Statistical Analysis Plan
Version 2.0, 20 July 2021

Protocol OP-107

Protocol Title: A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function

National Clinical Trial number: NCT03639610

Oncopeptides AB

STATISTICAL ANALYSIS PLAN

PROTOCOL OP-107

A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function

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VERSION HISTORY

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Version #	Chapter	Revision Summary	Reason(s) for Revision
V1.0	N/A	Initial release	N/A
V2.0	7.9.3 Laboratory Data	Added “Lipegfilgrastim” in the list of coded preferred term for defining G-CSF for analysis.	The coded preferred term, “Lipegfilgrastim” should be considered G-CSF for analysis.
		Added eGFR for analysis using toxicity grades.	This is to summarize eGFR toxicity grade data available.
	7.9.2 Adverse Events	Remove the clause regarding death before the start of subsequent anticancer treatment for the summary of death.	This is to summarize all death in a table regardless of the timing of the subsequent anticancer treatment started.
	7.9.7 Chest x-ray	Added a section of chest x-ray.	This is to document chest x-ray data by a listing.

APPROVAL SIGNATURES

STUDY TITLE: A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function

PROTOCOL NUMBER: OP-107 v.5.0. (Amendment 4 dated January 22, 2021)

SAP FINAL v2.0, July 20, 2021

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under curve
$AUC_{(0-\infty)}$	area under the concentration-time profile from 0 hours to infinity
$AUC_{(0-t)}$	area under the concentration-time profile from 0 hours to the last measurable concentration
CB	clinical benefit
CBR	clinical benefit rate
CKD-EPI	chronic kidney disease epidemiology collaboration
CI	confidence interval
cm	centimeters
CR	complete response
CTCAE	common terminology criteria for adverse events
CV%	coefficient of variation
DOCB	duration of clinical benefit
DOR	duration of response
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMD	extramedullary disease
EOT	end of treatment
FISH	fluorescence *in situ* hybridization
FLC	free light chain
ICH	International Council for Harmonisation
IFE	immunofixation
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
ISS	International Staging System
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
mAb	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
ml	milliliter
MM	multiple myeloma

MR	minimal response
NCA	non-compartmental analysis
NCI	National Cancer Institute
NDA	New drug application
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
F-U	follow-up
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PT	preferred Term
R-ISS	revised international staging system
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
S-Cr	serum creatinine
SD	standard deviation; stable disease (depending on context)
SDG	standardized drug groupings
SDTM	study data tabulation model
SFLC	serum free light chain
SMQ	standardized MedDRA query
SOC	system organ class
SPEP	serum protein electrophoresis
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
TTR	time to response
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood cells
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis and reporting for the study protocol OP-107 v.5.0. (Amendment 4 dated January 22, 2021) entitled; A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function. The purpose of the plan is to outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry. If the protocol is amended, this SAP will be revised as required. The plan will be finalized before the study database is locked.

The statistical principles applied in the design and planned analyses of this study are consistent with International Council for Harmonisation (ICH) guidelines E9 (Statistical Principles for Clinical Trials).

This SAP does not include the description of the population pharmacokinetic (PK) modeling analysis, which is described in a separate analysis plan.

2. STUDY OBJECTIVE

2.1 PRIMARY OBJECTIVES

- To evaluate the relationship between renal function and the PK parameters for melphalan during treatment with melflufen
- To assess the safety and tolerability of melflufen in patients with moderate (Cohort 1a and 1b) and severe (Cohort 2a and 2b) renal impairment

2.2 SECONDARY OBJECTIVES

- To assess the best tumor response as well as overall response rate (ORR)
- To assess the progression free survival (PFS)
- To assess duration of response (DOR) in patients with ≥ partial response (PR) (stringent complete response (sCR), complete response (CR), very good partial response (VGPR), PR) as best response

- To assess clinical benefit rate (CBR) and duration of clinical benefit (DOCB) (i.e., proportion of patients with ≥ minimal response (MR)) as best response
- To assess time to response (TTR) in patients with a PR or better and time to clinical benefit (CB) for patients with MR or better
- Overall Survival (OS)

2.3 EXPLORATORY OBJECTIVES

- To assess changes in renal function

3. STUDY DESCRIPTION

3.1 STUDY DESIGN

This multicenter study will enroll patients with relapsed refractory multiple myeloma (RRMM) following 2-4 lines of prior therapy.

Patients will be treated with melflufen 10-40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Patients ≥ 75 years of age will have a reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22.

3.2 STUDY TREATMENT

There are four Cohorts in the study: 1a, 1b, 2a and 2b.

- Cohort 1a (estimated glomerular filtration rate [eGFR] of ≥ 30 ml/min to < 45 ml/min): Patients will be treated with Melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

Following approval of Amendment 2, Cohort 1a will close for enrollment and Cohort 1b will open for a minimum of 6 additional patients.

- Cohort 1b (eGFR of ≥ 30 ml/min to < 45 ml/min): Patients will be treated with Melflufen 30 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

Cohort 2a will only open if recommended by Data Safety Monitoring Committee (DSMC) after evaluating data from Cohort 1a and 1b.

- Cohort 2a (eGFR of ≥ 15 ml/min to < 30 ml/min): Patients will be treated with melflufen 20 mg (recommended dose by DSMC) on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

Cohort 2b will only open if recommended by DSMC after evaluating data from Cohort 1a, 1b and 2a.

- Cohort 2b (eGFR of ≥ 15 ml/min to < 30 ml/min): Patients will be treated with melflufen 30 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

Patients ≥ 75 years of age will have a reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22. Patients will be assessed for response after each cycle according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar, 2011). Patients may continue treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue.

Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol. In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

3.3 DATA AND SAFETY MONITORING COMMITTEE

An independent DSMC will perform surveillance of efficacy/safety balance at regular intervals and on as needed basis during the study and assess the benefit/risk profile of the study, to safeguard the interest of study participants. The DSMC will consist of lead CRO global medical monitor investigator and Sponsor representative(s) and headed by an independent chairperson.

All reported grade 3-4 treatment-related non-hematological adverse events (AEs), as well as all serious adverse events (SAEs), and any treatment-related deaths due to hematologic or non-hematologic AEs, as well as efficacy and PK data will then be presented to the DSMC.

Cohort 2 will only be initiated following DSMC review of the PK and safety profile of at least 6 patients in Cohort 1. If the DSMC advises to proceed with Cohort 2, at least 6 patients with eGFR ≥ 15 ml/min to < 30 ml/min will be enrolled and analyzed for safety and PK data. The DSMC will advise if Cohort 2 should continue as planned. Cohort 2 will have two parts, Cohort 2a and 2b. After at least 6 patients in Cohort 2a with eGFR ≥ 15 ml/min to < 30 ml/min have been evaluated,

the DSMC may advise if a higher starting dose (Cohort 2b, 30 mg melflufen) should be investigated.

If the DSMC considers the benefit/risk profile different from previous knowledge of efficacy and safety the DSMC may recommend change to the protocol, additional safety monitoring or stopping further recruitment.

All activities and processes surrounding the DSMC will be outlined in the DSMC charter.

