# 16.1 Study Information

## 16.1.1 Protocol and protocol amendments

- Protocols
  - Original Protocol V1.0 20 Mar 2018
  - Protocol V2.0 18 Jun 2018
- Protocol Clarification Memos:
  - 21 Sep 2018
  - 25 Oct 2018
  - 17 Dec 2018
  - 30 Jan 2019

CCI

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

Protocol Number: EDO-S101-1004

*This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.*

**Study Sponsor:**

Mundipharma-EDO GmbH
St Alban Rheinweg 74
CH 4052 Basel
Switzerland

**Sponsor Signature**

PPD
PPD
PPD MD, PhD
PPD

**Date**

**IND Number:** CCI

**EudraCT Number:**

**Document Version (Date):** 1.0, 20 March, 2018

**Previous Version (Date):** N/A

# INVESTIGATOR STATEMENT

I understand that all documentation provided to me by Mundipharma EDO, or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Ethics Committee (EC). No changes will be made to the study protocol without the prior written approval of Mundipharma EDO and the IRB/EC, except where necessary to eliminate an immediate hazard to a patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

_____ _____
Investigator Signature Date

_____
Printed Name

# CLINICAL STUDY SYNOPSIS

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| **Name of Sponsor**<br>Mundipharma-EDO GmbH | | |
| **Name of Finished Product:**<br>Tinostamustine hydrochloride (Formerly EDO-S101) | | **Name of Active Ingredient:**<br>Tinostamustine hydrochloride |
| **Protocol No.:**<br>EDO-S101-1004 | **Temporary (T) No.:** | **<EUDRACT><IND> No.:** |
| **Short Title of the Study:**<br>Titanium 1<br>Phase 1/2 Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplantation for Treatment in Relapsed / Refractory Multiple Myeloma | | |
| **Full Title of the Study:**<br>Phase 1/2 Open-label Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplantation for Salvage Treatment in Relapsed / Refractory Multiple Myeloma (TITANIUM 1) | | |
| **Investigator(s)/Centre(s):** Multicenter study; 4 centers in Switzerland and between 6 and 7 centers in the US will be enrolling patients. The PI will be PPD MD, MRCP,MS, PPD . The Cordinating Investigator in Switzerland will be PPD MD, PhD, PPD | | |
| **Study Initiation:**<br>Q3 2018 | | **Phase of Development:**<br>Phase 1 / 2 |
| **Objectives:**<br>***Phase 1***<br>The primary objectives of Phase 1 of this study are to:<br>• Establish the safety, toxicity, and maximum tolerated dose (MTD) of the tinostamustine conditioning regimen.<br>• Identify the recommended Phase 2 dose (RP2D) of tinostamustine for use in the Phase 2 portion of the study.<br>The secondary objective of Phase 1 of this study is to: | | |

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- Investigate the pharmacokinetics (PK) of tinostamustine.

***Phase 2***

The primary objectives of Phase 2 of the study are to:

- Investigate the efficacy of the tinostamustine conditioning regimen at the RP2D dose.
- Investigate the safety of the tinostamustine conditioning regimen.

The secondary objective of Phase 2 of this study is to:

- Evaluate the PK of tinostamustine.

**Endpoints**

***Efficacy***

The primary efficacy endpoint in Phase 2 of the study is:

- Objective response rate (ORR): complete response [CR], very good partial response [VGPR] and partial response [PR] at Day 100 (±7 days) post-autologous stem cell transplant (ASCT).

Secondary efficacy endpoints among patients treated at the RP2D (in Phases 1 and 2) are:

- ORR, and, in patients who achieve CR, minimal residual disease-negativity (MRD-N), as determined by next-generation flow cytometry at Day 100 (±7 days) post-ASCT.

***Safety***

The safety endpoint in Phase 1 of the study is:

- Dose-limiting toxicities (DLT).

Additional safety endpoints in Phases 1 and 2 of the study are:

- Incidence of neutrophil and platelet engraftment failure.
- Duration of cytopenia (i.e., absolute neutrophil count [ANC] $\leq 0.5\times10^9$/L, platelet count $\leq 20\times10^9$/L).
- Cumulative incidence of treatment-related mortality (TRM).
- Transplant-related non-hematologic Grade 3 toxicity over time through Day 30, stratified by hematopoietic cell transplantation comorbidity index (HCT-CI).

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- Incidence of adverse events (AEs) and serious adverse events (SAEs).
- Change from baseline in standard safety hematology and clinical chemistry test results.

**Study Design (Methodology):**

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 multiple myeloma (MM). (ASCT is defined as salvage if the patient had already received a prior ASCT and undergoes a second ASCT after evidence of progressive disease [PD].)

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.

The total dose of tinostamustine will be administered on Day -1.

Phase 2 of the study employs a 2-step sequential design (Simon, 1989). In Stage 1 of Phase 2, up to 31 patients initially will be enrolled. 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, 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.

After provision of written informed consent, patients will be screened for study eligibility within 28 days before Day 0 (the day of ASCT). Patients who have a minimum of $2\times10^6$ CD34+ cells/kg cryopreserved and are otherwise determined to be eligible, based on screening assessments, will be enrolled and receive the tinostamustine conditioning regimen. The tinostamustine dose will be administered 24 hours pre-ASCT (i.e., Day -1).

On Day 1, ASCs will be administered intravenously (IV) according to standard institutional practice.

Patients will receive supportive measures (including growth factor support post-ASCT, antimicrobial prophylaxis, red blood cell and platelet transfusion, and treatment for neutropenic fever) according to

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standard institutional practice.

During in-patient hospitalization, patients will be assessed daily for toxicity through Month 1 Day 30 (±5 days) post-ASCT or until all transplant-related toxicity resolves. Patients will be discharged from the study center once the following engraftment criteria are met:

- Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
- Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.

Thereafter, patients will attend study center visits at Month 2 Day 60 (±5 days) and Day 100 (±7 days).

**Definition of DLT**

Toxicity will be assessed by the Investigator using the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

In Phase 1 of the study, DLT is defined as the occurrence of any of the following events occurring within 30 days post-ASCT that are considered by the Investigator to be at least possibly related to tinostamustine:

- Delayed engraftment (>30 days after ASCT). Engraftment will be considered delayed if the subject has not met criteria for both neutrophil and platelet engraftment:
  - Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
  - Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.
- QTcF >500 msec or >60 msec increase from baseline, with a duration of >30 minutes, or ≥Grade 3 QTcF interval prolongation accompanied by ventricular arrhythmia. Baseline QTcF interval will be the mean value determined during triplicate ECG(s) at Day -1 (-1day), before study drug administration; the mean QTcF will be confirmed by the cental laboratory.
- Grade 4 non-hematologic toxicity
- Grade 3, non-hematologic toxicity related to treatment, **with the exception of:**
  - Nausea or vomiting

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- Diarrhea
- Fatigue, dehydration, or glucose intolerance
- Skin rash, dry skin, or pruritus responsive to topical or systemic steroids
- Fever (>40ºC for ≤24 hours)
- Infection
- Dyspnea, hypoxia, or pneumonitis
- Abdominal pain
- Dysphagia, oral mucositis, oral pain, or anorexia
- Flu-like syndrome
- Engraftment syndrome
- Weight loss
- Pain, pain in extremity, headache, or insomnia
- Hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia
- Increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, or alkaline phosphatase
- Alopecia

**Dose Escalation Scheme**

In Phase 1, up to 3 patients initially are to be enrolled in each cohort. The first patient enrolled in the initial cohort must complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, before additional patients may be enrolled in that initial cohort. (If the first patient experiences a DLT, then a lower dose will be explored for the second patient, and so on.)

- If the first patient does not experience a DLT or experiences engraftment without a ≥Grade 3 toxicity, the next 2 patients may be enrolled simultaneously.

After 3 patients in a cohort complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, and have safety evaluations

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performed through that time, and:

- None of these 3 patients experience a DLT, then enrollment of the next cohort may commence with approval from the Safety Committee.
- 1 of 3 patients within a cohort experiences a DLT, then up to 3 additional patients are to be enrolled sequentially at that dose level. If none of the additional 3 patients has a DLT (i.e., 1 of 6 patients has a DLT), then enrollment at the next scheduled dose may commence with approval from the Safety Committee.
- If ≥2 patients within a cohort experience a DLT, then the DLT dose level will have been reached and the previous lower dose level will be considered the MTD. (If ≥2 patients in the initial dose cohort experience DLTs, then the dose will be reduced to one level lower and the same procedure will be followed.)

A total of 6 patients are planned to be treated at the MTD to confirm the RP2D before enrollment of patients in Phase 2 of the study. If the MTD is not confirmed at this stage, the dose will be reduced to one level lower and the same procedure will be followed.

Note that enrollment in the next dose cohort can begin only when the last patient enrolled in the current dose cohort completes the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, provided that <2 patients in the current dose cohort experienced a DLT.

Although decisions regarding dose escalation will be made based on review of data through Day 30 post-ASCT, safety data will also be collected from all patients continuing in the study and this will be reviewed periodically by the Safety Committee. Any detected toxicity may necessitate further refinement of the RP2D.

**Definition of MTD:**

The MTD is defined as the highest dose level at which ≤1 of 6 patients experiences DLT through 30 days post-ASCT.

**Definition of RP2D:**

The RP2D may be equal to or higher than the preliminary MTD, but less than the non-tolerated dose (i.e., the dose at which ≥2 of 6 patients experienced DLT). The RP2D will be determined in discussion with the Sponsor, Medical Monitor, and Investigators.

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**Number of Subjects:**

***Phase 1***

A total of 9-12 patients are planned to be enrolled in Phase 1.

***Phase 2***

A total of up to 71 patients are planned to be enrolled in Phase 2.

***Criteria for Inclusion/Exclusion:***

***Inclusion Criteria***

Patients must meet all of the following criteria to be eligible for enrollment:

1. Patient has MM and:
   a. Has received prior ASCT after standard first-line induction treatment.
   b. Has evidence of PD, with progression-free interval ≥6 months in Phase 1 ≥18 months in Phase 2.

      Progression Free Inteval is defined as the time from date of ASCT to PD.
   c. Received treatment with ≤3 prior lines of therapy.

      A line of therapy is defined as 1 or more cycles of a planned treatment program. When patients have undergone sequential phases of treatment without intervening progression, such as induction, collection of peripheral blood stem cells, transplantation and consolidation/maintenance, this is considered to be 1 line of treatment. A new line of therapy is initiated as a result of PD or relapse (Garderet et al, 2017).
2. CR, VGPR, PR, or minimal response (MR) to latest of salvage chemotherapy at relaps, as determined by the International Myeloma Working Group (IMWG) criteria.
3. Is, in the Investigator's opinion, a candidate for consolidation therapy with tinostamustine followed by ASCT. (Note that patients planned to receive tandem ASCT are not eligible for the Phase 1 portion of the study.)
4. Has available autologous peripheral blood stem cell (PBSC) product with CD34 cell dose $\geq 2\times10^6$ cells/kg. The product could be from a collection prior to first ASCT or later second collection. (Note that, although not required, in Phase 1, the Investigator should consider enrolling patient

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with a large number of available PBSCs to permit subsequent ASCT, as patients in Stage 1 may received a dose lower that that determined to be effective.)

5. Age 18-75 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status score <3 at Screening.
7. Creatinine clearance ≥40 mL/min, as determined by a local laboratory using the Cockcroft-Gault equation within 28 days before ASCT.
8. Left ventricular ejection fraction (LVEF) ≥40% within 28 days before ASCT.
9. Adequate pulmonary function, defined as forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO) >50% predicted within 28 days before ASCT.
10. Adequate liver function, as defined by an ALT and AST ≤2.5 × the upper limit of normal (ULN) and bilirubin ≤1.5 × ULN within 28 days before ASCT.
11. Potassium within the local laboratory's normal range. (Potassium supplementation is permissible.)

***Exclusion Criteria***

Patients meeting any of the following criteria are not eligible for enrollment in the study:

1. History of central nervous system (CNS) disease involvement.
2. Myocardial infarction (MI) or stroke within 6 months before Screening.
3. Uncontrolled acute infection.
4. HCT-CI >6 points.
5. Concurrent malignant disease with the exception of treated basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease shall be documented since then.
6. Major coagulopathy or bleeding disorder.
7. Other serious medical condition that could potentially interfere with the completion of treatment according to this protocol or that would impair tolerance to therapy or prolong hematological recovery.

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8. Lack of cooperation to allow study treatment as outlined in this protocol.
9. Pregnancy or lactating female patients.
10. The use of any anti-cancer investigational agents within 21 days prior to the expected start of trial treatment and interval of 14 days to last administration of salvage treatment.
11. Receiving treatment with drugs known to prolong the QT/QTc interval.
12. QTc interval (Fridericia's formula) >450 msec, based on the mean of triplicate Screening 12-lead ECGs.

**Test Treatment, Dose, and Mode of Administration:**

Tinostamustine (formerly EDO-S101) CCI [redacted] The drug substance is a class 4 cytotoxic agent and should be handled with care by experienced health care professionals.

For administration, tinostamustine powder is reconstituted with 20 mL saline (0.9%) and then further diluted with 230 mL saline (0.9%) to a final volume of 250 mL. CCI [redacted]

In Phase 1 of the study, the starting dose of tinostamustine 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. In Phase 2, patient will receive tinostamustine at the RP2D identified in Phase 1. The total tinostamustine dose will be administered on Day -1. Tinostamustine will be administered by IV infusion through a peripheral vein over 1 hour.

Twenty-four hours after the tinostamustine infusion, ASCs will be infused via central venous catheter on Day 1. If the CD34+ product is of large volume, the infusion can be given over 2 days.

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Patients may receive the following supportive care:

- IV hydration and anti-emetics, in accordance with institutional guidelines.
- Growth factor support with pegfilgrastim or equivalent agent post-ASCT, in accordance with institutional guidelines.
- Standard supportive care, in accordance with institutional guidelines, including blood product transfusions, antimicrobial prophylaxis, and treatment for febrile neutropenia.

**Duration of Treatment and Study Duration:**

All patients will receive 1 dose~~s~~ of tinostamustine on Day~~s~~ -1 followed by ASCT on Day 1.

The anticipated accrual is 9-12 patients/year in Phase 1. Recruitment will continue during the evaluation period needed for Stage 1 of Phase 2. All patients will be followed for a maximum of 130 (±7 days) post-ASCT thus yielding a study of total duration of approximately 2.5 to 3.5 years.

**Criteria for Evaluation:**

***Efficacy Assessment(s):***

Response will be determined by the Investigator using the IMWG criteria. In addition, response of each subject will be evaluated by two independent reviewers, otherwise not involved in the clinical trial. In order to assess response, M protein component is to be measured in serum and/or urine, free light chain (FLC) testing is to be performed. Note that in the case of immunoglobulin A (IgA) MM, MM IgA values should be used. Bone marrow aspirate or biopsy and imaging studies (e.g., computed tomography, magnetic resonance imaging) are to be performed as clinically indicated. For patients with CR, based on serum and urine analysis, bone marrow aspirate and biopsies are to be performed at Day 100 (±7days), including the myeloma immunophenotype.

Confirmatory assessment: A second assessment of response will be conducted within Day 130 (±7days), the latest, to confirm the response. If the result is not confirmed by a second evaluation, the status is either Non Evaluable (NE) or the prior disease status remains valid. Confirmation should be obtained for biochemical markers but ius not necessary for bone marrow or imaging studies,

Assessment of M protein in serum and urine should be performed any time relapse is suspected.

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***Drug Concentration Measurements:***

Serial blood samples for PK analysis will be collected before, duration, and after tinostamustine administration according to the schedule in Table 1. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

***Bioanalytical Methods:***

A fully validated LC-MS/MS method for the determination of EDO-S101 and its metabolites (M2 and M8) in human plasma will be utilised. CCI [redacted]

***Safety Assessments:***

Safety will be assessed by documentation of AEs, safety laboratory tests (hematology and clinical chemistries), ECOG performance status, vital signs, physical examinations, electrocardiograms (ECGs), and Holter monitoring.

During in-patient hospitalization, patients will be assessed daily for hematologic engraftment until and including the day the patient has an ANC >0.5 $\times 10^9$/L and platelet count > $20 \times 10^9$/L without transfusion support.

To assess for early renal toxicity, creatinine, urea, and uric acid will be assessed on a daily basis from the start of tinostamustine treatment through Day 3 post-ASCT. In case of clinically significant renal toxicity, creatinine, urea, and uric acid will be assessed as long as clinically indicated.

**Statistical Methods:**

***Analysis Populations***

All patients who receive tinostamustine will be included in the safety set.

All patients in the safety set who had at least one post-ASCT response evaluation will be included in the full analysis set (FAS).

All patients in the FAS with no major protocol deviations will be included in the per-protocol (PP) set.

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All patients in the safety set with at least one quantifiable pre-dose and one quantifiable post-dose PK plasma concentration will be included in the PK set.

Dependent of the specific analysis, these sets will be taken from the cohort for Phase 1, for Phase 2 (RP2D), or both phases pooled.

***Efficacy Analyses:***

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Summaries for categorical variables will include frequency counts and percentages.

Superiority testing will be performed on FAS in Phase 2 cohort 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% (CIBMTR report, December 2017) and a 1-sided, 2-step chi-square test will be performed at the 2.5% level of significance for FAS.

For the primary endpoint, also an upper 1-sided 97.5% confidence interval will be calculated for FAS in addition to summary statistics.

For the primary endpoint in other sets and for the secondary endpoints of other responder rates in the FAS, also 2-sided 95% confidence intervals will be calculated in addition to summary statistics.

***Interim Analyses:***

In Phase 2 of the study, at the completion of the Stage 1 with 31 patients, an interim analysis will be performed using the FAS for the Phase 2 cohort to determine whether enrollment will continue in Stage 2. If >25 of 31 patients 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).

***Pharmacokinetic Analyses:***

PK analysis for tinostamustine and its metabolites will be performed using the PK set.

PK parameters at all doses will include maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($t_{max}$), half-life ($t_{½}$) area under the plasma concentration curve from 0 to 12 hours ($AUC_{0-12}$), area under the plasma concentration curve from time 0 to time t ($AUC_{0-t}$), apparent total

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clearance (CL/F), apparent volume of distribution (Vd/F), and terminal disposition rate constant ($\lambda_z$). The initial calculation of PK parameters will be performed using non-compartmental analysis. Plasma concentrations and PK parameters will be summarized by dose.

Summaries will include the number of observations (n), arithmetic or geometric mean, SD or coefficient of variation (CoV), median, minimum, and maximum.

***Safety Analyses:***

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

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, SD, median, minimum, and maximum. Summaries for categorical variables will include frequency counts and percentages.

**Sample Size Rationale**

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

For Phase 1, a formal sample size determination/power calculation was not performed. Based on experience from previously published similar studies, a total number of 9 (minimum) to 15 (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% (CIBMTR report, December 2017) 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 drug is at least 90%.

In the methodology proposed by Simon (Simon, 1989), a Phase 2 design can be represented by 4 numbers: N1, R1, N, and R. N1 is the sample size in the first stage. R1 is the critical value in the first stage. If R1 or fewer responses occur in the N1 patients, the study treatment is rejected. N is the combined sample size for both the first and second stages. R is the critical value in the combined sample. If R or fewer of the N patients respond, the study treatment is rejected at the end.

The design is found with PASS Sample Size Software through an exhaustive search of all possible designs (combinations of R1, N1, R and N) that control alpha (0.025) and beta (0.20, meaning power is

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| **Name of Sponsor**<br>Mundipharma-EDO GmbH | | |
| **Name of Finished Product:**<br>Tinostamustine hydrochloride (Formerly EDO-S101) | | **Name of Active Ingredient:**<br>Tinostamustine hydrochloride |
| **Protocol No.:**<br>EDO-S101-1004 | **Temporary (T) No.:** | **<EUDRACT><IND> No.:** |
| 0.80). With the minimax approach, the design is selected that has the lowest N.<br>Per the minimax design, 31 patients are to be enrolled in Stage 1. If >25 of 31 patients (in the FAS) in Stage 1 experience a response to treatment, then enrollment will continue in 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. Thus, a total of up to 71 patients will be enrolled in Phase 2.<br>If the total number of patients who experience a response is ≥62 of 71, then the study is considered a success. | | |
| **Schedule of Events**<br>The schedule of events is presented in Table 1. | | |

**Table 1: Schedule of Events (Phases 1 and 2)**

| Procedure | Screening | Conditioning | ASCT | Post-ASCT Follow-up[1] | | | |
|---|---|---|---|---|---|---|---|
| | D-28 to -1 | D-1 | D0 | M1 | M2 | D100 (±7 days) | D130 (±7 days) |
| Written informed consent[2] | X | | | | | | |
| Eligibility review | X | | X | | | | |
| Demographics | X | | | | | | |
| Medical history | X | | | | | | |
| HCT-CI | X | | | | | | |
| Cancer history, including history of prior ASCT and other treatments | X | | | | | | |
| ECHO or MUGA scan | X | | | | | | |
| Pulmonary function testing[3] | X | | | | | | |
| Infectious disease screening[4] | X | | | | | | |
| Pregnancy test[5] | X | | | | | | |
| ECOG performance status | X | | X | X | X | X | |
| Complete physical examination | X | | | | | | |
| Targeted physical examination | | X | X | X | X | X | |
| Height | X | | | | | | |
| Weight | X | | X | X | X | X | |
| Vital signs[6] | X | X | X[7] | X | X | X | |
| Continuous Holter monitoring | | X[9] | | | | | |
| 12-lead ECG[10] | X[11] | X[11] | | X | | | |
| Hematology[12] | X | Repeat daily until hospital discharge | | | | | |
| Kidney function tests (creatinine, urea, and uric acid) | | Daily from the start of tinostamustine through Day 3post-ASCT | | | | | |
| Clinical chemistries[13] | X | X | X | X | X | X | |

| Procedure | Screening | Conditioning | ASCT | Post-ASCT Follow-up[1] | | | |
|---|---|---|---|---|---|---|---|
| | **D-28 to -1** | **D-1** | **D0** | **M1** | **M2** | **D100 (±7 days)** | **D130 (±7 days)** |
| Coagulation parameters: PT and/or INR, aPTT | X | | X | X | | X | |
| Urinalysis[14] | X | | | | | | |
| Tinostamustine administration[15] | | X | | | | | |
| PK sample collection | | X[16] | | | | | |
| ASCT[17] | | | X | | | | |
| Disease assessments | | | | | | | |
| Skeletal survey[18] | X | | | | | | |
| Bone marrow aspirate and biopsy[19] | X | | | | | D100 (±7 days)[20] | |
| Serum / urine M protein quantitation | X | | | X | X | X | X |
| Immunoglobulin quantitation (IgA, IgG, and IgM [required]; IgD, IgE [optional]) | X | | | X | X | X | X |
| Free light chain analysis | X | | | X | X | X | X |
| Disease response assessment[21] | X | | | X | X | X | |
| Evaluation for MRD-N | | | | | | D100 (±7 days)[20] | |
| AE monitoring[22] | AEs, including SAEs, are to be documented from the provision of written informed consent through Day 100. | | | | | | |
| Prior/concomitant medications[23] | All medications administered within 28 days before Day 0 through Day 100 are to be documented. | | | | | | |

1. Patients will be evaluated daily on an inpatient basis until engraftment criteria are met and the patient is discharged from the hospital. Thereafter, study center visits will be performed on an outpatient basis. Visit M1: D30 ( ±5days); visit M2: D60 (±5days)
2. Written informed consent is to be obtained before the performance of any study-related procedures.
3. Pulmonary function testing is to include $FEV_1$, FVC, and DLCO.
4. Infectious disease marker testing is to include, at a minimum, human immunodeficiency virus (HIV) types 1 and 2, hepatitis B virus (HBV) panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus (HCV), Treponema pallidum, CMV, and Epstein-Barr virus.
5. Urine or serum pregnancy testing will be performed for women of childbearing potential. Pregnancy testing is to be repeated on study any time pregnancy is suspected.
6. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Vital signs are to be measured after patient is sitting for 3-5 minutes.
7. Perform assessment both pre- and post-treatment.
8. ECGs (12-lead) are to be performed after the patient is supine for 5 minutes. Repeat ECGs as clinically indicated. All ECGs will be reviewed centrally.

9. Continuous Holter monitoring will be performed on Day -1, the day of tinostamustine administration. Holter monitoring will commence 15 minutes prior to the start of the infusion on Day -1 and will continue through 24 hours following the end of infusion. Patients should be resting comfortably in the supine or semisupine position for 15 minutes prior to each of the following timepoints: 0 [before start of infusion] then after start of the infusion at 15, 30, 45, and 60 minutes and 3, 6, and 24 hours following the start of the infusion. At time 0 and at all time points after infusion, ECGs readings will be extracted in triplicate, with each ECG separated by 5 minutes (±2 minutes), for establishment of baseline for the purposes of cardiac safety analyses. The Holter monitor flashcards will be sent to eResearch Technology, Inc., for processing.
10. The Investigator's interpretation of ECGs is to be used for patient management during the study; the central reader interpretation of ECGs extracted from Holter monitoring will be used to determine all ECG data for study endpoints including baseline QTcF interval for cardiac safety analyses and DLTs.
11. A triplicate ECG will be performed during Screening to determine patient eligibility for the study. Furthermore, on Day -1, a triplicate ECG is to be performed before study drug administration and a single ECGs will be performed at 30 and 60 minutes after the start of study drug administration for assessment by the site. Another single ECG will be performed at visit on day 30 (±5 days). ECGs are to be repeated by the Investigator, as clinically indicated.
12. Hematology parameters minimally include WBC count and differential (lymphocytes, monocytes, basophils, eosinophils, neutrophils), red blood cell (RBC) count, hematocrit, hemoglobin, and platelet count.
13. Serum chemistry parameters minimally include alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase, (AST), bicarbonate, bilirubin (total, direct, and indirect), calcium, magnesium, chloride, glucose, lactate dehydrogenase (LDH), phosphate, potassium, sodium, and total protein.
14. Urinalysis includes appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.
15. The tinostamustine dose will be administered one day before ASCT (Day -1), at least 24 hours pre-ASCT.
16. Blood samples for PK are to be collected immediately pre-infusion of tinostamustine and 30, 45, and 60 (±5) minutes and then at 3, 6, and 24 hours (±15 minutes) and then 48 hours (±30 minutes) after the start of infusion. Blood samples for PK assessment should be collected following the 15-minute supine resting periods described for the continuous Holter recordings. PK samples are to be collected from the arm opposite of that used for tinostamustine administration.
17. On Day 1, ASCs will be administered IV according to standard institutional practice. If the CD34+ product is of large volume, the infusion can be given over 2 days.
18. A skeletal survey (plain radiographs, or any other method used as standard care at the site, of the skull, spine, ribs, pelvis, humeri and femora) will be performed at Screening if not performed within the previous 3 months. Thereafter, skeletal survey and/or other imaging studies are to be performed as clinically indicated.
19. Bone marrow aspirate and trephine biopsy are to be performed during Screening. Bone marrow aspirate and biopsy are to be repeated during treatment as clinically indicated, at the Investigator's discretion, and at any time CR is suspected.
20. Any patient who achieves a CR will have peripheral blood and bone marrow collected at Day 100 (±7 days) for assessment of evidence of MRD-N via next-generation flow cytometry.
21. Disease response will be assessed by the Investigator using the IMWG Criteria. Confirmation should be obtained for biochemical markers but is not necessary for bone marrow or imaging studies. There is no specific time interval required between the 2 evaluations, the the confirmatory tests ideally should be performed approximately 4 weeks after the initial evaluation.
22. AEs will be documented as occurring 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 [ASC] infusion); or after ASCT (i.e., after the start of ASC infusion).
23. Concomitant 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 ASC infusion); or after ASCT (i.e., after the start of ASC infusion).

