defined as a prior medication.

If the start date or the end date of a concomitant medication is missing, the following imputation rules will be applied:

- For either the start or end date, if the year is missing or if the day, month, and year are all missing, do not impute.
- If both the start and stop dates are missing the month or day, the start date will be imputed first. If the imputed stop date is before the start date (imputed or non-imputed), then the stop date will be imputed using the start date.
- For the start date, if the day (or the day and the month) are missing, but all other date components match with the first dose date of study drug, use the first dose date of study drug. Otherwise, if the day (or the day and the month) are missing, but some of the other date components do not match with the first dose date of study drug, use the earliest possible date. For example, use Jan 1 if the day and the month are missing; use the first day of the actual month if only the day is missing.
- For the end date, if only the day is missing, use the last day of the month; if the day and the month are missing, use Dec 31.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A separate summary table for each will be organized to display the anatomical main class (1st level) of each coded medication and, within that, the pharmacological subgroup (3rd level) of the coded medication. The summary tables will display counts and percentages of patients who reported using at least one medication in each represented pharmacological subgroup.

A listing of concomitant medications will be generated for the Safety Population and will display entries from the Concomitant Medications eCRF page, ordered within patient by the "Date Started." The listing will display the recorded term from the CRF and, adjacent to that, the WHO Drug pharmacological subgroup and the anatomical main class that appears in the tables.

IX. Pharmacokinetic Analyses

Pharmacokinetic data are not within the scope of this SAP. These data will be reported by a third-party vendor and their analysis described in a separate report.

X. References

Please refer to the References section of the Mundipharma-EDO GmbH EDO-S101-1004 protocol for all referenced items in the analysis plan, as well as other supportive materials.