4. SAMPLE SIZE AND POWER CALCULATION

Enrollment of approximately 35 PK evaluable patients is considered sufficient for a reliable assessment of the PK parameters, at least 6 patients per cohort.

5. ANALYSIS ENDPOINTS

5.1 PRIMARY ENDPOINTS

- PK parameters of melphalan
- Frequency and grade of AE's

5.2 SECONDARY ENDPOINTS

- ORR
- CBR
- PFS
- DOR
- DOCB
- TTR
- Best response during the study (sCR, CR, VGPR, PR, MR, stable disease (SD) or progressive disease (PD))
- OS

5.3 EXPLORATORY ENDPOINTS

- Renal function: The level of eGFR determined at baseline and the start of each cycle

6. ANALYSIS POPULATIONS

Safety Analysis Set

The safety analysis set is defined as all patients who received at least one or partial dose of melflufen or dexamethasone. The safety analysis set will be the primary population for the summaries of all exposure, efficacy and safety data. Demographics and disposition data will also be summarized based on the safety analysis set.

All listings will be presented based on the safety analysis set.

PK Analysis Set

All patients that have received at least one melflufen dose and have sufficient PK samples taken after this infusion (three samples as scheduled post-infusion), i.e. patients with at least one treatment cycle with three measurable melphalan concentrations within the same cycle.

This analysis set will be used for the PK analysis.

Efficacy Analysis Set

All patients that complete 2 doses of melflufen and have relevant baseline and follow-up disease assessments after the second dose of melflufen. This analysis set will be used for sensitivity analysis of all the efficacy parameters.

Relevant disease assessments: Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum free light chain (SFLC), and immunofixation (IFE) in serum and urine.

Note: All of these relevant lab parameters at different timepoints will be considered for follow-up disease assessments as long as taken after the second dose of melflufen.

7. ANALYTICAL PLAN AND STATISTICAL METHODS

7.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All statistical analyses will be performed using SAS statistical analysis software (SAS, SAS/GRAPH and SAS/STAT; version 9.4 or higher of SAS for Windows [SAS Institute Inc.; Cary, NC, USA]).

Descriptive statistics for continuous variables will include the number of patients with non-missing data (n), arithmetic mean, standard deviation (SD), median, minimum and maximum. Summary statistics for categorical variables will contain count and percentage based on the number of patients in the selected analysis population. Percentages will be presented to one decimal, except for zero and one hundred percent, which will be presented as 0% and 100% respectively.

For descriptive statistics of continuous variables, the accuracy of the minimum and maximum and should match the original data, for the mean and median one more decimal point in addition to the original data will be presented, and for SD two more decimal points in addition to the original data will be presented. For the derived variables (e.g., time since diagnosis) minimum and maximum will be presented with one decimal after point; mean, median and SD will be applied following the rule above. Presented decimal places should however not be greater than 4.

For PK descriptive statistics significant figures will be used for precision: mean, geometric mean and median values are shown with 4 significant figures, and standard deviation and CV% with 3 significant figures.

Any data categorization will be done based on the original data, before rounding is applied.

Unless otherwise specified, the denominators for the percentages will be based on the number of patients with non-missing data in the population used in each column. For the summaries presented by time points, the denominator will be the number of patients with non-missing data at each time point. A “missing” category will be included for any parameter for which information is missing, without a percentage.

By default the data collected in the electronic case report form (eCRF) and by external vendors will be used for analysis unless it is specified that additional derivation is required.

There will be no formal statistical analysis in this study. Results will be presented using descriptive statistics by cohort (Cohort 1a, Cohort 1b, Cohort 2a and Cohort 2b) and overall.

For treated patients all data collected will be presented in the listings. Some derived parameters will also be presented in the listings: i.e. derived international staging system (ISS) and revised international staging system (R-ISS), cytogenetics abnormalities risk-level, best confirmed response during the study, and PK parameters.

7.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

In general the baseline is the last available assessment prior to the first dose of study drug (the earliest of melflufen and dexamethasone start date).

Where assessments are made on the day of first treatment and the time is available for comparison, the time should be used to recognize whether or not the assessment was prior to the first treatment and thus should be used as a baseline. If only the date is in place and time is not available, for assessments on the day of first treatment that are per protocol scheduled to take place prior to treatment, it will be assumed that the assessment is pre-dose, and is a valid baseline assessment. Refer to the protocol for the study visit schedule.

Note that for this study there is no study day 0, so the day immediately prior to study day 1 is study day -1. For any events on or after the first dose of study drug, study day is calculated as: event date – date of first administration of study treatment + 1. As such, the first dose date was study day 1. For any events before the first dose date, study day is calculated as: event date – date of first administration of study treatment. As such, one day before first dose date was study day -1.

Because unscheduled assessments are not associated with any scheduled time point, they are excluded from all summaries by time point. Unscheduled visits will be considered for the baseline values derivations. Unscheduled assessments will be considered when deriving myeloma response parameters as described in the Section 7.7 and for analysis of laboratory parameters by worst toxicity grade as specified in the Section 7.8.3 of this SAP. All unscheduled assessments will be presented in the respective listings.

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

7.3 HANDLING OF MISSING DATA

If only a partial date is available and is required for a calculation (e.g., time since diagnosis, time since most recent relapse, determination of whether a medication is concomitant or an AE is treatment-emergent), the following standards will be applied:

- Start dates (e.g., AE onset date or start date of medication, date of diagnosis, date of relapse). For missing start day only - day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first dose date, informed consent date), then the

partial date will be imputed to equal the date being used for the calculation, unless there is a complete end date which is earlier.

- For missing start day and month - day and month will be imputed as the first day of the year (i.e., 01 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation, unless there is a complete end date which is earlier.
- Stop dates (e.g., AE resolution date or stop date of medication). For missing stop day only - day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
- For missing stop day and month - day and month will be imputed as the last day of the year (i.e., 31 December).

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009).

In case of incomplete date of relapse, for the purpose of calculation of the time since most recent relapse, the rules mentioned above for the partial start date will be used. However, for the date of frontline transplant in calculation of time since frontline transplant to relapse and for the date of relapse in derivation of refractory status, the simplified approach of assigning first day of a month in case of missing day and 01 January in case of missing month and day will be used. This simple approach will be also applied to impute the partial date of relapse in the calculation of time since the frontline transplant to relapse with the following exception in order to avoid yielding a negative duration due to imputation: The partial date of relapse will be imputed to the date of frontline transplant in case the partial date falls in the same month and year (if only day is missing) or in the same year (if day and month are missing).

If time is not available but is required for a calculation (e.g., timing of AE vs study drug administration), the most conservative approach should be used, i.e. assuming that the time of AE was after study drug administration or that the time of concomitant medication was after AE.

AEs with missing relationship are considered related for the purposes of summaries. In case of multiple cases, the information regarding the number of imputed relationships will be provided in the footnote of the respective summaries.

AEs with missing severity are considered severe (grade 3) for the purposes of summaries. Imputed

relationship and severity will not be included in the listings.

eGFR will be derived using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (See Section 7.6.3) if eGFR is not reported but serum creatinine is available for the corresponding visit.