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AK-DACi | Alkylating deacetylase inhibitor |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ASC | Autologous stem cell |
| ASCT | Autologous stem cell transplantation |
| AST | Aspartate aminotransferase |
| $AUC_{0\ 12}$ | Area under the plasma concentration curve from 0 to 12 hours |
| $AUC_{0\text{-}t}$ | Area under the plasma concentration curve from time 0 to time t |
| CA | Competent Authorities |
| CL/F | Apparent total clearance |
| $C_{max}$ | Maximum plasma concentration |
| CNS | Central nervous system |
| CoV | Coefficient of variation |
| CR | Complete response |
| CRA | Clinical Research Associate |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P450 |
| DLCO | Carbon monoxide diffusing capacity |
| DLT | Dose-limiting toxicity |
| DNA | Deoxyribonucleic acid |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |

| Abbreviation | Definition |
|---|---|
| EDTA | Ethylenediaminetetraacetic acid |
| FAS | Full analysis set |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FLC | Free light chain |
| FVC | Forced vital capacity |
| GCP | Good Clinical Practice |
| HBV | Hepatitis B virus |
| hCG | Human chorionic gonadotropin |
| HCT-CI | Hematopoietic cell transplantation comorbidity index |
| HCV | Hepatitis C virus |
| HDACi | Histone-deacetylase inhibitor |
| HIV | Human immunodeficiency virus |
| HPβCD | Hydroxyl-propyl-β-cyclodextrin |
| $IC_{50}$ | 50% inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| ID | Identification |
| Ig | Immunoglobulin |
| IMWG | International Myeloma Working Group |
| IRB | Institutional review board |
| IRC | Independent Review Committee |
| IV | Intravenous(ly) |
| LVEF | Left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGMT | O6-methylguanine-DNA methyltransferase |
| MI | Myocardial infarction |
| MM | Multiple myeloma |

| Abbreviation | Definition |
|---|---|
| MR | Minimal response |
| MRD-N | Minimal residual disease-negativity |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| ORR | Objective response rate |
| PBSC | Peripheral blood stem cell |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PP | Per-protocol |
| PR | Partial response |
| RP2D | Recommended Phase 2 dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| sCR | Stringent complete response |
| SD | Stable disease |
| SD | Standard deviation |
| SUSAR | Serious and unexpected suspected adverse reaction |
| $t_{1/2}$ | half-life |
| $t_{max}$ | Time to maximum plasma concentration |
| TRM | Treatment-related mortality |
| ULN | Upper limit of normal |
| US | United States |
| Vd/F | Apparent volume of distribution |
| VGPR | Very good partial response |
| WHO-DD | World Health Organisation Drug Dictionary |
| λz | Terminal disposition rate constant |

# TABLE OF CONTENTS

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# 1. STUDY PERSONNEL AND ADMINISTRATIVE STRUCTURE

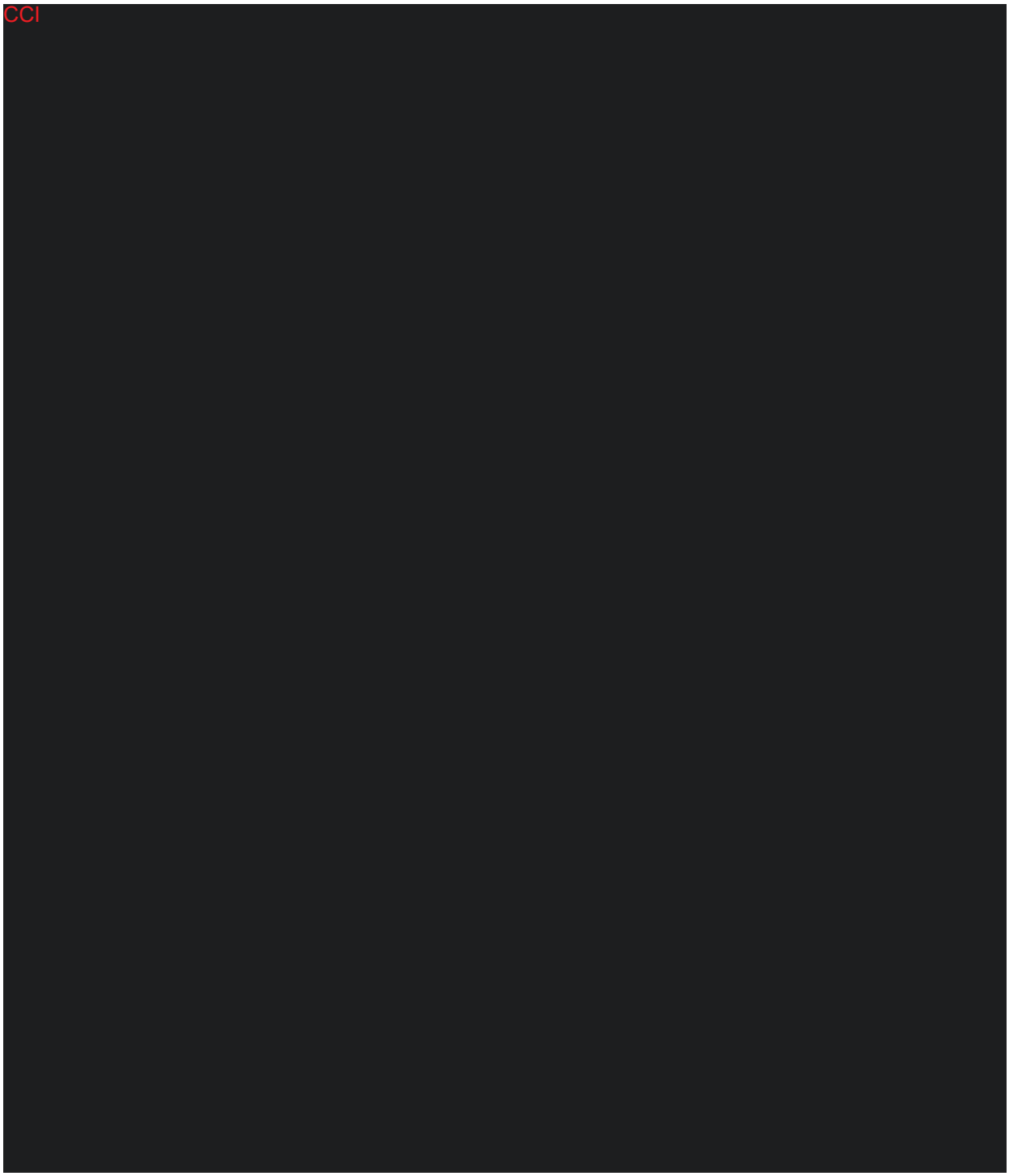
**Study Sponsor:**

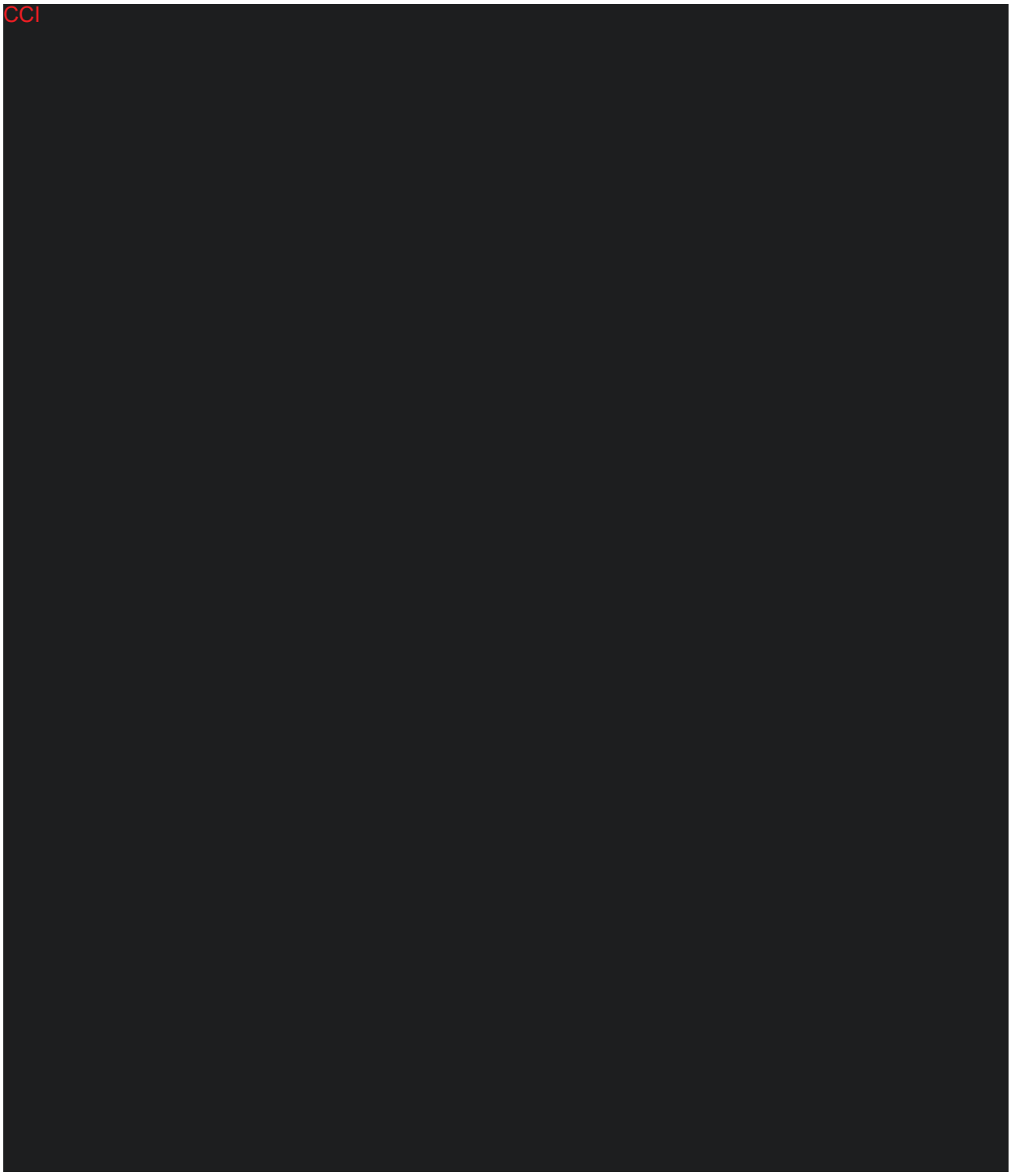
Mundipharma-EDO GmbH
St Alban Rheinweg 74
CH 4052 Basel
Switzerland

**Sponsor Signatory:**

PPD MD PhD

CCI

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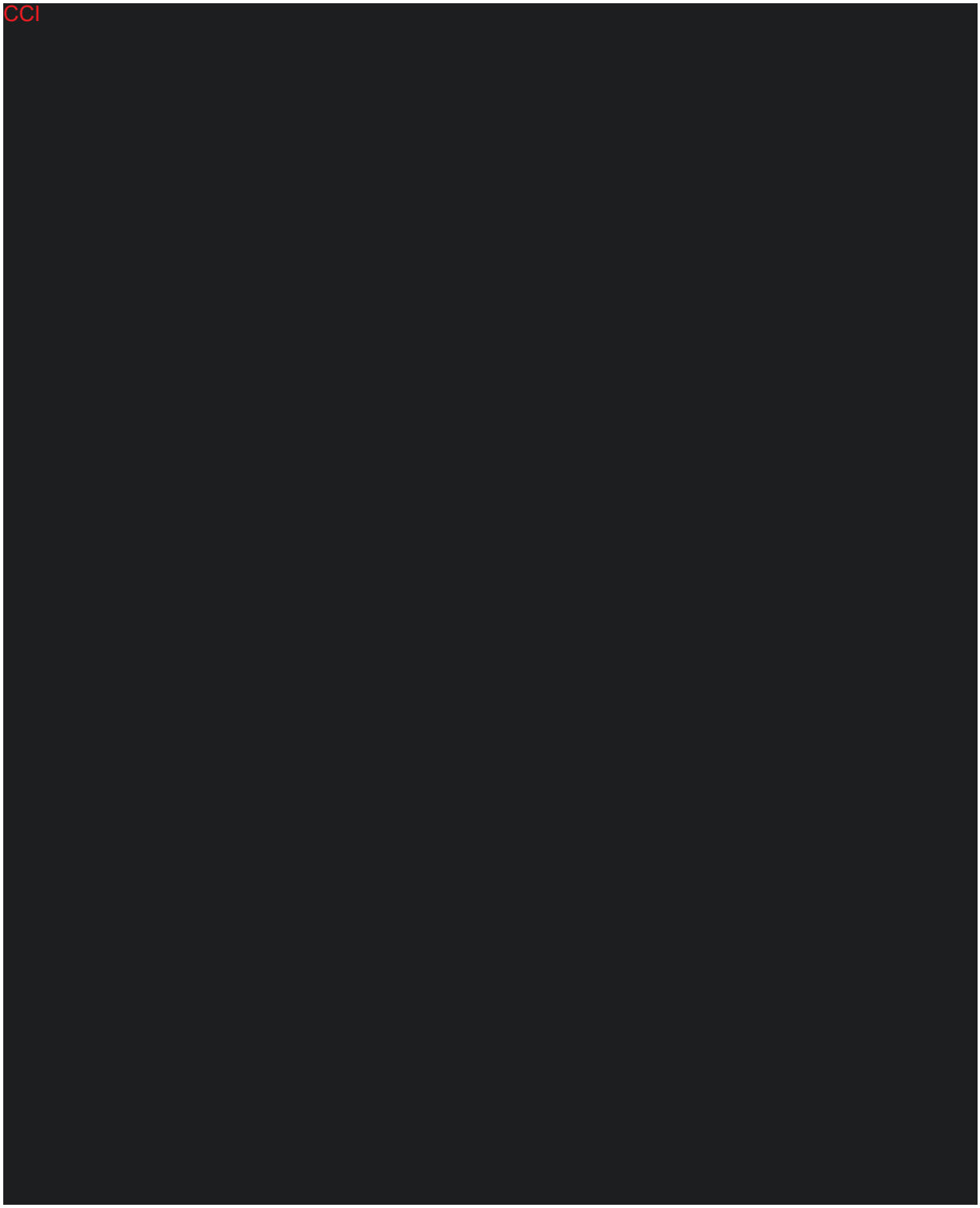

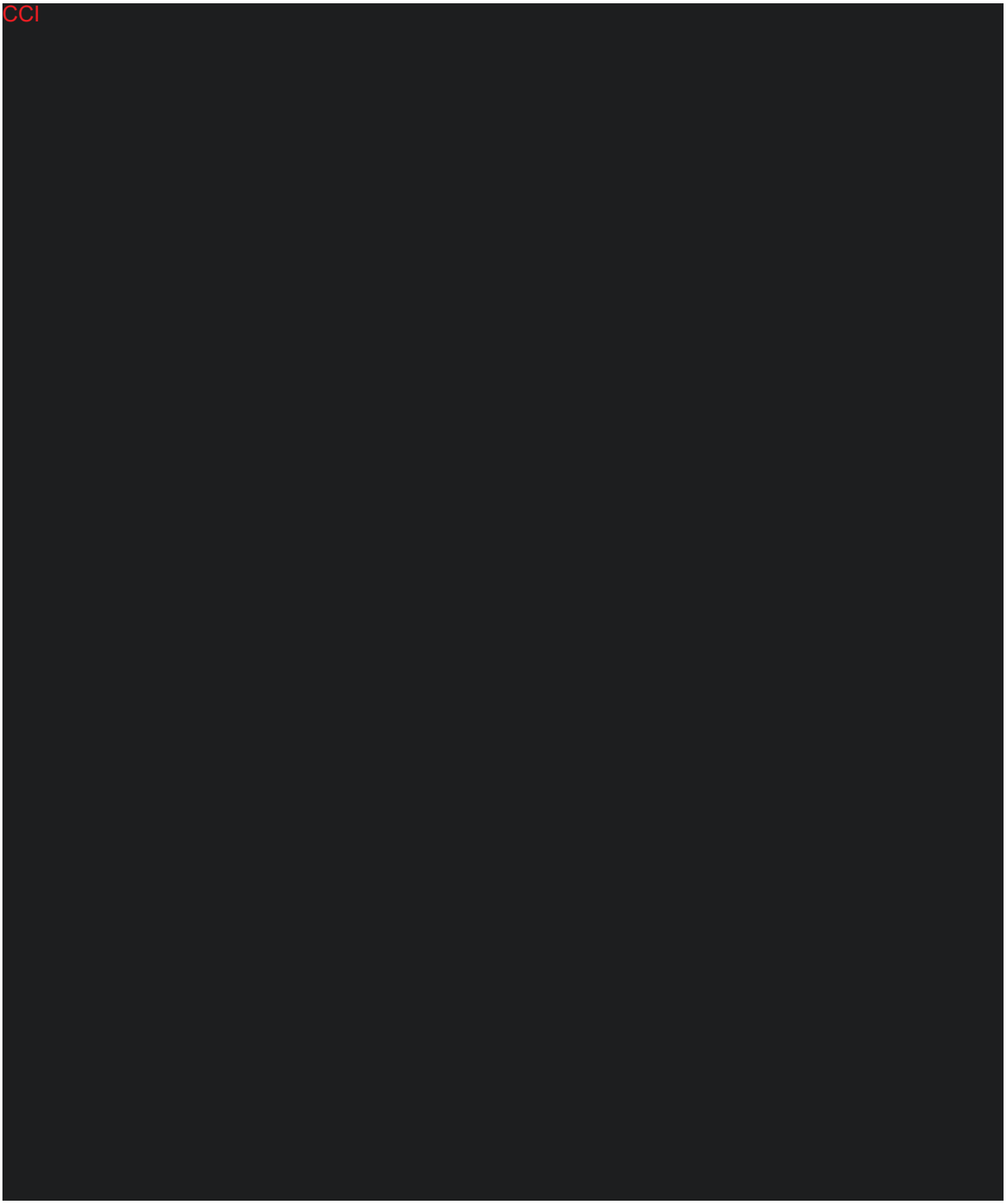
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# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1. Objectives

### 3.1.1. Phase 1

#### 3.1.1.1. Primary Objectives

The primary objectives of Phase 1 of this study are to:

- Establish the safety, toxicity, and MTD of the tinostamustine conditioning regimen.
- Identify the RP2D of tinostamustine for use in the Phase 2 portion of the study.

#### 3.1.1.2. Secondary Objectives

The secondary objective of Phase 1 of this study is to:

- Investigate the PK of tinostamustine.

### 3.1.2. Phase 2

#### 3.1.2.1. Primary Objectives

The primary objectives of Phase 2 of the study are to:

- Investigate the efficacy of the tinostamustine conditioning regimen at the RP2D.
- Investigate the safety of the tinostamustine conditioning regimen.

#### 3.1.2.2. Secondary Objectives

The secondary objective of Phase 2 of this study is to:

- Evaluate the PK of tinostamustine.

## 3.2. Study Endpoints

### 3.2.1. Efficacy

#### 3.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint in Phase 2 of the study is:

- Objective response rate (ORR): complete response [CR] plus partial response [PR] at Day 100 (±7 days) post-ASCT.

#### 3.2.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints among patients treated at the RP2D (in Phases 1 and 2) are:

- ORR and, in patients who achieve CR, minimal residual disease-negativity (MRD-N), as determined by next-generation flow cytometry at Day 100 (±7 days) post-ASCT.

### 3.2.2. Safety

The safety endpoint in Phase 1 of the study is:

- DLTs

Additional safety endpoints in both Phases 1 and 2 of the study are:

- Incidence of neutrophil and platelet engraftment failure.
- Duration of cytopenia (i.e., absolute neutrophil count [ANC] $\leq 0.5\times10^9$/L; platelet count $\leq 20\times10^9$/L).
- Cumulative incidence of treatment-related mortality (TRM).
- Transplant-related non-hematologic Grade 3 toxicity over time through Day 30, stratified by hematopoietic cell transplantation comorbidity index (HCT-CI).
- Incidence of adverse events (AEs) and serious adverse events (SAEs).
- Change from baseline in standard safety hematology and clinical chemistry test results.

# 4. INVESTIGATIONAL PLAN

## 4.1. Overall Study Design and Plan

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. (ASCT is defined as salvage if the patient had already received a prior ASCT and undergoes a second ASCT after evidence of progressive disease [PD].)

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.

In Phase 2 of the study, all patients will receive tinostamustine at the RP2D administered in Phase 1 according to the same schedule.

Phase 2 of the study employs a 2-step sequential design (Simon, 1989). 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, 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.

After provision of written informed consent, patients will be screened for study eligibility within 28 days before Day 0 (the day of ASCT). Patients who have a minimum of $2\times10^6$ CD34+ cells/kg cryopreserved and are otherwise determined to be eligible, based on screening assessments, will be enrolled and receive the tinostamustine conditioning regimen. The tinostamustine dose will be administered 24 hours pre-ASCT (i.e., Day -1).

On Day 1, ASCs will be administered intravenously (IV) according to standard institutional practice.

Patients will receive standard supportive measures (including growth factor support post-ASCT, antimicrobial prophylaxis, red blood cell and platelet transfusion and treatment for neutropenic fever) according to standard institutional practice.

During in-patient hospitalization, patients will be assessed daily for toxicity through Month 1 Day 30 (±5 days) post-ASCT or until all transplant-related toxicity resolves. Patients will be

discharged from the study center once the following engraftment criteria are met:

- Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
- Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.

Thereafter, patients are to be followed at Month 2 Day 60 (±5 days) and Day 100 (±7 days).

## 4.2. Justification for the Study Design

Goals of Phase 1 oncology studies include estimation of the initial safety and tolerability of a study drug, establishment of an MTD, and determination of a recommended range of doses for evaluation in future clinical studies, based on safety and PK (Ahn, 1998; Gatsonis, Greenhouse, 1992; Dillman, Koziol, 1992); the primary objectives of the current study are consistent with those typical of Phase 1 oncology studies.

Phase 1 of the study employs a traditional 3+3 dose escalation design. The dose escalation scheme to be followed is based on a modified Fibonacci sequence schema, which is commonly employed in Phase 1 dose-finding oncology studies (Storer, 1989).

After identification of the RP2D in the Phase 1 portion of the study, the potential efficacy of conditioning with tinostamustine followed by ASCT will be investigated in the Phase 2 portion of the study. Phase 2 utilizes a Simon 2-stage minimax design, a common design in Phase 2 oncology clinical studies by which the expected sample size is minimized if the treatment regimen has minimal activity (Simon, 1989).

# 5. STUDY POPULATION

Patients with relapsed/refractory MM who have received prior ASCT after standard first-line induction treatment are planned to be enrolled.

## 5.1. Inclusion Criteria

Patients must meet all of the following criteria to be considered eligible for study entry:

1. Patient has MM and:
   a. Has received prior ASCT after standard first-line induction treatment.
   b. Has evidence of PD, with progression-free interval ≥6 months in Phase 1 ≥18 months in Phase 2.

      Progression Free Interval is defined as the time from date of ASCT to PD.
   c. Received treatment with ≤3 prior lines of therapy.

      A line of therapy is defined as 1 or more cycles of a planned treatment program. When patients have undergone sequential phases of treatment without intervening progression, such as induction, collection of peripheral blood stem cells, transplantation and consolidation/maintenance, this is considered to be 1 line of treatment. A new line of therapy is initiated as a result of PD or relapse (Garderet et al, 2017).
2. CR, PR, or minimal response (MR) to salvage chemotherapy, as determined by the International Myeloma Working Group (IMWG) criteria.
3. Is, in the Investigator's opinion, a candidate for consolidation therapy with tinostamustine followed by ASCT. (Note that patients planned to receive tandem ASCT are not eligible for the Phase 1 portion of the study.)
4. Has available autologous PBSC product with CD34 cell dose ≥$2\times10^6$ cells/kg. The product could be from a collection prior to first ASCT or later second collection. (Note that, although not required, in Phase 1, the Investigator should consider enrolling patient with a large number of available PBSCs to permit subsequent ASCT, as patients in Stage 1 may received a dose lower than that determined to be effective.)
5. Age 18-75 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status score <3 at Screening.
7. Creatinine clearance ≥40 mL/min, as determined by a local laboratory using the Cockcroft-Gault equation within 28 days before ASCT.
8. Left ventricular ejection fraction (LVEF) ≥40% within 28 days before ASCT.

9. Adequate pulmonary function, defined as forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO) >50% predicted within 28 days before ASCT.
10. Adequate liver function, as defined by an alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper limit of normal (ULN) and bilirubin ≤1.5 × ULN within 28 days before ASCT.
11. Potassium within the local laboratory's normal range. (Potassium supplementation is permissible.)

## 5.2. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study entry:

1. History of central nervous system (CNS) disease involvement.
2. Primary or secondary plasma cell leukemia at any time point prior to transplant
2. Myocardial infarction (MI) or stroke within 6 months before Screening.
3. Uncontrolled acute infection.
4. HCT-CI >6 points.
5. Concurrent malignant disease with the exception of treated basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease shall be documented since then.
6. Major coagulopathy or bleeding disorder.
7. Other serious medical condition that could potentially interfere with the completion of treatment according to this protocol or that would impair tolerance to therapy or prolong hematological recovery.
8. Lack of cooperation to allow study treatment as outlined in this protocol.
9. Pregnancy or lactating female patients.
10. The use of any anti-cancer investigational agents within 21 days prior to the expected start of trial treatment and interval of 14 days to last administration of salvage treatment.
11. Receiving treatment with drugs known to prolong the QT/QTc interval.
12. QTc interval (Fridericia's formula) >450 msec, based on the mean of triplicate Screening 12-lead ECGs.

## 5.3. Source of Patients

This will be a multinational, multicenter study. Each study center is required to obtain local Institutional Review Board (IRB)/Ethics Committee (EC) and national regulatory approval to conduct the study before enrollment of patients may commence. Patients meeting the entry criteria who are known or referred to the study center will be eligible for enrollment.

# 6. STUDY CONDUCT

## 6.1. Patient Identification and Enrollment

To ensure accurate and timely monitoring of patient enrollment, the following procedures will be implemented:

- Patients who are candidates for enrollment into the study will be assigned a sequential and unique patient number by the Investigator after the patient has provided written informed consent. Once a patient number has been assigned, it cannot be reused.
- Patients who have provided written informed consent will be evaluated for eligibility by the Investigator to ensure that the entry criteria (see Section 5.1 and Section 5.2) have been satisfied and that the patient is eligible for participation in this clinical study. An eligibility form will be provided by the Sponsor, or designee for this evaluation.
- The Investigator or the Investigator's research staff will provide eligibility information to the Sponsor or designee. After confirmation, the Sponsor or designee will provide the Investigator with written verification of each patient's enrollment.
- No patient may be enrolled prior to confirmation of a patient's eligibility by the Sponsor or designee.
- Patients who are enrolled but not treated with tinostamustine followed by ASCT will be replaced.
- Investigators will be notified by the Sponsor or designee when enrollment in a given dose cohort / study part is closed and enrollment into the next dose cohort / study part can begin. (Investigators will be consulted in all dose escalation decisions.)
- Investigators will be notified by the Sponsor or designee if the study is placed on administrative hold, when it is completed, or is closed to further patient enrollment.

## 6.2. Patient Management

All patients must provide written informed consent before any samples are collected or evaluations performed in this study that are not part of standard patient care. Patients will be evaluated for study eligibility during the Screening period, within 28 days before baseline (Day 1; the Day of ASCT).

Patients who are determined to be eligible, based on Screening assessments, will return to the clinic to receive the tinostamustine conditioning regimen; the tinostamustine dose will be administered 24 hours pre-ASCT (on Day -1).

On Day 1, ASCs will be administered IV according to standard institutional practice.

During in-patient hospitalization, patients will be assessed daily for toxicity through Month 1 Day 30 (±5 days) post-ASCT or until all transplant-related toxicity resolves. Patients will be discharged from the study center once engraftment criteria are met (see Section 8.3).

Thereafter, patients are to be followed at Month 2 Day 60 (±5 days) and Day 100 (±7 days).

