STATISTICAL ANALYSIS PLAN

O-12-M1

AN OPEN-LABEL PHASE I/IIA STUDY OF THE SAFETY AND EFFICACY OF MELPHALAN-FLUFENAMIDE (MELFLUFEN) AND DEXAMETHASONE COMBINATION FOR PATIENTS WITH RELAPSED AND/OR RELAPSED-REFRACTORY MULTIPLE MYELOMA

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STATISTICAL ANALYSIS PLAN (SAP) SIGNATURE PAGE

Statistical analysis plan (SAP) Version 2.0 (dated 22AUG2017) for protocol O-12-M1.

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STATISTICAL ANALYSIS PLAN (SAP) SIGNATURE PAGE (CONTINUED)

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	09NOV2016	PPD	Not Applicable. First Version.
2.0	12JUL2017	PPD	Updated the definition for the derived EOT to take death date into account. Refer to "latest output shells" throughout document instead of to the specific version (except where output shells used for DSMC was referenced). Updated MedDRA to version 20.0 and WHO-DD to version dated 01MAR2017. Removed 21-day and 28-day cycle length by-group from study drug administration section. Action taken with melflufen updated from "increased" to "other" in text. Missing grades or relationships will not be indicated and analyzed as "worst case", but will be counted as "missing". Section 9.3 – Added text for presentation of major protocol deviations as obtained from the CTMS report. Section 15.2.2 – Histogram for disease response rate replaced with swimmers plot for time to disease response. Section 16.1.9 – added all categories displayed in overview TEAE tables. Section 16.1.10 – time to onset of grade III and/or IV TEAEs limited to neutropenia and thrombocytopenia. Section 16.2 – Added text to explain that counts of Neutropenia and

			Thrombocytopenia will be based on worst grade per cycle.
2.0	22AUG2017	PPD	Addition of textbook reference ranges for the white blood cell (email 13Jul2017) differential percentages. Incorporate Sponsor comments.

CTMS: Clinical Trials Management System. EOT: End of Treatment. MedDRA: Medical Dictionary for Regulatory Activities. TEAE: Treatment-emergent adverse event. WHO-DD: World Health Organization-Drug Dictionary.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AEs	Adverse events
ASH	American Society of Hematology
ATC	Anatomical Therapeutic Chemical
BLQ	Below the lower limit of quantification
CAT/CT	Computerized axial tomography
CBRR	Clinical benefit response rate
CFB	Change from Baseline
CI	Confidence intervals
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicities
DR	Data review
DSMC	Data safety monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEmITT	Efficacy-evaluable Modified Intent-to-Treat
EHA	European Hematology Association
EOS	End of study
EOT	End of Treatment
FISH	Fluorescence in situ hybridization
ICH	International Conference of Harmonisation
Ig	Immunoglobulin
IMiD	Immunomodulatory drugs
IMWG	International Myeloma Working Group
ISS	International Staging System
IV	Intravenous
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
M-protein	Monoclonal protein
MR	Minimal response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
ORR	Objective response rate

Abbreviation	Term
OR	Objective response
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PI	Proteasome inhibitor
PICC	Peripherally inserted central catheter
PK	Pharmacokinetic
PO	Per os
PP	Per Protocol
PR	Partial response
PT	Preferred Term
QTc	Corrected QT
QTcF	Corrected QT interval using Fridericia's formula
SAF	Safety
SAP	Statistical analysis plan
sCR	Stringent complete response
SD	Standard deviation
SD	Stable disease
SFLC	Serum free light chain
SI	International system of units
SOC	System Organ Class
TEAEs	Treatment-emergent AEs
ULQ	Above the upper limit of quantification
USA	United States of America
VGPR	Very good partial response
WHO-DD	World Health Organization-Drug Dictionary

1. INTRODUCTION

The document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol O-12-M1. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

With reference to the latest version of the data review (DR) plan [1], the statistical analysis plan (SAP) also contains definitions of analysis sets and derived variables for the dry run and final analysis.

CCI Biostatistics is not responsible for performing the following analyses:

- Pharmacokinetic (PK) analyses: To be performed by Oncopeptides AB.
- Holter electrocardiogram (ECG) assessments: To be performed by CCI .
- Data related to correlative studies: To be analyzed by CCI .

The aforementioned are therefore not included in the scope of this SAP.

The SAP is based on protocol Version 6.0, dated 06JUL2016 including protocol amendments 01 to 05 [2] and electronic case report form (eCRF) Version 12.0, dated 30AUG2016 [3].

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

2.1.1. PHASE I

The primary objective of Phase I of the study is to determine the maximum tolerated dose (MTD), after one treatment cycle, of the combination of melflufen and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma.

Phase I was completed in SEP2014 and the MTD was determined by the data safety monitoring committee (DSMC) at the meeting held on 19SEP2014 as 40 mg melflufen.

2.1.2. PHASE IIA

The primary objective of Phase IIa of the study is to evaluate the objective response rate (ORR) (partial response [PR] or better) and the clinical benefit response rate (CBRR) (minimal response [MR] or better) to the combination of melflufen and dexamethasone and melflufen as single-agent at the MTD as determined in Phase I.

2.2. SECONDARY OBJECTIVES

The secondary objectives of Phase IIa of the study are to evaluate the following in all efficacy-evaluable patients:

- Duration of disease response.
- Time to disease progression.
- Progression-free survival (PFS).
- Overall survival (OS).

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are to:

- Identify mechanisms of response and or resistance to melflufen.
- Evaluate pharmacokinetics on patients enrolled at selected sites that are to be trained in the process of sample handling (not included in the scope of this SAP).
- Review ECG assessments to screen for major effects on the corrected QT (QTc) interval conducted at selected sites. Should a signal be detected further evaluations are to be conducted in future studies (not included in the scope of this SAP).

2.4. SAFETY OBJECTIVES

As part of the secondary objectives of the study the safety and tolerability of the combination of melflufen and dexamethasone and of melflufen as single-agent are to be evaluated.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is an open-label, Phase I/IIa, multisite study conducted in Europe and the United States of America (USA) in patients with relapsed and or relapsed/refractory multiple myeloma. From this point onwards Phase I and Phase II (in lieu of Phase IIa) are used to reference the different phases of the study. Cycles are also used (in lieu of treatment cycles) to reference the relevant treatment period in which a patient received study drug. Phase I followed the standard 3 + 3 modified Fibonacci design with 3 to 6 patients, depending on dose limiting toxicity (DLT) observed, tested at each dose level. Up to five dose levels of melflufen (administered as 30-minute infusions on Day 1 at 15 mg, 25 mg, 40 mg, 55 mg and 70 mg) were to be evaluated during Phase I in combination with a fixed dose of dexamethasone (administered as 40 mg intravenous [IV]/per os [PO] on Days 1, 8 and 15 of each 21-day cycle).

With reference to Section 2.1.1 Phase I of this SAP, Phase I was completed and the MTD was determined as 40 mg melflufen. At the time of determining MTD only four (15 mg, 25 mg, 40 mg, 55 mg) of the five dose escalation cohorts had been evaluated.

An additional 49 patients are to be enrolled and treated at the MTD in Phase II, resulting in a total of 55 patients treated at the MTD. This includes the Phase I MTD patients and the Phase II 40 mg dose cohort and is referred to as combination regimen (Phase I + Phase II).

Based on protocol Version 5.0, including protocol amendments 01 to 04 a cohort of ≥ 20 patients are to be enrolled to single-agent melflufen (administered as 40 mg on Day 1 of each 28-day cycle). All study procedures are to remain the same for the single-agent patients except for dexamethasone administration that is to be used as an anti-emetic prophylaxis at lower doses only.

In the event that the risk-benefit balance of single-agent melflufen is determined to be sub optimal, the DSMC may at any time and without any further protocol amendment recommend that subsequent patients are to be treated with the combination regimen in order to optimize efficacy. In this case, patients are to follow the same dexamethasone dose, schedule and dose modification guidelines as previously described in accordance with protocol Version 4.0, dated 27JAN2015 for the combination regimen. Ongoing patients in the single-agent cohort may have weekly dexamethasone doses added at the discretion of the investigator.

For both Phase I and Phase II patients, the planned cycle length was increased from 21 to 28 days following a decision by the DSMC on 18MAY2015. Patients enrolled prior to 18MAY2015 are subject to a planned 21-day cycle length, but based on the investigator's judgment the cycle length for ongoing patients may be increased to 28 days. Patients enrolled after 18MAY2015 are to follow the protocol planned 28-day cycle length. This includes the Phase II single-agent patients. However, if any patient is subject to delayed hematologic recovery, the investigator may decide to increase the cycle length beyond the planned 21 or 28 days.

Patients are to be assessed for disease response after each cycle with confirmation of disease

response according to the International Myeloma Working Group (IMWG) response criteria (Appendix 6 Disease Response Criteria of this SAP) regardless of dose level treated.

According to the protocol, melflufen and/or dexamethasone dose modification guidelines are provided for patients experiencing toxicity and requiring dose modification.

Patients are to be assessed at the start of each cycle according to the assessments outlined on Day 1 of each cycle in Section 8.1 of protocol Version 6.0, including protocol amendments 01 to 05 [2]. To initiate a new cycle of study drug the following criteria are to be met:

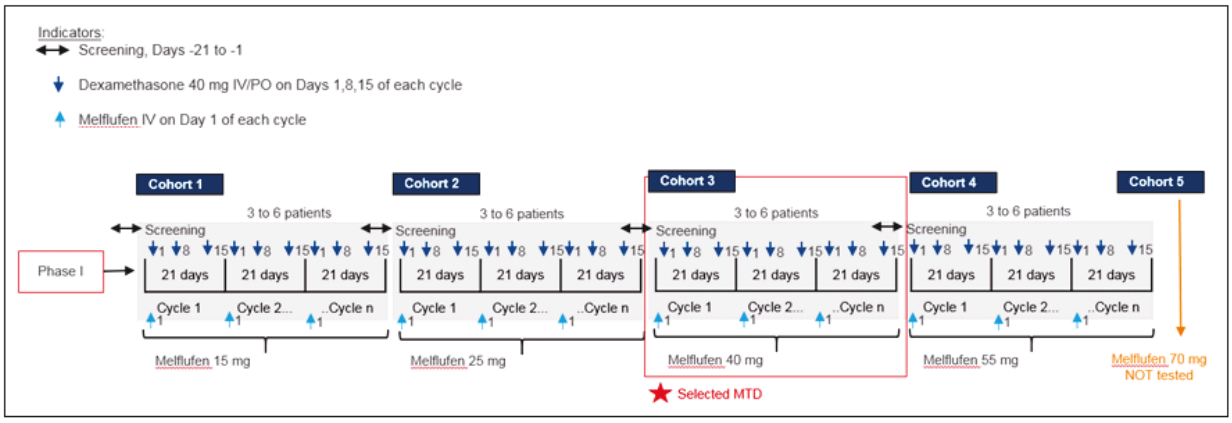
- Absolute neutrophil count ≥ 1.0 x 10E9/L.
- Platelet count ≥ 50.0 x 10E9/L.
- All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except alopecia).
- Absence of any other dose-limiting toxicities (DLTs).

Patients in both Phase I and Phase II may continue with study drug for up to 8 cycles, until the patient experiences unacceptable toxicity, disease progression, withdraws consent, and/or study drug is discontinued at the discretion of the investigator. However, patients who benefit from the treatment at the end of 8 cycles may continue treatment at the discretion of the investigator and after approval by Oncopeptides AB for each individual case. Section 8.3 of protocol Version 6.0, including protocol amendments 01 to 05 [2] specifies that the End of Treatment (EOT) visit should be performed within 30 days following study drug discontinuation or prior to initiation of any subsequent treatment (whichever occurs first).

Following disease progression or initiation of subsequent treatment, the post-study follow-up period includes documentation of secondary malignancies, subsequent treatment, disease status and survival. Follow-up is to occur every 3 months for up to 2 years. Patients that discontinue study drug for reasons other than disease progression are to continue to have disease response assessments performed monthly (for confirmation of disease response/progression) until disease progression or initiation of subsequent treatment.