The handling of dropouts and missing disease status assessments for the efficacy variables is described in their definitions in the relevant sections.

7.4 PATIENT DISPOSITION

Disposition summary will be based on the safety analysis set and presented by cohort and overall. The disposition of patients includes:

- Number (%) of patients in safety, PK and efficacy analysis sets
- Number (%) of patients permanently discontinued from the treatment along with the primary reasons for permanent treatment discontinuation
- Number (%) of death reported up to the end of treatment visit
- Number (%) of patients who had PFS follow-up (F-U) and by the following categories using counts and percentages based on the number of patients who had PFS F-U
    - Progressive disease (PD) and confirmed PD
    - Diagnosed with a second primary malignancy
    - Started subsequent therapy
- Number (%) of patients who had OS F-U and by the following categories using counts and percentages based on the number of patients who had OS F-U
    - Diagnosed with a second primary malignancy
    - Started subsequent therapy
    - Survival status at the last OS-FU
- Number (%) of patients discontinued from the study and reasons for study discontinuation

Treatment discontinuations due to AE specific to COVID-19 or other pandemic-related reasons will be presented separately.

All patient disposition information will be presented in the respective listings.

7.5 PROTOCOL DEVIATIONS

Major protocol deviations will be summarized by the deviation type for the safety analysis set by cohort and overall. All protocol deviations will also be provided in a listing. Separate listings for major protocol deviations, COVID-19 pandemic-related protocol deviations, and major COVID-19 pandemic-related protocol deviations will also be provided.

7.6 PATIENT CHARACTERISTICS

7.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

The following demographic and baseline characteristics will be summarized descriptively for the safety analysis set by cohort and overall:

- Age (years)
- Age categories (<65, ≥ 65 to ≤75, >75)
- Sex
- Race
- Ethnicity
- Baseline fertility status
- Baseline height (cm)
- Baseline weight (kg)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status

A listing will be provided for patient's demographic and baseline characteristics.
Separate listings will be provided for pregnancy test and ECOG results.

7.6.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Medical history will be summarized by Medical Dictionary of Regulatory Activities (MedDRA) (version 24.0 or higher), System Organ Class (SOC) and preferred term (PT) using number (n) and percentage (%) of patients having at least one occurrence of a disease for the safety analysis set by cohort and overall. Any medical history of COVID-19 will be presented as separate PTs specific to COVID-19 or SARS-CoV-2.
A listing will be provided for patient medical history.

7.6.3 MULTIPLE MYELOMA DISEASE HISTORY

The following disease characteristics at diagnosis will be summarized descriptively for the safety analysis set by cohort and overall:

- Stage of disease (ISS and R-ISS)
- Heavy chain and light chain subtypes
- Evidence of lytic bone disease
- Evidence of extramedullary disease (EMD)

The following disease characteristics at baseline/study entry will be summarized descriptively for the safety analysis set by cohort and overall:

- Stage of disease (ISS and R-ISS), eCRF reported and derived (see Table 1.)
- Heavy chain and light chain subtypes
- Evidence of lytic bone disease
- Evidence of EMD
- Disease status
- Time since diagnosis in years (calculated as [date of first dose of study drugs (the earliest of melflufen and dexamethasone first dose) – date of diagnosis+1]/365.25). Partial dates will be imputed according to the section 7.3 of this SAP
- Time since most recent relapse/progression in months (calculated as [date of first dose of study drugs (the earliest of melflufen and dexamethasone first dose) – date of most recent relapse/progression+1]/30.4375)
- Baseline SPEP, UPEP, kappa/lambda values; For descriptive statistics, in case of the second SPEP value being available as >0 g/L, the SPEP value will be derived as follows; Otherwise, in case of the second SPEP value being 0 g/L or not available, descriptive statistics will be produced without considering the second SPEP.
    - If there are more than one heavy chain subtypes (IgG, IgA, IgD, IgE, IgM) at study entry, the worst/higher values between the two available SPEP values will be used for descriptive statistics.
    - If there is only one heavy chain subtype (IgG, IgA, IgD, IgE, IgM) at study entry, the sum of the two available SPEP values will be used for descriptive statistics.
- Baseline maximum bone marrow plasma cells involvement (%) as values and by categories (<30%, ≥30 to <60%, ≥60%) (Note: The maximum bone marrow plasma cells involvement will be defined as the highest value amongst any of the available test results from the following bone marrow lab parameters: plasma cells ratio from bone marrow test, immature plasma cells/total cells based on bone marrow biopsy test or bone marrow aspiration/differential test.)
- Laboratory assessments
    - Baseline β2 microglobulin (mg/L) as continuous values and categories (< 3.5, ≥3.5 to ≤5.5 and > 5.5)

- Baseline platelet count (10^9/L) as continuous values and categories (<75, ≥75 to ≤ 100, >100 to ≤ 150, >150)
- Baseline absolute neutrophil count (ANC) (10^9/L) as continuous values and categories (<1.0, ≥1.0 to ≤1.5, and >1.5)
- Baseline hemoglobin (g/L) as continuous values and categories (<80, ≥80 to ≤100, >100)
- Baseline lactate dehydrogenase (LDH) (u/L) as continuous values and categories (<1.5xULN and ≥1.5xULN)
- Baseline albumin (g/L) as continuous values and categories (<35, ≥35)
- Baseline creatinine as continuous values
- Baseline eGFR (mL/min/1.73m2) as continuous values and categories (< 15, ≥15 to <30 , ≥30 to <45, ≥45)
- Screening eGFR (mL/min/1.73m2) as continuous values and categories (< 15, ≥15 to <30 , ≥30 to <45, ≥45) (Note: The latest available screening value (including unscheduled if available) will be used for analysis.)
- Baseline corrected calcium as continuous values

For patients for whom only creatinine clearance was calculated at baseline as a basis for enrolment values for renal function will be recalculated as eGFR using CKD-EPI formula:

$$eGFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018 \text{ [if female]} * 1.159 \text{ [if black]}$$

*Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

In addition to the above, ISS Stage and Revised ISS (R-ISS) Stage will be derived at study entry [Palumbo, 2015], (see Table 1).

ISS will be derived from screening serum β2 microglobulin and screening albumin. This derived ISS will in turn be used with screening serum LDH and high-risk cytogenetics at study entry as defined by the R-ISS guidelines to derive R-ISS. Derived ISS and R-ISS will be referred as "Derived ISS" and "Derived R-ISS" respectively. (Note: This derivation will consider the latest available screening value for β2 microglobulin, albumin, and serum LDH (including unscheduled if available).