## 6.3. Patient Adherence

All patients are required to adhere to the protocol-specified dosing and visit schedules. If a patient misses a scheduled visit, attempts should be made to reschedule the visit within the visit windows specified in Table 1. Failure to attend scheduled study visits may result in discontinuation from the study.

## 6.4. Treatment Discontinuation Criteria

Once tinostamustine has been infused it will be medically negligent to stop transplant and supportive therapy for the particular patient. In the event of consent withdrawal during or following conditioning or the development of complications that, in the Investigator's opinion, puts the patient at risk with continued protocol-specified treatment, the Medical Monitor should be contacted immediately to discuss management of the patient.

## 6.5. Study Discontinuation Criteria

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Patient non-adherence to protocol requirements.
- Patient unwillingness to continue in the study.
- Any other reason, based upon the medical judgment of the Investigator.

The reason for study withdrawal is to be documented in the patient's source documents and electronic case report form (eCRF).

## 6.6. Study Completion

A patient is considered to have completed the study if they complete the Day 100 (±7 days) visit and a confirmatory response assessment at D130 (±7 days) visit, the latest.

## 6.7. Study Termination

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of tinostamustine.

## 6.8. Investigator Compliance

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol. The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance documents.

## 6.9. Safety Committee

A Safety Committee will be involved in the conduct of this study. The Safety Committee will be comprised of Sponsor personnel, the Medical Monitor, the Investigator or representative thereof at each active study center, and a biostatistician (as needed). Ad hoc participants may be part of the committee at the request of the Sponsor or other Safety Committee members. The Safety Committee has the responsibility for monitoring the clinical study's progress and the safety of the participating patients. The Safety Committee will evaluate study conduct during the course of the clinical study, based upon data defined for this clinical study.

In Phase 1, the Safety Committee will review all safety data from all patients enrolled in each cohort to confirm any DLTs that were experienced and make a determination regarding enrollment in the next cohort. If a DLT necessitates enrollment of additional patients into a cohort, the Safety Committee will review all of the safety data for that cohort after those additional patients before a determination regarding enrollment in the next cohort is made. Based on evaluation of the data, the Safety Committee may decide that enrollment at an intermediate dose level not specified in this protocol may take place.

In addition, after identification of the MTD, the Safety Committee will review all safety data collected to date to confirm that no unexpected, significant, or unacceptable risk to patients enrolled in the study has been discovered.

# 7. STUDY DRUG

Mundipharma EDO or its designee will supply tinostamustine to the pharmacies at all participating study centers. All study drug must be stored in a safe and locked place with no access by unauthorized personnel.

## 7.1. Study Drug Supply

Tinostamustine (formerly EDO-S101) CCI [redacted] The drug substance is a class 4 cytotoxic agent and should be handled with care by experienced health care professionals.

## 7.2. Study Drug Packaging and Labeling

CCI [redacted]

Study drug will be labeled in accordance with applicable regulatory requirements. Study drug labels will not contain any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated.

## 7.3. Study Drug Storage

Tinostamustine vials are stored at CCI [redacted]

## 7.4. Study Drug Accountability

The Investigator or delegate will maintain accurate records of receipt and condition of study drug, including dates of receipt. In addition, accurate records will be kept of the date administered, quantity administered, and the patient to whom study drug was administered. Any reasons for departure from the protocol-specified dispensing regimen must also be recorded.

The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug. The site identification (ID) number and patient initials and ID number are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, they are to record the date dispensed, amount dispensed, and their initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused supplies.

A Clinical Research Associate (CRA) will review study drug accountability records during routine monitoring visits. At the completion of the study, there will be a final reconciliation of all study drug.

## 7.5. Study Drug Dose

In Phase 1 of the study, the starting dose of tinostamustine is 180 mg/m$^2$, with escalation to 220, 260, and then 300 mg/m$^2$ 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.

In Phase 2, patient will receive tinostamustine at the RP2D identified in Phase 1.

### 7.5.1. Dose Escalation Procedure

In Phase 1, up to 3 patients initially are to be enrolled in each cohort. The first patient enrolled in the initial cohort must complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, before additional patients may be enrolled in that initial cohort. (If the first patient experiences a DLT, then a lower dose will be explored for the second patient and so on.)

- If the first patient does not experience a DLT (see Section 7.5.2) or experiences engraftment without a ≥Grade 3 toxicity, the next 2 patients may be enrolled simultaneously.

After 3 patients in a cohort complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, and have safety evaluations performed through that time, and:

- None of these 3 patients experience a DLT (see Section 7.5.2), then enrollment of the next cohort may commence with approval from the Safety Committee.
- 1 of 3 patients within a cohort experiences a DLT (see Section 7.5.2), then up to 3 additional patients are to be enrolled sequentially at that dose level. If none of the additional 3 patients has a DLT (i.e., 1 of 6 patients has a DLT), then enrollment at the next scheduled dose may commence with approval from the Safety Committee.
- If ≥2 patients within a cohort experience a DLT (see Section 7.5.2), then the DLT dose level will have been reached and the previous lower dose level will be considered the MTD. (If ≥2 patients in the initial dose cohort experience DLTs, then the dose will be reduced to one level lower and the same procedure will be followed.)

A total of 6 patients are planned to be treated at the MTD to confirm the RP2D before enrollment of patients in Phase 2 of the study. If the MTD is not confirmed at this stage, the dose will be reduced to one level lower and the same procedure will be followed.

Note that enrollment in the next dose cohort can begin only when the last patient enrolled in the current dose cohort completes the study through engraftment without a ≥Grade 3 toxicity or

through 30 days post-ASCT without a DLT, whichever occurs first,, provided that <2 patients in the current dose cohort experienced a DLT.

Although decisions regarding dose escalation will be made based on review of data through Day 30 post-ASCT, safety data will also be collected from all patients continuing in the study and this will be reviewed periodically by the Safety Committee. Any detected toxicity may necessitate further refinement of the RP2D.

### 7.5.2. Definition of Dose-limiting Toxicity

Toxicity will be assessed by the Investigator using the US NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. The centralized laboratory assessment of ECGs will be used for the determination of DLT.

In Phase 1 of the study, DLT is defined as the occurrence of any of the following events occurring within 30 days post-ASCT that are considered by the Investigator to be at least possibly related to tinostamustine:

- Delayed engraftment (>30 days after ASCT). Engraftment will be considered delayed if the subject has not met criteria for both neutrophil and platelet engraftment:
  - Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
  - Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.
- QTcF >500 msec or >60 msec increase from baseline, with a duration of >30 minutes, based on the mean of triplicate 12-lead ECGs, or ≥Grade 3 QTcF interval prolongation accompanied by ventricular arrhythmia.

  Baseline QTcF interval will be the mean value determined during triplicate ECG(s) at Day -1 (-1), before study drug administration confirmed by the cental laboratory.
- Grade 4 non-hematologic toxicity
- Grade 3, non-hematologic toxicity related to treatment, **with the exception of:**
  - Nausea or vomiting
  - Diarrhea
  - Fatigue, dehydration, or glucose intolerance
  - Skin rash, dry skin, or pruritus responsive to topical or systemic steroids
  - Fever (>40ºC for ≤24 hours)
  - Infection

- Dyspnea, hypoxia, or pneumonitis
- Abdominal pain
- Dysphagia, oral mucositis, oral pain, or anorexia
- Flu-like syndrome
- Engraftment syndrome
- Weight loss
- Pain, pain in extremity, headache, or insomnia
- Hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia
- Increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, or alkaline phosphatase
- Alopecia

### 7.5.3. Definition of Maximum Tolerated Dose

The MTD is defined as the highest dose level at which ≤1 of 6 patients experiences DLT through 30 days post-ASCT.

### 7.5.4. Definition of Recommended Phase 2 Dose

The RP2D may be equal to or higher than the preliminary MTD, but less than the non-tolerated dose (i.e., the dose at which ≥2 of 6 patients experienced DLT). The RP2D will be determined in discussion with the Sponsor, Medical Monitor, and Investigators.

## 7.6. Study Drug Preparation and Administration

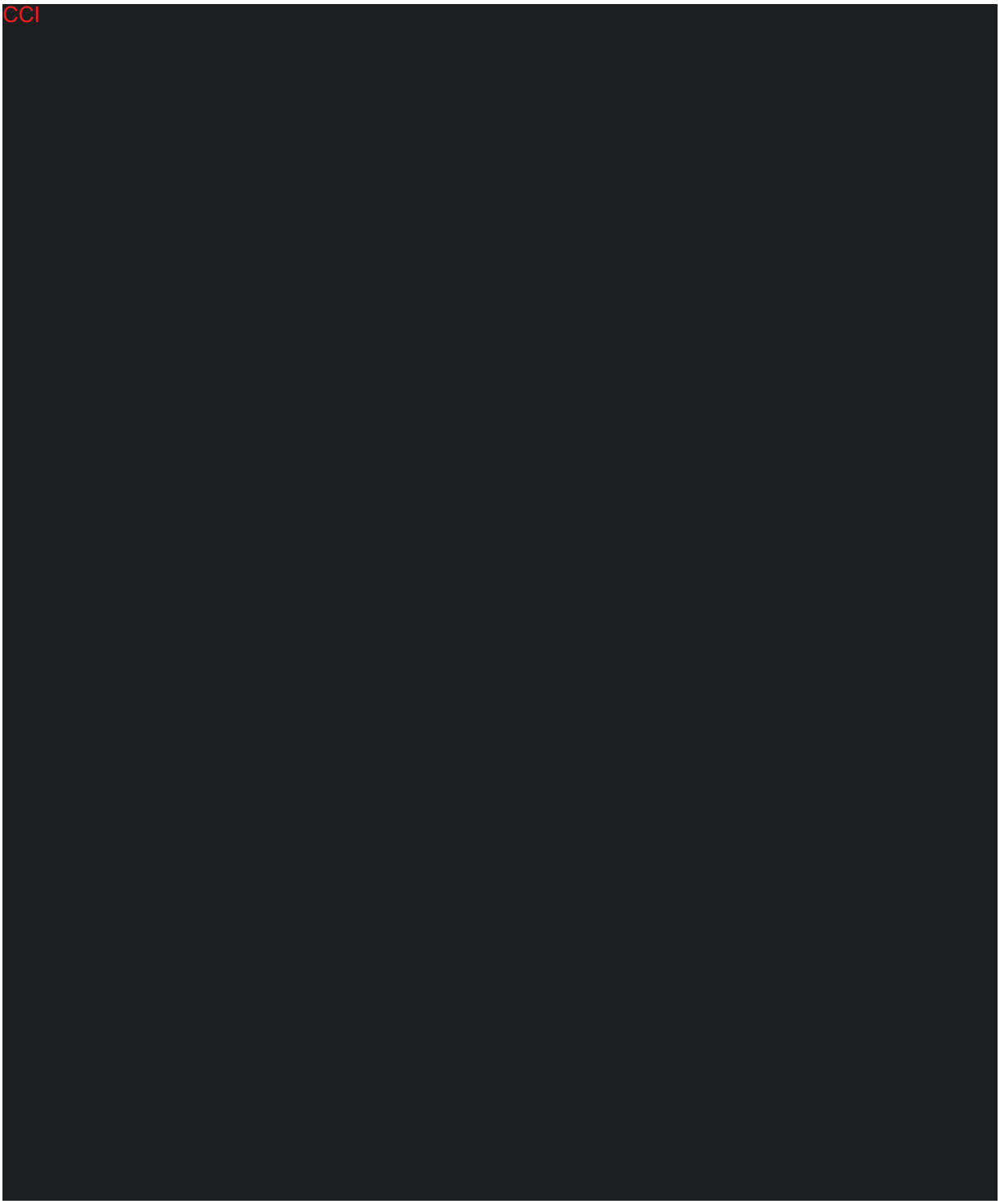
### 7.6.1. Study Drug Preparation

For administration, tinostamustine powder is reconstituted with 20 mL saline (0.9%) and then further diluted with 230 mL saline (0.9%) to a final volume of 250 mL. CCI [redacted]

Please refer to the study specific Pharmacy Manual to ensure the correct preparation of tinostamustine.

### 7.6.2. Study Drug Administration

Tinostamustine is to be administered IV through a peripheral vein over 45 minutes.


CCI


## 7.8. Prior and Concomitant Medications and Procedures

All prescription and non-prescription medications and therapies, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 28 days prior to the first dose of tinostamustine through Day 100 (±7 days) must be recorded in the eCRF. Concomitant 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 [ASC] infusion); or after ASCT (i.e., after the start of ASC infusion).

On PK sample collection days (Table 1), both the date and time of concomitant medications and therapies must be recorded.

The Investigator should contact the study medical monitor with any questions or clarifications regarding concomitant medications.

### 7.8.1. Prohibited Medications

The following medications and treatments are prohibited during study participation:

- Any investigational agent or device other than tinostamustine, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.
- Any anti-neoplastic treatment with activity against MM.
- Medications known to prolong the QT/QTc interval, will be excluded. The use of other concomitant medications that present a low risk of QT/QTc prolongation may be considered, with the approval of the Medical Monitor. (Refer to the crediblemeds list of drugs with known risk of TdP: http://crediblemeds.org.)

### 7.8.2. Permitted Medications and Supportive Therapies

Medications and treatments other than those specified in Section 7.8.1, including palliative and supportive care for disease-related symptoms, are permitted during the study. Patients should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate.

Patients may receive the following supportive care:

- IV hydration and anti-emetics, in accordance with institutional guidelines.
- Growth factor support with pegfilgrastim or equivalent agent post-ASCT, in accordance with institutional guidelines.
- Standard supportive care, in accordance with institutional guidelines, including blood product transfusions, antimicrobial prophylaxis (e.g., anti-bacterial, *Pneumocystis carinii*, anti-fungal, herpes simplex virus/varicella zoster virus), and treatment for febrile neutropenia.
- Bisphosphonates may be administered after ASCT according to local institutional practice.
- After adequate blood count recovery (ANC $>1.0\times10^9$/L and platelet count $>80\times10^9$/L) as well as resolution of mucositis and fever, if present, radiation may be administered for the following indications after consultation with the Medical Monitor:
  - Palliation of pain from bone lesions
  - Prevention of pathologic fractures
  - Relief of spinal cord compression or nerve root compression

  The radiation oncologist is to determine the dose and duration of radiation to be administered. Radiation to the liver or lungs should be avoided.

## 7.9. Blinding

This is an open-label study; no blinding methods will be employed.

# 8. TRANSPLANT PROCEDURES

## 8.1. Conditioning

See Section 7.6 for details regarding tinostamustine preparation and administration.

## 8.2. 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.

## 8.3. Engraftment

During in-patient hospitalization, patients will be assessed daily for hematologic engraftment, starting on the first day the ANC is $<0.5\times10^9$/L until and including the day engraftment criteria are met, as follows:

- Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
- Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.

# 9. STUDY ASSESSMENTS

## 9.1. Baseline Assessments

### 9.1.1. Informed Consent

All patients must provide written informed consent before any samples are collected or evaluations performed in this study that are not part of standard patient care.

### 9.1.2. Demographics

Patient demographics, including age, sex, race, and ethnicity, are to be documented in the source documents and in the eCRF at Screening.

### 9.1.3. Medical History, Including Cancer History

A complete medical history, including prior and concomitant illnesses and conditions as well as prior surgeries and other procedures, is to be documented in the source documents and in the eCRF at Screening. MM history, including the date of diagnosis and details regarding prior ASCT and all other previous treatment for MM and best response to such treatments, also is to be documented and recorded in the eCRF.

### 9.1.4. Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI)

The HCT-CI is a validated comorbidity index that comprises 17 different categories of organ dysfunction (Sorror et al. 2007; Maruyama et al. 2007; Barba et al. 2010; Frina et al. 2009). Positive findings are summated into a total score. 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. HCT-CI score is to be documented in the source documents and in the eCRF at Screening.

The HCT-CI is accessible at: http://www.hctci.org/Home/Calculator.

### 9.1.5. Prior and Concomitant Medications

All prior medications and supplements the patient received within 28 days before baseline and all medications and supplements the patient receives through Day 100 are to be documented in the source documents and in the eCRF. Concomitant 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 ASC infusion); or after ASCT (i.e., after the start of ASC infusion).

### 9.1.6. Echocardiogram or Multi-gated Acquisition Scan

LVEF is to be determined by multi-gated acquisition scan or echocardiography during Screening.

#### 9.1.7. Pulmonary Function Testing

The following PFTs are to be measured during Screening

- $FEV_1$
- FVC
- DLCO

Patients who have difficulty making an appropriate seal on the mouthpiece to perform PFTs effectively should be fitted with a facial mask for PFT measurements.

#### 9.1.8. Screening Serologies

Blood samples for infectious disease marker testing, including, at a minimum, human immunodeficiency virus (HIV) types 1 and 2, hepatitis B virus (HBV) panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus (HCV), Treponema pallidum, cytomegalovirus, and Epstein-Barr virus, are to be collected during Screening. Any patient with a positive result is not eligible for study participation.

#### 9.1.9. Pregnancy Testing

Serum or urine β-human chorionic gonadotropin (hCG) pregnancy testing is to be performed for female patients of childbearing potential (i.e., premenopausal or not surgically sterile) during Screening. Any patient with a positive result is not eligible for study participation. Pregnancy testing is to be repeated any time pregnancy is suspected.

### 9.2. Safety Measurements

#### 9.2.1. Physical Examination,

Physical examinations are to be performed at each study center visit. Complete physical examinations are to be performed at the time points designated in Table 1. The complete physical examination includes assessment of the following:

- General appearance
- Head, eyes, ears, nose, and throat
- Cardiovascular system
- Respiratory system
- Gastrointestinal system (abdomen)
- Lymphatic system
- Musculoskeletal system
- Skin

- Psychiatric
- Neurological – A complete neurologic examination, including assessment of mental status, memory, cranial nerves, motor function, and reflexes, is to be performed as part of the complete physical examination.

Targeted (i.e., symptom-directed) physical examinations are to be conducted at the time points designated in Table 1.

Abnormal physical examination findings that are considered by the Investigator to be clinically significant are to be reported as an AE, if the finding represents a change from baseline.

### 9.2.2. Height and Weight

Height is to be measured for all patients during Screening.

Body weight is to be measured during Screening and at the time points designated in Table 1. The patient's height documented during Screening and weight documented prior to the commencement of tinostamustine on Day -1 are to be used to calculate the tinostamustine dose.

### 9.2.3. ECOG Performance Status

ECOG performance status is to be determined at the time points designated in Table 1. The ECOG performance status scale, with corresponding Karnofsky performance status score equivalents, is presented in Table 4.

**Table 4: Eastern Cooperative Oncology Group Performance Status Scale, with Equivalent Karnofsky Performance Status Scores**

| ECOG[1] | | Karnofsky[2] | |
|---|---|---|---|
| **Score** | **Criterion** | **%** | **Criterion** |
| 0 | Normal activity | 100 | Normal; no complaints; no evidence of disease |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 1 | Symptoms but ambulatory | 80 | Normal activity with effort; some signs or symptoms of disease |
| | | 70 | Cares for self; unable to carry on normal activity or do active work |
| 2 | In bed <50% of time | 60 | Requires occasional assistance but is able to care for most of his/her needs |
| | | 50 | Requires considerable assistance and frequent medical care |
| 3 | In bed >50% of time | 40 | Disabled, requires special care and assistance |
| | | 30 | Severely disabled; hospitalization is indicated though death is not imminent |
| 4 | 100% bedridden | 20 | Very sick; hospitalization is necessary |
| | | 10 | Moribund; fatal processes progressing rapidly |
| 5 | Dead | 0 | Dead |

1 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

2 Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer. 1984;53:2002-2007.

### 9.2.4. Vital Signs

Vital signs, including blood pressure, pulse and respiration rates, and body temperature, are to be measured at the time points designated in Table 1. Pulse rate and blood pressure will be measured with the patient in a sitting position after a 5-minute rest.

Vital signs abnormalities that are considered by the Investigator to be clinically significant are to be reported as AEs, if the finding represents a change from baseline.

### 9.2.5. Holter Monitoring

Continuous Holter monitoring will be performed on Day -1, the day of tinostamustine administration. Holter monitoring will commence 15 minutes prior to the start of the infusion on Day -1 and will continue through 24 hours following the end of infusion.

Patients should be resting comfortably in the supine or semisupine position for 15 minutes prior to each of the following timepoints: 0 [before start of infusion] then after start of the infusion at 15, 30, 45, 60 and 75 minutes and 3, 6, and 24 hours following the start of the infusion.

At time 0 and at all time points after infusion, ECGs readings will be extracted for establishment of baseline and for the purposes of Dose Limiting Toxicities determination and for cardiac safety analyses.

The Holter monitor flashcards will be sent to eResearch Technology, Inc., for processing. The analysis methodology will be described in a separate ECG cardiac safety statistical analysis plan.

Note that because the ECG recordings are stored on flashcards, results will not be available in "real time" at the study center.

The ECGs extracted from the Holter monitoring will be used for the determination of DLTs.

### 9.2.6. 12-Lead Electrocardiogram

A triplicate ECG will be performed during Screening to determine patient eligibility for the study. Furthermore, on Day -1 (-1 day), a triplicate ECG is to be performed before study drug administration and a single ECGs will be performed at 30 and 60 minutes after the start of study drug administration for assessment by the site. Another single ECG will be performed at visit on D30 (±5 days). ECGs are to be repeated by the Investigator, as clinically indicated.

ECGs (12-lead) are to be performed in after the patient is supine for 5 minutes.

All ECGs will be reviewed centrally. The Investigator or the Sponsor may request expedited central review of ECGs, as clinically indicated.

The Investigator's interpretation of ECGs is to be used for patient management during the study; the central reader interpretation of ECGs extracted from Holter monitoring will be used to determine all ECG data for study endpoints including baseline QTcF interval for cardiac safety analyses and DLTs.

### 9.2.7. Safety Laboratory Tests

#### 9.2.7.1. Hematology, Serum Chemistries, and Urinalysis

Blood samples are to be collected for assessment of hematology, coagulation studies, and clinical chemistry parameters and urine samples for urinalysis, according to the schedule defined in Table 1. Laboratory samples are to be collected after vital signs are measured.

The following safety laboratory parameters will be measured:

**Hematology**

- Hematocrit
- Hemoglobin
- Red blood cell count
- White blood cell count
- Platelet count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

**Serum Chemistries**

- ALT
- AST
- Bilirubin (total, direct, and indirect)
- Magnesium
- Glucose
- Phosphate
- Sodium
- Creatinine*
- Uric acid
- Alkaline phosphatase
- Bicarbonate
- Calcium
- Chloride
- Lactate dehydrogenase
- Potassium
- Total protein
- Blood urea nitrogen

*To be fractionated if abnormal.

**Coagulation Studies**

- Prothrombin time and/or International normalized ratio
- Activated partial thromboplastin time

**Urinalysis**

- Color
- Specific gravity
- Glucose
- Blood
- pH
- Protein
- Ketones

Safety laboratory tests may be repeated as necessary during treatment at a schedule determined by the Investigator, based on the patient's clinical status.

Laboratory abnormalities that are considered by the Investigator to be clinically significant are to be reported as AEs, if the finding represents a change from baseline.

### 9.2.8. Adverse Events

#### 9.2.8.1. Definitions

##### *9.2.8.1.1. Adverse Event*

An AE is defined in the ICH Guideline for GCP as "any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment" (ICH E6:1.2).

Worsening of a pre-existing medical condition, (i.e., diabetes, migraine headaches, gout) should be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (i.e., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AEs.

In the case of death, only record "Fatal" for the event causing death. AEs that are ongoing at the end of the study or time of death are to be noted as "continuing." Classification of AEs is to be done by the Investigator according to the NCI CTCAE, version 4.03.

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual patient represents a significant change from baseline. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should not be recorded as AEs; however, laboratory value changes requiring therapy are considered AEs.

##### *9.2.8.1.2. Suspected Adverse Reaction*

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, "reasonable possibility" and/or at least possibly related means there is evidence to suggest a causal relationship between the drug and

the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### *9.2.8.1.3. Serious Adverse Event*

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

- is fatal
- is life-threatening (i.e., places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 hospitalization, or the development of drug dependency or drug abuse.

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any AE that does not meet one of the definitions of serious (i.e., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the Investigator to meet the "important medical event" criterion for classification as an SAE.

#### *9.2.8.1.4. Unexpected Adverse Event*

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application, as amended.

*9.2.8.1.5. Serious and Unexpected Suspected Adverse Reaction*

A serious and unexpected suspected adverse reaction (SUSAR) is any event that meets all 3 of the following definitions:

1) suspected adverse reaction (Section 9.2.8.1.2);

2) serious (Section 9.2.8.1.3); and

3) unexpected (Section 9.2.8.1.4).

### 9.2.8.2. Adverse Event Assessment

All AEs will be collected and recorded 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. This includes AEs the patient reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during scheduled study visits.

Each AE is to be assessed by the Investigator with regard to the following categories.

**Serious/Non-Serious**

AEs that meet the criteria specified in Section 9.2.8.1 are to be considered serious.

**Relationship to Study Drug**

The relationship of each AE to study drug is to be assessed by the Investigator according to categories in Table 5.

**Table 5: Criteria for Determination of Adverse Event Relationship to Study Drug**

| Relationship Between Study Drug and AE: | | | | | |
|---|---|---|---|---|---|
| | Category | | | | |
| **AE (is):** | **None** | **Unlikely** | **Possibly** | **Likely** | **Definitely** |
| Clearly the result of an external factor | Yes | No | No | No | No |
| Probably/possibly the result of another factor | No | Yes | Yes | No | No |
| Has a chronological relationship with the time of administration and/or represents a known reaction to Study Drug | No | No | Yes | Yes | Yes |
| Disappears or decreases after discontinuation of the Study Drug | NA | NA | NA | Yes | Yes |
| Recurs on renewed administration (re-challenge) | No | No | NA | NA | Yes or NA** |

**A re-challenge is not required; if done, re-challenge would be expected to be positive.
NA = not applicable

**Intensity**

The intensity of each AE is to be assessed by the Investigator according to the NCI CTCAE, version 4.03. If the AE is not included in the NCI CTCAE, version 4.03, then the Investigator is to determine the intensity of the AE according to the following criteria:

- Mild (Grade 1): Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2): Minimal, local, or non-invasive intervention indicated; limited age-appropriate instrumental activities of daily living.
- Severe (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; incapacitating with inability to work or perform normal daily activity.
- Life-threatening (Grade 4): consequences: urgent intervention indicated.
- Death (Grade 5) related to an AE.

#### 9.2.8.3. Recording Adverse Events

All AEs occurring from the from the time written informed consent is obtained through the Day 100 (±7 days) visit are to be recorded in the source documents and in the eCRF. AEs will be documented as occurring pre-conditioning (i.e., pre-tinostamustine); during conditioning (i.e., after the start of the first tinostamustine infusion through immediately before the start of ASC infusion); or after ASCT (i.e., after the start of ASC infusion). All AE reports are to contain the following details regarding the AE: a brief description, onset date, duration, intensity, treatment required, relationship to study drug, study drug action taken, outcome, and whether the event is classified as serious.

#### 9.2.8.4. Reporting Serious Adverse Events

SAEs will be collected and recorded throughout the study period, beginning with the signing of the informed consent form (ICF) through the Day 100 (±7 days) visit, or after the end of the study if thought to be related to study drug.

The Investigator must report all SAEs to the Sponsor within 24 hours of discovery.

A completed SAE report is to be sent to the Medical Monitor's attention within 24 hours of discovering the event. The initial report should include at least the following information:

- Patient's ID number;
- Description and date of the event;
- Criterion for serious; and

- Preliminary assignment of causality to study drug.

The Medical Monitor will contact the Investigator via telephone for follow-up information regarding the SAE, as appropriate.