The study design is schematically displayed below in Figure 1: Phase I and Figure 2: Phase II, respectively.

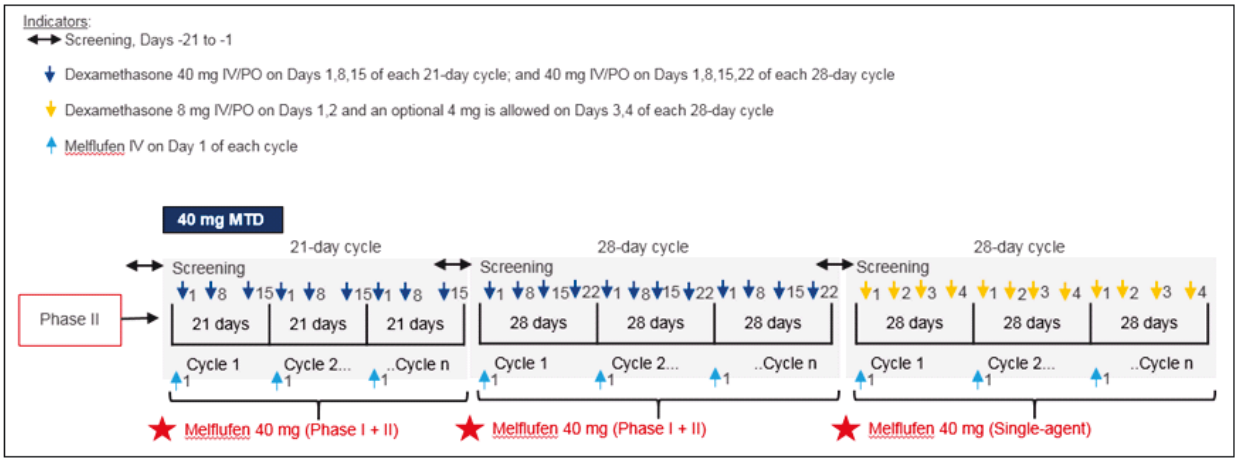
Figure 1: Phase I



DLT: Dose-limiting toxicity. IV: Intravenous. MTD: Maximum tolerated dose. PO: Per os.

Dose reductions are not permitted during Cycle 1 of Phase I, unless the patient experiences a dose-limiting toxicity (DLT). Dose reductions are permitted in subsequent cycles of Phase I.

Figure 2: Phase II



IV: Intravenous. MTD: Maximum tolerated dose. PO: Per os.

Dose reductions are permitted during Cycle 1 of Phase II and subsequent cycles of Phase II.

3.2. SCHEDULE OF EVENTS

Schedule of events is presented in Section 8.1 of protocol Version 6.0, including protocol amendments 01 to 05 [2].

3.3. CHANGES/CLARIFICATIONS TO ANALYSIS FROM PROTOCOL AND ELECTRONIC CASE REPORT FORM (ECRF) DATA COLLECTION

The analysis sets described in the SAP are more comprehensive than those described in protocol Version 6.0, including protocol amendments 01 to 05 [2]. The analysis sets of the study are expanded to include the following:

- Modified Intent-to-Treat (mITT) Analysis Set.
- Per Protocol (PP) Analysis Set.

The modified Intent-to-Treat (mITT) Analysis Set is introduced to allow the inclusion of the 40 mg MTD Phase I patients as well as the Phase II patients who have not necessarily completed at least two full cycles of study drug (intent-to-treat principle). Also, as per the International Conference of Harmonisation (ICH) guidelines it is recommended to test patients who are more compliant with the protocol by looking at the PP Analysis Set. International Conference of Harmonisation (ICH) Chapter 5.2.2 states the following: "The 'per protocol' set of subjects, sometimes described as the 'valid cases', the 'efficacy' sample or the 'evaluable subjects' sample, defines a subset of the subjects in the full analysis set who are more compliant with the protocol and is characterised by criteria such as the following:

- The completion of a certain pre-specified minimal exposure to the treatment regimen.
- The availability of measurements of the primary variable(s).
- The absence of any major protocol violations including the violation of entry criteria".

Within the context of the clinical study report (CSR) transparency with regards such factors is important and this aids in producing the relevant table summaries to address the ICH requirements.

Due to the initial design of the eCRF and the development of the analyses over time, external data in EXCEL format, not included in the standard data transfer are to be incorporated in the analysis datasets and presented in the output following review and authorization by Oncopeptides AB. This includes:

- Appendix 2: Assignment of Patients to Disease Status (Relapsed/Refractory) to Prior Therapy (EXCEL spreadsheet), of the DR report.
- Appendix 3: Assignment of Patients to a Planned 21-day versus 28-day Cycle (EXCEL spreadsheet), of the DR report.
- Appendix 4: Hematopoietic growth factors (EXCEL spreadsheet), of the DR report.
- Appendix 5: Standardized transfusions (EXCEL spreadsheet), of the DR report.

4. PLANNED ANALYSES

The following formal analyses are to be performed for the study:

- Analyses for the conduct of DSMC meetings.
- Final analysis.

4.1. DATA SAFETY MONITORING COMMITTEE (DSMC)

A DSMC SAP (DSMC_Charter_O-12-M1.doc) and SAP output shells (20150409 O-12-M1 DSMC Outputs Draft V5.0.doc) were created as separate documents describing the methodology and presentation of results as provided by CCI Biostatistics on several occasions for various DSMC meetings. Similar output was requested in preparation for the American Society of Hematology (ASH) poster presentations and the European Hematology Association (EHA) meeting.

4.2. INTERIM ANALYSIS

No interim analysis is planned for the study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in the SAP are to be performed by CCI Biostatistics. The following study documents require Oncopeptides AB's authorization, unless otherwise specified:

- Statistical Analysis Plan (SAP) and latest SAP output shells.
- Appendix 1: Assignment of Patients to Analysis Sets and Identification of Major Analysis Set Deviations (EXCEL spreadsheet), of the DR report.
- Additional EXCEL spreadsheets as detailed in Section 3.3 Changes/Clarifications to Analysis from Protocol and electronic Case Report Form (eCRF) Data Collection of this SAP.
- CCI Biostatistics' and CCI Data Management's authorization of the final data issues log and the data handling report.

5. ANALYSIS SETS

With reference to the latest authorized version of the DR plan [1] the following analysis sets are defined for analysis purposes.

5.1. ALL PATIENTS SCREENED ANALYSIS SET

All patients who provided written informed consent prior to performing any specific study-related procedures.

5.2. SAFETY (SAF) ANALYSIS SET

All patients who received at least one dose, or part thereof, of study drug are to be included in the Safety (SAF) Analysis Set. The first occurrence of either melflufen or dexamethasone is to be considered for all patients except for Phase II single-agent patients. Dexamethasone is to be regarded as anti-emetic prophylaxis in the single-agent cohort. Therefore only the first occurrence of melflufen is to be considered for Phase II single-agent patients. The SAF Analysis Set is regarded as primary for the safety analyses.

5.3. MODIFIED INTENT-TO-TREAT (MITT) ANALYSIS SET

All patients considered to be valid for the SAF Analysis Set and who received at least one dose of study drug at MTD as initial dose. This includes the 40 mg MTD Phase I patients as well as the Phase II patients. The mITT Analysis Set is regarded as primary for PFS and OS analyses.

In the event that a deviation in planned versus actual study drug is present, patients are to be analyzed according to planned study drug (enrolled dose cohort).

5.4. EFFICACY-EVALUABLE MODIFIED INTENT-TO-TREAT (EEMITT) ANALYSIS SET

All patients considered to be valid for the mITT Analysis Set, who have a Baseline efficacy assessment (measurable disease assessment) and for whom at least one post-baseline efficacy assessment (disease response assessment), following completion of at least two full cycles of study drug, is available, are to be included in the Efficacy-evaluable Modified Intent-to-Treat (EEmITT) Analysis Set. The EEmITT Analysis Set is regarded as primary for disease response efficacy endpoints including response rates, time to response and duration of response analyses as well as disease progression. Refer to Table 2: Dose Cohorts of this SAP for the presentation of summaries.

In the event that a deviation in planned versus actual study drug is present, patients are to be analyzed according to actual study drug (actual initial dose of melflufen received as indicated on the Melflufen Administration eCRF).

5.5. PER PROTOCOL (PP) ANALYSIS SET

The PP Analysis Set includes all patients who completed the study according to protocol and had no major analysis set deviations. Analysis set deviations are defined as major if they have an influence on the efficacy outcome or the effect of the study drug within the patient. Only patients included in the EEmITT Analysis Set are eligible for inclusion in the PP Analysis Set. Patients who are withdrawn from the study due to lack of efficacy or drug-related (relationship to either melflufen or dexamethasone) reasons are to be included in the PP Analysis Set if they are otherwise valid. The PP Analysis Set is regarded as confirmation of the primary efficacy results obtained from the EEmITT Analysis Set.

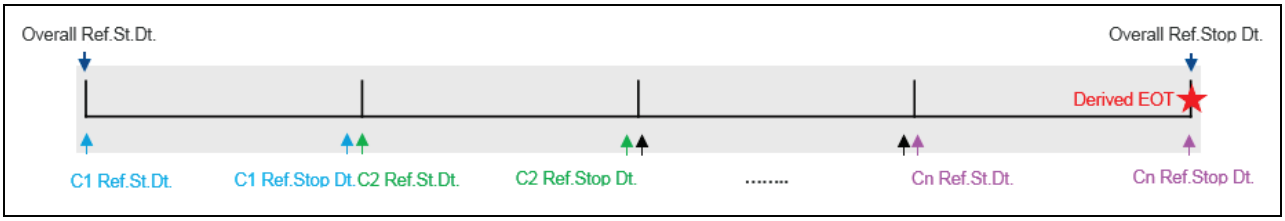
The PP Analysis Set is further defined by the following valid course criteria:

- Compliance with study drug (melflufen and dexamethasone).
- Sufficient evidence of the study indication.
- Adherence to the visit schedule.
- Eligible in accordance with the protocol specified inclusion/exclusion criteria.
- Use of prohibited prior/concomitant medication and/or therapy.
- No deviation in planned versus actual study drug.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATES, REFERENCE STOP DATES AND REFERENCE DAYS

Table 1: Reference Dates



C: Cycle. Dt: Date. EOT: End of Treatment. Ref: Reference. St: Start. Cn: Represents a patient's last cycle.

Date of first and last dose of study drug is to be based on the earliest (minimum) and the latest (maximum) dose date of the two study drugs (melflufen and dexamethasone) in the combination regimen, where relevant. Study drug details are to be obtained as indicated on the Melflufen Administration and Dexamethasone Administration eCRFs. With reference to Table 1: Reference Dates, the overall reference start date is defined as the date of first dose of study drug (Cycle 1 Day 1 is the day of the first dose of study drug). The first occurrence of either melflufen or dexamethasone is to be considered for all patients except for Phase II single-agent patients. Dexamethasone is regarded as anti-emetic prophylaxis in the single-agent cohort. Therefore only the first occurrence of melflufen is to be considered for Phase II single-agent patients. The overall reference start date is to be presented in selected by-patient data listings where an assessment date or event date is presented.

The last occurrence of either melflufen or dexamethasone (latest [maximum]) is to be considered for all patients except for Phase II single-agent patients initially enrolled as per protocol amendment 04. Only the last occurrence of melflufen is to be considered for Phase II single-agent patients as the last dose date, unless the investigator decides to switch a patient to combination regimen: Phase I + II (per protocol amendment 05) for which the last occurrence of either melflufen or dexamethasone (latest [maximum]) is to be considered.

Reference start and stop dates are also defined for each cycle. The reference start date of Cycle x is defined as the date of first dose of study drug on Cycle x Day 1. The first occurrence of either melflufen or dexamethasone is to be identified as described for the overall reference start date. The reference stop date of Cycle x is defined as the day before Day 1 of the subsequent cycle (Cycle [x+1] Day 1). The reference stop date of the last cycle (i.e., the overall reference stop date) is defined as the derived EOT date (refer to Section 6.2 Derived Timepoints of this SAP).