Table 1: Standard Risk Factors for MM and the Revised ISS (R-ISS)

Standard Risk Factors for MM and the Revised -ISS (R-ISS)	
Prognostic Factor	**Criteria**
ISS Stage	
Stage I	Serum B2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
Stage II	Not ISS stage I or III
Stage III	Serum B2-microglobulin ≥ 5.5 mg/L
Chromosomal abnormalities (CA) by interphase florescent in situ hybridization (iFISH)	
High-Risk	Presence of del(17p) and/or translocation of t(4:14) and/or translocation of t(14:16)
Standard-Risk	No high-risk CA
Lactate Dehydrogenase (LDH)	
Normal	Serum LDH =< upper limit of normal (ULN)
High	Serum LDH > ULN
A new model for risk stratification of MM R-ISS	
Stage I	ISS stage I and standard-risk CA by iFISH and normal LDH
Stage II	Not R-ISS stage I or III
Stage III	ISS stage III and either high-risk CA by iFISH or LDH

A separate summary dedicated to cytogenetics investigations at diagnosis and study entry will be presented, including type of cytogenetic analysis (iFISH, karyotype), and the number and percentage of patients having particular types of cytogenetic abnormalities. Cytogenetics abnormalities at study entry will also be pooled by risk level (high-risk, standard-risk and unknown) as follows depending on the type of cytogenetic analysis:

- High-risk based on iFISH is defined in case the following abnormalities were found: deletion (17p), gain 1q (+1q), gain (1q21); t (4;14), t(4;14) (p16;q32), t (14;16), t (14;16) (q32;q23), t(14;20), t(14;20) (q32;q11).
- Standard-risk based on iFISH consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk based on iFISH.
- Unknown: consists of patients for whom the iFISH procedure was not done or unevaluable.
- High-risk based on karyotype is defined in case the following abnormalities were found: deletion (13) or deletion (13q).
- Standard-risk based on karyotype consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk based on karyotype.

- Unknown: consists of patients for whom the karyotype procedure was not done or unevaluable.

Bone lesion assessments at screening will be analyzed descriptively with the number and percent of patients, including the number and percent of patients for whom skeletal survey was performed, method of skeletal survey, result of exam, bone lesions locations. The same information will be presented for the other imaging procedures.

Listings will be provided for MM history, bone lesion assessments and bone marrow aspirate.

7.6.4 PRIOR MM THERAPIES

The following information related to prior MM therapies will be summarized for the safety analysis set by cohort and overall:

- Number and percentage of patients who had a transplant.
- Number of patients who had a salvage transplant (defined as any transplant where the patient has already had one or more transplants in earlier lines). Planned tandem autologous or autologous-allogeneic are considered as one transplant.
- Frontline transplant type (allogeneic or autologous); Frontline transplant is the first transplant per patient irrespective in which therapy line it was applied. The number and percentage of patients having frontline transplant per prior therapy line will be presented.
- Number and percentage of patients with the tandem transplant.
- Number and percentage of patients with at least one prior autologous transplant, and number and percentage of patients with two or more prior autologous transplants
- Number of prior autologous transplants
- Time from frontline transplant to the earliest relapse following frontline transplant (not necessarily after the prior therapy line when frontline transplant occurred) in years (as continuous variable as well as per categories < 1 year, ≥1 year to <1.5 years, ≥1.5 years to ≤2 years, >2 years; To be calculated as [date of earliest relapse following the frontline transplant – date of frontline transplant +1]/365.25. Partial dates will be imputed according to the section 7.3 of this SAP)
- Number of prior systemic therapy lines
- Best response to the last prior line of systemic therapy

- Refractory status to the last prior line of systemic therapy
- Number and percentage of patients with any prior lines including: immunomodulatory drugs (IMiD's), proteasome inhibitors (PI's), alkylators, anti-CD38 monoclonal antibodies (mAb), other mAb and others
- Number and percentage of patients receiving any of above agents in the last prior line.
- The number and percentage of patients refractory to any of the above agents in at least one prior regimen
- The number and percentages patients refractory to any of the above agents in the last prior line
- Number and percentage of patients who received IMiD and PI (double-class) in any of prior lines of therapies
- Number and percentage of patients, double refractory to PI and IMiD in any of prior lines of therapies);
- Number and percentage of patients who received IMiD, PI, and anti-CD38 mAb (triple-class) in any of prior lines of therapies
- Number and percentage of patients, that are refractory and/or intolerant to a PI, an IMiD, and an Anti-CD38 mAb (Triple class refractory) in any of prior lines of therapies. Intolerance is defined when a patient stopped treatment due to toxicity, and as well as did not receive a drug in the same therapeutic drug class again prior to entering the current study.
- Number and percentage of patients with prior radiotherapy

The next list of drugs is associated with each drug class using World Health Organization Drug Dictionary (WHODD) version March 2021 or higher:

- IMiD is defined as WHODD Standardized Drug Groupings (SDG) "Antineoplastic thalidomide analogues"
- PI is defined as WHODD SDG "Antineoplastic proteasome inhibitors"
- Alkylators is defined as WHODD SDG "Antineoplastic alkylating drugs"
- Anti-CD38 mAb is defined as WHODD SDG "Antineoplastic CD38 antigen inhibitors"
- Other mAb is defined as WHODD SDG "Monoclonal antibodies – antineoplastics" excluding SDG "Antineoplastic CD38 antigen inhibitors"

- Other antineoplastic drugs for the treatment of MM will be referred to as 'Other". Will be identified by manual review of the drugs not included into the categories above.

Refractory is defined as non-responsive disease (achieving SD or PD as the best response) while on therapy, or reason for termination was PD, or relapse/progression within 60 days after stop date of treatment. A patient is to be deemed as refractory to a therapy line in case of refractory to at least one of the agents in the therapy line whereas a patient is deemed as non-refractory to a therapy line in case of non-refractory to all of agents in the therapy line. Otherwise, a patient's refractory status to the therapy line will be considered unknown.

All patient details of prior MM therapies will be presented in the respective listings.

7.6.5 PRIOR AND CONCOMITANT MEDICATION

All concomitant medications will be coded using the WHODD version March 2021 or higher.

A medication is considered prior if stopped before the date of the first dose of study drug (the earliest of melflufen and dexamethasone start date). Concomitant medications are defined as medications with start date or end date on or after the date of first dose of study drug and start date within 30 days after the date of the last dose of study drug (the latest of melflufen and dexamethasone end date) or are ongoing at the time of first dose of study drug.

The number and percentages of patients with at least one concomitant medication will be summarized by the Anatomical Therapeutic Chemical (ATC) class (ATC 2 and ATC 4) and preferred name. Summaries will be presented by safety analysis set by cohort and overall. Patients may have more than one medication per ATC class and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. The summaries will be ordered by descending frequency of ATC class and preferred name within each ATC class in the total group. Prior medications will be presented separately in the same way. Separate summaries will be provided for the number and percentage of patients with the following medication categories: "Haemapoetic growth factors" (WHODD SDG "Colony stimulating factors") and by preferred terms, as well as "Transfusions" (including next PTs: "Platelets", "Erythrocytes").

A listing of prior and concomitant medications will be provided.

All prior and concomitant surgical/medical procedures performed within 21 days of study entry until the EOT visit will be listed.

7.7 PHARMACOKINETICS ANALYSIS

PK parameters will be calculated and provided by the Sponsor using Non-Compartmental Analysis (NCA) and the software Phoenix WinNonlin® version 8.2 or later (Certara L.P., U.S.A.). The following PK parameters will be assessed for melphalan.