The Investigator, or designated party, should notify the appropriate IRB/EC of SAEs occurring at the study center and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

SAEs that are considered as possible or probably related to the investigational product, and as unexpected (i.e., SUSARs), will be reported to the concerned Competent Authorities (CAs) and IRBs/ECs by the Sponsor or Sponsor's designee as required by applicable local regulations. Per regulation, any fatal or life-threatening SUSAR will be reported to the CAs/IRBs/ECs within 7 calendar days, and additional information within an additional 8 calendar days. The Sponsor or Sponsor's designee is required to submit any other SUSAR to the CAs/IRBs/ECs within 15 calendar days of notification. The Sponsor or its designee is also responsible for notifying the investigational sites of all expedited SAEs. The Investigator must keep copies of all expedited SAE information including correspondence with the Sponsor on file.

#### 9.2.8.5. Follow-Up of Adverse Events

The Investigator must continue to follow all SAEs and non-serious AEs considered to be at least possibly related to study drug either until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

#### 9.2.8.6. Reporting Safety Information

The Investigator must promptly report to his or her IRB/EC all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs reasonably or possibly associated with the use of Study Drug according to the IRB/EC's procedures.

The Sponsor will assess the severity and frequency of adverse drug reactions in adults versus pediatric patients, and will submit findings annually in the Development Safety Update Report/Annual Report.

#### 9.2.8.7. Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. The Investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Medical Monitor, in conjunction with the Investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be noted in the eCRF.

#### 9.2.8.8. Pregnancy

Pregnancy is considered unlikely in this study, given the population of patients to be enrolled. Nonetheless, pregnancies occurring within 12 months after the patient's last dose of tinostamustine will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 9.2.8.4.

The patient is to be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient until completion of the pregnancy, and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth are to be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to tinostamustine should also be reported.

## 9.3. Disease Assessments

### 9.3.1. Myeloma Protein Measurements in Serum and Urine

#### 9.3.1.1. Serum

Blood samples for quantitation of immunoglobulin (Ig) (IgA, IgG, and IgM are required; IgD and IgE are optional) and M-protein and assessment of M-protein by immunofixation in serum are to be collected from all patients at the time points designed in Table 1. Note that in the case of IgA MM, MM IgA values should be used.

All samples will be analyzed by the local laboratory. Assessments of response will be evaluated by two independednt reviewers.

#### 9.3.1.2. Urine

Twenty-four hour urine samples for quantitation of M-protein and assessment of M-protein by immunofixation are to be collected from all patients during Screening. For patients with positive findings at Screening, such samples also are to be collected at the time points designed in Table 1. Patients with negative Screening results need not provide urine samples for M-protein quantitation and assessment after Screening.

All samples will be analyzed by the local laboratory. Assessments of response will be evaluated by two independednt reviewers.

### 9.3.2. Free Light Chain Testing

Serum samples for free light chain (FLC) testing are to be collected from all patients during Screening and at the time points designed in Table 1. The free kappa/lambda ratio is to be recorded in the eCRF.

A serum sample for FLC testing also is to be collected in order to confirm stringent complete response (sCR).

### 9.3.3. Bone Marrow Examination

Bone marrow aspiration to be performed for all patients during Screening, and for patients who achieve a CR, on Day 100 (±7 days) post-ASCT. Bone marrow aspiration and biopsy are to be repeated during treatment as clinically indicated.

Approximately 5mL of the same sample (i.e., "first-pull"), collected in ethylenediaminetetraacetic acid (EDTA) tubes, will be used for assessment of MRD-N using next-generation flow cytometry.

### 9.3.4. Skeletal Survey and Other Imaging Studies

Skeletal surveys (plain radiographs, or any other method used as standard care at the site, of the skull, spine, ribs, pelvis, humeri and femora) are to be performed during Screening. If a skeletal survey has been performed within 3 months before Baseline, then this evaluation need not be repeated during Screening.

A skeletal survey is to be repeated during the study as clinically indicated.

Other appropriate imaging studies (e.g., magnetic resonance imaging, CT, X-ray) to evaluate the patient's disease are to be performed during Screening per standard of care, as determined by the Investigator. Appropriate imaging studies are to be repeated as necessary to confirm CR.

### 9.3.5. Assessment of Disease Response

The Investigator will perform tests that will allow evaluation of response to therapy according to the IMWG Criteria, as outlined in Table 6. Patients who are determined to have CR are then to have additional tests performed that will allow further characterization of the CR.

Assessment of disease response using non-invasive procedures will be performed at the time points designed in Table 1. Appropriate imaging studies and bone marrow aspirates/biopsies must be repeated only in patients suspected of having a CR, based on non-invasive procedures.

**Table 6: IMWG Response Criteria**

| Response | IMWG Criteria |
|---|---|
| Complete response (CR)[1] | • Negative immunofixation of serum and urine, and<br>• Disappearance of any soft tissue plasmacytomas, and<br>• <5% plasma cells in bone marrow |

| Response | IMWG Criteria |
|---|---|
| Stringent complete response (sCR) | CR as defined above plus<br>• Normal FLC ratio, and<br>• Absence of clonal plasma cells (PC) by immunohistochemistry or 2-4 color flow cytometry. |
| Immunophenotypic CR | Stringent CR plus<br>• Absence of phenotypically aberrant PC (clonal) in bone marrow (BM) with a minimum of one million of total BM cells analyzed by multiparametric flow cytometry (with >4 colors) |
| Molecular CR | CR plus<br>• Negative allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR), sensitivity $10^{-5}$ |
| Very good partial response (VGPR)[1] | • Serum and urine M-component detectable by immunofixation but not on electrophoresis, or<br>• ≥90% or greater reduction in serum M-component plus urine M component <100 mg per 24 hours |
| Partial response (PR) | • ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 hours<br>• If the serum and urine M-protein are unmeasurable a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria<br>• If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30%<br>• In addition to the above criteria, if present at Baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required |
| Stable disease (SD) | Not meeting criteria for CR, VGPR, PR or progressive disease. |

| Response | IMWG Criteria |
|---|---|
| Progressive disease (PD)[2] | • Increase of 25% from lowest response value in any one or more of the following:<br>• Serum M-component (absolute increase must be ≥0.5 g/dL) and/or<br>• Urine M-component (absolute increase must be ≥200 mg/24 hours) and/or<br>• Only in patients without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)<br>• Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be >10%)<br>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<br>• Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder |

Source:. Rajkumar, et al. Blood 2011;117(18):4691-5.
All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at Baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
1 Note clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients requires in addition a >90% decrease in the difference between involved and uninvolved free light chain FLC levels.
2 Note clarifications to IMWG criteria for coding PD: Clarified than bone marrow criteria for progressive disease are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia. Note that the "lowest response value" does not need to be a confirmed value.

The Investigator's assessment of disease response will be used for patient management during the study.

Confirmation of responses should be obtained for biochemical markers but is not necessary for bone marrow or imaging studies. The confirmatory tests should be performed by Day 130+/-7 days. The response date is not the date of confirmation but the initial date when the assessment met the end point. In other words, the second test is confirmatory. If the result is not confirmed by a second evaluation, the status is either non-evaluable and the prior disease status remains valid.

### 9.3.6. Independent Review Committee

An Independent Review Committee (IRC) will be established under the direction of the Sponsor to provide an objective, unbiased, independent review of objective response, using the IMWG criteria (Table 6), as demonstrated based on the pertinent clinical data from the study.

A formal, written IRC charter will be established outlining the composition of the IRC, the data to be evaluated, and the manner of committee meetings.

## 9.4. Pharmacokinetics

Serial blood samples for PK analysis will be collected after each tinostamustine dose according to the schedule in Table 1. Blood samples for PK assessment should be collected following the 15-minute supine, resting periods described for the continuous Holter recordings. PK samples are to be collected from the arm opposite of that used for tinostamustine administration.

The calendar date and exact 24-hour clock time of blood sample collection for PK assessments will be documented in the source document and the eCRF.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

# 10. STATISTICAL ANALYSES

## 10.1. Statistical Basis for Sample Size

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 15 (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%.

In the methodology proposed by Simon (Simon, 1989), a Phase 2 design can be represented by 4 numbers: N1, R1, N, and R. N1 is the sample size in the first stage. R1 is the critical value in the first stage. If R1 or fewer responses occur in the N1 patients, the study treatment is rejected. N is the combined sample size for both the first and second stages. R is the critical value in the combined sample. If R or fewer of the N patients respond, the study treatment is rejected at the end.

The design is found with PASS Sample Size Software through an exhaustive search of all possible designs (combinations of R1, N1, R and N) that control alpha (0.025) and beta (0.20, meaning power is 0.80). With the minimax approach, the design is selected that has the lowest N.

Per the minimax design, 31 patients are to be enrolled in Stage 1. If >25 of 31 patients (in the 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.

## 10.2. Statistical and Analytical Plan

An overview of the statistical methodology to be employed is provided in the following subsections. Details regarding the statistical methodology will be documented in a formal Statistical Analysis Plan (SAP) prior to database lock.

### 10.2.1. General Methods

Statistical analyses will be primarily descriptive in nature. Statistical hypothesis testing is neither intended nor appropriate within this context except for the primary endpoint. Confidence intervals will be based on asymptotic methods.

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 (n, %) of patients within each classification.

Dependent of the specific analysis, the analysis sets as defined in Section 10.2.2 will be taken from the cohort for Phase 1, for Phase 2 (RP2D) or both phases pooled. Unless specified otherwise below, this will be further defined in the SAP.

### 10.2.2. Analysis Populations

All patients who receive tinostamustine will be included in the safety set.

All patients in the safety set who had at least one post-ASCT response evaluation will be included in the full analysis set (FAS).

All patients in the FAS with no major protocol deviations will be included in the per-protocol (PP) set.

All patients in the safety set with at least one quantifiable pre-dose and one quantifiable post-dose PK plasma concentration will be included in the PK set.

### 10.2.3. Missing Data

Analyses will be based on observed data only; no data will be imputed.

### 10.2.4. Disposition of Patients

Patients who are screened for study entry and do not meet the eligibility criteria will be documented. The numbers and proportions of patients who complete the study and who are early terminations will be summarized. Reasons for study discontinuation after the start of study treatment will be tabulated.

### 10.2.5. Demographics and Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized. Data to be tabulated will include demographic and baseline characteristics such as sex, age, race, height, weight, and body mass index, and MM-specific diagnostic and historical information. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and raw and coded data will be summarized.

### 10.2.6. Extent of Exposure

Descriptive statistics for the percent of expected dose received and the actual dose received will be summarized. A tabular summary and listing of drug 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.

### 10.2.7. Prior and Concomitant Medications

Tabulations of prior and concomitant medications, coded using the World Health Organization Drug Dictionary (WHO-DD), will be produced. All prior and concomitant medications administered will be presented in a data listing.

### 10.2.8. Efficacy Analyses

Superiority testing will be performed on FAS in the Phase 2 cohort 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% (CIBMTR report, December 2017) and a 1-sided 2-step chi-square test will be performed at the 2.5% level of significance for FAS.

For the primary endpoint, also an upper 1-sided 97.5% confidence interval will be calculated for FAS in addition to summary statistics.

For the primary endpoint in other sets and for the secondary endpoints of other responder rates in the FAS, also 2-sided 95% confidence intervals will be calculated in addition to summary statistics.

Response assessments as determined by the Investigator and IRC will be compared, with agreement determined by Kappa coefficient.

Disease assessment variables and their changes from baseline will be summarized visit wise.

### 10.2.9. Pharmacokinetic Analyses

PK analysis for tinostamustine and its metabolites will be performed using the PK set.

PK parameters at all doses will include $C_{max}$, time to maximum plasma concentration ($t_{max}$), $t_{1/2}$, area under the plasma concentration curve from 0 to 12 hours ($AUC_{0-12}$), area under the plasma concentration curve from time 0 to time t ($AUC_{0-t}$), apparent total clearance (CL/F), apparent volume of distribution (Vd/F), and terminal disposition rate constant ($\lambda z$). The initial calculation of PK parameters will be performed using non-compartmental analysis. Plasma concentrations and PK parameters will be summarized by dose.

Summaries will include the number of observations (n), arithmetic or geometric mean, SD or coefficient of variation (CoV), median, minimum, and maximum.

### 10.2.10. Safety Analyses

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

Adverse Events will be coded using MedDRA and raw and coded data will be summarized.

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.

### 10.2.11. Interim Analyses

In Phase 2 of the study, at the completion of the Stage 1 with 31 patients, an interim analysis will be performed using the FAS for the Phase 2 cohort to determine whether enrollment will continue in Stage 2. If >25 of 31 patients in Stage 1 experience a response to treatment, then enrollment will continue in 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 in the ongoing Stage 2 recruitment.

## 10.3. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report.

# 11. ETHICAL, LEGAL, AND ADMINISTRATIVE CONSIDERATIONS

## 11.1. Good Clinical Practice

This study will be conducted according to the protocol and in compliance with ICH GCP, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

The Investigator confirms this by signing the protocol.

## 11.2. Informed Consent

Written informed consent will be obtained from each patient prior to undergoing any protocol-specific tests or procedures that are not part of routine care.

The Sponsor or designee will provide an ICF template to the Investigator for use in developing a study center-specific consent documents. Prior to submission of the study center-specific ICF to the IRB/EC, these documents must be reviewed and approved by the Sponsor or designee. Any changes requested by the IRB/EC must also be approved by the Sponsor or designee. The final IRB/EC-approved ICF must be provided to the Sponsor or designee. Revisions to the ICF required during the study must be approved by the Sponsor r designee, and a copy of the revised ICF provided to the Sponsor or designee.

Before recruitment and enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the ICF in a language they understand. After the Investigator or designee is assured that the patient understands the commitments of participating in the study, the patient will be asked to sign and date the ICF, as appropriate.

A copy of the fully signed and dated ICF will be given to the patient. The original will be maintained in the patient's medical record at the study center. All active patients will sign an updated ICF if revisions are made to the ICF during the course of the study.

## 11.3. Institutional Review Board/Ethics Committee

Federal and European regulations and ICH require that approval be obtained from an IRB/EC prior to participation of patients in research studies. Approval by the Competent Authority, if applicable, or as required by local laws and regulations, is also required in Europe. Prior to the 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/EC.

All IRB/EC approvals must be dated and signed by the IRB/EC Chairperson or designee and must identify the IRB/EC by name and address, the clinical protocol by title and/or protocol number, and the date approval or favorable opinion was granted for the clinical research.

No drug will be released to the site to dose a patient until written IRB/EC authorization has been received by the Sponsor or designee.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB/EC. The Investigator must supply the Sponsor or designee with written documentation of the approval of the continued clinical research.

The Investigator, sponsor, or designee as applicable, will make all attempts to ensure that the IRB/EC is constituted and operates in accordance with Federal and ICH GCP and any local regulations.

## 11.4. Amending the Protocol

Any changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee and the IRB/EC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/EC for approval prior to patients being enrolled into the amended protocol.

The Sponsor may make administrative changes (i.e., changes that do not significantly affect patient safety or the study's scope or scientific quality) without any further approvals.

All amendments will be distributed to all protocol recipients.

## 11.5. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from the Sponsor.

Patient confidentiality will be strictly maintained to the extent possible under the law. Patient names must not be disclosed. Patients will be identified in the eCRFs and other documents submitted to the Sponsor or its designated representative, by their initials, birth date, and/or assigned patient number. Documents that identify the patient (e.g., the signed ICF) should not to be submitted to the Sponsor or its designated representative, and must be maintained in confidence by the Investigator.

## 11.6. Publication Policy

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. The initial planned publication will be a multicenter report of the study outcome. Additional publications from a given center can only occur after the publication of the multicenter results. A prepublication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher.

# 12. STUDY MANAGEMENT

## 12.1. Data Quality Assurance

The Sponsor or its designated representative will conduct a study center visit to verify the qualifications of each investigator, inspect study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

## 12.2. Case Report Forms and Source Documentation

The Investigator and designees agree to maintain accurate eCRFs and source documentation as part of case histories. Source documents are the originals of any documents used by the Investigator or subinvestigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the study.

The Sponsor or designee will provide eCRFs to the study center. eCRFs will be completed for each patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of informed consent, study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected/data are available, preferably on the same day that a patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

## 12.3. Monitoring

A CRA, or other representative of the Sponsor, will conduct a study center visit to verify the qualifications of each Investigator, inspect study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

During the course of the study, the CRA will make study center visits to review protocol compliance, compare eCRFs and individual patients' medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements in respect to GCP. eCRFs will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

## 12.4. Inspections

Regulatory authorities and/or quality assurance personnel from the Sponsor or its designated representative, may wish to carry out such source data checks and/or in-center audit inspections.

The Investigator assures the Sponsor of the necessary support at all times. In the event of an audit, the Investigator agrees to allow the sponsor's representatives and any regulatory agencies access to all study records.

## 12.5. Financial Disclosure Reporting Obligations

Investigators and subinvestigators are required to provide financial disclosure information to the sponsor to permit the sponsor to fulfill its regulatory obligation. Investigators and subinvestigators must commit to promptly updating the information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

## 12.6. Archiving Study Records

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local requirements.

ICH requires that patient identification codes be retained for at least 15 years after the completion or discontinuation of the study.

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

Protocol Number: EDO-S101-1004

*This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.*

**Study Sponsor:**

Mundipharma-EDO GmbH
St Alban Rheinweg 74
CH 4052 Basel
Switzerland

**Sponsor Signature**

PPD

PPD , MD

PPD

Date PPD

**IND Number:** CCI

**EudraCT Number:** CCI

**Document Version (Date):** 2.0, 18 June 2018

**Previous Version (Date):** 1.0, 20 March 2018

# INVESTIGATOR STATEMENT

I understand that all documentation provided to me by Mundipharma EDO, or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Ethics Committee (EC). No changes will be made to the study protocol without the prior written approval of Mundipharma EDO and the IRB/EC, except where necessary to eliminate an immediate hazard to a patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

_____ _____
Investigator Signature Date

_____
Printed Name

# CLINICAL STUDY SYNOPSIS

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| **Name of Sponsor**<br>Mundipharma-EDO GmbH | | |
| **Name of Finished Product:**<br>Tinostamustine hydrochloride (Formerly EDO-S101) | | **Name of Active Ingredient:**<br>Tinostamustine hydrochloride |
| **Protocol No.:**<br>EDO-S101-1004 | **Temporary (T) No.:** | **<EUDRACT><IND> No.:**<br>CCI [redacted] |
| **Short Title of the Study:**<br>Titanium 1<br>Phase 1/2 Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplantation for Treatment in Relapsed / Refractory Multiple Myeloma | | |
| **Full Title of the Study:**<br>Phase 1/2 Open-label Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplantation for Salvage Treatment in Relapsed / Refractory Multiple Myeloma (TITANIUM 1) | | |
| **Investigator(s)/Centre(s):** Multicenter study; up to 18 centers in the US and Europe will be enrolling patients. | | |
| **Study Initiation:**<br>Q3 2018 | | **Phase of Development:**<br>Phase 1 / 2 |

**Objectives:**

***Phase 1***

The primary objectives of Phase 1 of this study are to:

- 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 Phase 2 portion of the study.

The secondary objective of Phase 1 of this study is to:

- Investigate the pharmacokinetics (PK) of tinostamustine.

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***Phase 2***

The primary objectives of Phase 2 of the study are to:

- Investigate the efficacy of the tinostamustine conditioning regimen at the RP2D dose.
- Investigate the safety of the tinostamustine conditioning regimen.

The secondary objective of Phase 2 of this study is to:

- Evaluate the PK of tinostamustine.

**Endpoints**

***Efficacy***

The primary efficacy endpoint in Phase 2 of the study is:

- Objective response rate (ORR): complete response [CR], very good partial response [VGPR] and partial response [PR] at Day 100 (±7 days) post-autologous stem cell transplant (ASCT).

Secondary efficacy endpoints among patients treated at the RP2D (in Phases 1 and 2) are:

- ORR, and, in patients who achieve CR, minimal residual disease-negativity (MRD-N), as determined by next-generation flow cytometry at Day 100 (±7 days) post-ASCT.

***Safety***

The safety endpoint in Phase 1 of the study is:

- Dose-limiting toxicities (DLT).

Additional safety endpoints in Phases 1 and 2 of the study are:

- Incidence of neutrophil and platelet engraftment failure.
- Duration of cytopenia (i.e., absolute neutrophil count [ANC] $\leq 0.5\times10^9$/L, platelet count $\leq 20\times10^9$/L).
- Cumulative incidence of treatment-related mortality (TRM).
- Transplant-related non-hematologic Grade 3 toxicity over time through Day 30, stratified by hematopoietic cell transplantation comorbidity index (HCT-CI).
- Incidence of adverse events (AEs) and serious adverse events (SAEs).

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- Change from baseline in standard safety hematology and clinical chemistry test results.

**Study Design (Methodology):**

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 multiple myeloma (MM). (ASCT is defined as salvage if the patient had already received a prior ASCT and undergoes a second ASCT after evidence of progressive disease [PD].)

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.

The total dose of tinostamustine will be administered on Day -1.

Phase 2 of the study employs a 2-step sequential design (Simon, 1989). In Stage 1 of Phase 2, up to 31 patients initially will be enrolled. 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, 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.

After provision of written informed consent, patients will be screened for study eligibility within 28 days before Day 1 (the day of ASCT). Patients who have a minimum of $2\times10^6$ CD34+ cells/kg cryopreserved and are otherwise determined to be eligible, based on screening assessments, will be enrolled and receive the tinostamustine conditioning regimen. The tinostamustine dose will be administered 24 hours pre-ASCT (i.e., Day -1).

On Day 1, ASCs will be administered intravenously (IV) according to standard institutional practice.

Patients will receive supportive measures (including growth factor support post-ASCT, antimicrobial prophylaxis, red blood cell and platelet transfusion, and treatment for neutropenic fever) according to standard institutional practice.

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During in-patient hospitalization, patients will be assessed daily for toxicity through Month 1 Day 30 (±5 days) post-ASCT or until all transplant-related toxicity resolves. Patients will be discharged from the study center once the following engraftment criteria are met:

- Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
- Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.

Thereafter, patients will attend study center visits at Month 2 Day 60 (±5 days) and Day 100 (±7 days).

**Definition of DLT**

Toxicity will be assessed by the Investigator using the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

In Phase 1 of the study, DLT is defined as the occurrence of any of the following events occurring within 30 days post-ASCT that are considered by the Investigator to be at least possibly related to tinostamustine:

- Delayed engraftment (>30 days after ASCT). Engraftment will be considered delayed if the subject has not met criteria for both neutrophil and platelet engraftment:
  - Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
  - Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.
- QTcF >500 msec or >60 msec increase from baseline, with a duration of >30 minutes, or ≥Grade 3 QTcF interval prolongation accompanied by ventricular arrhythmia. Baseline QTcF interval will be the mean value determined during triplicate ECG(s) at Day -1 (-1day), before study drug administration; the mean QTcF will be confirmed by the cental laboratory.
- Grade 4 non-hematologic toxicity
- Grade 3, non-hematologic toxicity related to treatment, **with the exception of:**
  - Nausea or vomiting
  - Diarrhea

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- Fatigue, dehydration, or glucose intolerance
- Skin rash, dry skin, or pruritus responsive to topical or systemic steroids
- Fever (>40ºC for ≤24 hours)
- Infection
- Dyspnea, hypoxia, or pneumonitis
- Abdominal pain
- Dysphagia, oral mucositis, oral pain, or anorexia
- Flu-like syndrome
- Engraftment syndrome
- Weight loss
- Pain, pain in extremity, headache, or insomnia
- Hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia
- Increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, or alkaline phosphatase
- Alopecia

**Dose Escalation Scheme**

In Phase 1, up to 3 patients initially are to be enrolled in each cohort. The first patient enrolled in the initial cohort must complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, before additional patients may be enrolled in that initial cohort. (If the first patient experiences a DLT, then a lower dose will be explored for the second patient, and so on.)

- If the first patient does not experience a DLT or experiences engraftment without a ≥Grade 3 toxicity, the next 2 patients may be enrolled simultaneously.

After 3 patients in a cohort complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, and have safety evaluations performed through that time, and:

- None of these 3 patients experience a DLT, then enrollment of the next cohort may commence

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with approval from the Safety Committee.

- 1 of 3 patients within a cohort experiences a DLT, then up to 3 additional patients are to be enrolled sequentially at that dose level. If none of the additional 3 patients has a DLT (i.e., 1 of 6 patients has a DLT), then enrollment at the next scheduled dose may commence with approval from the Safety Committee.
- If ≥2 patients within a cohort experience a DLT, then the DLT dose level will have been reached and the previous lower dose level will be considered the MTD. (If ≥2 patients in the initial dose cohort experience DLTs, then the dose will be reduced to one level lower and the same procedure will be followed.)

A total of 6 patients are planned to be treated at the MTD to confirm the RP2D before enrollment of patients in Phase 2 of the study. If the MTD is not confirmed at this stage, the dose will be reduced to one level lower and the same procedure will be followed.

Note that enrollment in the next dose cohort can begin only when the last patient enrolled in the current dose cohort completes the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, provided that <2 patients in the current dose cohort experienced a DLT.

Although decisions regarding dose escalation will be made based on review of data through Day 30 post-ASCT, safety data will also be collected from all patients continuing in the study and this will be reviewed periodically by the Safety Committee. Any detected toxicity may necessitate further refinement of the RP2D.

**Definition of MTD:**

The MTD is defined as the highest dose level at which ≤1 of 6 patients experiences DLT through 30 days post-ASCT.

**Definition of RP2D:**

The RP2D may be equal to or higher than the preliminary MTD, but less than the non-tolerated dose (i.e., the dose at which ≥2 of 6 patients experienced DLT). The RP2D will be determined in discussion with the Sponsor, Medical Monitor, and Investigators.

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**Number of Subjects:**

***Phase 1***

A total of 9-12 patients are planned to be enrolled in Phase 1.

***Phase 2***

A total of up to 71 patients are planned to be enrolled in Phase 2.

***Criteria for Inclusion/Exclusion:***

***Inclusion Criteria***

Patients must meet all of the following criteria to be eligible for enrollment:

1. Patient has MM and:
   a. Has received prior ASCT after standard first-line induction treatment.
   b. Has evidence of PD, with progression-free interval ≥6 months in Phase 1 ≥18 months in Phase 2.

      Progression Free Inteval is defined as the time from date of ASCT to PD.
   c. Received treatment with ≤3 prior lines of therapy.

      A line of therapy is defined as 1 or more cycles of a planned treatment program. When patients have undergone sequential phases of treatment without intervening progression, such as induction, collection of peripheral blood stem cells, transplantation and consolidation/maintenance, this is considered to be 1 line of treatment. A new line of therapy is initiated as a result of PD or relapse (Garderet et al, 2017).
2. CR, VGPR, PR, or minimal response (MR) to latest of salvage chemotherapy at relaps, as determined by the International Myeloma Working Group (IMWG) criteria.
3. Is, in the Investigator's opinion, a candidate for consolidation therapy with tinostamustine followed by ASCT. (Note that patients planned to receive tandem ASCT are not eligible for the Phase 1 portion of the study.)
4. Has available autologous peripheral blood stem cell (PBSC) product with CD34 cell dose ≥$2\times10^6$ cells/kg. The product could be from a collection prior to first ASCT or later second collection. (Note that, although not required, in Phase 1, the Investigator should consider enrolling patient

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with a large number of available PBSCs to permit subsequent ASCT, as patients in Stage 1 may received a dose lower that that determined to be effective.)

5. Age 18-75 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status score <3 at Screening.
7. Creatinine clearance ≥40 mL/min, as determined by a local laboratory using the Cockcroft-Gault equation within 28 days before ASCT.
8. Left ventricular ejection fraction (LVEF) ≥40% within 28 days before ASCT.
9. Adequate pulmonary function, defined as forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO) >50% predicted within 28 days before ASCT.
10. Adequate liver function, as defined by an ALT and AST ≤2.5 × the upper limit of normal (ULN) and bilirubin ≤1.5 × ULN within 28 days before ASCT.
11. Potassium within the local laboratory's normal range. (Potassium supplementation is permissible.)