Study days (relative to the overall reference start date) are to be used to indicate the relative day on which assessments started/stopped.

Cycle days (relative to the reference start date of Cycle x) are to be used to indicate the relative day on

which assessments started/stopped within an individual cycle. Cycle days for Screening assessments are to be defined relative to the overall reference start date and derived EOT or post-study follow-up assessments are to be defined relative to the last melflufen dose date.

6.1.1. DERIVATIONS

Study day is to be calculated relative to overall reference start date.

If the date of the event is on or after the overall reference start date:

- Study day = (<Date of event> – <overall reference start date>) + 1.

If the date of the event is prior to the overall reference start date:

- Study day = (<Date of event> – <overall reference start date>).

Study days are only presented for patients with a least one dose of study drug or part thereof. Unless otherwise specified, if an assessment date is partial or missing, study day, and any corresponding durations are to be presented as partial or missing in the by-patient data listings.

Cycle day is to be calculated relative to reference start date of Cycle x per individual cycle, except for Screening assessments to be calculated relative to the overall reference start date and derived EOT or post-study follow-up assessments to be calculated relative to the last melflufen dose date.

If the date of the event of Cycle x is on or after the reference date:

- Cycle day = (<Date of event> – <reference date>) + 1.

If the date of the event of Cycle x is prior to the reference date:

- Cycle day = (<Date of event> – <reference date>).

6.2. DERIVED TIMEPOINTS

Following data investigation, some patients were identified with the EOT visit occurring after the specified 30 days from study drug discontinuation (Section 8.3 of protocol Version 6.0, including protocol amendments 01 to 05 [2]). To ensure inclusion of as much data as possible for the analyses and to obtain the actual cycle length of a patient's last cycle, a reference point (i.e., a derived EOT date) was introduced by CCI Biostatistics. For patients with no actual EOT visit recorded or patients with an actual EOT visit occurring within 30 days of the last cycle's Day 1 melflufen dose date, the last study drug date of melflufen + 30-day gap period is to be used as the derived EOT date. The derived EOT date is defined as the latest reference date of either the last melflufen dose date + 30-day gap period or the actual EOT visit date, or the death date should it occur first. If subsequent treatment is initiated within the last cycle, derived EOT is calculated as the start date of subsequent treatment administration. Please refer to 20170824 EOT derivation.xls EXCEL spreadsheet for authorized derived EOT dates based on the above definition and review and authorization from Oncopeptides team.

For patients with no assessments recorded at the actual EOT visit, the last non-missing post-baseline

assessment (scheduled or unscheduled) up to and including the derived EOT date is to be carried forward to allow change from Baseline (CFB) at EOT calculations. The last observation carried forward (LOCF) data handling convention is to be used to prevent exclusion of data for patients with no assessments recorded at the actual EOT visit. Change from Baseline (CFB) calculations for which the LOCF data handling convention is to be applied include plasmacytoma, laboratory (hematology, serum chemistry, coagulation, and quantitative urinalysis), 12-lead ECG, and vital signs assessments.

6.2.1. Derivations

- Derived EOT date = min(max[<Last melflufen dose date> + 30, <actual EOT visit date>], <first subsequent treatment date>, <death date>).

6.3. Cycle Length, Cycle Assignment, and Cycle Completion

As described in Section 3.1 General Description of this SAP, the planned cycle length was increased from 21 to 28 days.

The actual cycle length (duration) is defined as the difference in days from Day 1 of a patient's current cycle (Cycle x) to the day before Day 1 of the subsequent cycle (Cycle [x + 1] Day 1). The actual cycle length (duration) of a patient's last cycle is defined as the difference in days from Day 1 of the last cycle to the derived EOT date + 1 (refer to Section 6.2 Derived Timepoints of this SAP). The total number of cycles completed (derived sum) is based on patients returning at the start of a subsequent cycle who are considered to have completed the previous cycle (refer to Section 6.1 Reference Start Dates, Reference Stop Dates and Reference Days of this SAP) plus the addition of the patient's last cycle ending with the derived EOT as reference point.

6.3.1. Derivations

Cycle length (days): Calculated relative to the day before Day 1 of the subsequent cycle:

- Cycle x length (days) = ({[Date of Cycle {x + 1} Day 1]} – Date of Cycle x Day 1). Where x = 1 to n.

Cycle length (days) of last cycle: Calculated relative to the derived EOT date (refer to Section 6.2 Derived Timepoints of this SAP):

- Cycle n length (days) = (Date of derived EOT – Date of Cycle n Day 1) + 1.

The number of cycles completed is indicated on the End of Treatment eCRF. However, the total number of cycles completed is to be derived based on the actual administration data as indicated on the Melflufen Administration eCRF. Patients returning at the start of the subsequent cycle (Cycle [x + 1] Day 1) are to be considered to have completed the previous cycle (Cycle x Day 1). The patient's derived EOT date is to be used to account for a patient's last cycle in lieu of the subsequent cycle.

- Total number of cycles completed (derived sum) $= \sum_{x=1}^{n-1} (Cycle\ [x+1] Day\ 1 - Cycle\ x\ Day\ 1) + 1.$

Where n represents a patient's last cycle. An example below is presented for illustration purposes:

For n=3, i.e., x=1 to (n-1)					
x=1	Cycle (1 + 1) Day 1 – Cycle 1 Day 1	→	Cycle 2 Day 1 – Cycle 1 Day 1	=	1
x=2	Cycle (2 + 1) Day 1 – Cycle 2 Day 1	→	Cycle 3 Day 1 – Cycle 2 Day 1	=	1
	Cycle 3 Day 1 to derived EOT date			→	1
	Total number of cycles completed (derived sum)			=	3

EOT: End of Treatment. The derived EOT date is to be used to account for the patient's last cycle.

The following data are to be assigned to the cycle during which the procedure/medication/event started based on cycle reference start and stop dates. If the procedure/medication/event date is on or after the cycle reference start date and on or before the cycle reference stop date, then the procedure/medication/event is to be assigned to the relevant cycle.

- Concomitant procedures (including standardized transfusions): Cycle occurrence is to be assigned based on the date of the procedure.
- Concomitant medications (including hematopoietic growth factors): Cycle occurrence is to be assigned based on the start date of the medication.
- Adverse events (AEs): Cycle occurrence is to be assigned based on the start date of the event.
- Neutropenia and thrombocytopenia/events of special interest: Cycle occurrence is to be assigned based on the date of laboratory assessment. Adverse events (AEs), hematopoietic growth factors and standardized transfusions are included in the events of special interest and are to be handled as described above.

For the handling of partial dates for AEs, medications, prior therapies, and/or procedures refer to Appendix 2 Partial Date Conventions of this SAP.

6.4. BASELINE

Baseline is defined as the last non-missing assessment (scheduled or unscheduled up to and including Cycle 1 Day 1) prior to the first dose of study drug (overall reference start date). In the case where the last non-missing assessment and the overall reference start date coincide, the assessment is to be considered as occurring prior to the start of study drug and is to be used as the Baseline assessment. However, AEs and medications commencing on the overall reference start date (Cycle 1 Day 1) are to be considered post-baseline, i.e., as treatment-emergent AEs (TEAEs) or concomitant medications.

For serum free light chain (SFLC) assay differences Baseline is defined as the difference in the last non-missing involved SFLC assay and uninvolved SFLC assay where both SFLC assays are obtained from the same identified last non-missing SFLC assessment:

- Involved kappa: SFLC difference at Baseline = ($Kappa_{Baseline}$ - $Lambda_{Baseline}$).

- Involved lambda: SFLC difference at Baseline = ($Lambda_{Baseline}$ - $Kappa_{Baseline}$).

Section 15.1.1 Laboratory Assessments of this SAP details the identification of involved and uninvolved SFLC assays.

Post-baseline is defined as any assessment (scheduled or unscheduled) obtained after the first dose of study drug (overall reference start date). For SFLC assay differences, post-baseline is defined as the difference in the involved SFLC assay and the uninvolved SFLC assay where both SFLC assays are obtained from the same identified post-baseline SFLC assessment:

- Involved kappa: SFLC difference at post-baseline = ($Kappa_{Visit}$ - $Lambda_{Visit}$).
- Involved lambda: SFLC difference at post-baseline = ($Lambda_{Visit}$ - $Kappa_{Visit}$).

If one of the components required in the calculation is not available, no SFLC difference is to be presented.

6.5. Premature Discontinuation, End of Treatment (EOT) and End of Study (EOS)

At the time patients discontinue study drug, a visit is to be scheduled as soon as possible (within 30 days following study drug discontinuation or prior to initiation of subsequent treatment [whichever occurs first]). The EOT visit is to be followed by the post-study follow-up assessments.

At the time patients have completed the post-study follow-up assessments, End of Study (EOS) assessments are to be performed. However, EOS assessments are also to be performed when:

- A patient is not willing to participate in the post-study follow-up assessments.
- Death occurs during the treatment period or post-study follow-up period.

End of Treatment (EOT) and EOS assessments are collected as indicated on the eCRF. Derived EOT timepoints are to be presented in the relevant output for which data is presented by visit.

6.6. Retests and Unscheduled Visits

In general, for by-visit summaries, data recorded at nominal visits are to be presented. Unscheduled assessments are not to be included in by-visit summaries, but are to contribute to Baseline, abnormal results as per specified criteria or best/worst case results where required (e.g., shift [cross tabulation] tables and duration of laboratory assessments).

For any incidence summaries of laboratory grades, all visits are to be taken into account including unscheduled visits.

In the case of a retest (same sample collection date), the latest available result for that visit is to be used for by-visit summaries.

By-patient data listings are to include scheduled, unscheduled, and retest data (if applicable). Unscheduled assessments are also to be included in the by-patient figures.

6.7. WINDOWING CONVENTIONS

No visit windowing is to be performed for the study.

6.8. STATISTICAL OUTPUT CONVENTIONS

The default summary statistics for quantitative variables are listed below in the preferred order. If the original data has N decimal places, the default summary statistics are to be presented with the following decimal precision (using SAS® function ROUND as the very last step prior to presentation):

- Number (n) of patients in each category.
- Mean: N + 1.
- Standard deviation (SD): N + 2.
- Minimum: N.
- Median: N + 1.
- Maximum: N.
- Missing: 0.

The default summary statistics for qualitative variables are as follows:

- Number (n) of patients in each category.
- Percentage (%) of patients in each category presented to 1 decimal place (using SAS® function ROUND as the very last step prior to presentation) and calculated relative to either one of the following, unless otherwise specified:
  - Total number of patients in the relevant analysis set.
  - Total number of patients in the relevant analysis set with data available (observed cases).

The number (n) of patients with missing results for qualitative or quantitative variables is to be presented as part of a missing category or missing statistic, where applicable.

Confidence Intervals (CIs)

- Confidence intervals (CIs), 25th and 75th percentiles are to be presented to 1 decimal place.
- Presentation of CIs are to be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of CIs are to be separated by a hyphen, i.e., [xx.x-xx.x].

6.9. COMMON CALCULATIONS

For quantitative assessments, CFB is to be calculated as:

- CFB = (Test value at visit x – Baseline value).

Percentage CFB (% CFB) is to be calculated as:

- % CFB = (Test value at visit x – Baseline value)/Baseline value × 100.

6.10. SOFTWARE VERSION

All analyses are to be conducted using SAS® Version 9.2 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable.

7.2. MULTISITE STUDIES

The study is to be conducted by multiple investigators at multiple clinical sites internationally. The following countries are to host selected sites: USA (sites 501, 502 and 503), Denmark (site 601), Italy (site 801), Sweden (site 901), and the Netherlands (site 701). Summaries are to include combined data across all sites only. Individual site data are to be available in by-patient data listings.

7.3. MISSING DATA

Missing efficacy data are to be handled as described in Section 15.2.1 Missing Data Methods for Primary Efficacy Variables of this SAP. For the handling of partial dates for AEs, medications, prior therapies, and/or procedures refer to Appendix 2 Partial Date Conventions of this SAP.