- Maximum drug concentration (C_{max})

  C_{max} is defined as the maximum drug concentration observed in plasma per treatment cycles with PK sampling.

- Time of maximum concentration (T_{max})

  Time of maximum plasma concentration (T_{max}) is defined as the time at which the C_{max} occurs.

- Area under the concentration-time profile from 0 hours to the last measurable concentration ($AUC_{(0-t)}$)

  $AUC_{(0-t)}$ is defined as the area under the concentration-time curve from start of dosing (time 0) to the time of the last measured concentration. $AUC_{(0-t)}$ will be estimated using the Linear Up Log Down calculation method.

- Area under the concentration-time profile from 0 hours to infinity ($AUC_{(0-\infty)}$)

  $AUC_{(0-\infty)}$ is defined as the total area under the concentration-time curve from start of infusion (time 0) to the limit as the end time becomes arbitrarily large.

- Half-life (t½)

  The apparent t½ is defined as the time required for the drug concentration to decrease by a factor of one-half in the terminal phase. t½ will be estimated as ln(2) / Ke, Ke referring to terminal phase elimination rate constant of the apparent log-linear decrease as defined by 3 data points.

  Blood samples for PK analysis of melphalan concentrations in plasma, will be collected at the following time points:

Table 4. PK sampling schedule

	Cycle 1 and 2
Sample 1, time point	5-10 minutes after the end of melflufen infusion
Sample 2, time point	2-3 hour after the end of melflufen infusion
Sample 3 time point	5-7 hours after the end of melflufen infusion

Date and time of sample collection or reason for not being collected will be recorded in the eCRF. Concentrations and corresponding PK parameters will be provided as external files and appended to the study database.

Actual time points relative to start of melflufen infusion in minutes will be derived and used by the Pharmacokinetist for calculating parameters. Actual time in minutes will be calculated as datetime of blood sampling minus datetime of start of infusion.

All PK parameters to be calculated for melphalan are listed in Table 5. The derivation of PK parameters is done by the Pharmacokineticist. All parameters will be presented in a listing in minimum.

Table 5. PK parameters to be calculated

Phoenix WinNonLin ID	**Unit**	**Parameter code**	**CDISC submission value**
Rsq		R2	R Squared
Rsq_adjusted		R2ADJ	R Squared Adjusted
Corr_XY		CORRXY	Correlation Between TimeX and Log ConcY
No_points_lambda_z		LAMZNPT	Number of Points for Lambda z
Lambda_z	min	LAMZ	Lambda z
Lambda_z_int	ng/mL	LAMZINT	Lambda z Intercept
Lambda_z_lower	min	LAMZLL	Lambda z Lower Limit
Lambda_z_upper	min	LAMZUL	Lambda z Upper Limit
Lambda_z_span	min	LAMZSPN	Lambda z Span
*HL_Lambda_z	min	LAMZHL	Half-Life Lambda z
*Tmax	min	TMAX	Time of Cmax
*Cmax	ng/mL	CMAX	Max Conc
Cmax_D	ng/mL/mg	CMAXD	Max Conc Norm by Dose

Tlast	min	TLST	Time of Last Nonzero Conc
Clast	ng/mL	CLST	Last Nonzero Conc
Clast_pred	ng/mL	CLSTP	Last Nonzero Conc Pred
*AUClast	min*ng/mL	AUCLST	AUC to Last Nonzero Conc
AUClast_D	min*ng/mL	AUCLSTD	AUC to Last Nonzero Conc Norm by Dose
AUCall	min*ng/mL	AUCALL	AUC All
*AUCINF_obs	min*ng/mL	AUCIFO	AUC Infinity Obs
AUCINF_D_obs	min*ng/mL/mg	AUCIFOD	AUC Infinity Obs Norm by Dose
AUC_%Extrap_obs	%	AUCPEO	AUC %Extrapolation Obs
Vss_obs	L	VSSO	Vol Dist Steady State Obs
Vz_obs	L	VZO	Vz Obs
AUCINF_pred	min*ng/mL	AUCIFP	AUC Infinity Pred
AUCINF_D_pred	min*ng/mL/mg	AUCIFPD	AUC Infinity Pred Norm by Dose
AUC_%Extrap_pred	%	AUCPEP	AUC %Extrapolation Pred
Vss_pred	L	VSSP	Vol Dist Steady State Pred
Vz_pred	L	VZP	Vz Pred
Cl_pred	L/min	CLP	Total CL Pred
AUMClast	min*min*ng/mL	AUMCLST	AUMC to Last Nonzero Conc
AUMCINF_obs	min*min*ng/mL	AUMCIFO	AUMC Infinity Obs
AUMC_%Extrap_obs	%	AUMCPEO	AUMC % Extrapolation Obs
AUMCINF_pred	min*min*ng/mL	AUMCIFP	AUMC Infinity Pred
AUMC_%Extrap_pred	%	AUMCPEP	AUMC % Extrapolation Pred
MRTlast	min	MRTIVLST	MRT Intravasc to Last Nonzero Conc
MRTINF_obs	min	MRTIVIFO	MRT Intravasc Infinity Obs
MRTINF_pred	min	MRTIVIFP	MRT Intravasc Infinity Pred

* Summarized with descriptive statistics as continuous variables and with the geometric mean and geometric coefficient of variation.

C_{max} and T_{max} will be presented with the same number of decimals as the concentration measurements and time points, while the derived PK variables will be presented with an appropriate number of significant digits based on the general practice.

It may be necessary to exclude individual PK profiles because they are erroneous or abnormal, e.g. protocol violation, documented sample handling errors etc. Such data will not be used for analysis and any excluded data should be flagged in the listings and the reason for exclusion should be documented.

Statistical methods

Descriptive statistics (arithmetic mean with corresponding SD, geometric mean with corresponding SD , geometric coefficient of variation (CV%), median with minimum and maximum) for drug concentrations by time point and PK variables will be provided for melphalan.

Geometric mean and geometric CV% will be calculated as follows:

$Geometric\ mean = \text{GeoMean} = exp[\{ln(y_1) + \cdots + ln(y_n)\}/n]$,
$Geometric\ standard\ deviation = GeoSD = exp[SD\{ln(y_1), \ldots, ln(y_n)\}]$, and
$Geometric\ CV\ (\%) = GeoCV = 100 \times \sqrt{exp\{ln(GeoSD)\}^2 - 1}$,

where SD is the arithmetic standard deviation.

7.8 EFFICACY ENDPOINTS AND ANALYSIS

All efficacy analyses will be produced on the safety analysis set and efficacy analysis set by cohort and overall.

All tumor response and progression-depended objectives are assessed by investigators according to the IMWG-URC (Rajkumar, 2011).

7.8.1 RESPONSE RATES

For analysis of response rates, all percentages calculations will be based on the respective analysis set. For analysis of the best confirmed response rates, a category of 'non-evaluable' will be added and included in the percentage calculation for patients who cannot be categorized for the best confirmed response (as described below). For analysis of the best unconfirmed response rates, the same approach will be used.

Best Overall Confirmed Response

Best overall confirmed response during the study, including follow-up tumor response assessments (sCR, CR, VGPR, PR, MR, SD or PD), collected prior to the new therapy initiation, and assessed by the investigator according to IMWG-URC, will be summarized descriptively.