***Exclusion Criteria***

Patients meeting any of the following criteria are not eligible for enrollment in the study:

1. History of central nervous system (CNS) disease involvement.
2. Myocardial infarction (MI) or stroke within 6 months before Screening.
3. Uncontrolled acute infection.
4. HCT-CI >6 points.
5. Concurrent malignant disease with the exception of treated basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease shall be documented since then.
6. Major coagulopathy or bleeding disorder.
7. Other serious medical condition that could potentially interfere with the completion of treatment according to this protocol or that would impair tolerance to therapy or prolong hematological recovery.

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8. Lack of cooperation to allow study treatment as outlined in this protocol.
9. Pregnancy or lactating female patients.
10. The use of any anti- cancer investigational agents within 21 days prior to the expected start of trial treatment and interval of 14 days to last administration of salvage treatment.
11. Receiving treatment with drugs known to prolong the QT/QTc interval.
12. QTc interval (Fridericia's formula) >450 msec, based on the mean of triplicate Screening 12-lead ECGs.

**Test Treatment, Dose, and Mode of Administration:**

Tinostamustine (formerly EDO-S101) CCI [redacted] The drug substance is a class 4 cytotoxic agent and should be handled with care by experienced health care professionals.

For administration, tinostamustine powder is reconstituted with 20 mL saline (0.9%) and then further diluted with saline (0.9%) to a final volume of 50 mL. CCI [redacted]

In Phase 1 of the study, the starting dose of tinostamustine 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. In Phase 2, patient will receive tinostamustine at the RP2D identified in Phase 1. The total tinostamustine dose will be administered on Day -1. Tinostamustine will be administered by IV infusion through a peripheral vein over 1 hour.

Twenty-four hours after the tinostamustine infusion, ASCs will be infused via central venous catheter on

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Day 1. If the CD34+ product is of large volume, the infusion can be given over 2 days.

Patients may receive the following supportive care:

- IV hydration and anti-emetics, in accordance with institutional guidelines.
- Growth factor support with pegfilgrastim or equivalent agent post-ASCT, in accordance with institutional guidelines.
- Standard supportive care, in accordance with institutional guidelines, including blood product transfusions, antimicrobial prophylaxis, and treatment for febrile neutropenia.

**Duration of Treatment and Study Duration:**

All patients will receive 1 doses of tinostamustine on Days -1 followed by ASCT on Day 1.

The anticipated accrual is 9-12 patients/year in Phase 1. Recruitment will continue during the evaluation period needed for Stage 1 of Phase 2. All patients will be followed for a maximum of 130 (±7 days) post-ASCT thus yielding a study of total duration of approximately 2.5 to 3.5 years.

**Criteria for Evaluation:**

***Efficacy Assessment(s):***

Response will be determined by the Investigator using the IMWG criteria. In addition, response of each subject will be evaluated by two independent reviewers, otherwise not involved in the clinical trial. In order to assess response, M protein component is to be measured in serum and/or urine, free light chain (FLC) testing is to be performed. Note that in the case of immunoglobulin A (IgA) MM, MM IgA values should be used. Bone marrow aspirate or biopsy and imaging studies (e.g., computed tomography, magnetic resonance imaging) are to be performed as clinically indicated. For patients with CR, based on serum and urine analysis, bone marrow aspirate and biopsies are to be performed at Day 100 (±7days), including the myeloma immunophenotype.

Confirmatory assessment: A second assessment of response will be conducted between 107 and 130 to confirm the response. If the result is not confirmed by a second evaluation, the status is either Non Evaluable (NE) or the prior disease status remains valid. Confirmation should be obtained for biochemical markers but ius not necessary for bone marrow or imaging studies,

Assessment of M protein in serum and urine should be performed any time relapse is suspected.

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***Drug Concentration Measurements:***

Serial blood samples for PK analysis will be collected before, duration, and after tinostamustine administration according to the schedule in Table 1. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

***Bioanalytical Methods:***

A fully validated LC-MS/MS method for the determination of EDO-S101 and its metabolites (M2 and M8) in human plasma will be utilised. CCI [redacted]

***Safety Assessments:***

Safety will be assessed by documentation of AEs, safety laboratory tests (hematology and clinical chemistries), ECOG performance status, vital signs, physical examinations, electrocardiograms (ECGs), and Holter monitoring.

During in-patient hospitalization, patients will be assessed daily for hematologic engraftment until and including the day the patient has an ANC >0.5 $\times 10^9$/L and platelet count > $20 \times 10^9$/L without transfusion support.

To assess for early renal toxicity, creatinine, urea, and uric acid will be assessed on a daily basis from the start of tinostamustine treatment through Day 3 post-ASCT. In case of clinically significant renal toxicity, creatinine, urea, and uric acid will be assessed as long as clinically indicated.

**Statistical Methods:**

***Analysis Populations***

All patients who receive tinostamustine will be included in the safety set.

All patients in the safety set who had at least one post-ASCT response evaluation will be included in the full analysis set (FAS).

All patients in the FAS with no major protocol deviations will be included in the per-protocol (PP) set.

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| All patients in the safety set with at least one quantifiable pre-dose and one quantifiable post-dose PK plasma concentration will be included in the PK set.<br>Dependent of the specific analysis, these sets will be taken from the cohort for Phase 1, for Phase 2 (RP2D), or both phases pooled. | | |
| ***Efficacy Analyses:***<br>Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Summaries for categorical variables will include frequency counts and percentages.<br>Superiority testing will be performed on FAS in Phase 2 cohort 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% (CIBMTR report, December 2017) and a 1-sided, 2-step chi-square test will be performed at the 2.5% level of significance for FAS.<br>For the primary endpoint, also an upper 1-sided 97.5% confidence interval will be calculated for FAS in addition to summary statistics.<br>For the primary endpoint in other sets and for the secondary endpoints of other responder rates in the FAS, also 2-sided 95% confidence intervals will be calculated in addition to summary statistics. | | |
| ***Interim Analyses:***<br>In Phase 2 of the study, at the completion of the Stage 1 with 31 patients, an interim analysis will be performed using the FAS for the Phase 2 cohort to determine whether enrollment will continue in Stage 2. If >25 of 31 patients 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). | | |
| ***Pharmacokinetic Analyses:***<br>PK analysis for tinostamustine and its metabolites will be performed using the PK set.<br>PK parameters at all doses will include maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($t_{max}$), half-life ($t_{½}$) area under the plasma concentration curve from 0 to 12 hours ($AUC_{0-12}$), area under the plasma concentration curve from time 0 to time t ($AUC_{0-t}$), apparent total clearance (CL/F), | | |

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apparent volume of distribution (Vd/F), and terminal disposition rate constant ($\lambda_z$). The initial calculation of PK parameters will be performed using non-compartmental analysis. Plasma concentrations and PK parameters will be summarized by dose.

Summaries will include the number of observations (n), arithmetic or geometric mean, SD or coefficient of variation (CoV), median, minimum, and maximum.

***Safety Analyses:***

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

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, SD, median, minimum, and maximum. Summaries for categorical variables will include frequency counts and percentages.

**Sample Size Rationale**

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

For Phase 1, a formal sample size determination/power calculation was not performed. 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% (CIBMTR report, December 2017) 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 drug is at least 90%.

In the methodology proposed by Simon (Simon, 1989), a Phase 2 design can be represented by 4 numbers: N1, R1, N, and R. N1 is the sample size in the first stage. R1 is the critical value in the first stage. If R1 or fewer responses occur in the N1 patients, the study treatment is rejected. N is the combined sample size for both the first and second stages. R is the critical value in the combined sample. If R or fewer of the N patients respond, the study treatment is rejected at the end.

The design is found with PASS Sample Size Software through an exhaustive search of all possible designs (combinations of R1, N1, R and N) that control alpha (0.025) and beta (0.20, meaning power is

| | | |
|---|---|---|
| **Name of Sponsor**<br>Mundipharma-EDO GmbH | | |
| **Name of Finished Product:**<br>Tinostamustine hydrochloride (Formerly EDO-S101) | | **Name of Active Ingredient:**<br>Tinostamustine hydrochloride |
| **Protocol No.:**<br>EDO-S101-1004 | **Temporary (T) No.:** | **<EUDRACT><IND> No.:**<br>CCI |
| 0.80). With the minimax approach, the design is selected that has the lowest N.<br>Per the minimax design, 31 patients are to be enrolled in Stage 1. If >25 of 31 patients (in the FAS) in Stage 1 experience a response to treatment, then enrollment will continue in 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. Thus, a total of up to 71 patients will be enrolled in Phase 2.<br>If the total number of patients who experience a response is ≥62 of 71, then the study is considered a success. | | |
| **Schedule of Events**<br>The schedule of events is presented in Table 1. | | |

**Table 1: Schedule of Events (Phases 1 and 2)**

| Procedure | Screening | Conditioning | ASCT | Post-ASCT Follow-up[1] | | | |
|---|---|---|---|---|---|---|---|
| | D-28 to -1 | D-1 | D0 | M1 | M2 | D100 (±7 days) | D130 (±7 days) |
| Written informed consent[2] | X | | | | | | |
| Eligibility review | X | | X | | | | |
| Demographics | X | | | | | | |
| Medical history | X | | | | | | |
| HCT-CI | X | | | | | | |
| Cancer history, including history of prior ASCT and other treatments | X | | | | | | |
| ECHO or MUGA scan | X | | | | | | |
| Pulmonary function testing[3] | X | | | | | | |
| Infectious disease screening[4] | X | | | | | | |
| Pregnancy test[5] | X | | | | | | |
| ECOG performance status | X | | X | X | X | X | |
| Complete physical examination | X | | | | | | |
| Targeted physical examination | | X | X | X | X | X | |
| Height | X | | | | | | |
| Weight | X | | X | X | X | X | |
| Vital signs[6] | X | X | X[7] | X | X | X | |
| Continuous Holter monitoring | | X[9] | | | | | |
| 12-lead ECG[10] | X[11] | X[11] | | X | | | |
| Hematology[12] | X | Repeat daily until hospital discharge | | | | | |
| Kidney function tests (creatinine, urea, and uric acid) | | Daily from the start of tinostamustine through Day 3post-ASCT | | | | | |

| Procedure | Screening | Conditioning | ASCT | Post-ASCT Follow-up[1] | | | |
|---|---|---|---|---|---|---|---|
| | **D-28 to -1** | **D-1** | **D0** | **M1** | **M2** | **D100 (±7 days)** | **D130 (±7 days)** |
| Clinical chemistries[13] | X | X | X | X | X | X | |
| Coagulation parameters: PT and/or INR, aPTT | X | | X | X | | X | |
| Urinalysis[14] | X | | | | | | |
| Tinostamustine administration[15] | | X | | | | | |
| PK sample collection | | X[16] | | | | | |
| ASCT[17] | | | X | | | | |
| Disease assessments | | | | | | | |
| Skeletal survey[18] | X | | | | | | |
| Bone marrow aspirate and biopsy[19] | X | | | | | D100 (±7 days)[20] | |
| Serum / urine M protein quantitation | X | | | X | X | X | X |
| Immunoglobulin quantitation (IgA, IgG, and IgM [required]; IgD, IgE [optional]) | X | | | X | X | X | X |
| Free light chain analysis | X | | | X | X | X | X |
| Disease response assessment[21] | X | | | X | X | X | |
| Evaluation for MRD-N | | | | | | D100 (±7 days)[20] | |
| AE monitoring[22] | AEs, including SAEs, are to be documented from the provision of written informed consent through Day 100. | | | | | | |
| Prior/concomitant medications[23] | All medications administered within 28 days before Day 1 through Day 100 are to be documented. | | | | | | |

1. Patients will be evaluated daily on an inpatient basis until engraftment criteria are met and the patient is discharged from the hospital. Thereafter, study center visits will be performed on an outpatient basis. Visit M1: D30 ( ±5days); visit M2: D60 (±5days)
2. Written informed consent is to be obtained before the performance of any study-related procedures.
3. Pulmonary function testing is to include $FEV_1$, FVC, and DLCO.
4. Infectious disease marker testing is to include, at a minimum, human immunodeficiency virus (HIV) types 1 and 2, hepatitis B virus (HBV) panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus (HCV), Treponema pallidum, CMV, and Epstein-Barr virus.
5. Urine or serum pregnancy testing will be performed for women of childbearing potential. Pregnancy testing is to be repeated on study any time pregnancy is suspected.
6. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Vital signs are to be measured after patient is sitting for 3-5 minutes.

7. Perform assessment both pre- and post-treatment.
8. ECGs (12-lead) are to be performed after the patient is supine for 5 minutes. Repeat ECGs as clinically indicated. Screening ECGs will be reviewd centrally. Regarding other 12 lead ECGs: the investigator or the sponsor may request expedited central review of ECGs, as clinically indicated.
9. Continuous Holter monitoring will be performed on Day -1, the day of tinostamustine administration. Holter monitoring will commence 15 minutes prior to the start of the infusion on Day -1 and will continue through 24 hours following the end of infusion. Patients should be resting comfortably in the supine or semisupine position for 15 minutes prior to each of the following timepoints: 0 [before start of infusion] then after start of the infusion at 15, 30, 45, and 60 minutes and 3, 6, and 24 hours following the start of the infusion. At time 0 and at all time points after infusion, ECGs readings will be extracted in triplicate, with each ECG separated by 5 minutes (±2 minutes), for establishment of baseline for the purposes of cardiac safety analyses. The Holter monitor flashcards will be sent to eResearch Technology, Inc., for processing.
10. The Investigator's interpretation of ECGs is to be used for patient management during the study; the central reader interpretation of ECGs extracted from Holter monitoring will be used to determine all ECG data for study endpoints including baseline QTcF interval for cardiac safety analyses and DLTs.
11. A triplicate ECG will be performed during Screening to determine patient eligibility for the study. Furthermore, on Day -1, a triplicate ECG is to be performed before study drug administration and a single ECGs will be performed at 30 and 60 minutes after the start of study drug administration for assessment by the site. Another single ECG will be performed at visit on day 30 (±5 days). ECGs are to be repeated by the Investigator, as clinically indicated.
12. Hematology parameters minimally include WBC count and differential (lymphocytes, monocytes, basophils, eosinophils, neutrophils), red blood cell (RBC) count, hematocrit, hemoglobin, and platelet count.
13. Serum chemistry parameters minimally include alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase, (AST), bicarbonate, bilirubin (total, direct, and indirect), calcium, magnesium, chloride, glucose, lactate dehydrogenase (LDH), phosphate, potassium, sodium, and total protein.
14. Urinalysis includes appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.
15. The tinostamustine dose will be administered one day before ASCT (Day -1), at least 24 hours pre-ASCT.
16. Blood samples for PK are to be collected immediately pre-infusion of tinostamustine and 30, 45, and 60 (±5) minutes and then at 3, 6, and 24 hours (±15 minutes) and then 48 hours (±30 minutes) after the start of infusion. Blood samples for PK assessment should be collected following the 15-minute supine resting periods described for the continuous Holter recordings. PK samples are to be collected from the arm opposite of that used for tinostamustine administration.
17. On Day 1, ASCs will be administered IV according to standard institutional practice. If the CD34+ product is of large volume, the infusion can be given over 2 days.
18. A skeletal survey (plain radiographs, or any other method used as standard care at the site, of the skull, spine, ribs, pelvis, humeri and femora) will be performed at Screening if not performed within the previous 3 months. Thereafter, skeletal survey and/or other imaging studies are to be performed as clinically indicated.
19. Bone marrow aspirate and trephine biopsy are to be performed during Screening. Bone marrow aspirate and biopsy are to be repeated during treatment as clinically indicated, at the Investigator's discretion, and at any time CR is suspected.
20. Any patient who achieves a CR will have peripheral blood and bone marrow collected at Day 100 (±7 days) for assessment of evidence of MRD-N via next-generation flow cytometry.
21. Disease response will be assessed by the Investigator using the IMWG Criteria. Confirmation should be obtained for biochemical markers but is not necessary for bone marrow or imaging studies. There is no specific time interval required between the 2 evaluations, the the confirmatory tests ideally should be performed approximately 4 weeks after the initial evaluation.
22. AEs will be documented as occurring 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 [ASC] infusion); or after ASCT (i.e., after the start of ASC infusion).
23. Concomitant 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 ASC infusion); or after ASCT (i.e., after the start of ASC infusion).

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AK-DACi | Alkylating deacetylase inhibitor |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ASC | Autologous stem cell |
| ASCT | Autologous stem cell transplantation |
| AST | Aspartate aminotransferase |
| $AUC_{0\ 12}$ | Area under the plasma concentration curve from 0 to 12 hours |
| $AUC_{0\text{-}t}$ | Area under the plasma concentration curve from time 0 to time t |
| CA | Competent Authorities |
| CL/F | Apparent total clearance |
| $C_{max}$ | Maximum plasma concentration |
| CNS | Central nervous system |
| CoV | Coefficient of variation |
| CR | Complete response |
| CRA | Clinical Research Associate |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P450 |
| DLCO | Carbon monoxide diffusing capacity |
| DLT | Dose-limiting toxicity |
| DNA | Deoxyribonucleic acid |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |

| Abbreviation | Definition |
|---|---|
| EDTA | Ethylenediaminetetraacetic acid |
| FAS | Full analysis set |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FLC | Free light chain |
| FVC | Forced vital capacity |
| GCP | Good Clinical Practice |
| HBV | Hepatitis B virus |
| hCG | Human chorionic gonadotropin |
| HCT-CI | Hematopoietic cell transplantation comorbidity index |
| HCV | Hepatitis C virus |
| HDACi | Histone-deacetylase inhibitor |
| HIV | Human immunodeficiency virus |
| HPβCD | Hydroxyl-propyl-β-cyclodextrin |
| $IC_{50}$ | 50% inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| ID | Identification |
| Ig | Immunoglobulin |
| IMWG | International Myeloma Working Group |
| IRB | Institutional review board |
| IRC | Independent Review Committee |
| IV | Intravenous(ly) |
| LVEF | Left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGMT | O6-methylguanine-DNA methyltransferase |
| MI | Myocardial infarction |
| MM | Multiple myeloma |

| **Abbreviation** | **Definition** |
|---|---|
| MR | Minimal response |
| MRD-N | Minimal residual disease-negativity |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| ORR | Objective response rate |
| PBSC | Peripheral blood stem cell |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PP | Per-protocol |
| PR | Partial response |
| RP2D | Recommended Phase 2 dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| sCR | Stringent complete response |
| SD | Stable disease |
| SD | Standard deviation |
| SUSAR | Serious and unexpected suspected adverse reaction |
| $t_{1/2}$ | half-life |
| $t_{max}$ | Time to maximum plasma concentration |
| TRM | Treatment-related mortality |
| ULN | Upper limit of normal |
| US | United States |
| Vd/F | Apparent volume of distribution |
| VGPR | Very good partial response |
| WHO-DD | World Health Organisation Drug Dictionary |
| λz | Terminal disposition rate constant |

# TABLE OF CONTENTS

# LIST OF TABLES IN THE TEXT

# 1. STUDY PERSONNEL AND ADMINISTRATIVE STRUCTURE

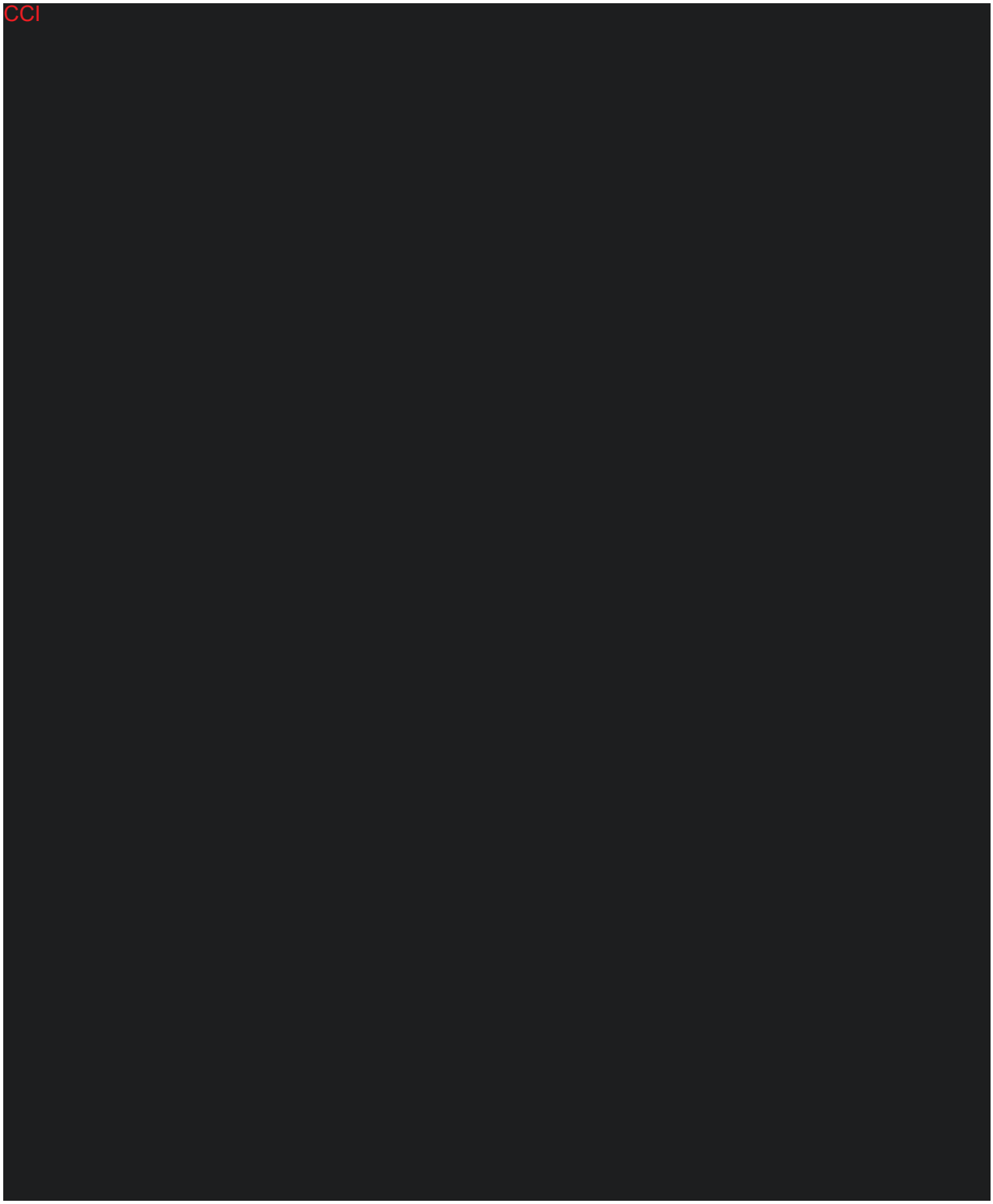
**Study Sponsor:**

Mundipharma-EDO GmbH
St Alban Rheinweg 74
CH 4052 Basel
Switzerland

**Sponsor Signatory:**

PPD, MD

CCI



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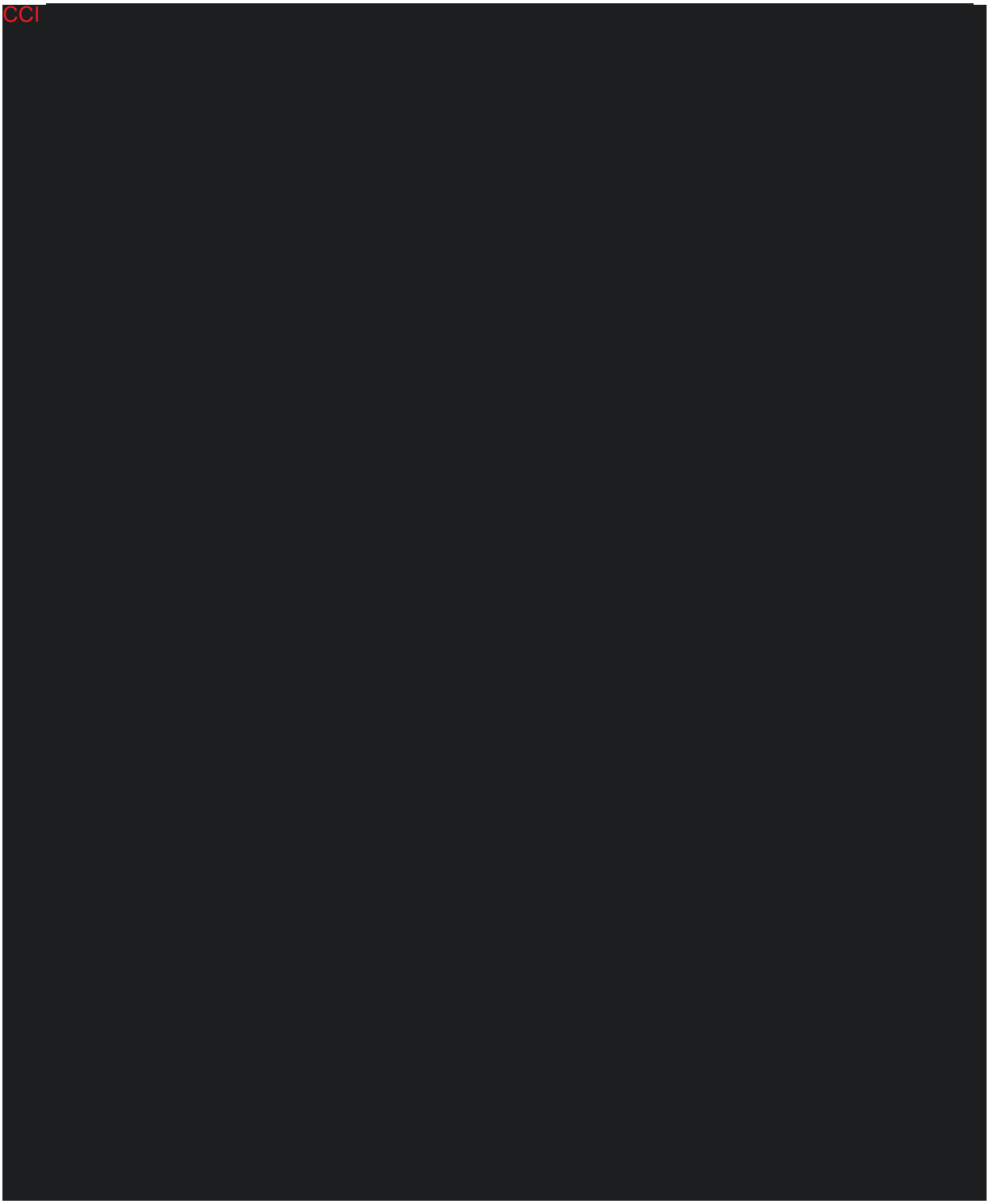