7.4. MULTIPLE COMPARISONS/MULTIPLICITY

Not applicable.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses are to be conducted as part of the efficacy analysis. Assignment of patients to the subgroup stratification levels is to be included in Appendix 1: Assignment of Patients to Analysis Sets and Identification of Major Analysis Set Deviations (EXCEL spreadsheet), of the DR report and authorized. It is to be noted that the study was not designed to detect cohort differences within subgroup stratification levels. With reference to the latest authorized version of the DR plan [1] the following subgroups are defined:

7.5.1. AGE (YEARS)

Age (years) (calculated relative to Screening) is classified as:

- < 65.
- ≥ 65 to ≤ 75.
- > 75.

7.5.2. BASELINE INTERNATIONAL STAGING SYSTEM (ISS)

Baseline International Staging System (ISS) is classified as:

- Stage I: Baseline beta2-microglobulin < 3.5 mg/L and Baseline serum albumin ≥ 3.5 g/dL (i.e., ≥ 35 g/L).
- Stage II: Neither Stage I nor Stage III. Baseline beta2-microglobulin < 3.5 mg/L and Baseline serum albumin < 3.5 g/dL (i.e., < 35 g/L); or Baseline beta2-microglobulin ≥ 3.5 to < 5.5 mg/L irrespective of the Baseline serum albumin.
- Stage III: Baseline beta2-microglobulin ≥ 5.5 mg/L.
- Unknown: Not categorized as Stage I, II, or III.

7.5.3. PRIOR THERAPIES

Number of lines of prior therapy

The number of lines of prior therapy is classified as:

- < 2. No patients are expected in this subgroup stratification level based on Inclusion Criterion 04.
- ≥ 2 to ≤ 3.
- > 3 to ≤ 5.
- > 5.

Type of prior therapy

The type of prior therapy transplant is classified as follows:

- Autologous.
- Allogeneic.
- Autologous/Allogeneic.
- No transplant.

7.5.4. REFRACTORY STATUS

Refractory status (refer to Section 13.1 Prior Therapies of this SAP) to lines of prior therapy containing any of the below listed medications in a regimen is to be derived (a.) across all lines of prior therapy (refractory status to any line) as well as (b.) by last line of prior therapy (refractory status to last line) and classified as:

- Alkylator (Melphalan, cyclophosphamide, or bendamustine).
- Proteasome inhibitor (PI) (Bortezomib, carfilzomib, or ixazomib).
- Immunomodulatory drugs (IMiD) (Lenalidomide, thalidomide, or pomalidomide).
- Monoclonal antibody (Elotuzumab or daratumumab).
- Double refractory (PI and IMiD).

- Double refractory and alkylator (PI and IMiD and alkylator).
- Non-refractory (i.e., relapsed) to all of the above.

7.5.5. BASELINE DISEASE RISK STATUS

Baseline disease risk status is classified as:

- High: Patients with the presence of at least one of del(17p), or t(4;14), or t(14;16), or t(14;20) or gain(1q) determined by Baseline fluorescence in situ hybridization (FISH), or nonhyperdiploid Baseline karyotype (i.e., hypodiploid), or karyotype del(13).
- Standard: Patients with any other cytogenetic abnormality including t(11;14) or t(6;14) determined by Baseline FISH and the absence of the high-risk genetics determined by Baseline FISH.
- Missing: Patients for whom Baseline disease risk status cannot be categorized as high or standard due to missing, indeterminate or other Baseline FISH, karyotype, or ploidy specification.

8. OUTPUT PRESENTATIONS

Appendix 1 Specific Programming Conventions for Outputs of this SAP details the conventions for presentation of data. The latest SAP output shells provided with the SAP describe the presentations for the study and therefore the format and content of the summary tables, by-patient data listings and figures to be provided by CCI Biostatistics.

Unless otherwise specified, data are to be presented and summarized for the SAF Analysis Set. If the number (n) of patients in the SAF Analysis Set and mITT differ by more than 10% (i.e., 5 patients) summaries are to be repeated for the mITT (i.e., the 40 mg MTD Phase I patients as well as the Phase II patients) as specified in the SAP output shells.

Data that is recorded in free text fields are not to be modified by CCI Biostatistics and are to be presented by the text "Specification (eCRF)" as indicated by the investigator on the eCRF. Selected presentations of laboratory data are to contain an assessment identifier indicating the origin of the data (i.e., eCRF, local laboratory data, or central laboratory data).

Table 2: Dose Cohorts

Phase I: Dose Escalation Cohort	Phase II: Dose Cohort MTD
Dose Escalation Cohort 15 mg (N=xxx) | 25 mg (N=xxx) | 40 mg (N=xxx) | 55 mg (N=xxx)	Dose Cohort MTD Phase I + II (N=xxx) | Single-agent (N=xxx) | Total (N=xxx

MTD: Maximum tolerated dose. N = Total number of patients in the relevant analysis set. The Total column is to be derived as the sum of the combination regimen (Phase I + Phase II) and the single-agent dose cohorts.

9. DISPOSITION

With reference to Section 6 General Considerations and Section 7 Statistical Considerations of this SAP summaries are to be provided by the relevant analysis set, phase, and dose cohort (refer to Table 2: Dose Cohorts of this SAP) as specified in the latest SAP output shells. There are no statistical comparisons planned between the dose cohorts for the study.

9.1. END OF STUDY (EOS)

All patients who provided informed consent are to be accounted for in the study. Data as indicated on the End of Study eCRF is to be presented in a by-patient data listing for the All Patients Screened Analysis Set. Accounting for the key study milestones the following are to be presented:

- Date of informed consent relative to overall reference start date.
- Date of Screening relative to overall reference start date.
- Date of first dose (overall reference start date) and last dose (overall reference stop date) of study drug.
- Study completion/discontinuation and the relevant primary reason for study discontinuation.

Data are to be summarized for:

- Patients who completed the study.
- The primary reasons for study discontinuation in the specified order:
  - Withdrawal of informed consent.
  - Lost to follow-up.
  - Death.
  - Investigator discretion.
  - Termination of the study by the sponsor.
  - Other/Specification (eCRF).

A patient's study participation status (study completion/study discontinuation) is to be based on the End of Study eCRF as indicated by the investigator. Patients who have completed the 2-year post-study follow-up period are considered to have completed the study.

9.2. END OF TREATMENT (EOT)

Data as indicated on the End of Treatment eCRF is to be presented.

- The total number of cycles completed (to be listed as indicated on the eCRF and to be summarized based on the derived sum [refer to Section 6.3.1 Derivations of this SAP]).
- The date of last dose of study drug (melflufen and dexamethasone) (to be presented as indicated on the eCRF).

- The best overall disease response on treatment (to be presented as indicated on the eCRF).
- Study drug discontinuation and the relevant primary reason for discontinuation.
- Post-study follow-up participation/Specification (eCRF).

With reference to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP disease response assessments are based on the investigator's by-cycle assessments as indicated on the Disease Response Assessment eCRF. The best overall disease response on treatment is based on the investigator's assessment as indicated on the End of Treatment eCRF and is to be used in the primary endpoint analysis (refer to Section 15.2.2 Analysis of Primary Efficacy Variables of this SAP).

Data are to be summarized for:

- Patients who discontinued study drug including primary reasons for discontinuation of study drug in the specified order:
  - Disease progression.
  - Adverse events (AEs).
    - As per ICH E3 Structure and Content of Clinical Study Reports and the eCRF design AE data as indicated on the Adverse Events/Serious Adverse Events eCRF is not to be detailed in the presentation of disposition output.
  - Requiring other anti-neoplastic therapies.
  - Protocol deviation.
  - Withdrawal of informed consent.
  - Lost to follow-up.
  - Death.
  - Pregnancy.
  - Investigator discretion.
  - Termination of the study by the sponsor.
  - Other/Specification (eCRF).
- Patients who participated in the post-study follow-up period (as indicated on the End of Treatment eCRF).

9.3. ANALYSIS SETS

Major analysis set deviations are defined as any factor affecting the efficacy outcome or the treatment of the patient and are to be identified and authorized by Oncopeptides AB at the final DR meeting. Data are to be summarized for the All Patients Screened Analysis Set:

- Number (n) and percentage (%) of patients included or excluded from the hierarchical analysis sets and the reason(s) for exclusion. (Appendix 1: Assignment of Patients to Analysis Sets and Identification of Major Analysis Set Deviations [EXCEL spreadsheet], of the DR report). The authorized EXCEL spreadsheet is to be imported into SAS® for use in the analysis datasets and presentation in the output.

Inclusion/exclusion criteria exceptions are defined as criteria with a response of "missing" or "no" to

any inclusion criteria or a response of "missing" or "yes" to any exclusion criteria. The exceptions are to be based on the protocol amendment in effect at the time of informed consent provided.

Major protocol deviations [as obtained from the Clinical Trials Management System (CTMS) report], major analysis set deviations, analysis set assignment, and inclusion/exclusion criteria exceptions are to be presented in by-patient data listings for the All Patients Screened Analysis Set.

Screen failures as indicated on the Screen Failure eCRF are to be included in the relevant dose cohorts as enrolled and indicated on the Demography eCRF. CCI

9.4. VISIT DATES

With reference to the presentation of visits as tabulated in Appendix 1 Specific Programming Conventions for Outputs the following variables are to be presented:

- Visits (including date of visit).
- Cycle day.
- Planned visit window.
- Actual cycle length (days).
- Patient status of continuing to a subsequent cycle.
- Total number of cycles completed (derived) (refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP).

For this presentation the cycle day is to be calculated relative to the reference start date of Cycle x per individual cycle. Visits outside the planned protocol visit window (± 3 days) are to be flagged. Disease response assessments for patients who discontinue study drug for reasons other than disease progression are to be flagged. These patients are to have monthly disease response assessments until disease progression or initiation of subsequent treatment. The initiation of subsequent treatment is to be flagged in the by-patient data listing to facilitate identification.

Following disease progression or initiation of subsequent treatment, post-study follow-up visits are to occur every 3 months for up to 2 years after the derived EOT.

Details of actual cycle length are presented in Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP. Patient status of continuing to a subsequent cycle is to be presented as indicated on the Study Status and Study Continuation eCRFs.

10. DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics as indicated on the Demography eCRF are to be presented.

Data are to be summarized for:

- Age (years): Calculated relative to Screening (refer to Section 7.5 Examination of Subgroups of this SAP).
- Age (years) category:
  - < 65.
  - ≥ 65 to ≤ 75.
  - > 75.
- Gender (including childbearing potential for female patients). Percentage (%) of childbearing potential status is to be calculated relative to the total number of female patients with data.
- Race.
  - American Indian or Alaska Native.
  - Black or African American.
  - Asian.
  - Caucasian/White.
  - Native Hawaiian or other Pacific Islander.
  - Other/Specification (eCRF).
- Ethnicity.
  - Hispanic or Latino.
  - Not Hispanic or Latino.
  - Not collected as per local laws.

The following are also to be presented in the by-patient data listing:

- Date of birth.
- Protocol version signed.

11. MEDICAL AND/OR SURGICAL HISTORY

Medical and/or surgical history conditions are defined as any prior significant conditions as indicated on the Medical and Surgical History eCRF.

Patients (n and %) with medical and/or surgical history conditions are to be summarized by System Organ Class (SOC), and Preferred Term (PT). If a medical and/or surgical history condition occurs more than once for a patient per level of summarization the patient is only counted once per Medical Dictionary for Regulatory Activities (MedDRA) SOC or PT. System Organ Classes (SOCs) are to be sorted by total decreasing frequency. Preferred Terms (PTs) are to be sorted by total decreasing frequency within each SOC. If SOCs or PTs have the same total frequency they are to be sorted alphabetically.

Partial dates are not to be imputed and as such study day is to be presented as missing. Uncoded medical and/or surgical history conditions (i.e., conditions with no dictionary coding information available) are only to be presented if applicable using the investigator's Verbatim Term (eCRF) presented as PT within the text "UNCODED" as SOC.