Confirmed response: Two consecutive assessments with the same response result made at any time. In case at the second consecutive assessment (made at any time) the response is higher than

the previous one, then confirmed response (linked to the first assessment visit) will be the first one (e.g., PR – VGPR consecutive pair will lead to a PR confirmed response at the first visit). In case the second consecutive response is lower than the first one, then confirmed response (linked to the first assessment visit) will be the second one (e.g. CR-VGPR consecutive pair will lead to a VGPR confirmed response at the first visit).

Best Unconfirmed Response

Defined as the best response achieved on study, i.e. a response may not be confirmed by a consecutive assessment. Will be presented similarly to best overall confirmed response.

Overall Response Rate

The ORR will be estimated as the proportion of patients who achieve a confirmed response of sCR, CR, VGPR, or PR as their best response, as assessed by the investigator. The denominator is the number of patients in the analysis population for particular cohort. The exact binomial two-sided 95% confidence interval (CI) for ORR will be calculated.

Clinical Benefit Rate

The CBR is the proportion of patients who achieve a confirmed minimal response or better (sCR, CR, VGPR, PR and MR) as their best response, as assessed by the investigator. CBR will be summarized using the same method as for ORR.

All the details of myeloma response assessment will be presented in a listing.

7.8.2 TIME TO EVENT PARAMETERS

Progression-Free Survival

The PFS is defined as the time from the date of first study drug (the earliest of melflufen and dexamethasone start date) initiation to the date of first documentation of confirmed PD or death due to any cause, whichever occurs first. PFS time, in months, is calculated as (PFS date – date of first study drug initiation +1)/30.4375.

Additional conventions for the PFS date derivation and censoring are defined in the Table 2 below:

Table 2. Conventions for PFS date derivation and censoring

Situation	Date of Progression or Censoring	Outcome
No post-baseline response assessments, except in the case of death	Date of initiation of therapy (the earliest of melflufen and dexamethasone start date)	Censored
New anticancer therapy started before documentation of PD or death	Date of last response assessment prior to start of new anticancer therapy	Censored
Death or PD immediately after more than 1 consecutively missed response assessment visit*	Date of last response assessment visit without documentation of PD that is before the first missed visit	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
Alive and without PD documentation	Date of last response assessment	Censored
Death or PD between planned response assessments	Date of death or first response assessment showing PD, whichever occurs first	Progressed
Death before first response assessment	Date of death	Progressed

*unless there was an unscheduled visit showing absence of PD between the last scheduled missing response assessment and date of PD identification

The distribution of PFS will be summarized using the Kaplan-Meier (K-M) method. The median PFS will be estimated from the 50th percentile of the corresponding K-M estimates. The 95% CI for median PFS will be constructed using the method of Brookmeyer (Brookmeyer, 1982).

K-M plots will also be produced.

A patient data listing will be provided for PFS follow-up.

Duration of Response (DOR)

DOR is defined as the time in months from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression according to the IMWG-URC or to death due to any cause. DOR is defined only for patients with a confirmed PR or better.

DOR is to be censored and summarized using the same methods as for PFS.

DOR will be derived as (DOR date – date of first documented confirmed response (≥PR) + 1)/30.4375.

Duration of Clinical Benefit (DOCB)

DOCB will be calculated as time in months from the first evidence of confirmed assessment of sCR, CR, VGPR, PR or MR to first confirmed disease progression, or to death due to any cause. Duration of clinical benefit is defined only for patients with a confirmed MR or better. DOCB will be censored and summarized using the same method as for PFS.

DOCB will be derived as (DOCB date – date of first documented confirmed response (≥MR) + 1)/30.4375.

Time to Response (TTR)

TTR will be calculated as time in months from first dose of study drug to first documented confirmed response in a patient that has responded with PR or better. TTR will be presented descriptively for patients with a response. Will be derived as (date of first documented confirmed response (≥PR) – date of study drug initiation +1)/30.4375.

Time to CB will be presented for confirmed response of MR or better and analyzed similarly to TTR.

Overall Survival (OS)

OS defined as time in months from date of study drug initiation to death due to any cause. Patients still alive at the end of study, or lost to follow-up, will be censored at last day known alive. Will be derived as (OS date – date of study drug initiation +1)/30.4375.

A patient data listing will be provided for overall survival follow-up.

7.8.3 EFFICACY ASSESSMENTS

Myeloma specific laboratory tests results, including SPEP, UPEP, serum and urine IFE, and SFLC will be summarized descriptively by assessment visit, and this will include change from baseline summary using descriptive statistics for continuous variables. In case the second SPEP value is available as >0 g/L at a given time point, see the section 7.6.3 for the derivation.

All the myeloma specific laboratory tests results and other efficacy assessments (i.e. extramedullary plasmacytoma assessment) will be presented in the listings.

7.9 SAFETY ENDPOINTS AND ANALYSIS

All analyses of safety will be based on the safety analysis set.

7.9.1 EXPOSURE TO STUDY TREATMENT

Exposure analysis will be based on the safety analysis set by cohort and overall.

Duration of melflufen treatment in weeks is defined as (date of last dose – date of first dose + 29 days) divided by 7.

If a patient discontinued from treatment and the end of treatment (EOT) visit happened prior to 29 days after last dose, then the duration of melflufen is defined as (date of EOT – date of first dose +1) divided by 7.

If a patient died prior to 29 days after last dose, then the duration of melflufen is defined as (date of death – date of first dose +1) divided by 7.

Duration of dexamethasone treatment in weeks is defined as (date of last dose – date of first dose + 1) divided by 7.

Overall duration of treatment with study drug in weeks is defined as the longest duration of dexamethasone or melflufen treatment.

The duration of study treatment exposure will be summarized descriptively and presented for overall treatment duration and also separately for melflufen and dexamethasone and will include: treatment duration in weeks, number of cycles received (and also additionally number of doses for dexamethasone), cumulative dose (in mg) of study drug received per patient, average dose of study drug (mg/week for melflufen and mg/week for dexamethasone), the total number and percentage of patients receiving a dose per cycle (for overall treatment and melflufen), average duration of infusion (min) for melflufen. Patients who received only a partial dose of melflufen for a given cycle will be considered as having received treatment for that cycle.

Average dose of melflufen in mg/week is defined as the cumulative dose divided by the duration of melflufen treatment (the same for dexamethasone).

Dose modification information will be summarized descriptively for any drug (melflufen and/or dexamethasone) for overall and then also separately for melflufen and dexamethasone by cycle. The number of patients with each action by frequency will be presented based on the melflufen/dexamethasone administration eCRF page.

A dose delay is defined as a consecutive dose of melflufen administered on day 33 or later

following a preceding dose of melflufen (day at the moment of melflufen administration is defined as a difference between Cycle X Day 1 (CXD1) date and C(X-1)D1 date +1). Dose delays will be categorized as delays in weeks as 1 (day 33 to 39), 2 (day 40 to 46), 3 (day 47 to 53), 4 (day 54 to 60), and >4 weeks (day 61 or later) for each cycle.