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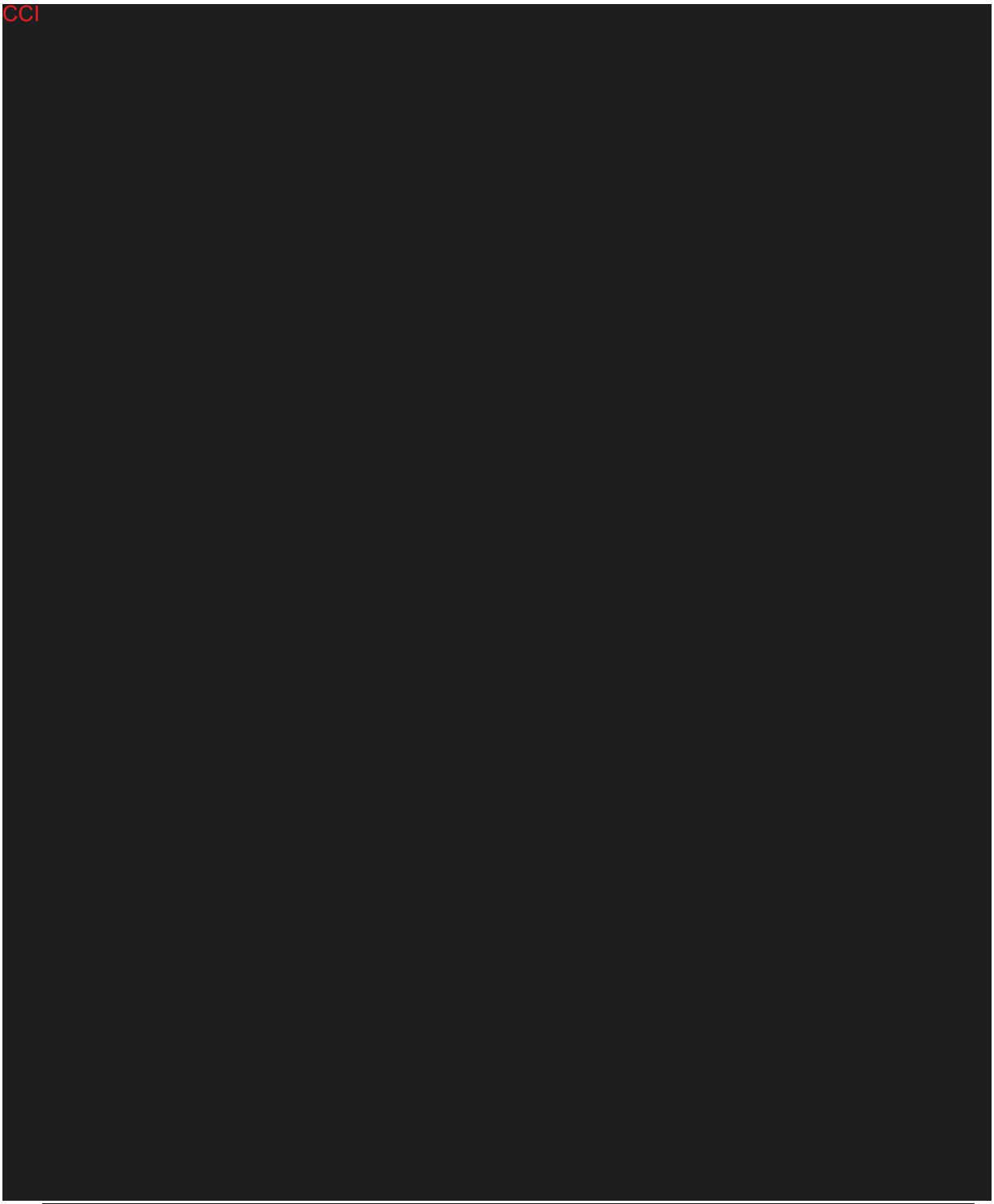

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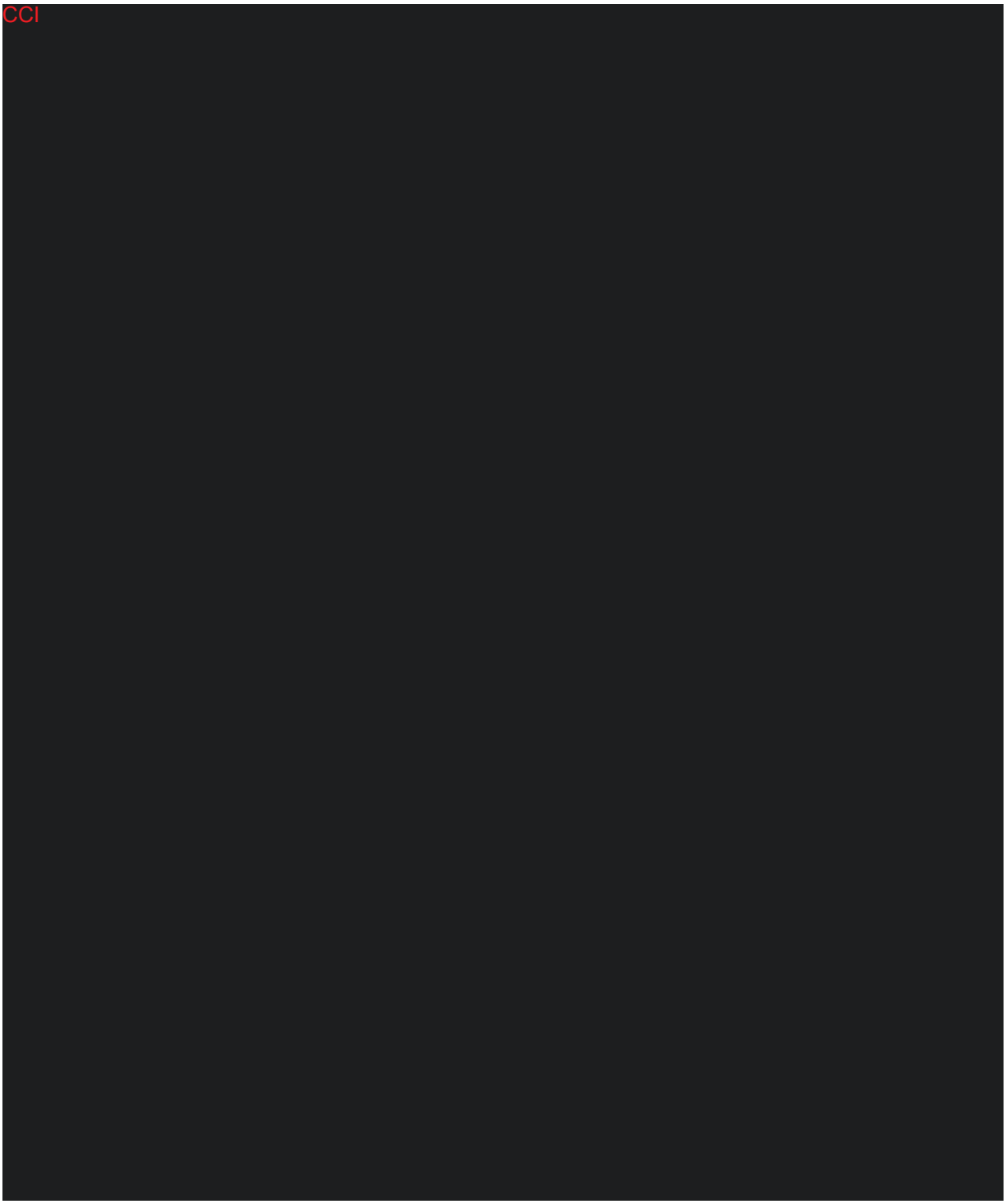


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# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1. Objectives

### 3.1.1. Phase 1

#### 3.1.1.1. Primary Objectives

The primary objectives of Phase 1 of this study are to:

- Establish the safety, toxicity, and MTD of the tinostamustine conditioning regimen.
- Identify the RP2D of tinostamustine for use in the Phase 2 portion of the study.

#### 3.1.1.2. Secondary Objectives

The secondary objective of Phase 1 of this study is to:

- Investigate the PK of tinostamustine.

### 3.1.2. Phase 2

#### 3.1.2.1. Primary Objectives

The primary objectives of Phase 2 of the study are to:

- Investigate the efficacy of the tinostamustine conditioning regimen at the RP2D.
- Investigate the safety of the tinostamustine conditioning regimen.

#### 3.1.2.2. Secondary Objectives

The secondary objective of Phase 2 of this study is to:

- Evaluate the PK of tinostamustine.

## 3.2. Study Endpoints

### 3.2.1. Efficacy

#### 3.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint in Phase 2 of the study is:

- Objective response rate (ORR): complete response [CR] plus partial response [PR] at Day 100 (±7 days) post-ASCT.

#### 3.2.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints among patients treated at the RP2D (in Phases 1 and 2) are:

- ORR and, in patients who achieve CR, minimal residual disease-negativity (MRD-N), as determined by next-generation flow cytometry at Day 100 (±7 days) post-ASCT.

### 3.2.2. Safety

The safety endpoint in Phase 1 of the study is:

- DLTs

Additional safety endpoints in both Phases 1 and 2 of the study are:

- Incidence of neutrophil and platelet engraftment failure.
- Duration of cytopenia (i.e., absolute neutrophil count [ANC] $\leq 0.5\times10^9$/L; platelet count $\leq 20\times10^9$/L).
- Cumulative incidence of treatment-related mortality (TRM).
- Transplant-related non-hematologic Grade 3 toxicity over time through Day 30, stratified by hematopoietic cell transplantation comorbidity index (HCT-CI).
- Incidence of adverse events (AEs) and serious adverse events (SAEs).
- Change from baseline in standard safety hematology and clinical chemistry test results.

# 4. INVESTIGATIONAL PLAN

## 4.1. Overall Study Design and Plan

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. (ASCT is defined as salvage if the patient had already received a prior ASCT and undergoes a second ASCT after evidence of progressive disease [PD].)

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.

In Phase 2 of the study, all patients will receive tinostamustine at the RP2D administered in Phase 1 according to the same schedule.

Phase 2 of the study employs a 2-step sequential design (Simon, 1989). 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, 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.

After provision of written informed consent, patients will be screened for study eligibility within 28 days before Day 1 (the day of ASCT). Patients who have a minimum of 2×10$^6$ CD34+ cells/kg cryopreserved and are otherwise determined to be eligible, based on screening assessments, will be enrolled and receive the tinostamustine conditioning regimen. The tinostamustine dose will be administered 24 hours pre-ASCT (i.e., Day -1).

On Day 1, ASCs will be administered intravenously (IV) according to standard institutional practice.

Patients will receive standard supportive measures (including growth factor support post-ASCT, antimicrobial prophylaxis, red blood cell and platelet transfusion and treatment for neutropenic fever) according to standard institutional practice.

During in-patient hospitalization, patients will be assessed daily for toxicity through Month 1 Day 30 (±5 days) post-ASCT or until all transplant-related toxicity resolves. Patients will be

discharged from the study center once the following engraftment criteria are met:

- Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
- Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.

Thereafter, patients are to be followed at Month 2 Day 60 (±5 days) and Day 100 (±7 days).

## 4.2. Justification for the Study Design

Goals of Phase 1 oncology studies include estimation of the initial safety and tolerability of a study drug, establishment of an MTD, and determination of a recommended range of doses for evaluation in future clinical studies, based on safety and PK (Ahn, 1998; Gatsonis, Greenhouse, 1992; Dillman, Koziol, 1992); the primary objectives of the current study are consistent with those typical of Phase 1 oncology studies.

Phase 1 of the study employs a traditional 3+3 dose escalation design. The dose escalation scheme to be followed is based on a modified Fibonacci sequence schema, which is commonly employed in Phase 1 dose-finding oncology studies (Storer, 1989).

After identification of the RP2D in the Phase 1 portion of the study, the potential efficacy of conditioning with tinostamustine followed by ASCT will be investigated in the Phase 2 portion of the study. Phase 2 utilizes a Simon 2-stage minimax design, a common design in Phase 2 oncology clinical studies by which the expected sample size is minimized if the treatment regimen has minimal activity (Simon, 1989).

# 5. STUDY POPULATION

Patients with relapsed/refractory MM who have received prior ASCT after standard first-line induction treatment are planned to be enrolled.

## 5.1. Inclusion Criteria

Patients must meet all of the following criteria to be considered eligible for study entry:

1. Patient has MM and:
   a. Has received prior ASCT after standard first-line induction treatment.
   b. Has evidence of PD, with progression-free interval ≥6 months in Phase 1 ≥18 months in Phase 2.

      Progression Free Interval is defined as the time from date of ASCT to PD.
   c. Received treatment with ≤3 prior lines of therapy.

      A line of therapy is defined as 1 or more cycles of a planned treatment program. When patients have undergone sequential phases of treatment without intervening progression, such as induction, collection of peripheral blood stem cells, transplantation and consolidation/maintenance, this is considered to be 1 line of treatment. A new line of therapy is initiated as a result of PD or relapse (Garderet et al, 2017).
2. CR, PR, or minimal response (MR) to salvage chemotherapy, as determined by the International Myeloma Working Group (IMWG) criteria.
3. Is, in the Investigator's opinion, a candidate for consolidation therapy with tinostamustine followed by ASCT. (Note that patients planned to receive tandem ASCT are not eligible for the Phase 1 portion of the study.)
4. Has available autologous PBSC product with CD34 cell dose ≥$2\times10^6$ cells/kg. The product could be from a collection prior to first ASCT or later second collection. (Note that, although not required, in Phase 1, the Investigator should consider enrolling patient with a large number of available PBSCs to permit subsequent ASCT, as patients in Stage 1 may received a dose lower than that determined to be effective.)
5. Age 18-75 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status score <3 at Screening.
7. Creatinine clearance ≥40 mL/min, as determined by a local laboratory using the Cockcroft-Gault equation within 28 days before ASCT.
8. Left ventricular ejection fraction (LVEF) ≥40% within 28 days before ASCT.

9. Adequate pulmonary function, defined as forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO) >50% predicted within 28 days before ASCT.
10. Adequate liver function, as defined by an alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper limit of normal (ULN) and bilirubin ≤1.5 × ULN within 28 days before ASCT.
11. Potassium within the local laboratory's normal range. (Potassium supplementation is permissible.)

## 5.2. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study entry:

1. History of central nervous system (CNS) disease involvement.
2. Primary or secondary plasma cell leukemia at any time point prior to transplant
2. Myocardial infarction (MI) or stroke within 6 months before Screening.
3. Uncontrolled acute infection.
4. HCT-CI >6 points.
5. Concurrent malignant disease with the exception of treated basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease shall be documented since then.
6. Major coagulopathy or bleeding disorder.
7. Other serious medical condition that could potentially interfere with the completion of treatment according to this protocol or that would impair tolerance to therapy or prolong hematological recovery.
8. Lack of cooperation to allow study treatment as outlined in this protocol.
9. Pregnancy or lactating female patients.
10. The use of any anti- cancer investigational agents within 21 days prior to the expected start of trial treatment and interval of 14 days to last administration of salvage treatment.
11. Receiving treatment with drugs known to prolong the QT/QTc interval.
12. QTc interval (Fridericia's formula) >450 msec, based on the mean of triplicate Screening 12-lead ECGs.

## 5.3. Source of Patients

This will be a multinational, multicenter study. Each study center is required to obtain local Institutional Review Board (IRB)/Ethics Committee (EC) and national regulatory approval to conduct the study before enrollment of patients may commence. Patients meeting the entry criteria who are known or referred to the study center will be eligible for enrollment.

# 6. STUDY CONDUCT

## 6.1. Patient Identification and Enrollment

To ensure accurate and timely monitoring of patient enrollment, the following procedures will be implemented:

- Patients who are candidates for enrollment into the study will be assigned a sequential and unique patient number by the Investigator after the patient has provided written informed consent. Once a patient number has been assigned, it cannot be reused.
- Patients who have provided written informed consent will be evaluated for eligibility by the Investigator to ensure that the entry criteria (see Section 5.1 and Section 5.2) have been satisfied and that the patient is eligible for participation in this clinical study. An eligibility form will be provided by the Sponsor, or designee for this evaluation.
- The Investigator or the Investigator's research staff will provide eligibility information to the Sponsor or designee. After confirmation, the Sponsor or designee will provide the Investigator with written verification of each patient's enrollment.
- No patient may be enrolled prior to confirmation of a patient's eligibility by the Sponsor or designee.
- Patients who are enrolled but not treated with tinostamustine followed by ASCT will be replaced.
- Investigators will be notified by the Sponsor or designee when enrollment in a given dose cohort / study part is closed and enrollment into the next dose cohort / study part can begin. (Investigators will be consulted in all dose escalation decisions.)
- Investigators will be notified by the Sponsor or designee if the study is placed on administrative hold, when it is completed, or is closed to further patient enrollment.

## 6.2. Patient Management

All patients must provide written informed consent before any samples are collected or evaluations performed in this study that are not part of standard patient care. Patients will be evaluated for study eligibility during the Screening period, within 28 days before baseline (Day 1; the Day of ASCT).

Patients who are determined to be eligible, based on Screening assessments, will return to the clinic to receive the tinostamustine conditioning regimen; the tinostamustine dose will be administered 24 hours pre-ASCT (on Day -1).

On Day 1, ASCs will be administered IV according to standard institutional practice.

During in-patient hospitalization, patients will be assessed daily for toxicity through Month 1 Day 30 (±5 days) post-ASCT or until all transplant-related toxicity resolves. Patients will be discharged from the study center once engraftment criteria are met (see Section 8.3).

Thereafter, patients are to be followed at Month 2 Day 60 (±5 days) and Day 100 (±7 days).

## 6.3. Patient Adherence

All patients are required to adhere to the protocol-specified dosing and visit schedules. If a patient misses a scheduled visit, attempts should be made to reschedule the visit within the visit windows specified in Table 1. Failure to attend scheduled study visits may result in discontinuation from the study.

## 6.4. Treatment Discontinuation Criteria

Once tinostamustine has been infused it will be medically negligent to stop transplant and supportive therapy for the particular patient. In the event of consent withdrawal during or following conditioning or the development of complications that, in the Investigator's opinion, puts the patient at risk with continued protocol-specified treatment, the Medical Monitor should be contacted immediately to discuss management of the patient.

## 6.5. Study Discontinuation Criteria

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Patient non-adherence to protocol requirements.
- Patient unwillingness to continue in the study.
- Any other reason, based upon the medical judgment of the Investigator.

The reason for study withdrawal is to be documented in the patient's source documents and electronic case report form (eCRF).

## 6.6. Study Completion

A patient is considered to have completed the study if they complete the Day 100 (±7 days) visit and a confirmatory response assessment between D107 visit and D130 visit, the latest.

## 6.7. Study Termination

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of tinostamustine.

## 6.8. Investigator Compliance

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol. The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance documents.

## 6.9. Safety Committee

A Safety Committee will be involved in the conduct of this study. The Safety Committee will be comprised of Sponsor personnel, the Medical Monitor, the Investigator or representative thereof at each active study center, and a biostatistician (as needed). Ad hoc participants may be part of the committee at the request of the Sponsor or other Safety Committee members. The Safety Committee has the responsibility for monitoring the clinical study's progress and the safety of the participating patients. The Safety Committee will evaluate study conduct during the course of the clinical study, based upon data defined for this clinical study.

In Phase 1, the Safety Committee will review all safety data from all patients enrolled in each cohort to confirm any DLTs that were experienced and make a determination regarding enrollment in the next cohort. If a DLT necessitates enrollment of additional patients into a cohort, the Safety Committee will review all of the safety data for that cohort after those additional patients before a determination regarding enrollment in the next cohort is made. Based on evaluation of the data, the Safety Committee may decide that enrollment at an intermediate dose level not specified in this protocol may take place.

In addition, after identification of the MTD, the Safety Committee will review all safety data collected to date to confirm that no unexpected, significant, or unacceptable risk to patients enrolled in the study has been discovered.

# 7. STUDY DRUG

Mundipharma EDO or its designee will supply tinostamustine to the pharmacies at all participating study centers. All study drug must be stored in a safe and locked place with no access by unauthorized personnel.

## 7.1. Study Drug Supply

CCI [redacted]

CCI [redacted] The drug substance is a class 4 cytotoxic agent and should be handled with care by experienced health care professionals.

## 7.2. Study Drug Packaging and Labeling

CCI [redacted]

Study drug will be labeled in accordance with applicable regulatory requirements. Study drug labels will not contain any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated.

## 7.3. Study Drug Storage

Tinostamustine vials are stored CCI [redacted]

## 7.4. Study Drug Accountability

The Investigator or delegate will maintain accurate records of receipt and condition of study drug, including dates of receipt. In addition, accurate records will be kept of the date administered, quantity administered, and the patient to whom study drug was administered. Any reasons for departure from the protocol-specified dispensing regimen must also be recorded.

The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug. The site identification (ID) number and patient initials and ID number are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, they are to record the date dispensed, amount dispensed, and their initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused supplies.

A Clinical Research Associate (CRA) will review study drug accountability records during routine monitoring visits. At the completion of the study, there will be a final reconciliation of all study drug.

## 7.5. Study Drug Dose

In Phase 1 of the study, the starting dose of tinostamustine is 180 mg/m$^2$, with escalation to 220, 260, and then 300 mg/m$^2$ 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.

In Phase 2, patient will receive tinostamustine at the RP2D identified in Phase 1.

### 7.5.1. Dose Escalation Procedure

In Phase 1, up to 3 patients initially are to be enrolled in each cohort. The first patient enrolled in the initial cohort must complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, before additional patients may be enrolled in that initial cohort. (If the first patient experiences a DLT, then a lower dose will be explored for the second patient and so on.)

- If the first patient does not experience a DLT (see Section 7.5.2) or experiences engraftment without a ≥Grade 3 toxicity, the next 2 patients may be enrolled simultaneously.

After 3 patients in a cohort complete the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first, and have safety evaluations performed through that time, and:

- None of these 3 patients experience a DLT (see Section 7.5.2), then enrollment of the next cohort may commence with approval from the Safety Committee.
- 1 of 3 patients within a cohort experiences a DLT (see Section 7.5.2), then up to 3 additional patients are to be enrolled sequentially at that dose level. If none of the additional 3 patients has a DLT (i.e., 1 of 6 patients has a DLT), then enrollment at the next scheduled dose may commence with approval from the Safety Committee.
- If ≥2 patients within a cohort experience a DLT (see Section 7.5.2), then the DLT dose level will have been reached and the previous lower dose level will be considered the MTD. (If ≥2 patients in the initial dose cohort experience DLTs, then the dose will be reduced to one level lower and the same procedure will be followed.)

A total of 6 patients are planned to be treated at the MTD to confirm the RP2D before enrollment of patients in Phase 2 of the study. If the MTD is not confirmed at this stage, the dose will be reduced to one level lower and the same procedure will be followed.

Note that enrollment in the next dose cohort can begin only when the last patient enrolled in the current dose cohort completes the study through engraftment without a ≥Grade 3 toxicity or through 30 days post-ASCT without a DLT, whichever occurs first,, provided that <2 patients in the current dose cohort experienced a DLT.

Although decisions regarding dose escalation will be made based on review of data through Day 30 post-ASCT, safety data will also be collected from all patients continuing in the study and this will be reviewed periodically by the Safety Committee. Any detected toxicity may necessitate further refinement of the RP2D.

### 7.5.2. Definition of Dose-limiting Toxicity

Toxicity will be assessed by the Investigator using the US NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. The centralized laboratory assessment of ECGs will be used for the determination of DLT.

In Phase 1 of the study, DLT is defined as the occurrence of any of the following events occurring within 30 days post-ASCT that are considered by the Investigator to be at least possibly related to tinostamustine:

- Delayed engraftment (>30 days after ASCT). Engraftment will be considered delayed if the subject has not met criteria for both neutrophil and platelet engraftment:
  - Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
  - Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.
- QTcF >500 msec or >60 msec increase from baseline, with a duration of >30 minutes, based on the mean of triplicate 12-lead ECGs, or ≥Grade 3 QTcF interval prolongation accompanied by ventricular arrhythmia.

  Baseline QTcF interval will be the mean value determined during triplicate ECG(s) at Day -1 (-1), before study drug administration confirmed by the cental laboratory.
- Grade 4 non-hematologic toxicity
- Grade 3, non-hematologic toxicity related to treatment, **with the exception of:**
  - Nausea or vomiting
  - Diarrhea
  - Fatigue, dehydration, or glucose intolerance

- Skin rash, dry skin, or pruritus responsive to topical or systemic steroids
- Fever (>40ºC for ≤24 hours)
- Infection
- Dyspnea, hypoxia, or pneumonitis
- Abdominal pain
- Dysphagia, oral mucositis, oral pain, or anorexia
- Flu-like syndrome
- Engraftment syndrome
- Weight loss
- Pain, pain in extremity, headache, or insomnia
- Hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia
- Increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, or alkaline phosphatase
- Alopecia

#### 7.5.3. Definition of Maximum Tolerated Dose

The MTD is defined as the highest dose level at which ≤1 of 6 patients experiences DLT through 30 days post-ASCT.

#### 7.5.4. Definition of Recommended Phase 2 Dose

The RP2D may be equal to or higher than the preliminary MTD, but less than the non-tolerated dose (i.e., the dose at which ≥2 of 6 patients experienced DLT). The RP2D will be determined in discussion with the Sponsor, Medical Monitor, and Investigators.

## 7.6. Study Drug Preparation and Administration

#### 7.6.1. Study Drug Preparation

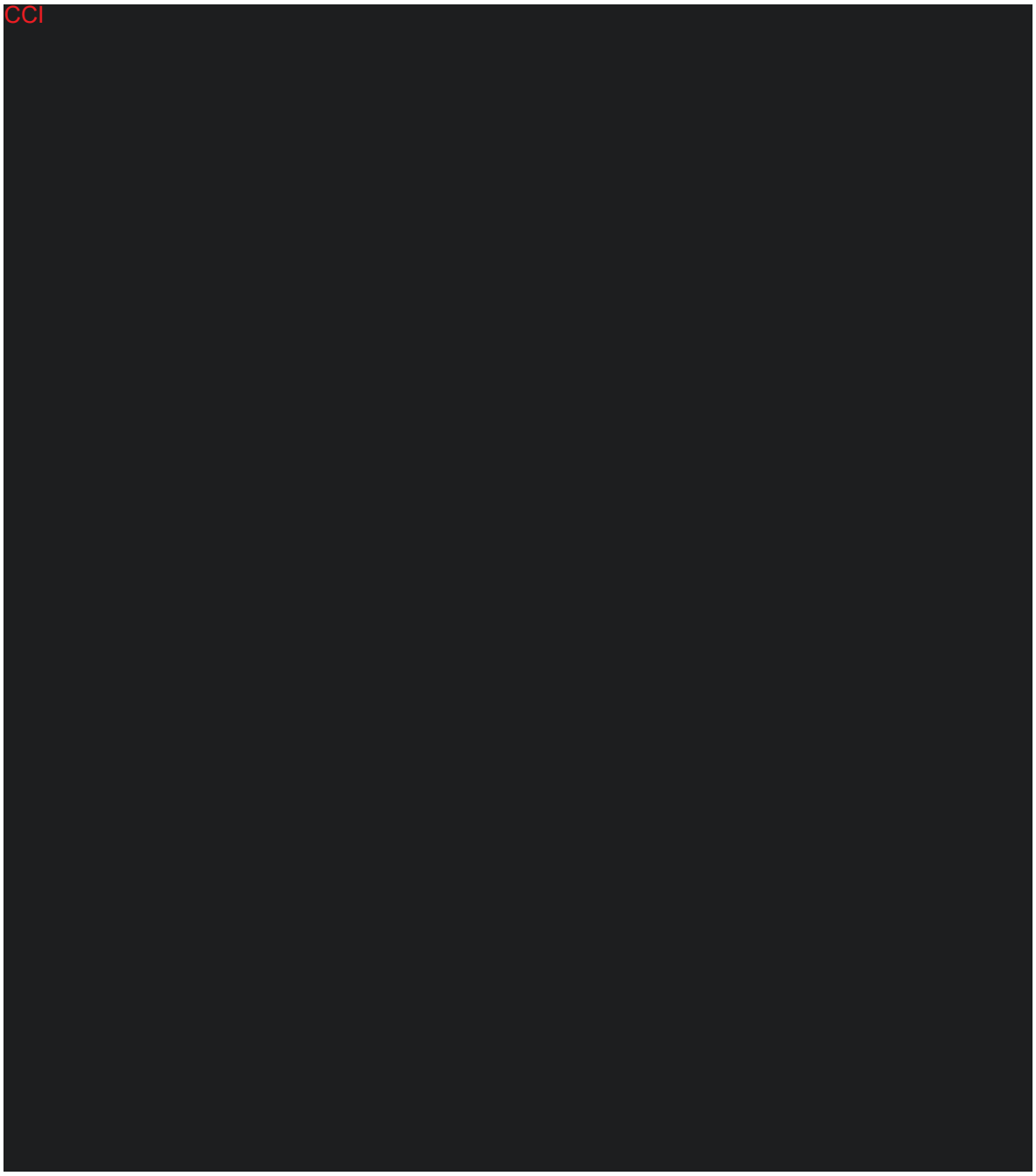
For administration, tinostamustine powder is reconstituted with 20 mL saline (0.9%) and the solution must be further diluted with saline (0.9%) to a final volume of 50 mL. CCI [redacted]

Please refer to the study specific Pharmacy Manual to ensure the correct preparation of tinostamustine.