Medical and/or surgical history conditions are coded using MedDRA Version 20.0.

12. DISEASE CHARACTERISTICS OF MULTIPLE MYELOMA

12.1. DISEASE CHARACTERISTICS SINCE/AT INITIAL DIAGNOSIS

Disease characteristics at initial diagnosis as indicated on the History of Multiple Myeloma eCRF are to be summarized for:

- Time since initial diagnosis (years): Calculated relative to overall reference start date.
- Age at initial diagnosis (years): Calculated relative to date of initial diagnosis.
- Stage at initial diagnosis.
  - Durie-Salmon.
    - IA; IB.
    - IIA; IIB.
    - IIIA; IIIB.
    - Unknown.
  - International Staging System (ISS).
    - I.
    - II.
    - III.
    - Unknown.
- Disease type at initial diagnosis.
  - Immunoglobulin (Ig) (A, D, E, G, M).
  - Other/Specification (eCRF).
- Light chain type at initial diagnosis.
  - Kappa.
  - Lambda.
  - Unknown.
- Evidence of lytic bone disease at initial diagnosis.
  - Yes.
  - No.
  - Unknown.
- Evidence of extramedullary disease at initial diagnosis.
  - Yes.
  - No.
  - Unknown.
- Conventional karyotype at initial diagnosis.

- Not detected.
- Unknown.
- Not done.
- Abnormal karyotype/Specification (eCRF).

- Fluorescence in situ hybridization (FISH) at initial diagnosis.
  - Unknown.
  - Not done.
  - Del17p13.
  - T(4;14)(p16.3;q32.3).
  - T(14;16)(q32.3;q23).
  - +1q21;Amp1q21.
  - Del(13);13q14.3.
  - Other/Specification (eCRF).

- Ploidy at initial diagnosis.
  - Unknown.
  - Not done.
  - Hyperdiploid.
  - Hypodiploid.

Multiple categories for disease type, light chain type and FISH results may be selected resulting in percentages not necessarily adding up to 100%.

12.1.1. DERIVATIONS

Time since initial diagnosis (years): Calculated relative to overall reference start date using the following SAS® code:

- Time since initial diagnosis (years) = int((intck("month", <date of initial diagnosis>, <date of first dose of study drug>) - (day(<date of first dose of study drug>) < day(<date of initial diagnosis>)))/12).

Age (years): Calculated relative to date of initial diagnosis using the following SAS® code:

- Age (years) = int((intck("month", <date of birth>, <date of initial diagnosis>) - (day(<date of initial diagnosis>) < day(<date of birth>)))/12).

For the handling of partial initial diagnosis dates refer to Appendix 2 Partial Date Conventions of this SAP.

12.2. DISEASE CHARACTERISTICS AT BASELINE

Both local and central laboratory results are to be obtained regarding the evaluation of multiple myeloma. Refer to Section 15.1.3.1 Central/Local Laboratory Data of this SAP for the handling of local/central laboratory assessments in view of Baseline derivations.

Disease characteristics at Baseline are only to be presented for the SAF Analysis Set. Unless the relevant eCRF is specified as assessment identifier, results are to be obtained from central laboratory when available and local laboratory otherwise. Disease characteristics at Baseline (refer to Section 6.4 Baseline of this SAP) are to be summarized for:

- Baseline ISS category (refer to Section 7.5.2 Baseline International Staging System (ISS) of this SAP).
  - I.
  - II.
  - III.
  - Unknown.
- Current disease status category (as indicated by the investigator on the History of Multiple Myeloma eCRF).
  - Relapsed.
  - Relapsed/Refractory.
  - Primary refractory.
  - Unknown.
- Eastern Cooperative Oncology Group (ECOG) (as indicated by the investigator on the ECOG Performance Status eCRF).
  - Performance status:
    - Grade 0: Normal activity, fully active, able to carry on all pre-disease performance without restriction.
    - Grade 1: Symptoms, but fully ambulatory, restricted in physically strenuous but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
    - Grade 2: Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
    - Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
    - Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
    - Grade 5: Dead.
- Serum chemistry (as indicated on the Local Laboratory/Serum Chemistry eCRF, but converted to international system of units [SI], where required).
  - Creatinine (µmol/L).
  - Creatinine clearance (mL/min) (eCRF).
  - Corrected calcium (mmol/L) (derived) (refer to Section 12.2.1 Derivations of this SAP).
  - Albumin (g/L).
- Special chemistry.
  - Serum beta2-microglobullin (mg/L).
- Serum electrophoresis.

- Monoclonal protein (M-protein) abs (g/L). Multiple assessments are to be presented in the by-patient data listing, if applicable.
  - The sum of the measurable results is to be used as analyzable result when multiple assessments of the same test are available at the same visit. Refer to Appendix 4 Specific Myeloma Central Laboratory Evaluations of this SAP for mapping of laboratory panels to the correct laboratory system/variable for the analysis.

- Urine electrophoresis.
  - Monoclonal protein (M-protein) (mg/24h). Multiple assessments are to be presented in the by-patient data listing, if applicable.
    - The sum of the measurable results is to be handled in the same manner as described for serum electrophoresis.

- Serum immunology.
  - Immunoglobulin (Ig) (A, D, E, G, M).

- Serum chemistry.
  - Protein total (g/L).
  - Serum free light chain (SFLC) assay kappa (mg/L).
  - Serum free light chain (SFLC) assay lambda (mg/L).
    - The involved SFLC assay (refer to Section 15.1.1 Laboratory Assessments of this SAP) is to be flagged in the by-patient data listing to enable the correct subtraction of kappa and lambda results to calculate the CFB and % CFB.
  - Serum free light chain (SFLC) kappa/lambda ratio.
    - Normal.
    - Abnormal.

- Urine chemistry.
  - Protein urine (mg/24h).

- Serum interpretation (as per central laboratory data).
  - Monoclonal Ig (A, D, E, G, M) kappa or lambda.

- Urine interpretation (as per central laboratory data).
  - Free light chain kappa or lambda.

- Bone marrow aspirate.
  - Plasma cells (%).

12.2.1. DERIVATIONS

Corrected calcium (mmol/L) calculated using the following formula [5] [7]:

- Corrected calcium (mmol/L) = Serum calcium (mmol/L) + 0.02 × [40 (g/L) - serum albumin (g/L)].

Refer to Section 6.4 Baseline of this SAP for the Baseline and post-baseline definitions for SFLC assays.

12.3. BONE MARROW ASPIRATION AT BASELINE

Bone marrow aspiration at Baseline as indicated on the Local Lab/Bone Marrow Aspiration eCRF is to be presented. Bone marrow aspiration at Baseline is to be summarized for:

- Cytogenetics.
  - Indeterminate/Inadequate specimen.
  - None detected.
  - Abnormal karyotype.
- Fluorescence in situ hybridization (FISH).
  - Indeterminate/Inadequate specimen.
  - Del17p13.
  - T(4;14)(p16.3;q32.3).
  - T(14;16)(q32.3;q23).
  - +1q21;Amp1q21.
  - Del(13);13q14.3.
  - Other/Specification (eCRF).
- Baseline disease risk status category (derived) (refer to Section 7.5.5 Baseline Disease Risk Status of this SAP).
  - High.
  - Standard.
  - Missing.
- Ploidy.
  - Indeterminate.
  - Hyperdiploid.
  - Hypodiploid.

13. THERAPIES, MEDICATIONS AND/OR PROCEDURES

13.1. PRIOR THERAPIES

Based on protocol Version 6.0, including protocol amendments 01 to 05 [2] a line of prior therapy consists of at least one or more cycles of a planned treatment regimen (including single-agent or combination therapy or a sequence of treatments administered in a planned manner). A new line of prior therapy starts when a planned course is modified as a result of disease progression, relapse or toxicity or when a planned period of observation is interrupted by the need for additional treatment of the disease. As per the eCRF design, radiation therapy forms part of the options for a line of prior therapy, although as advised by Oncopeptides AB, radiation therapy is not to be considered as a line of prior therapy.

According to the IMWG Consensus panel 1 on uniform reporting criteria in clinical studies [4] the following definitions are relevant to the classification per medication within each line of prior therapy:

- Relapsed status: Defined as a patient with a disease response of MR or better to the medication within each line of prior therapy and who progressed later than 60 days after the last dose of the stop date of the individual medication.
- Refractory status: Defined as a patient who has never achieved a disease response of MR or better the medication within each line of prior therapy.
- Relapsed/Refractory status: Defined as a patient with a disease response of MR or better the medication within each line of prior therapy and who progressed while on prior therapy or within 60 days of the last dose of the stop date of the individual medication.

In addition to the classification per medication within each line of prior therapy, a patient can also have an overall status of relapsed, relapsed/refractory or primary refractory. The following definitions to derive the overall status to the classification of prior therapy are:

- Overall relapsed status: Defined as a patient who never progressed while on prior therapy or within 60 days of last dose of prior therapy.
- Overall primary refractory status: Defined as a patient who never responded to any line of prior therapy.
- Overall relapsed/refractory status: Defined as a patient who might be refractory to one specific line of prior therapy, but responded to other lines of prior therapy.

The subcategories relapsed, refractory, or relapsed/refractory status to any line of prior therapy, to last line of prior therapy as well as overall status are to be derived per individual medication in regimen. Prior therapy derivations (Appendix 2: Assignment of Patients to Disease Status [Relapsed/Refractory] to Prior Therapy [EXCEL spreadsheet], of the DR report), are to be authorized by Oncopeptides AB at the final DR meeting. The overall status as indicated by the investigator on the History of Multiple Myeloma eCRF is to be compared with the derived overall status (derived by

CCI Biostatistics) to ensure results are comparable, but the derived results are to be summarized.

Prior therapies as indicated on the Prior Therapy eCRF are to be summarized as follows:

- Number of lines of prior therapy (including a summary of number of lines of prior therapy category).
  - Total number of lines of prior therapy that a patient received based on the maximum result of the raw.PT.PTPRG variable.
- Type of prior therapy (transplant category) (refer to Section 7.5.3 Prior Therapies of this SAP).
- Best disease response to last line of prior therapy (as indicated by the investigator on the Prior Therapy eCRF).
- Status of (a.) any line of prior therapy and (b.) last line of prior therapy, regardless of regimen.
- Patients with (a.) any line of prior therapy and (b.) last line of prior therapy including regimen containing:
  - Alkylator (Melphalan, cyclophosphamide, bendamustine).
  - Proteasome inhibitor (PI) (Bortezomib, carfilzomib or ixazomib).
  - Immunomodulatory drug (IMiD) (Lenalidomide, thalidomide, or pomalidomide).
  - Monoclonal antibody (Elotuzumab, or daratumumab).
  - Double refractory, defined as PI and IMiD.
  - Double refractory and alkylator, defined as PI and IMiD and alkylator.

The number (n) of patients with (a.) any line of prior therapy including regimen containing at least one of the specified medications of interest is to be used as denominator for the calculation of relapsed, refractory, and relapsed/refractory status to any line of prior therapy across stratification levels. Similarly, the number (n) of patients with (b.) the last line of prior therapy including regimen containing at least one of the specified medications of interest is to be used as denominator for the calculation of relapsed, refractory, and relapsed/refractory status to last line of prior therapy across stratification levels.

- The derived subcategories are to be repeated for:
  - Relapsed, refractory, or relapsed/refractory status to any line of prior therapy to regimen containing an alkylator, PI, IMiD, monoclonal antibody, PI and IMiD, PI and IMiD and alkylator.
  - Relapsed, refractory, or relapsed/refractory status to last line of prior therapy to regimen containing an alkylator, PI, IMiD, monoclonal antibody, PI and IMiD, PI and IMiD and alkylator.

Medications of interest are to be selected based on code. Prior therapies are to be coded using the World Health Organization-Drug Dictionary (WHO-DD)01MAR2017. Refer to Appendix 2 Partial Date Conventions of this SAP for the handling of partial dates for prior therapies. Instead of handling missing disease progression dates as a worst-case scenario through imputation, the prior therapy stop date of the line of prior therapy containing a missing disease progression date is to be compared to the subsequent line of prior therapy's start date, to determine if the subsequent line's start date is within 60 days of the line containing the missing disease progression date.