A separate table will present the number and percentage of patients with delayed cycles for post-cycle 1 (those with day 33 and later at the moment of melflufen administration following a preceding dose of melflufen) as well as the number of delayed cycles by delay categories (1 week, 2 weeks, 3 weeks, 4 weeks and >4 weeks).

Number of patients with a dose delay due to COVID-19 pandemic will be summarized.

All melflufen and dexamethasone administration details will be presented in the respective listings.

7.9.2 ADVERSE EVENTS

All AE summaries will be presented based on the safety analysis set by cohort and overall.

All AEs will be coded using the MedDRA (version 24.0 or higher), for toxicity assessment the National Cancer Institute Common Toxicity Criteria Adverse Event (NCI CTCAE) version 4.03 will be used.

The summaries of AEs will be based on treatment-emergent adverse events (TEAEs).

TEAEs are defined as AEs that start on or after the first day of study treatment (the earliest of melflufen and dexamethasone start date) administration and within 30 days after the last administration of study treatment (the latest of melflufen and dexamethasone end date), or before start of subsequent anticancer treatment (whichever occurs first) or that worsen on or after the first day of study treatment.

An overall summary of AEs will be presented. It will include the number and percentage of patients (as well as total event count) with at least one pre-treatment condition (started prior to the first dose of melflufen and/or dexamethasone), patients with at least one TEAE, patients with at least one grade 3, grade 4 and grade 3/4 TEAE, patients with at least one serious TEAE, and patients with TEAEs leading to death.

The overall summary will include the treatment related TEAEs analyzed separately for treatment related TEAEs (melflufen and/or dexamethasone related), melflufen related TEAEs, and dexamethasone related TEAE. It will include the number and percentage of patients (as well as total event count) with each corresponding treatment related TEAEs; patients with grade 3, grade

4 and grade 3/4 TEAEs; This summary will include the number (%) of patients with study treatment related serious TEAEs as well as melflufen-related serious TEAEs, and dexamethasone related serious TEAE separately along with the number (%) of patients with respective treatment related TEAEs leading to death. In addition the number and percentage of patients with TEAEs leading to dose reduction, dose held and dose discontinuation will be presented for overall (melflufen and/or dexamethasone), and separately for melflufen and dexamethasone.

The number and percentage of patients experiencing TEAEs, as well as total event count (except for summaries by toxicity grade), will be summarized by MedDRA SOC and PT for:

- TEAEs
- Non-serious TEAEs
- Treatment-related (related to melflufen and/or dexamethasone) TEAEs
- Melflufen-related TEAEs
- Dexamethasone-related TEAEs
- Serious TEAEs
- Treatment-related serious TEAEs
- Melflufen-related serious TEAEs
- Dexamethasone-related serious TEAEs
- TEAEs by CTCAE toxicity grade
- Treatment related (related to melflufen and/or dexamethasone) TEAEs by CTCAE toxicity grade
- Melflufen-related TEAEs by CTCAE toxicity grade
- Dexamethasone-related TEAEs by CTCAE toxicity grade
- Serious TEAEs by CTCAE toxicity grade
- Treatment-related serious TEAEs by CTCAE toxicity grade
- Melflufen-related serious TEAEs by CTCAE toxicity grade
- Dexamethasone-related serious TEAEs by CTCAE toxicity grade
- TEAEs resulting in any treatment modification (hold, reduction, delay, interruption and discontinuation) for any study drug and also separately for melflufen and dexamethasone

The number and percentage of patients with grouped AEs – TEAEs defined as follows:

- Thrombocytopenia (SMQ “Haematopoietic thrombocytopenia” – Broad scope)

- Neutropenia (PTs: “Neutropenia”, “Febrile neutropenia”, “Neutrophil count decreased”, “Neutropenic sepsis”, “Neutropenic infection”, “Cyclic neutropenia”, “Band neutrophil count decreased”, “Band neutrophil percentage decreased”, “Neutrophil percentage decreased”, “Agranulocytosis”, “Granulocyte count decreased”, “Granulocytopenia”)
- Anemia (standardized MedDRA query (SMQ) “Haematopoietic erythropenia” – Broad scope)
- Myelodysplastic syndrome (PTs: “5q minus syndrome”, “Chronic myelomonocytic leukemia”, “Myelodysplastic syndrome”, “Myelodysplastic syndrome transformation”, “Myelodysplastic syndrome unclassifiable”, “Refractory anemia with an excess of blasts”, “Refractory anemia with ringed sideroblasts”,”Refractory cytopenia with multilineage dysplasia”, “Refractory cytopenia with unilineage dysplasia”, “Sideroblastic anemia”)
- Second primary malignancies ((SMQ “Malignant or unspecified tumours” and HLT “Myelodysplastic syndromes”), excluding HLGT “Plasma cell neoplasms”)
- Febrile neutropenia (PT “Febrile neutropenia”)
- Infections (SOC “Infections and infestations”)
- Infective pneumonia – broad scope (SMQ “Infective pneumonia”)
- Infective pneumonia – narrow scope (SMQ “Infective pneumonia” – Narrow terms)
- Hemorrhage (SMQ “Haemorrhages” - Narrow terms)
- Thrombocytopenia concomitant to hemorrhage: Hemorrhage with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 thrombocytopenia. Grade 3/4 thrombocytopenia resolution date is to be identified based on the laboratory data as a first day when thrombocytopenia assessment is grade 2 or lower (grade ≤ 2 for toxicity “Platelet count decreased”).
- Neutropenia concomitant to infection: Infection with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 neutropenia. Grade 3/4 neutropenia resolution date is to be identified based on the laboratory data as a first day when neutropenia assessment is grade 2 or lower (grade ≤ 2 for toxicity “Neutrophil count decreased”).

The groups above will be summarized as a separate summaries for all by SOC, PT and all by SOC, PT, CTCAE toxicity grade analyses.

By SOC, PT grouped AE summaries will also be presented by cycle.

For by-cycle reporting, an AE is assigned to particular cycle if started at or after the date and time of the study treatment (earliest of melflufen and dexamethasone administration at particular cycle) administration at particular cycle and prior to the date of treatment administration in subsequent cycle. If a patient discontinued somewhere in between the cycles, the AE is assigned to the cycle in which the discontinuation has happened.

A patient reporting the same TEAE more than once will only be counted once when calculating incidence:

- within a given SOC
- within a given SOC and PT combination or MedDRA SMQ

The maximum CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations.

TEAEs reported with a causality assessment of "Probably Related" and "Possibly Related" are to be considered as "Related" for the analysis purposes. AEs having both onset and end dates missing will be considered TEAEs; in case of a missing start date and a complete end date, the AE will be considered a TEAE unless the end date is prior to the date of the first dose of study drug.

A separate summary will present the number and percentage of patients who died during the study treatment period (between the first dose of treatment (the earliest of melflufen and dexamethasone start date) and within 30 days after last dose of treatment (the latest of melflufen and dexamethasone end date)) and on follow-up (more than 30 days after last treatment dose along with the reason for deaths as well as the number of patients died within 60 days after first treatment dose.