### 7.6.2. Study Drug Administration

Tinostamustine is to be administered IV through a peripheral vein over 1 hour.

CCI




## 7.8. Prior and Concomitant Medications and Procedures

All prescription and non-prescription medications and therapies, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 28 days prior to the first dose of tinostamustine through Day 100 (±7 days) must be recorded in the eCRF. Concomitant 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 [ASC] infusion); or after ASCT (i.e., after the start of ASC infusion).

On PK sample collection days (Table 1), both the date and time of concomitant medications and therapies must be recorded.

The Investigator should contact the study medical monitor with any questions or clarifications regarding concomitant medications.

### 7.8.1. Prohibited Medications

The following medications and treatments are prohibited during study participation:

- Any investigational agent or device other than tinostamustine, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.
- Any anti-neoplastic treatment with activity against MM.
- Medications known to prolong the QT/QTc interval, will be excluded. The use of other concomitant medications that present a low risk of QT/QTc prolongation may be considered, with the approval of the Medical Monitor. (Refer to the crediblemeds list of drugs with known risk of TdP: http://crediblemeds.org.)

### 7.8.2. Permitted Medications and Supportive Therapies

Medications and treatments other than those specified in Section 7.8.1, including palliative and supportive care for disease-related symptoms, are permitted during the study. Patients should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate.

Patients may receive the following supportive care:

- IV hydration and anti-emetics, in accordance with institutional guidelines.
- Growth factor support with pegfilgrastim or equivalent agent post-ASCT, in accordance with institutional guidelines.
- Standard supportive care, in accordance with institutional guidelines, including blood product transfusions, antimicrobial prophylaxis (e.g., anti-bacterial, *Pneumocystis carinii*, anti-fungal, herpes simplex virus/varicella zoster virus), and treatment for febrile neutropenia.
- Bisphosphonates may be administered after ASCT according to local institutional practice.
- After adequate blood count recovery (ANC $>1.0\times10^9$/L and platelet count $>80\times10^9$/L) as well as resolution of mucositis and fever, if present, radiation may be administered for the following indications after consultation with the Medical Monitor:
  - Palliation of pain from bone lesions
  - Prevention of pathologic fractures
  - Relief of spinal cord compression or nerve root compression

  The radiation oncologist is to determine the dose and duration of radiation to be administered. Radiation to the liver or lungs should be avoided.

## 7.9. Blinding

This is an open-label study; no blinding methods will be employed.

# 8. TRANSPLANT PROCEDURES

## 8.1. Conditioning

See Section 7.6 for details regarding tinostamustine preparation and administration.

## 8.2. 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.

## 8.3. Engraftment

During in-patient hospitalization, patients will be assessed daily for hematologic engraftment, starting on the first day the ANC is $<0.5\times10^9$/L until and including the day engraftment criteria are met, as follows:

- Neutrophil engraftment is defined as the first of 3 consecutive days with ANC $>0.5\times10^9$/L.
- Platelet engraftment will be defined as the first of 3 consecutive days of platelet count $>20\times10^9$/L without platelet transfusion in the prior 7 days.

# 9. STUDY ASSESSMENTS

## 9.1. Baseline Assessments

### 9.1.1. Informed Consent

All patients must provide written informed consent before any samples are collected or evaluations performed in this study that are not part of standard patient care.

### 9.1.2. Demographics

Patient demographics, including age, sex, race, and ethnicity, are to be documented in the source documents and in the eCRF at Screening.

### 9.1.3. Medical History, Including Cancer History

A complete medical history, including prior and concomitant illnesses and conditions as well as prior surgeries and other procedures, is to be documented in the source documents and in the eCRF at Screening. MM history, including the date of diagnosis and details regarding prior ASCT and all other previous treatment for MM and best response to such treatments, also is to be documented and recorded in the eCRF.

### 9.1.4. Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI)

The HCT-CI is a validated comorbidity index that comprises 17 different categories of organ dysfunction (Sorror et al. 2007; Maruyama et al. 2007; Barba et al. 2010; Frina et al. 2009). Positive findings are summated into a total score. 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. HCT-CI score is to be documented in the source documents and in the eCRF at Screening.

The HCT-CI is accessible at: http://www.hctci.org/Home/Calculator.

### 9.1.5. Prior and Concomitant Medications

All prior medications and supplements the patient received within 28 days before baseline and all medications and supplements the patient receives through Day 100 are to be documented in the source documents and in the eCRF. Concomitant 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 ASC infusion); or after ASCT (i.e., after the start of ASC infusion).

### 9.1.6. Echocardiogram or Multi-gated Acquisition Scan

LVEF is to be determined by multi-gated acquisition scan or echocardiography during Screening.

### 9.1.7. Pulmonary Function Testing

The following PFTs are to be measured during Screening

- $FEV_1$
- FVC
- DLCO

Patients who have difficulty making an appropriate seal on the mouthpiece to perform PFTs effectively should be fitted with a facial mask for PFT measurements.

### 9.1.8. Screening Serologies

Blood samples for infectious disease marker testing, including, at a minimum, human immunodeficiency virus (HIV) types 1 and 2, hepatitis B virus (HBV) panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus (HCV), Treponema pallidum, cytomegalovirus, and Epstein-Barr virus, are to be collected during Screening. Any patient with a positive result is not eligible for study participation.

### 9.1.9. Pregnancy Testing

Serum or urine β-human chorionic gonadotropin (hCG) pregnancy testing is to be performed for female patients of childbearing potential (i.e., premenopausal or not surgically sterile) during Screening. Any patient with a positive result is not eligible for study participation. Pregnancy testing is to be repeated any time pregnancy is suspected.

## 9.2. Safety Measurements

### 9.2.1. Physical Examination,

Physical examinations are to be performed at each study center visit. Complete physical examinations are to be performed at the time points designated in Table 1. The complete physical examination includes assessment of the following:

- General appearance
- Head, eyes, ears, nose, and throat
- Cardiovascular system
- Respiratory system
- Gastrointestinal system (abdomen)
- Lymphatic system
- Musculoskeletal system
- Skin

- Psychiatric
- Neurological – A complete neurologic examination, including assessment of mental status, memory, cranial nerves, motor function, and reflexes, is to be performed as part of the complete physical examination.

Targeted (i.e., symptom-directed) physical examinations are to be conducted at the time points designated in Table 1.

Abnormal physical examination findings that are considered by the Investigator to be clinically significant are to be reported as an AE, if the finding represents a change from baseline.

### 9.2.2. Height and Weight

Height is to be measured for all patients during Screening.

Body weight is to be measured during Screening and at the time points designated in Table 1. The patient's height documented during Screening and weight documented prior to the commencement of tinostamustine on Day -1 are to be used to calculate the tinostamustine dose.

### 9.2.3. ECOG Performance Status

ECOG performance status is to be determined at the time points designated in Table 1. The ECOG performance status scale, with corresponding Karnofsky performance status score equivalents, is presented in Table 4.

**Table 4: Eastern Cooperative Oncology Group Performance Status Scale, with Equivalent Karnofsky Performance Status Scores**

| ECOG[1] | | Karnofsky[2] | |
|---|---|---|---|
| **Score** | **Criterion** | **%** | **Criterion** |
| 0 | Normal activity | 100 | Normal; no complaints; no evidence of disease |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 1 | Symptoms but ambulatory | 80 | Normal activity with effort; some signs or symptoms of disease |
| | | 70 | Cares for self; unable to carry on normal activity or do active work |
| 2 | In bed <50% of time | 60 | Requires occasional assistance but is able to care for most of his/her needs |
| | | 50 | Requires considerable assistance and frequent medical care |
| 3 | In bed >50% of time | 40 | Disabled, requires special care and assistance |
| | | 30 | Severely disabled; hospitalization is indicated though death is not imminent |
| 4 | 100% bedridden | 20 | Very sick; hospitalization is necessary |
| | | 10 | Moribund; fatal processes progressing rapidly |
| 5 | Dead | 0 | Dead |

1 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

2 Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer. 1984;53:2002-2007.

### 9.2.4. Vital Signs

Vital signs, including blood pressure, pulse and respiration rates, and body temperature, are to be measured at the time points designated in Table 1. Pulse rate and blood pressure will be measured with the patient in a sitting position after a 5-minute rest.

Vital signs abnormalities that are considered by the Investigator to be clinically significant are to be reported as AEs, if the finding represents a change from baseline.

### 9.2.5. Holter Monitoring

Continuous Holter monitoring will be performed on Day -1, the day of tinostamustine administration. Holter monitoring will commence 15 minutes prior to the start of the infusion on Day -1 and will continue through 24 hours following the end of infusion.

Patients should be resting comfortably in the supine or semisupine position for 15 minutes prior to each of the following timepoints: 0 [before start of infusion] then after start of the infusion at 15, 30, 45, 60 and 75 minutes and 3, 6, and 24 hours following the start of the infusion.

At time 0 and at all time points after infusion, ECGs readings will be extracted for establishment of baseline and for the purposes of Dose Limiting Toxicities determination and for cardiac safety analyses.

The Holter monitor flashcards will be sent to eResearch Technology, Inc., for processing. The analysis methodology will be described in a separate ECG cardiac safety statistical analysis plan.

Note that because the ECG recordings are stored on flashcards, results will not be available in "real time" at the study center.

The ECGs extracted from the Holter monitoring will be used for the determination of DLTs.

### 9.2.6. 12-Lead Electrocardiogram

A triplicate ECG will be performed during Screening to determine patient eligibility for the study. Furthermore, on Day -1 (-1 day), a triplicate ECG is to be performed before study drug administration and a single ECGs will be performed at 30 and 60 minutes after the start of study drug administration for assessment by the site. Another single ECG will be performed at visit on D30 (±5 days). ECGs are to be repeated by the Investigator, as clinically indicated.

ECGs (12-lead) are to be performed in after the patient is supine for 5 minutes.

All screening ECGs will be reviewed centrally. Regarding other 12-lead ECGs: the Investigator or the Sponsor may request expedited central review of ECGs, as clinically indicated. ECGs will be reviewed centrally. The Investigator or the Sponsor may request expedited central review of ECGs, as clinically indicated.

The Investigator's interpretation of ECGs is to be used for patient management during the study; the central reader interpretation of ECGs extracted from Holter monitoring will be used to determine all ECG data for study endpoints including baseline QTcF interval for cardiac safety analyses and DLTs.

### 9.2.7. Safety Laboratory Tests

#### 9.2.7.1. Hematology, Serum Chemistries, and Urinalysis

Blood samples are to be collected for assessment of hematology, coagulation studies, and clinical chemistry parameters and urine samples for urinalysis, according to the schedule defined in Table 1. Laboratory samples are to be collected after vital signs are measured.

The following safety laboratory parameters will be measured:

**Hematology**

- Hematocrit
- Hemoglobin
- Red blood cell count
- White blood cell count
- Platelet count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

**Serum Chemistries**

- ALT
- AST
- Bilirubin (total, direct, and indirect)
- Magnesium
- Glucose
- Phosphate
- Sodium
- Creatinine*
- Uric acid
- Alkaline phosphatase
- Bicarbonate
- Calcium
- Chloride
- Lactate dehydrogenase
- Potassium
- Total protein
- Blood urea nitrogen

*To be fractionated if abnormal.

**Coagulation Studies**

- Prothrombin time and/or International normalized ratio
- Activated partial thromboplastin time

**Urinalysis**

- Color
- Specific gravity
- Glucose
- Blood
- pH
- Protein
- Ketones

Safety laboratory tests may be repeated as necessary during treatment at a schedule determined by the Investigator, based on the patient's clinical status.

Laboratory abnormalities that are considered by the Investigator to be clinically significant are to be reported as AEs, if the finding represents a change from baseline.

### 9.2.8. Adverse Events

#### 9.2.8.1. Definitions

##### *9.2.8.1.1. Adverse Event*

An AE is defined in the ICH Guideline for GCP as "any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment" (ICH E6:1.2).

Worsening of a pre-existing medical condition, (i.e., diabetes, migraine headaches, gout) should be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (i.e., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AEs.

In the case of death, only record "Fatal" for the event causing death. AEs that are ongoing at the end of the study or time of death are to be noted as "continuing." Classification of AEs is to be done by the Investigator according to the NCI CTCAE, version 4.03.

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual patient represents a significant change from baseline. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should not be recorded as AEs; however, laboratory value changes requiring therapy are considered AEs.

##### *9.2.8.1.2. Suspected Adverse Reaction*

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, "reasonable possibility" and/or at least possibly related means there is evidence to suggest a causal relationship between the drug and

the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### *9.2.8.1.3. Serious Adverse Event*

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

- is fatal
- is life-threatening (i.e., places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 hospitalization, or the development of drug dependency or drug abuse.

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any AE that does not meet one of the definitions of serious (i.e., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the Investigator to meet the "important medical event" criterion for classification as an SAE.

#### *9.2.8.1.4. Unexpected Adverse Event*

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application, as amended.

*9.2.8.1.5. Serious and Unexpected Suspected Adverse Reaction*

A serious and unexpected suspected adverse reaction (SUSAR) is any event that meets all 3 of the following definitions:

1) suspected adverse reaction (Section 9.2.8.1.2);

2) serious (Section 9.2.8.1.3); and

3) unexpected (Section 9.2.8.1.4).

### 9.2.8.2. Adverse Event Assessment

All AEs will be collected and recorded 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. This includes AEs the patient reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during scheduled study visits.

Each AE is to be assessed by the Investigator with regard to the following categories.

**Serious/Non-Serious**

AEs that meet the criteria specified in Section 9.2.8.1 are to be considered serious.

**Relationship to Study Drug**

The relationship of each AE to study drug is to be assessed by the Investigator according to categories in Table 5.

**Table 5: Criteria for Determination of Adverse Event Relationship to Study Drug**

| Relationship Between Study Drug and AE: | | | | | |
|---|---|---|---|---|---|
| | Category | | | | |
| **AE (is):** | **None** | **Unlikely** | **Possibly** | **Likely** | **Definitely** |
| Clearly the result of an external factor | Yes | No | No | No | No |
| Probably/possibly the result of another factor | No | Yes | Yes | No | No |
| Has a chronological relationship with the time of administration and/or represents a known reaction to Study Drug | No | No | Yes | Yes | Yes |
| Disappears or decreases after discontinuation of the Study Drug | NA | NA | NA | Yes | Yes |
| Recurs on renewed administration (re-challenge) | No | No | NA | NA | Yes or NA** |

**A re-challenge is not required; if done, re-challenge would be expected to be positive.
NA = not applicable

**Intensity**

The intensity of each AE is to be assessed by the Investigator according to the NCI CTCAE, version 4.03. If the AE is not included in the NCI CTCAE, version 4.03, then the Investigator is to determine the intensity of the AE according to the following criteria:

- Mild (Grade 1): Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2): Minimal, local, or non-invasive intervention indicated; limited age-appropriate instrumental activities of daily living.
- Severe (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; incapacitating with inability to work or perform normal daily activity.
- Life-threatening (Grade 4): consequences: urgent intervention indicated.
- Death (Grade 5) related to an AE.

#### 9.2.8.3. Recording Adverse Events

All AEs occurring from the from the time written informed consent is obtained through the Day 100 (±7 days) visit are to be recorded in the source documents and in the eCRF. AEs will be documented as occurring pre-conditioning (i.e., pre-tinostamustine); during conditioning (i.e., after the start of the first tinostamustine infusion through immediately before the start of ASC infusion); or after ASCT (i.e., after the start of ASC infusion). All AE reports are to contain the following details regarding the AE: a brief description, onset date, duration, intensity, treatment required, relationship to study drug, study drug action taken, outcome, and whether the event is classified as serious.

#### 9.2.8.4. Reporting Serious Adverse Events

SAEs will be collected and recorded throughout the study period, beginning with the signing of the informed consent form (ICF) through the Day 100 (±7 days) visit, or after the end of the study if thought to be related to study drug.

The Investigator must report all SAEs to the Sponsor within 24 hours of discovery.

A completed SAE report is to be sent to the Medical Monitor's attention within 24 hours of discovering the event. The initial report should include at least the following information:

- Patient's ID number;
- Description and date of the event;
- Criterion for serious; and

- Preliminary assignment of causality to study drug.

The Medical Monitor will contact the Investigator via telephone for follow-up information regarding the SAE, as appropriate.

The Investigator, or designated party, should notify the appropriate IRB/EC of SAEs occurring at the study center and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

SAEs that are considered as possible or probably related to the investigational product, and as unexpected (i.e., SUSARs), will be reported to the concerned Competent Authorities (CAs) and IRBs/ECs by the Sponsor or Sponsor's designee as required by applicable local regulations. Per regulation, any fatal or life-threatening SUSAR will be reported to the CAs/IRBs/ECs within 7 calendar days, and additional information within an additional 8 calendar days. The Sponsor or Sponsor's designee is required to submit any other SUSAR to the CAs/IRBs/ECs within 15 calendar days of notification. The Sponsor or its designee is also responsible for notifying the investigational sites of all expedited SAEs. The Investigator must keep copies of all expedited SAE information including correspondence with the Sponsor on file.

#### 9.2.8.5. Follow-Up of Adverse Events

The Investigator must continue to follow all SAEs and non-serious AEs considered to be at least possibly related to study drug either until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

#### 9.2.8.6. Reporting Safety Information

The Investigator must promptly report to his or her IRB/EC all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs reasonably or possibly associated with the use of Study Drug according to the IRB/EC's procedures.

The Sponsor will assess the severity and frequency of adverse drug reactions in adults versus pediatric patients, and will submit findings annually in the Development Safety Update Report/Annual Report.

#### 9.2.8.7. Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. The Investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Medical Monitor, in conjunction with the Investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be noted in the eCRF.

#### 9.2.8.8. Pregnancy

Pregnancy is considered unlikely in this study, given the population of patients to be enrolled. Nonetheless, pregnancies occurring within 12 months after the patient's last dose of tinostamustine will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 9.2.8.4.

The patient is to be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient until completion of the pregnancy, and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth are to be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to tinostamustine should also be reported.

## 9.3. Disease Assessments

### 9.3.1. Myeloma Protein Measurements in Serum and Urine

#### 9.3.1.1. Serum

Blood samples for quantitation of immunoglobulin (Ig) (IgA, IgG, and IgM are required; IgD and IgE are optional) and M-protein and assessment of M-protein by immunofixation in serum are to be collected from all patients at the time points designed in Table 1. Note that in the case of IgA MM, MM IgA values should be used.

All samples will be analyzed by the local laboratory. Assessments of response will be evaluated by two independednt reviewers.

#### 9.3.1.2. Urine

Twenty-four hour urine samples for quantitation of M-protein and assessment of M-protein by immunofixation are to be collected from all patients during Screening. For patients with positive findings at Screening, such samples also are to be collected at the time points designed in Table 1. Patients with negative Screening results need not provide urine samples for M-protein quantitation and assessment after Screening.

All samples will be analyzed by the local laboratory. Assessments of response will be evaluated by two independednt reviewers.

### 9.3.2. Free Light Chain Testing

Serum samples for free light chain (FLC) testing are to be collected from all patients during Screening and at the time points designed in Table 1. The free kappa/lambda ratio is to be recorded in the eCRF.

A serum sample for FLC testing also is to be collected in order to confirm stringent complete response (sCR).

### 9.3.3. Bone Marrow Examination

Bone marrow aspiration to be performed for all patients during Screening, and for patients who achieve a CR, on Day 100 (±7 days) post-ASCT. Bone marrow aspiration and biopsy are to be repeated during treatment as clinically indicated.

Approximately 5mL of the same sample (i.e., "first-pull"), collected in ethylenediaminetetraacetic acid (EDTA) tubes, will be used for assessment of MRD-N using next-generation flow cytometry.

### 9.3.4. Skeletal Survey and Other Imaging Studies

Skeletal surveys (plain radiographs, or any other method used as standard care at the site, of the skull, spine, ribs, pelvis, humeri and femora) are to be performed during Screening. If a skeletal survey has been performed within 3 months before Baseline, then this evaluation need not be repeated during Screening.

A skeletal survey is to be repeated during the study as clinically indicated.

Other appropriate imaging studies (e.g., magnetic resonance imaging, CT, X-ray) to evaluate the patient's disease are to be performed during Screening per standard of care, as determined by the Investigator. Appropriate imaging studies are to be repeated as necessary to confirm CR.

### 9.3.5. Assessment of Disease Response

The Investigator will perform tests that will allow evaluation of response to therapy according to the IMWG Criteria, as outlined in Table 6. Patients who are determined to have CR are then to have additional tests performed that will allow further characterization of the CR.

Assessment of disease response using non-invasive procedures will be performed at the time points designed in Table 1. Appropriate imaging studies and bone marrow aspirates/biopsies must be repeated only in patients suspected of having a CR, based on non-invasive procedures.

**Table 6: IMWG Response Criteria**

| Response | IMWG Criteria |
|---|---|
| Complete response (CR)[1] | • Negative immunofixation of serum and urine, and<br>• Disappearance of any soft tissue plasmacytomas, and<br>• <5% plasma cells in bone marrow |

| Response | IMWG Criteria |
|---|---|
| Stringent complete response (sCR) | CR as defined above plus<br>• Normal FLC ratio, and<br>• Absence of clonal plasma cells (PC) by immunohistochemistry or 2-4 color flow cytometry. |
| Immunophenotypic CR | Stringent CR plus<br>• Absence of phenotypically aberrant PC (clonal) in bone marrow (BM) with a minimum of one million of total BM cells analyzed by multiparametric flow cytometry (with >4 colors) |
| Molecular CR | CR plus<br>• Negative allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR), sensitivity $10^{-5}$ |
| Very good partial response (VGPR)[1] | • Serum and urine M-component detectable by immunofixation but not on electrophoresis, or<br>• ≥90% or greater reduction in serum M-component plus urine M component <100 mg per 24 hours |
| Partial response (PR) | • ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 hours<br>• If the serum and urine M-protein are unmeasurable a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria<br>• If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30%<br>• In addition to the above criteria, if present at Baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required |
| Stable disease (SD) | Not meeting criteria for CR, VGPR, PR or progressive disease. |

| Response | IMWG Criteria |
|---|---|
| Progressive disease (PD)[2] | • Increase of 25% from lowest response value in any one or more of the following:<br>• Serum M-component (absolute increase must be ≥0.5 g/dL) and/or<br>• Urine M-component (absolute increase must be ≥200 mg/24 hours) and/or<br>• Only in patients without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)<br>• Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be >10%)<br>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<br>• Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder |

Source:. Rajkumar, et al. Blood 2011;117(18):4691-5.
All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at Baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
1 Note clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients requires in addition a >90% decrease in the difference between involved and uninvolved free light chain FLC levels.
2 Note clarifications to IMWG criteria for coding PD: Clarified than bone marrow criteria for progressive disease are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia. Note that the "lowest response value" does not need to be a confirmed value.

The Investigator's assessment of disease response will be used for patient management during the study.

Confirmation of responses should be obtained for biochemical markers but is not necessary for bone marrow or imaging studies. The confirmatory tests should be performed by Day 130. The response date is not the date of confirmation but the initial date when the assessment met the end point. In other words, the second test is confirmatory. If the result is not confirmed by a second evaluation, the status is either non-evaluable and the prior disease status remains valid.

### 9.3.6. Independent Review Committee

An Independent Review Committee (IRC) will be established under the direction of the Sponsor to provide an objective, unbiased, independent review of objective response, using the IMWG criteria (Table 6), as demonstrated based on the pertinent clinical data from the study.

A formal, written IRC charter will be established outlining the composition of the IRC, the data to be evaluated, and the manner of committee meetings.

## 9.4. Pharmacokinetics

Serial blood samples for PK analysis will be collected after each tinostamustine dose according to the schedule in Table 1. Blood samples for PK assessment should be collected following the 15-minute supine, resting periods described for the continuous Holter recordings. PK samples are to be collected from the arm opposite of that used for tinostamustine administration.

The calendar date and exact 24-hour clock time of blood sample collection for PK assessments will be documented in the source document and the eCRF.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

# 10. STATISTICAL ANALYSES

## 10.1. Statistical Basis for Sample Size

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%.

In the methodology proposed by Simon (Simon, 1989), a Phase 2 design can be represented by 4 numbers: N1, R1, N, and R. N1 is the sample size in the first stage. R1 is the critical value in the first stage. If R1 or fewer responses occur in the N1 patients, the study treatment is rejected. N is the combined sample size for both the first and second stages. R is the critical value in the combined sample. If R or fewer of the N patients respond, the study treatment is rejected at the end.

The design is found with PASS Sample Size Software through an exhaustive search of all possible designs (combinations of R1, N1, R and N) that control alpha (0.025) and beta (0.20, meaning power is 0.80). With the minimax approach, the design is selected that has the lowest N.

Per the minimax design, 31 patients are to be enrolled in Stage 1. If >25 of 31 patients (in the 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.

## 10.2. Statistical and Analytical Plan

An overview of the statistical methodology to be employed is provided in the following subsections. Details regarding the statistical methodology will be documented in a formal Statistical Analysis Plan (SAP) prior to database lock.

### 10.2.1. General Methods

Statistical analyses will be primarily descriptive in nature. Statistical hypothesis testing is neither intended nor appropriate within this context except for the primary endpoint. Confidence intervals will be based on asymptotic methods.

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 (n, %) of patients within each classification.

Dependent of the specific analysis, the analysis sets as defined in Section 10.2.2 will be taken from the cohort for Phase 1, for Phase 2 (RP2D) or both phases pooled. Unless specified otherwise below, this will be further defined in the SAP.

### 10.2.2. Analysis Populations

All patients who receive tinostamustine will be included in the safety set.

All patients in the safety set who had at least one post-ASCT response evaluation will be included in the full analysis set (FAS).

All patients in the FAS with no major protocol deviations will be included in the per-protocol (PP) set.

All patients in the safety set with at least one quantifiable pre-dose and one quantifiable post-dose PK plasma concentration will be included in the PK set.

### 10.2.3. Missing Data

Analyses will be based on observed data only; no data will be imputed.

### 10.2.4. Disposition of Patients

Patients who are screened for study entry and do not meet the eligibility criteria will be documented. The numbers and proportions of patients who complete the study and who are early terminations will be summarized. Reasons for study discontinuation after the start of study treatment will be tabulated.

### 10.2.5. Demographics and Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized. Data to be tabulated will include demographic and baseline characteristics such as sex, age, race, height, weight, and body mass index, and MM-specific diagnostic and historical information. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and raw and coded data will be summarized.

### 10.2.6. Extent of Exposure

Descriptive statistics for the percent of expected dose received and the actual dose received will be summarized. A tabular summary and listing of drug 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.

### 10.2.7. Prior and Concomitant Medications

Tabulations of prior and concomitant medications, coded using the World Health Organization Drug Dictionary (WHO-DD), will be produced. All prior and concomitant medications administered will be presented in a data listing.

### 10.2.8. Efficacy Analyses

Superiority testing will be performed on FAS in the Phase 2 cohort 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% (CIBMTR report, December 2017) and a 1-sided 2-step chi-square test will be performed at the 2.5% level of significance for FAS.

For the primary endpoint, also an upper 1-sided 97.5% confidence interval will be calculated for FAS in addition to summary statistics.

For the primary endpoint in other sets and for the secondary endpoints of other responder rates in the FAS, also 2-sided 95% confidence intervals will be calculated in addition to summary statistics.

Response assessments as determined by the Investigator and IRC will be compared, with agreement determined by Kappa coefficient.