Radiation therapy as indicated on the Prior Radiation Therapy eCRF is to be presented in a by-patient data listing. Radiation therapy is not considered a line of prior therapy and is not to be included in the prior therapy summaries. Any line of prior therapy containing radiation therapy mentions amongst other individual medications in a regimen is to be modified by CCI Biostatistics by omitting the radiation therapy from the line of prior therapy. These lines of prior therapy are not to form part of the number of lines of prior therapy.

13.2. MEDICATIONS/CONCOMITANT PROCEDURES

Medications as indicated on the Concomitant Medications eCRF are to be coded using the WHO-DD01MAR2017. However, the Anatomical Therapeutic Chemical (ATC) classification system is not included in the scope of coding. Concomitant procedures as indicated on the Concomitant Procedures eCRF are not to be coded.

Refer to Appendix 2 Partial Date Conventions of this SAP, for the handling of partial dates for medications and/or concomitant procedures. Medications and concomitant procedures are to be classified by cycle occurrence based on the start date of the medication or concomitant procedure (refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP).

13.2.1. MEDICATIONS

Medications are to be presented as:

- Prior medications (PM): Defined as medications which started and stopped prior to the first dose of the study drug (overall reference start date).
- Concomitant medications (CM): Defined as medications which are taken on or after the first dose of the study drug (overall reference start date) up to and including derived EOT or which are ongoing.
- Follow-up medications (FM): Defined as medications which are taken after derived EOT or which are ongoing.

Concomitant medications and follow-up medications are not mutually exclusive and a medication can therefore be classified as both CM/FM.

13.2.1.1. HEMATOPOIETIC GROWTH FACTORS AND STANDARDIZED TRANSFUSIONS

Hematopoietic growth factors as indicated on the Concomitant Medications eCRF and standardized transfusions as indicated on the Concomitant Procedures eCRF are to be identified and classified by the CCI medical advisor and authorized by Oncopeptides AB at the final DR meeting.

Patients who have received hematopoietic growth factors and/or standardized transfusions during the course of the study are to be summarized and the output is to be repeated for the following by-group variable:

- Overall.

- Melflufen dose reduced.
  - For this by-group variable, the total number of patients in the relevant analysis set (N) presents a subset of the number of patients in the Safety Analysis Set, i.e., the number (n) of patients with at least one melflufen dose reduction in at least one or more cycles.

The number (n) of patients treated in each cycle or overall is to be used as denominator for the percentage (%) calculation of patients who received hematopoietic growth factors and/or standardized transfusions during the course of the study.

13.2.2. Concomitant Procedures

Standardized transfusions are to be identified as noted in Section 13.2.1.1 Hematopoietic Growth Factors and Standardized Transfusions of this SAP.

The time (days) from a platelet transfusion to the subsequent melflufen dose is to be derived (refer to Section 13.2.3 Derivations of this SAP). In addition, the number of cycles in which platelet transfusions were administered within 1 week of subsequent melflufen dose (refer to Section 13.2.3 Derivations of this SAP) is to be classified as follows:

- < 2 cycles.
- ≥ 2 to ≤ 3 cycles.
- ≥ 4 cycles.
  - The number (n) of patients who received at least one platelet transfusion within 1 week of subsequent melflufen dose is to be used as denominator for the aforementioned category percentage (%) calculation.

13.2.3. Derivations

Time to subsequent melflufen dose (days) is to be derived using the following formula:

- Time to subsequent melflufen dose (days) = abs(<Date of platelet transfusion> - <date of subsequent melflufen dose>).
- Number of cycles in which platelet transfusions were administered within 1 week of subsequent melflufen dose

$$= \sum_{x=1}^{n} (\text{Time to subsequent melflufen dose [days]}) \leq 7.$$

Where n represents a patient's last cycle (i.e., in this case the last Day 1 melflufen dose).

14. STUDY DRUG ADMINISTRATION

Patients are to be treated with melflufen on Day 1 of each cycle. Patients following a 21-day cycle are to be treated with a maximum of 40 mg dexamethasone on Days 1, 8, 15. Similarly, patients following a 28-day cycle are to be treated with a maximum of 40 mg dexamethasone on Days 1, 8, 15, 22 and single-agent patients are to be treated with a maximum of 24 mg dexamethasone on Days 1, 2 (Days 3, 4 are optional for dexamethasone treatment) for anti-emetic purposes as per protocol amendment 04. Single-agent patients switching from protocol amendment 04 (as initially enrolled) to protocol amendment 05 may receive the combination regimen of melflufen and 40 mg dexamethasone.

Percentage (%) of patients with action(s) taken with melflufen/dexamethasone and patients with reason(s) for modification of melflufen/dexamethasone is to be calculated relative to the total number of patients treated in an individual cycle or overall. Multiple categories for action taken and reason(s) for modification are allowed resulting in percentages not necessarily adding up to 100%.

14.1. MELFLUFEN ADMINISTRATION

Study drug administration data as indicated on the Melflufen Administration eCRF are to be presented.

The following variables are to be presented in a by-patient data listing:

- Visit (containing cycles).
- Actual cycle length (days) (refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP).
- Date of study drug administration.
- Infusion data.
  - Type of device used.
    - Implanted port.
    - Peripherally inserted central catheter (PICC) line.
    - Central venous catheter.
  - Planned and actual dose per individual cycle.
  - Infusion preparation start time.
  - Infusion start time, stop time and duration, and volume infused.
- New cycle initiation criteria (refer to Section 3.1 General Description of this SAP) including action taken with study drug and reason(s) for dose modification.
- Relative dose data.
- Administration of anti-emetics.

The planned melflufen dose per individual cycle for patients enrolled in Phase I comprises 15 mg,

25 mg, 40 mg, or 55 mg and for patients enrolled in Phase II the planned melflufen dose per individual cycle comprises 40 mg. The actual dose per individual cycle is to be obtained as indicated on the Melflufen Administration eCRF, and is to be used in conjunction with the number of vials used for study drug administration. Vials to be used for melflufen preparation include:

- 15 mg Melflufen: (1 × 15 mg vial) or (1 × 20 mg vial).
- 25 mg Melflufen: (1 × 25 mg vial) or (2 × 20 mg vials).
- 40 mg Melflufen: (1 × 15 mg vial + 1 × 25 mg vial) or (2 × 20 mg vials).
- 55 mg Melflufen: 2 × 15 mg vials + 1 × 25 mg vial.

The 30-minute melflufen IV infusions are to be administered within 30 minutes from the start of the infusion preparation.

Relative dose data are to include planned cumulative dose (mg), actual cumulative dose (mg), percentage (%) relative dose and relative dose category:

- ≤ 50%.
- > 50% to ≤ 80%.
- > 80% to ≤ 100%.
- > 100%.

Planned cumulative dose (mg) is defined as the planned dose per individual cycle multiplied by the total number of melflufen IV infusions received. Actual cumulative dose (mg) is defined as the sum of the actual study drug doses across all cycles. Refer to Section 14.1.1 Derivations of this SAP.

Data to be summarized include:

- (*)Total number of cycles completed (based on the actual administration data as indicated on the Melflufen Administration eCRF). Refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP.
- (*)Total number of cycles with at least one melflufen dose reduction. This is defined as the sum of all cycles during which any patient experienced at least one melflufen dose reduction. Dose reduction is based on the action taken with melflufen.
- (*)Total number of cycles with at least one melflufen dose interruption. This is defined as the sum of all cycles during which any patient experienced at least one melflufen dose interruption. Dose interruption is based on the action taken with melflufen.
- (*)Number (n) of patients treated at least once.
- Number (n) of patients treated in cycle.
- Patients with action(s) taken with melflufen.
  - Interrupted.
  - Reduced.

- Delayed.
- Held.
- Other.
- Permanently discontinued.

- Reason(s) for modification of melflufen.
  - Adverse event (AE).
  - Other. As indicated by the investigator on the Melflufen Administration eCRF.
- (*)Actual cumulative dose (mg).
- (*)Relative dose (%).
- (*)Relative dose (%) category.
- Actual cycle length (days). Refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP.

Variables are to be summarized for each individual cycle, but variables marked with an asterisk (*) are to be summarized across all cycles only (i.e., Visit = "OVERALL").

14.1.1. Derivations

- Melflufen IV infusion duration (min) = <Infusion stop time> - <infusion start time>.
- Time from melflufen preparation to infusion (min) = <Infusion start time> - <preparation start time>.
  - The result is to be presented as a binary Yes/No response to the required 30 minutes allowed from infusion preparation to administration.
- Planned cumulative dose (mg) = (Planned dose × total number of melflufen IV infusions).
- Actual cumulative dose (mg) $= \sum_{x=1}^{n} \text{Cycle x Day 1 melflufen dose.}$
-

Where n represents a patient's last cycle (i.e., in this case the last Day 1 melflufen dose).

- Relative dose (%) = (Actual cumulative dose/planned cumulative dose) × 100.

14.2. Dexamethasone Administration

Study drug data as indicated on the Dexamethasone Administration and Dexamethasone Administration for Day 1 to Day 4 eCRFs are to be presented.

The following variables are to be presented in a by-patient data listing:

- Visit (containing cycles and cycle days).
- Actual cycle length (days) (refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle

Completion of this SAP).

- Date of study drug administration.
- Study drug route.
- Action taken with study drug and reason(s) for dose modification.
- Continuation to the subsequent cycle (as indicated on the Study Status and Study Continuation eCRFs).
- Total number of cycles completed (derived sum).
- Actual cumulative dose (mg) per individual cycle and overall

Actual cumulative dose (mg) per individual cycle is defined as the sum of the actual study drug doses per individual cycle. Overall actual cumulative dose (mg) is defined as the sum of the actual study drug doses across all cycles. Refer to Section 14.2.1 Derivations of this SAP.

Data to be summarized include:

- (*)Total number of cycles completed (based on the actual administration data as indicated on the Melflufen Administration eCRF). Refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP.
- (*)Total number of cycles with at least one dexamethasone dose reduction. This is defined as the sum of all cycles during which any patient experienced at least one dexamethasone dose reduction. Dose reduction is based on the action taken with dexamethasone.
- (*)Total number of cycles with at least one dexamethasone dose held. . This is defined as the sum of all cycles during which any patient experienced at least one dexamethasone dose held. Dose held is based on the action taken with dexamethasone.
- (*)Number (n) of patients treated at least once.
- Number (n) of patients treated in cycle.
- Patients with action(s) taken with dexamethasone.
  - Reduced.
  - Delayed.
  - Held.
  - Permanently discontinued.
- Reason(s) for modification of dexamethasone.
  - Adverse event (AE).
  - Other. As indicated by the investigator on the Dexamethasone Administration and Dexamethasone Administration for Day 1 to Day 4 eCRFs.
- Actual cumulative dose (mg). Includes summary across all cycles.

Variables are to be summarized for each individual cycle, but variables marked with an asterisk (*) are

to be summarized across all cycles only (i.e., Visit = “OVERALL”).

14.2.1. DERIVATIONS

- Actual cumulative dose per individual cycle (mg) $= \sum_{y=1}^{n} \text{Cycle x Day y dexamethasone dose.}$
-

Where x represents an individual cycle and n represents Day 1, 8, and 15 for patients following a 21-day cycle and Day 1, 8, 15, and 22 for patients following a 28-day cycle.

- Overall actual cumulative dose (mg) $= \sum_{x=1}^{n} \sum_{y=1}^{m} \text{Cycle x Day y dexamethasone dose.}$

Where n represents a patient’s last cycle and m represents Day 1, 8, and 15 for patients following a 21-day cycle and Day 1, 8, 15, and 22 for patients following a 28-day cycle.