Any AEs related to COVID-19 will be presented as separate PTs specific to COVID-19 or coronavirus.

Listings will be provided for patients experiencing AEs, SAEs, AEs resulting in drug withdrawal and events with fatal outcome.

7.9.3 LABORATORY DATA

Laboratory data will be summarized for the safety analysis set by cohort and overall.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units on Study Data Tabulation Model (SDTM) level. Hematology and

chemistry parameters will be summarized descriptively and changes from baseline to post-baseline visits for each parameter will be presented. Urinalysis results will only be listed.

All the data from both scheduled and unscheduled time points will be included in the CTCAE grade shift tables.

Shift tables for the change in CTCAE grade (with separate parts for decreased and increased grades) will be constructed for hematology and chemistry laboratory parameters, which have corresponding CTCAE grades to tabulate changes in NCI CTCAE (version 4.03) from baseline to worst post-baseline on study (up to and including EOT visit) CTCAE grade. Number of patients with grade 3 or higher toxicity will be summarized as counts and percentages by cycle. A separate listing of all laboratory results corresponding to grade 3 or 4 will be provided.

The following list of parameters that will be presented in the toxicity grades laboratory tables:

- Hematology
    - Hemoglobin (increase, decrease)
    - Platelets (decrease)
    - White blood cells (WBC) (increase, decrease)
    - ANC (decrease)
    - Lymphocyte count (increase, decrease)
- Serum Chemistry
    - Alanine aminotransferase (ALT) (increase)
    - Aspartate aminotransferase (AST) (increase)
    - Alkaline phosphatase (increase)
    - Total bilirubin (increase)
    - Creatinine (increase)
    - Calcium (increase, decrease)
    - Glucose (increase, decrease)
    - Albumin (decrease)
    - Potassium (increase, decrease)
    - Sodium (increase, decrease)
    - eGFR (decrease)

For hemoglobin, ANC and platelet counts, CTCAE grade shift tables will also be additionally presented by cycles. For this analysis by cycle, the maximum grade within each cycle is used for analysis.

Time from the date of the first study drug dose (earliest of melflufen and dexamethasone administration at particular cycle) in a particular cycle until the date of grade 3, grade 4 and grade 3/4 onset will be presented for each cycle for ANC and platelets. Time to onset of grade 3, grade 4 and grade 3/4 for ANC and platelets will also be presented overall (duration in days from the treatment start until the date of grade 3, grade 4 and grade 3/4 respectively) and for completed cycles.

For laboratory results reported with a prefix, for example "<" or ">", the value derived from the reported results without a prefix will be analyzed.

A separate table will be produced for incidence of grade 4 neutropenia (grade 4 toxicity "Neutrophil count decreased") and thrombocytopenia (grade 4 toxicity "Platelet count decreased") based on laboratory data for completed cycles (cycles having a subsequent cycle available). The table will include the number of patients dosed in each cycle, the number of patients dosed in completed cycle, the number and percentage of patients with grade 4 neutropenia and grade 4 thrombocytopenia, number and percentage of patients with G-CSF (concomitant medication with PT="Granulocyte Colony Stimulating Factor", "Filgrastim", "Pegfilgrastim", "Lenograstim", "Lipegfilgrastim")) in each cycle, the number and percentage of patients with platelets transfusion (concomitant medication with PT="Platelets") and erythrocytes transfusion (concomitant medication with PT="Erythrocytes" and "Red blood cells") at each cycle.

Concomitant medication is assigned to the particular cycle if taken between the date of the melflufen administration at a particular cycle and date of melflufen administration in subsequent cycle. If patient discontinued somewhere in between the cycles concomitant medication is assigned to the cycle in which the discontinuation has happened.

Another table will investigate the occurrence of grade 3 and 4 neutropenia and thrombocytopenia leading to melflufen dose reduction per cycle, based on the laboratory data,

All laboratory data will be listed, including CTCAE toxicity grades and normal ranges. A listing will be provided for urine pregnancy tests as well.

7.9.4 VITAL SIGNS

Vital signs will be summarized using descriptive statistics for the safety analysis set by cohort and overall.

Results and change from baseline to post-baseline time points for weight, blood pressure, pulse, respiratory rate and temperature will be presented.

A patient data listing will be provided to document height, weight, and vital signs data.

7.9.5 PHYSICAL EXAMINATION

Physical examination will only be listed without a summary.

7.9.6 12-LEAD ELECTROCARDIOGRAM (ECG)

ECG data will be summarized for the safety analysis set by cohort and overall.

ECG data (heart rate, PR interval, QRS interval, QT interval, QTc-Fridericia (QTcF) interval, RR interval) will be summarized using descriptive statistics, changes from baseline to EOT visit will also be evaluated.

Shift tables from baseline (Normal/Abnormal-clinically significant/Abnormal – not clinically significant) to EOT visit will be summarized for ECG interpretation data.

All ECG data collected will be presented in the listing.

7.9.7 CHEST X-RAY

Chest x-ray data will be listed without a summary.

7.10 OTHER ENDPOINTS AND ANALYSIS

7.10.1 ECOG

ECOG performance status will be summarized as counts and percentages using shift tables of baseline versus worst performance status (largest ECOG value) during the study. Also, the number of patients with decrease of ≥1 unit and ≥2 units respectively at the last available visit and at the EOT visit will be summarized as counts and percentages to reflect the level of improvement in ECOG values.

7.10.2 EGFR

The eGFR level at the start of each cycle and the changes from baseline over time will be presented using descriptive statistics.

A patient data listing will be provided to document eGFR level by cycle.

8. INTERIM ANALYSIS

The interim analysis took place to support accelerated New Drug Application (NDA) submission and was described in the separate interim SAP dated 28 June 2019.

An interim analysis for an interim clinical study report (iCSR) is planned when patients enrolled in Cohort 1a and 1b have been followed until progression or up to at least 6 months after first dose. The objective of this interim analysis is to evaluate PK, safety and efficacy in Cohort 1, moderately impaired patients, to support regulatory submissions. As no inferential statistical analyses are planned at the interim analysis, the interim has no impact on the statistical methods or presentation of data for the final report.

9. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

There are no deviations from analysis as described in the protocol.

10. PROGRAMMING SPECIFICATION

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the protocol number will be presented. On the next line a table/listing number followed by the title of the table/listing and population information will be displayed. Horizontal lines will appear after the column heading of the table/listing. Footnotes will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The SAS program name will appear bottom left in a string and the page number will appear on the bottom right corner of each table/listing. The date and time of creation of table/listing will appear bottom left under to the SAS program name line.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format, for example, 07MAY2002.

Shells for unique tables and listings are provided in a separate Mock-Up TFLs document.

11. REFERENCES

Rajkumar, S. V., J. L. Harousseau, B. Durie, et al. Consensus Recommendations for the Uniform Reporting of Clinical Trials: Report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011; 117(18):4691-4695.

Brookmeyer R, Crowley J. A Confidence interval for the median survival time. Biometrics; 1982; 38: 29-41.

Palumbo A, et al. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. Journal of Oncology 2015. 33:26, 2863-2869.