Disease assessment variables and their changes from baseline will be summarized visit wise.

### 10.2.9. Pharmacokinetic Analyses

PK analysis for tinostamustine and its metabolites will be performed using the PK set.

PK parameters at all doses will include $C_{max}$, time to maximum plasma concentration ($t_{max}$), $t_{1/2}$, area under the plasma concentration curve from 0 to 12 hours ($AUC_{0-12}$), area under the plasma concentration curve from time 0 to time t ($AUC_{0-t}$), apparent total clearance (CL/F), apparent volume of distribution (Vd/F), and terminal disposition rate constant ($\lambda z$). The initial calculation of PK parameters will be performed using non-compartmental analysis. Plasma concentrations and PK parameters will be summarized by dose.

Summaries will include the number of observations (n), arithmetic or geometric mean, SD or coefficient of variation (CoV), median, minimum, and maximum.

### 10.2.10. Safety Analyses

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

Adverse Events will be coded using MedDRA and raw and coded data will be summarized.

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.

### 10.2.11. Interim Analyses

In Phase 2 of the study, at the completion of the Stage 1 with 31 patients, an interim analysis will be performed using the FAS for the Phase 2 cohort to determine whether enrollment will continue in Stage 2. If >25 of 31 patients in Stage 1 experience a response to treatment, then enrollment will continue in 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 in the ongoing Stage 2 recruitment.

## 10.3. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report.

# 11. ETHICAL, LEGAL, AND ADMINISTRATIVE CONSIDERATIONS

## 11.1. Good Clinical Practice

This study will be conducted according to the protocol and in compliance with ICH GCP, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

The Investigator confirms this by signing the protocol.

## 11.2. Informed Consent

Written informed consent will be obtained from each patient prior to undergoing any protocol-specific tests or procedures that are not part of routine care.

The Sponsor or designee will provide an ICF template to the Investigator for use in developing a study center-specific consent documents. Prior to submission of the study center-specific ICF to the IRB/EC, these documents must be reviewed and approved by the Sponsor or designee. Any changes requested by the IRB/EC must also be approved by the Sponsor or designee. The final IRB/EC-approved ICF must be provided to the Sponsor or designee. Revisions to the ICF required during the study must be approved by the Sponsor r designee, and a copy of the revised ICF provided to the Sponsor or designee.

Before recruitment and enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the ICF in a language they understand. After the Investigator or designee is assured that the patient understands the commitments of participating in the study, the patient will be asked to sign and date the ICF, as appropriate.

A copy of the fully signed and dated ICF will be given to the patient. The original will be maintained in the patient's medical record at the study center. All active patients will sign an updated ICF if revisions are made to the ICF during the course of the study.

## 11.3. Institutional Review Board/Ethics Committee

Federal and European regulations and ICH require that approval be obtained from an IRB/EC prior to participation of patients in research studies. Approval by the Competent Authority, if applicable, or as required by local laws and regulations, is also required in Europe. Prior to the 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/EC.

All IRB/EC approvals must be dated and signed by the IRB/EC Chairperson or designee and must identify the IRB/EC by name and address, the clinical protocol by title and/or protocol number, and the date approval or favorable opinion was granted for the clinical research.

No drug will be released to the site to dose a patient until written IRB/EC authorization has been received by the Sponsor or designee.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB/EC. The Investigator must supply the Sponsor or designee with written documentation of the approval of the continued clinical research.

The Investigator, sponsor, or designee as applicable, will make all attempts to ensure that the IRB/EC is constituted and operates in accordance with Federal and ICH GCP and any local regulations.

## 11.4. Amending the Protocol

Any changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee and the IRB/EC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/EC for approval prior to patients being enrolled into the amended protocol.

The Sponsor may make administrative changes (i.e., changes that do not significantly affect patient safety or the study's scope or scientific quality) without any further approvals.

All amendments will be distributed to all protocol recipients.

## 11.5. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from the Sponsor.

Patient confidentiality will be strictly maintained to the extent possible under the law. Patient names must not be disclosed. Patients will be identified in the eCRFs and other documents submitted to the Sponsor or its designated representative, by their initials, birth date, and/or assigned patient number. Documents that identify the patient (e.g., the signed ICF) should not to be submitted to the Sponsor or its designated representative, and must be maintained in confidence by the Investigator.

## 11.6. Publication Policy

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. The initial planned publication will be a multicenter report of the study outcome. Additional publications from a given center can only occur after the publication of the multicenter results. A prepublication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher.

# 12. STUDY MANAGEMENT

## 12.1. Data Quality Assurance

The Sponsor or its designated representative will conduct a study center visit to verify the qualifications of each investigator, inspect study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

## 12.2. Case Report Forms and Source Documentation

The Investigator and designees agree to maintain accurate eCRFs and source documentation as part of case histories. Source documents are the originals of any documents used by the Investigator or subinvestigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the study.

The Sponsor or designee will provide eCRFs to the study center. eCRFs will be completed for each patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of informed consent, study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected/data are available, preferably on the same day that a patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

## 12.3. Monitoring

A CRA, or other representative of the Sponsor, will conduct a study center visit to verify the qualifications of each Investigator, inspect study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

During the course of the study, the CRA will make study center visits to review protocol compliance, compare eCRFs and individual patients' medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements in respect to GCP. eCRFs will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

## 12.4. Inspections

Regulatory authorities and/or quality assurance personnel from the Sponsor or its designated representative, may wish to carry out such source data checks and/or in-center audit inspections.

The Investigator assures the Sponsor of the necessary support at all times. In the event of an audit, the Investigator agrees to allow the sponsor's representatives and any regulatory agencies access to all study records.

## 12.5. Financial Disclosure Reporting Obligations

Investigators and subinvestigators are required to provide financial disclosure information to the sponsor to permit the sponsor to fulfill its regulatory obligation. Investigators and subinvestigators must commit to promptly updating the information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

## 12.6. Archiving Study Records

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local requirements.

ICH requires that patient identification codes be retained for at least 15 years after the completion or discontinuation of the study.

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**Date:** September 21, 2018

**To:** EDO-S101-1004 (TITANIUM 1) Investigators and Site Staff

**Protocol Title:** A Phase 1/2 Open-Label Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplant for Salvage Treatment in Relapsed/Refractory Multiple Myeloma (TITANIUM 1)

**Protocol Version:** 2.0, 18 June 2018

**Subject:** Protocol Clarification Memo

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Dear Investigators and Site Staff,

Please see below clarifications for EDO-S101-1004 version 2.0 protocol from 18 June 2018.

**Item 1:** Use of central line

Currently, Protocol Version 2.0 18 June 2018 states on the bottom of page 11, that Tinostamustine will be administered by IV infusion through a peripheral vein over 1 hour. This is also noted in section 7.6.2 on page 49.

It should say that Tinostamustine will be administered by IV infusion through a peripheral vein or a central line over 1 hour.

**Item 2:** Day of Autologous Stem Cell Transplant (ASCT)

Currently, Protocol Version 2.0 18 June 2018 states in the header of the Schedule of Events on pages 17 and 18, that ASCT is on Day 0.

It should say that the day of ASCT is study Day 1.

**Item 3:** Exclusion Criteria #2

Currently, Protocol Version 2.0 18 June 2018 has two Exclusion Criteria #2's listed on page 39. The one noted as "Primary or secondary plasma cell leukemia at any point prior to transplant" is not noted in the Clinical Study Synopsis exclusion criteria list on page 10.

This exclusion criteria should be included in the Clinical Study Synopsis.

**Item 4** Protocol Deviations

Currently, Protocol Version 2.0 18 June 2018 states that all protocol deviations and reasons for such deviations must be noted in the eCRF.

It should say that all protocol deviations and reasons for such deviations must be noted in the CTMS.

**Item 5** Confirmatory Response Assessment

Currently, Protocol Version 2.0 18 June 2018 states on pages 12 and 42 that a confirmatory response assessment will be done between D107 and D130. On the schedule of assessments on pages 17 and 18, it is listed as D130 (+/-7 days).

It should say that a confirmatory response assessment will be done between D107 and D130, ideally approximately 4 weeks after the initial evaluation.

**Item 6** Discharge Criteria

Currently, Protocol Version 2.0 18 June 2018 states on pages 6 and 37 that the following engraftment criteria need to be met in order for the patient to be discharged:

- Neutrophil engraftment is defined as the first of 3 consecutive days with ANC >0.5x$10^9$/L.
- Platelet engraftment will be defined as the first 3 consecutive days of platelet count >20x$10^9$/L without platelet transfusion in the prior 7 days.

It should say the following:

- Absolute neutrophil count >0.5x$10^9$/L.
- Patient is not platelet transfusion dependent.

**Item 7** Triplicate ECGs

Currently, Protocol Version 2.0 18 June 2018 states on footnote 9 of the schedule of assessments on page 19 that triplicate ECGs should be separated by 5 minutes (+/-2 minutes).

It should say that triplicate ECGs should be at least 1 minute apart.

**Item 8** Fractionated Creatinine

Currently, Protocol Version 2.0 18 June 2018 states on page 59, that creatinine is "*to be fractionated if abnormal".

This statement is unnecessary as the protocol only allows for subjects with a normal creatinine.

These clarifications do not impact patient safety. Please submit these clarifications to your IRB/IEC for their review, if required. In addition, file this letter and any IRB/IEC correspondence in your study files.

These clarifications will be incorporated into a subsequent protocol amendment should one be required.

I am available to discuss any questions or comments you may have.

Sincerely

PPD

PPD , MD
Mundipharma-EDO GmbH

Cc: EDO-S101-1004 Study Team
Cc: EDO-S101-1004 Trial Master File

**Date: October** 22, 2018

**To:** EDO-S101-1004 (TITANIUM 1) Investigators and Site Staff

**Protocol Title:** A Phase 1/2 Open-Label Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplant for Salvage Treatment in Relapsed/Refractory Multiple Myeloma (TITANIUM 1)

**Protocol Version:** 2.0, 18 June 2018

**Subject:** Protocol Clarification Memo

---

Dear Investigators and Site Staff,

Please see below clarifications for EDO-S101-1004 version 2.0 protocol from 18 June 2018.

**Item 2:** Day of Autologous Stem Cell Transplant (ASCT)

Currently, Protocol Clarification memo dated 21Sep18 and Protocol Version 2.0 18 June 2018 in all places except the header of the Schedule of Events on pages 17 and 18, that ASCT is on Day 1.

As is standard practice, it should say that the day of ASCT is study Day 0.

This clarification does not impact patient safety. Please submit this clarification to your IRB/IEC for their review, if required. In addition, file this letter and any IRB/IEC correspondence in your study files.

This clarification will be incorporated into a subsequent protocol amendment should one be required.

I am available to discuss any questions or comments you may have.

Sincerely,

PPD

PPD

PPD

MD PPD

Mundipharma-EDO GmbH

Cc: EDO-S101-1004 Study Team
Cc: EDO-S101-1004 Trial Master File

**Date:** 14 December 2018

**To:** EDO-S101-1004 (TITANIUM 1) Investigator and Site Staff

**Protocol Title:** A Phase 1/2 Open-Label Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplantation for Salvage Treatment in Relapsed/Refractory Multiple Myeloma (TITANIUM 1)

**Protocol Version: 2.0, 18 June 2018**

**Subject:** Protocol Clarification Memo

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Dear Investigator and Site Staff,

Please see below clarifications for EDO-S101-1004 version 2.0 protocol 18 June 2018. An amendment is forthcoming with these changes incorporated.

**Item 1:** Evaluation of PKs as an Endpoint, Synopsis Pgs. 3-4; Section 3.1.1.2 & 3.1.2.2, Section 3.2

Synopsis pages 3-5 and Section 3.1.1.2 lists "Investigate the pharmacokinetics (PK) of Tinostamustine" as a secondary objective of the phase I portion of the trial. Synopsis pages 3-5 Section 3.1.2.2 lists "Evaluate the PK of Tinostamustine" as a secondary objective of the phase II portion of the trial.

Synopsis pages 3-5 and protocol section 3.2 will be updated to reflect a third endpoint in the new section "3.2.3 Pharmacokinetics (PK)", with the description "Evaluate and investigate the pharmacokinetics (PK) of Tinostamustine".

**Item 2:** Exclusion of Hypersensitivity to IMP, Synopsis Pg.11; Section 5.2

Currently, Protocol Version 2.0 18 June 2018 does not include hypersensitivity to IMP as an exclusion criterion. The following protocol exclusion criteria will be updated to include the following text to the above sections.

*13. Subjects who are known to have any hypersensitivities or allergies to any ingredient of the investigational agent are not eligible to participate.*

**Item 3:** Infections Diseases Exclusion, Synopsis Pg.11; Section 5.2

Currently, Protocol Version 2.0 18 June 2018 does not include exclusion criterion regarding positive serology on any of the disease screened for as described in section 9.1.8 (pg. 55). The following protocol exclusion criteria will be updated to include the following text to the above sections.

*14. Subjects who are known to have or test positive for human immunodeficiency virus (HIV) types 1 and 2, hepatitis B virus (HBV) panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus (HCV), Treponema pallidum, cytomegalovirus, and Epstein-Barr virus, may not participate in this study.*

**Item 4:** Definition of People of Childbearing Potential, Section 5 "Study Population" New Sub-Section

Currently, Protocol Version 2.0 18 June 2018 does not define women or men of childbearing potential. The protocol will be amended to include the following text:

*A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.*

**Item 5:** Acceptable methods of highly effective contraception, Section 5 "Study Population" New Sub-Section

Currently, Protocol Version 2.0 18 June 2018 does not list acceptable methods of effective contraception. The protocol will be amended to include the following text:

*Methods that achieve a failure rate of less than 1% per year when consistently and correctly used are considered highly effective methods of birth control. Highly effective methods of birth control include: estrogen and progestogen combined hormonal contraception which inhibits ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine devices (IUD), bilateral tubal occulusion, vasectomized partner in a monogamous sexual relationship, and complete sexual abstinence. Acceptable, but less effective (>1% failure rate per year) methods such as male or female condom with spermicide, cap, diaphragm, or sponge with spermicide, or double barrier methods may be used in conjunction with another form of highly effective birth control.*

**Item 6:** Duration of contraception requirement, Section 5 "Study Population" New Sub-Section

Currently, Protocol Version 2.0 18 June 2018 does not provide a proposed duration for the contraception requirement. The protocol will be amended to include the following text:

*Males and females of child bearing potential, and their partners, must be willing to use at least two effective forms of birth control for at least ninety (90) days after the administration of the study drug to be eligible to participate. These requirements were created based on the recommendations by the Clinical Trial Faciliation Group (CTFG) "Recommendations related to contraception and pregnancy testing in clinical trials" (15Sep2014) due to the alkylating nature of the drug and the limited data on genetotoxicity.*

**Item 7:** Contraception Eligibility, Synopsis Pg.10; Pg. 39 Section 5.1

Currently, Protocol Version 2.0 18 June 2018 does not include guidance on pregnancy contraception and eligibility. The following protocol inclusion criteria will be updated to include the following text to the above sections.

*12. Males and females of child bearing potential, and their partners, must be willing to use at least two effective forms of birth control for at least ninety (90) days after the administration of the study drug to be eligible to participate.*

**Item 8:** Exclusion criteria #9, Synopsis Pg.11; Pg. 39 Section 5.2

Currently, Protocol Version 2.0 18 June 2018 states that patients who are found to be pregnant, are not eligible. Current exclusion criteria number 9 will be updated with the below language.

*9. Women who are pregnant or breastfeeding, or plan to become pregnant or breastfeed, are not eligible for study participation.*

**Item 9:** End of trial definition, Synopsis Pg.12

Currently, Protocol Version 2.0 18 June 2018 does not contain a clear and unambiguous definition of end of trial. In the protocol synopsis (Pg. 12) under "Duration of Treatment and Study Duration" the following text will be added: *The end of trial will be the last patient last visit (LPLV).*

**Item: 10:** Summary of known and potential risks and benefits to human subjects

Currently, Protocol Version 2.0 18 June 2018 does not include a summary of known and potential risks and benefits to human subjects. The following text will be added in a protocol amendment as new section 4.3 "Risks and Benefits" in the protocol:

*This study is investigating the use of Tinostamustine*

*On the sister study, Tinostamustine is being tested the first in human study in patients with relapsed or refractory haematological malignancies for which there are no available approved therapies. Preliminary signals show that the treatment with tinostamustine may offer benefit by overcoming tumor resistance and trigger response. As a result, this therapy may slow down or stop disease progression. Out of 37 patients evaluable for efficacy during the dose-escalation part of the study, approximately half have benefited from treatment.*

*The risks associated with the treatment with tinostamustine are expected to be similar to other alkylators, like bendamustine. The peripheral cell compartments show a differential sensitivity to tinostamustine, with lymphocytes being most sensitive and platelets most robust, but showing the most rapid decline at higher doses. Due to myelosuppression, patients may be more susceptible to infections. The analysis of the chemistry data showed no other meaningful or serious organ toxicity. ECGs during and after infusion showed small prolongations of the QTc interval during and post infusion. Mean change from baseline were up to 24 ms and were clinically not significant. Blood pressure and heart frequency showed no notable changes in any subjects at any dose levels. Patients may experience various types of gastrointestinal toxicity such as nausea, vomiting or diarrhea. At the studied doses these events were non-severe. Mundipharma-EDO considers the benefit and risk balance to be in favour of further development of this molecule in humans.*

***Possible Risks Include:***

- *Myelosuppression (thrombocytopenia, leukopenia, and neutropenia)*
- *Anemia*

- *Gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation)*
- *Cough*
- *Peripheral edema*
- *Pyrexia*
- *Decreased appetite*
- *Dyspnea*
- *Headache*
- *Asthenias*
- *Allergic reaction*
- *Infection*
- *QTc Prolongation*

*As noted above, the risks associated with the treatment with Tinostamustine are expected to be similar to other alkylators, like bendamustine. Additionally, patients undergoing any high-dose conditioning for transplant, will experience myelosuppression, which puts the patients at a higher risk for infection. Thus, the protocol was designed around current standard practices for monitoring the toxicity and safety of patients in this treatment setting. Patients are evaluated daily for hematologic parameters, signs of infection, and any other adverse reactions until engraftment is reached. After engraftment the patients are monitored monthly through 130 days but may be seen in between these timepoints if clinically indicated. Cardiac safety is monitored pre-infusion through 24 hours post infusion with a continuous holter monitor, in addition to ECGs being performed and read by the qualified site personnel before, during, and after the infusion. Other adverse reactions will be continuously monitored and treated as appropriate according to the protocol and local standard of care.*

*Since the purpose of this study is to evaluate the safety and preliminary efficacy of this regimen, it is unknown if this treatment will benefit individual patients directly. While the study may or may not improve the disease of the patients, they could benefit in the following ways:*

- *Helping others by contributing to medical research*
- *Monitoring of their condition while on the study with additional study services and evaluations.*

*While this investigational agent and regimen are being studied, the ongoing sister studies have shown some early promising results. Preliminary data shows that treatment with this agent may offer benefit by overcoming tumor resistance and trigger response. As a result, this therapy may slow down or stop disease progression. Therefore, Mundipharma-EDO considers the benefit and risk balance to be in favour of further development of this molecule in humans.*

**Item 11:** Very good partial response (VGPR), Synopsis Pg.4; Pg. 34 Section 3.2.1.1

Currently, Protocol Version 2.0 18 June 2018 does not include in the main body of the protocol (Pg. 34 Section 3.2.1.1) VGPR as a type of ORR, while the Synopsis on pg. 4 does list VGPR as a type of ORR. The main body of the protocol will be updated to add "Very Good Partial Response (VGPR)" in section 3.2.1.1.

**Item 12:** Inclusion criteria #2, Synopsis Pg.9; Pg. 38 Section 5.1

Currently, Protocol Version 2.0 18 June 2018 does not include VGPR in section 5.1 Pg. 38 for inclusion #2, while VGPR is listed under inclusion #2 in on Synopsis pg. 9. The following text will be added in a protocol amendment to the existing protocol inclusion criteria #2 to section 5.1.

*2. CR, VGPR, PR, or minimal response (MR) to latest of salvage chemotherapy at relapse, as determined by the International Myeloma Working Group (IMWG) criteria.*

**Item 13**: Plasma Cell Leukemia Exclusion #2, Synopsis Pg.10; Pg. 39 Section 5.2

Currently, Protocol Version 2.0 18 June 2018 does not include the first exclusion criterion #2 in the protocol synopsis, even though it is included in the body of the protocol in section 5.2. The following text will be added in a protocol amendment to the existing protocol exclusion criteria #2 to Pg. 10 of the protocol synopsis.

*2. Primary or secondary plasma cell leukemia at any time point prior to transplant.*

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***Item 14:*** Due to the updates to language, addition of new inclusion/exclusion criteria, and the re-numbering due to discrepancies, as noted in items 2, 3, 7, 8, 12, and 13 above, the Synopsis pages 9-11 and protocol sections 5.1 and 5.2 will be updated with the following inclusion/exclusion criteria and number sequencing. Of note, new criteria and criteria with updated language are in red italics.

***Inclusion Criteria***

Patients must meet all of the following criteria to be eligible for enrollment:

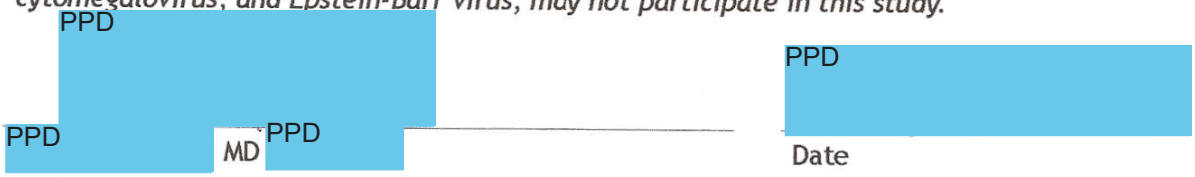
1. Patient has MM and:
   a. Has received prior ASCT after standard first-line induction treatment.
   b. Has evidence of PD, with progression-free interval ≥6 months in Phase 1 ≥18 months in Phase 2. Progression Free Interval is defined as the time from date of ASCT to PD.
   c. Received treatment with ≤3 prior lines of therapy.
   A line of therapy is defined as 1 or more cycles of a planned treatment program. When patients have undergone sequential phases of treatment without intervening progression, such as induction, collection of peripheral blood stem cells, transplantation and consolidation/maintenance, this is considered to be 1 line of treatment. A new line of therapy
   is initiated as a result of PD or relapse (Garderet et al, 2017).
2. CR, *VGPR*, PR, or minimal response (MR) to latest of salvage chemotherapy at relapse, as determined by the International Myeloma Working Group (IMWG) criteria.
3. Is, in the Investigator's opinion, a candidate for consolidation therapy with Tinostamustine followed by ASCT. (Note that patients planned to receive tandem ASCT are not eligible for the Phase 1 portion of the study.)
4. Has available autologous peripheral blood stem cell (PBSC) product with CD34 cell dose ≥2×106 cells/kg. The product could be from a collection prior to first ASCT or later second collection. (Note that, although not required, in Phase 1, the Investigator should consider enrolling patient with a large number of available PBSCs to permit subsequent ASCT, as patients in Stage 1 may received a dose lower that that determined to be effective.)
5. Age 18-75 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status score < 3 at Screening.
7. Creatinine clearance ≥40 mL/min, as determined by a local laboratory using the Cockcroft-Gault equation within 28 days before ASCT.
8. Left ventricular ejection fraction (LVEF) ≥40% within 28 days before ASCT.

9. Adequate pulmonary function, defined as forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO) >50% predicted within 28 days before ASCT.
10. Adequate liver function, as defined by an ALT and AST ≤2.5 × the upper limit of normal (ULN) and bilirubin ≤1.5 × ULN within 28 days before ASCT.
11. Potassium within the local laboratory's normal range. (Potassium supplementation is permissible.)
12. *Males and females of child bearing potential, and their partners, must be willing to use at least two effective forms of birth control for at least ninety (90) days after the administration of the study drug to be eligible to participate.*

***Exclusion Criteria***

Patients meeting any of the following criteria are not eligible for enrollment in the study:

1. History of central nervous system (CNS) disease involvement.
2. *Primary or secondary plasma cell leukemia at any time point prior to transplant.*
2. Myocardial infarction (MI) or stroke within 6 months before Screening.
3. Uncontrolled acute infection.
4. HCT-CI >6 points.
5. Concurrent malignant disease with the exception of treated basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease shall be documented since then.
6. Major coagulopathy or bleeding disorder.
7. Other serious medical condition that could potentially interfere with the completion of treatment according to this protocol or that would impair tolerance to therapy or prolong hematological recovery.
8. Lack of cooperation to allow study treatment as outlined in this protocol.
9. *Women who are pregnant or breastfeeding, or plan to become pregnant or breastfeed, are not eligible for study participation.*
10. The use of any anti- cancer investigational agents within 21 days prior to the expected start of trial treatment and interval of 14 days to last administration of salvage treatment.
11. Receiving treatment with drugs known to prolong the QT/QTc interval.
12. QTc interval (Fridericia's formula) >450 msec, based on the mean of triplicate Screening 12-lead ECGs.
13. *Subjects who are known to have any hypersensitivities or allergies to any ingredient of the investigational agent are not eligible to participate.*
14. *Subjects who are known to have or test positive for human immunodeficiency virus (HIV) types 1 and 2, hepatitis B virus (HBV) panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus (HCV), Treponema pallidum, cytomegalovirus, and Epstein-Barr virus, may not participate in this study.*



**Date:** January 30, 2019

**To:** EDO-S101-1004 (TITANIUM 1) Investigators and Site Staff

**Protocol Title:** A Phase 1/2 Open-Label Trial of Tinostamustine Conditioning and Autologous Stem Cell Transplant for Salvage Treatment in Relapsed/Refractory Multiple Myeloma (TITANIUM 1)

**Protocol Version:** 2.0, 18 June 2018

**Subject:** Protocol Clarification Memo

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Dear Investigators and Site Staff,

The purpose of this memo is to provide a list of recommended anti-emetic medications, to clarify performance of the bone marrow MRD assessment at day 100, and to clarify screening serology results. An amendment is forthcoming with these changes incorporated.

Recommended Anti-Emetics

Due to its association with QTc prolongation, ondansetron is prohibited around the time of tinostamustine dosing. Also, due to reported interactions with alkylating agents, aprepitant is also not allowed for nausea control. We, therefore, recommend the following anti-emetic medications for nausea control on day -1:

- Palonosetron
- Glucocortcoids-as single agent or in combination with palonosetron
- Olanzapine
- Lorazepam-in combination with other recommended anti-emetics

Given the short half-life of tinostamustine, ondansetron can be used up to 24 hours prior to tinostamustine dosing on day -1 and resumed 24 hours after the dose. In patients with mild hepatic dysfunction, this interval should be extended to 48 hours due to reports of delayed clearance of ondansetron in this population. Since aprepitant has a long half-life, it should not be administered at least 3 days prior to tinostamustine dosing. If needed, aprepitant can be given 24 hours after tinostamustine dosing.

Bone Marrow: Day 100 Assessment, in Phase 2 only

At day 100, subjects who meet laboratory criteria for CR only will undergo a bone marrow assessment. Samples will be obtained for pathology examination and MRD-N analysis.

Subjects who do not achieve CR at day 100 will not need a post-treatment bone marrow exam.

Screening Serologies

Protocol Version 2.0 18Jun18 notes in section 9.1.8. "Blood samples for infectious disease marker testing, including, at a minimum, human immunodeficiency virus (HIV) types 1 and 2, hepatitis B virus (HBV) panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus (HCV), Treponema pallidum, cytomegalovirus, and Epstein-Barr virus, are to be collected during Screening. Any patient with a positive result is not eligible for study participation."

This means patients with active and/or chronic infection.

Sincerely

PPD

PPD MD
Mundipharma-EDO GmbH

Cc: EDO-S101-1004 Study Team
Cc: EDO-S101-1004 Trial Master File