15. EFFICACY OUTCOMES

The EEmITT Analysis Set is regarded as primary for disease response efficacy endpoints including disease response rates, time to disease response and duration of disease response analyses as well as disease progression. The mITT Analysis Set is regarded as primary for PFS, OS and time to first subsequent treatment analyses. Unless otherwise specified, all efficacy outputs are to be summarized for each of the subgroups as defined in Section 7.5 Examination of Subgroups of this SAP and all figures are to be presented for the EEmITT Analysis Set. The following list provides a comprehensive overview of the primary and secondary endpoints of the study:

The primary endpoints of the study are to evaluate the following in all evaluable patients:

- Best overall disease response on treatment defined as the best overall disease response on treatment including progressive disease (PD), stable disease (SD), MR, PR, very good partial response (VGPR), complete response (CR), or stringent complete response (sCR).
- Objective response (OR) defined as the first occurrence of disease response including PR or better (i.e., PR, VGPR, CR, or sCR).
- Clinical benefit response (CBR) defined as the first occurrence of disease response including MR or better (i.e., MR, PR, VGPR, CR, or sCR).
- Objective response rate (ORR).
- Clinical benefit response rate (CBRR).

The secondary endpoints of the study are to evaluate the following in all evaluable patients:

- Duration of best overall disease response to treatment (months).
  - Per disease response hierarchy (including SD or better).
  - Duration of OR.
  - Duration of CBR.
- Time to disease response on treatment (months).
  - Time to first OR.
  - Time to first CBR.
  - Time to best overall disease response on treatment (only included in a figure and a by-patient data listing).
- Time to disease progression (months).
- Progression-free survival (PFS) (months).
  - Overall.
  - Per disease response hierarchy.
- Overall survival (OS) (months).
- Time to first subsequent treatment (months).

15.1. MULTIPLE MYELOMA

15.1.1. LABORATORY ASSESSMENTS

Appendix 4 Specific Myeloma Central Laboratory Evaluations of this SAP provides the complete list of laboratory assessments obtained from the local and central laboratories. Quantitative safety laboratory assessments are to be compared with the relevant laboratory reference ranges in SI units and are to be classified as:

- Low (L): Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High (H): Above the upper limit of the laboratory reference range.

The kappa/lambda ratio is to be classified as normal or abnormal based on the laboratory specific reference range.

Patients with a kappa/lambda SFLC ratio below the lower reference range are defined as having monoclonal lambda SFLC and patients with a kappa/lambda SFLC ratio above the upper reference range are defined as having a monoclonal kappa SFLC. If the SFLC ratio is above the upper reference range, kappa is considered to be the "involved" SFLC and lambda the "uninvolved" SFLC, and vice versa if the ratio is below the lower reference range. Involved SFLC assay results are to be flagged in the by-patient data listing to enable the correct subtraction of kappa and lambda results to calculate the CFB. Refer to Section 6.4 Baseline of this SAP for the Baseline and post-baseline definitions for SFLC assays.

The following figures are to be presented:

- The best serum or 24-hour urine M-protein or SFLC % CFB. The waterfall plot is to present the best % CFB for each patient, sorted by descending % CFB.
- Serum and urine M-protein and involved SFLC results are to be presented over time for individual patients. For the by-patient figure, the involved SFLC (kappa or lambda [mg/L]) results are to be converted to g/L to plot the involved SFLC assay together with the serum M-protein results on the same axis. The kappa/lambda ratio is not to be included in the figure presentation.

15.1.2. RESPONSE ASSESSMENT

The investigator is to assess disease response at every cycle starting on completion of Cycle 2 in accordance with the IMWG response criteria (refer to Appendix 6 Disease Response Criteria of this SAP). An assessment of a patient's disease response to study drug is based on the multiple myeloma laboratory assessments together with the investigator's clinical expertise and the confirmation of two consecutive disease response assessments can therefore not be performed on a data analysis level.

CCI Biostatistics is to derive a by-cycle disease response assessment based on the laboratory data to evaluate derived outcome in comparison to the investigator's by-cycle disease response

assessments as indicated on the Disease Response Assessment eCRF. In addition, CCI Biostatistics is to derive a best overall disease response on treatment based on derived by-cycle disease response assessments to evaluate derived outcome in comparison to the investigator's assessment as indicated on the EOT eCRF. However, despite any potential differences, analysis of disease response assessments is to be based on the investigator's by-cycle assessments or EOT assessment, as specified. The disease response hierarchy from best to worst includes sCR, CR, VGPR, PR, MR, SD, and PD.

15.1.3. Data Conventions

15.1.3.1. Central/Local Laboratory Data

For the current study laboratory results related to disease response evaluations of multiple myeloma are obtained from both local and central laboratories. From a scientific standpoint it is preferable to have only one source of laboratory assessments. The database is to contain both sets of results such that local and central laboratory assessments are to be used interchangeably for analysis purposes [6]. However, preference is to be given to central laboratory assessments when available, otherwise local laboratory assessments are to be used. In the by-patient data listings the assessment identifier of the data (i.e., eCRF, central laboratory data or local laboratory data) is to be presented.

15.1.3.2. Analyzable Result

Based on the current data, entries exist such that some patients have multiple results for M-protein assessments at one or more visit(s). The sum of the measurable results is to be used as analyzable result when multiple assessments of the same test are available at the same visit.

15.1.3.1. Evaluable Disease Response Assessment

Disease response assessments recorded prior to the initiation of subsequent treatment are to be defined as evaluable disease response assessments for efficacy outputs. This is to ensure exclusion of disease response assessments subject to subsequent treatment administration.

15.1.3.2. Best Serum or 24-hour Urine Monoclonal-Protein (M-Protein) or Serum Free Light Chain (SFLC) % Change from Baseline (CFB)

The best % CFB is defined as the CFB to the minimum (lowest) analyzable serum or 24-hour urine M-protein or SFLC result post-baseline up to and including derived EOT (LOCF assessment).

For patients with measurable serum M-protein at Baseline, it is the best % CFB based on analyzable post-baseline serum M-protein results up to and including derived EOT. For patients with non-measurable serum M-protein, but measurable 24-hour urine M-protein, it is the best % CFB based on analyzable post-baseline 24-hour urine M-protein results up to and including derived EOT. For patients with non-measurable serum M-protein and non-measurable 24-hour urine M-protein, it is the best % CFB based on analyzable post-baseline SFLC results up to and including derived EOT. The best SFLC % CFB is to be based on the minimum (lowest) involved kappa/lambda analyzable result

post-baseline, where both kappa and lambda are obtained from the same identified post-baseline SFLC assessment.

The CFB and % CFB are to be presented for all test results available per the analyzable flags in the listing and the best % CFB (CFB to minimum [lowest] analyzable result post-baseline based on serum or 24-hour urine M-protein or SFLC results up to and including derived EOT [LOCF assessment]) is to be flagged to facilitate identification of the same result in the corresponding figure.

Refer to Section 6.1 Reference Start Dates, Reference Stop Dates and Reference Days of this SAP for Baseline and post-baseline SFLC assessment.

15.2. PRIMARY EFFICACY

The primary objectives described in the SAP are more comprehensive than those described in protocol Version 6.0, including protocol amendments 01 to 05 [2] and in view of the protocol specified Phase II objectives, the following efficacy endpoints are:

- Best overall disease response on treatment defined as the best overall disease response on treatment including PD, SD, MR, PR, VGPR, CR, or sCR.
- Objective response (OR) defined as the first occurrence of disease response including PR or better (i.e., PR, VGPR, CR, or sCR).
- Clinical benefit response (CBR) defined as the first occurrence of disease response including MR or better (i.e., MR, PR, VGPR, CR, or sCR).
- Objective response rate (ORR).
- Clinical benefit response rate (CBRR).

The aforementioned is to be evaluated in the combination regimen and the single-agent dose cohorts. Following the approval of protocol Version 6.0, ongoing patients in the single-agent cohort may have weekly dexamethasone doses added at the discretion of the investigator. The addition of the weekly dexamethasone can influence the effect of study drug, but with the "Total" column in the SAP output shells, all cycles from the single-agent patients are to be included for analysis purposes.

15.2.1. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLES

Missing primary efficacy variables are not to be imputed. The EEmITT Analysis Set is to be used as primary for the efficacy endpoints. Per definition the EEmITT Analysis Set is not to include patients with no Baseline efficacy assessment (measurable disease assessment) and no post-baseline efficacy assessment (disease response assessment), following completion of at least two full cycles of study drug.

15.2.2. ANALYSIS OF PRIMARY EFFICACY VARIABLES

The best overall disease response on treatment based on the investigator's assessment as indicated on the End of Treatment eCRF is to be summarized per the individual disease responses within the

hierarchy as well as for the following disease response combinations:

- Stringent complete response (sCR) + CR.
- Stringent complete response (sCR) + CR + VGPR.
- Objective response rate (ORR): sCR + CR + VGPR + PR.
- Clinical benefit response rate (CBRR): sCR + CR + VGPR + PR + MR.

The primary objective of Phase II is to test the null hypothesis (H_0) that the ORR of melflufen and dexamethasone combination is below the specified response rate:

- H_0: ORR < 15%.

The alternative hypothesis (H_A) is that the ORR of melflufen and dexamethasone combination is equal to or greater than the specified response rate:

- H_A: ORR ≥ 15%.

The ORR is considered to be the more conservative endpoint when assessing ORR and CBR given that ORR is obtained based on the first occurrence of PR or better. The outcome of disease response assessments are related to the binomial distribution, because a patient either experiences a given response or not. The Clopper-Pearson method is to be used to calculate a 95% confidence interval (CI) for the binomial proportion. The following SAS® code is to be used:

```
proc freq data=dd;
        by treatment;
        tables response / nocum norow binomial alpha=0.05;
        exact binomial;
run;
```

Notes:

- The treatment variable refers to the relevant dose cohorts.
- The FREQUENCY procedure computes the CI for the lowest level of the response variable, unless specified otherwise.

An ORR ≥ 15% may indicate that melflufen in combination with dexamethasone is considered promising for the treatment of multiple myeloma. Similarly, an ORR ≥ 15% for melflufen as single-agent at the MTD may indicate that melflufen is considered to have single activity for the treatment of multiple myeloma.

The following figure is to be presented:

- Swimlane plot of disease response (PR or better) based on the investigator's by-cycle assessments as indicated on the Disease Response Assessment eCRF is to be presented in a swimmers plot.
- Swimlane plot of disease response (SD or MR) based on the investigator's by-cycle assessments as indicated on the Disease Response Assessment eCRF is to be presented in a swimmers plot.

In the disease response assessment by-patient data listing the following are to be presented:

- First dose of study drug (overall reference start date).
- Visit (containing cycles and cycle days).
- Date and method of the disease response assessment.
- Investigator's by-cycle disease response assessment.
- Best overall disease response assessment on treatment.
- First occurrence of an OR, CBR or PD.

15.2.3. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLES

The PP Analysis Set is characterized by specific criteria and it defines a subset of patients in the EEmITT Analysis Set who are more compliant with the protocol and who represent the scientific model. Within the context of the CSR transparency with regards to these factors is important and this aids in producing the relevant table summaries to address the ICH requirements. If the EEmITT Analysis Set and the PP Analysis Set therefore differ by more than 10% (i.e., 5 patients) then the output is to be repeated for the PP Analysis Set to confirm the results obtained from the EEmITT Analysis Set. This applies to all efficacy output with the exception of OS, time to first subsequent treatment, and shift presentations of X-ray and imaging assessments and plasmacytoma evaluations.

If the mITT Analysis Set and the EEmITT Analysis Set differ by more than 10% (i.e., 5 patients) then the PFS output is to be repeated for the EEmITT Analysis Set to confirm the results obtained from the mITT Analysis Set.

15.3. SECONDARY EFFICACY

The secondary objectives of the study are expanded to include:

- Duration of best overall disease response to treatment (months).
  - Per disease response hierarchy (including SD or better).
  - Duration of OR.
  - Duration of CBR.
- Time to disease response on treatment (months).
  - Time to first OR.
  - Time to first CBR.
- Time to disease progression (months).
- Progression-free survival (PFS) (months).
  - Overall.
  - Per disease response hierarchy.
- Overall survival (OS) (months).

- Time to first subsequent treatment.

15.3.1. Secondary Efficacy Variables and Derivations

Survival analysis (duration of time until the occurrence of a specified event) estimates the underlying distribution of the survival time variable and assesses the dependence of the survival time variable on the independent variables. Analysis of survival data must take censoring into account and correctly use both the censored observations and the uncensored observations. The overall reference start date is referenced as the date of first dose of study drug in the time to event calculations.

The LIFETEST procedure in SAS® is a nonparametric procedure for analyzing survival data to compute the Kaplan-Meier curve, which is a nonparametric maximum likelihood estimate of the survival function. From the Kaplan-Meier statistics the following are to be presented based on the relevant time to specified event:

- 25th percentile.
- Median (including 95% CI).
- 75th percentile.

This is calculated using the following SAS® code:

```
proc lifetest data=dd outsurv=dd1 method=KM alpha=0.05 alphaqt=0.05 conftype=linear
plots=(survival(strata=individual));
                time <survival time> * <censoring indicator>;
                by treatment;
run;
```

With the following indicators for the censoring of patients:

- 1 = Patients that have an event.
- 0 = Patients that do not have an event, i.e., censored patients.

Note:

- The treatment variable refers to the relevant dose cohorts.

15.3.1.1. Duration of Best Overall Disease Response to Treatment

Duration of best overall disease response to treatment (months) is to be summarized per disease response hierarchy (including SD or better). Duration of best overall disease response to treatment (months) is defined as the time from the date of the first occurrence of the best overall disease response on treatment to the date of the first occurrence of evaluable PD or death. For patients who do not experience evaluable PD or death the date of the last evaluable disease response assessment (i.e., SD or better) is to be used (censored).

Duration of best overall disease response to treatment (months) per disease response hierarchy:

- Patients with an event: Formula = (<date of first occurrence of evaluable PD or death> - <date of

first occurrence of best overall disease response to treatment>)/365.25 × 12.

- Patients with no event: Censored formula = (<date of the last evaluable disease response assessment (i.e., SD or better)> - <date of first occurrence of best overall disease response on treatment>)/365.25 × 12.

Duration of OR (months):

- Patients with an event: Formula = (<date of first occurrence of evaluable PD or death> - <date of first occurrence of PR or better>)/365.25 × 12.
- Patients with no event: Censored formula = (<date of the last evaluable disease response assessment (i.e., SD or better)> - <date of first occurrence of PR or better>)/365.25 × 12.

Duration of CBR (months):

- Patients with an event: Formula = (<date of first occurrence of evaluable PD or death>) - <date of first occurrence of MR or better>)/365.25 × 12.
- Patients with no event: Censored formula = (<date of the last evaluable disease response assessment (i.e., SD or better)>) - <date of first occurrence of MR or better>)/365.25 × 12.

15.3.1.2. TIME TO DISEASE RESPONSE ON TREATMENT

Time to first OR (months) is defined as the time from the date of the first dose of study drug (overall reference start date) to the date of the first occurrence of PR or better. For patients who do not experience an OR the date of the last available disease response assessment (i.e., MR or SD or PD) on treatment is to be used (censored).

Time to first CBR (months) is defined as the time from the date of the first dose of study drug (overall reference start date) to the date of the first occurrence of MR or better. For patients who do not experience a CBR the date of the last available disease response assessment (i.e., SD or PD) on treatment is to be used (censored).

Time to first OR (months):

- Patients with an event: Formula = (<date of first occurrence of PR or better> - <date of first dose of study drug>)/365.25 × 12.
- Patients with no event: Censored formula = (<date of the last available disease response assessment (i.e., MR or SD or PD) on treatment > - <date of first dose of study drug>)/365.25 × 12.

Time to first CBR (months):

- Patients with an event: Formula = (<date of first occurrence of MR or better> - <date of first dose of study drug>)/365.25 × 12.
- Patients with no event: Censored formula = (<date of the last available disease response assessment (i.e., SD or PD) on treatment> - <date of first dose of study drug>)/365.25 × 12.

The following figures (Kaplan-Meier plots) are to be presented for the EEmITT Analysis Set:

- Time to first OR.
- Time to first CBR.
- Time to best overall disease response on treatment.

15.3.1.3. TIME TO DISEASE PROGRESSION

Time to disease progression (months) is defined as the time from the date of the first dose of study drug (overall reference start date) to the date of the first occurrence of evaluable PD. For patients who do not experience evaluable PD the date of the last evaluable disease response assessment (i.e., SD or better) is to be used (censored).

Time to disease progression (months):

- Patients with an event: Formula = (<date of first occurrence of evaluable PD> - <date of first dose of study drug>)/365.25 × 12.
- Patients with no event: Censored formula = (<date of the last evaluable disease response assessment (i.e., SD or better)> - <date of first dose of study drug>)/365.25 × 12.

The time to disease progression is to be presented in a figure (Kaplan-Meier plot). The following variables are to be presented in the by-patient data listing:

- Date of first dose of study drug (overall reference start date).
- Date of disease progression.
- Date of death.
- Date of last evaluable disease response (SD or better).
- Time to disease progression (months) and PFS (months).

15.3.1.4. PROGRESSION-FREE SURVIVAL (PFS)

Progression-free survival (PFS) (months) is defined as the time from the date of the first dose of study drug (overall reference start date) to the date of the first occurrence of evaluable PD or death. For patients who do not experience evaluable PD or death, but who started non-protocol anticancer treatment before documentation of PD or death, who are lost to follow-up or who are alive without documentation of PD or death at the date of last contact, the date of the last evaluable disease response assessment (i.e., SD or better) is to be used (censored).

Progression-free survival (PFS) (months):

- Patients with an event: Formula = (day(<date of first occurrence of evaluable PD or death> - <date of first dose of study drug>)/365.25 × 12.
- Patients with no event: Censored formula = (<date of the last evaluable disease response assessment (i.e., SD or better)> - <date of first dose of study drug>)/365.25 × 12.

Progression-free survival (PFS) is to be presented in a figure (Kaplan-Meier plot) for the mITT Analysis

Set. Summarized PFS output and the PFS figure are to be repeated per disease response hierarchy.

15.3.1.5. OVERALL SURVIVAL (OS)

Overall survival (OS) data is to be presented as indicated on the Survival Follow Up eCRF. Overall survival (OS) (months) is defined as the time from the date of the first dose of study drug (overall reference start date) to death. For patients who do not experience death the last date that a patient is known to be alive or the date of last contact (whichever is latest) is to be used (censored).

Overall survival (OS) (months):

- Patients with an event: Formula = (<date of death> - <date of first dose of study drug>)/365.25 × 12.
- Patients with no event: Censored formula = (<maximum of date last known to be alive and date of last contact> - <date of first dose of study drug>)/365.25 × 12.

Overall survival (OS) is to be presented in a figure (Kaplan-Meier plot) for the mITT Analysis Set. The following variables are to be presented in the by-patient data listing:

- Date of first dose of study drug (overall reference start date).
- Date and method of contact.
- Date of death (including primary reason for death and autopsy information).
- Date of last contact.
- Anti-cancer status (including type of, start date of and time to subsequent treatment).
- Secondary malignancy (including type and date).
- Date last known to be alive.
- Overall survival (OS) (months).

15.3.1.6. TIME TO FIRST SUBSEQUENT TREATMENT

The use of subsequent treatments are indicated on the Survival Follow Up eCRF. Presentation of time to first subsequent treatment is not to be repeated for any subgroups. Time to first subsequent treatment (months) start is defined as the time from the date of the derived EOT to the date of the first subsequent treatment. For patients who are not receiving subsequent treatment the date of last contact is to be used (censored).

Time to first subsequent treatment (months):

- Patients with an event: Formula = (<date of first subsequent treatment> - <date of derived EOT>)/365.25 × 12.
- Patients with no event: Censored formula = (<date of last contact> - <date of derived EOT>)/365.25 × 12.

15.4. EXPLORATORY EFFICACY

Not applicable.

15.5. OTHER EFFICACY ASSESSMENTS

Presentation of OS, time to first subsequent treatment, and shift presentations of X-ray and imaging assessments and plasmacytoma evaluations are not to be repeated for any subgroups.

15.5.1. X-RAY AND IMAGING ASSESSMENTS

X-ray and imaging assessments as indicated on the Chest X-ray, Imaging Assessment, Screening and Imaging Assessment eCRFs are to be presented in a by-patient data listing for the SAF Analysis Set. The following variables are to be presented:

- Visit (containing cycles and cycle days).
- Date and category of the imaging assessment.
- Presence of lytic bone lesions or plasmacytomas.
- Anatomical site.
- Procedure type.
- Result as indicated by the investigator on the Chest X-ray, Imaging Assessment, Screening and Imaging Assessment eCRFs:
  - Normal.
  - Abnormal, not clinically significant (ANCS).
  - Abnormal, clinically significant (ACS).
- Reason for assessment and change since previous assessment are to be presented.

Imaging assessments are classified as:

- Chest X-ray.
  - Chest radiography.
- Imaging.
  - Skeletal survey.
  - Computerized axial tomography (CAT or CT)/positron emission tomography (PET) scan.
  - Other imaging procedure.

Chest X-rays are scheduled to be performed at Screening and EOT. Only selected variables (visit, date of assessment, category/assessment, and result/specification) as indicated on the Chest X-ray eCRF are to be presented for the chest X-ray category amongst other imaging variables.

A shift table is to summarize the data based on the Baseline and derived EOT result for the mITT Analysis Set. The results are to be presented as judged by the investigator as follows:

- Normal.
- Abnormal, not clinically significant (ANCS).
- Abnormal, clinically significant (ACS).

For summary purposes, the imaging procedure type (e.g., bone scan, magnetic resonance imaging [MRI], skeletal survey etc.) is to be the same for Baseline and derived EOT. Percentage (%) of patients in each category is to be calculated relative to the total number of patients in the relevant analysis set, with assessments available at Baseline and the relevant post-baseline assessment.

15.5.2. PLASMACYTOMA EVALUATION

Plasmacytoma evaluation as indicated on the Plasmacytoma Evaluation Screening and Plasmacytoma Measurement eCRFs is to be presented in a by-patient data listing. The following variables are to be presented:

- Visit (containing cycles and cycle days).
- Date of assessment.
- Plasmacytoma number and category.
- Anatomical site.
- Procedure.
- Lesion measurement and result.
- Change since the previous assessment.

Plasmacytomas are classified as:

- Soft tissue.
- Lytic bone.
- Other.

Soft tissue and lytic bone plasmacytomas are to be included in the presentation of total plasmacytoma size, but other plasmacytoma site codes are only to be presented in the by-patient data listing.

Soft tissue plasmacytomas total size is to include liver (visceral), lung (visceral), node or soft tissue all plasmacytomas as indicated on the Plasmacytoma Evaluation Screening and Plasmacytoma Measurement eCRFs. Lytic bone plasmacytomas total size is to include lytic bone plasmacytomas as indicated on the Plasmacytoma Evaluation Screening and Plasmacytoma Measurement eCRFs.

A total plasmacytoma size is to be calculated by adding the lesion measurements (mm^2) within the plasmacytoma categories (i.e., soft tissue or lytic bone).

A by-visit presentation (at Baseline and derived EOT) for the mITT Analysis Set is to summarize the observed and CFB results in derived total plasmacytomas size by plasmacytoma category.

15.5.2.1. DERIVATIONS

- Plasmacytoma total size = $\sum_{x=1}^{n}(\text{lesion } 1_x \times \text{lesion } 2_x).$

Where n represents the total number of plasmacytomas reported for a patient within the plasmacytoma categories (i.e., soft tissue or lytic bone).

16. SAFETY OUTCOMES

The Safety Analysis Set is to be regarded as primary for the safety analyses.

16.1. ADVERSE EVENTS (AEs)

Adverse events (AEs) are to be presented as indicated on the Adverse Events/Serious Adverse Events eCRF. Progression of malignancy is not to be reported as an AE.

For the purpose of the analysis, AEs are to be assigned to a cycle as detailed in Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP. Refer to Appendix 2 Partial Date Conventions of this SAP for the handling of partial dates for AEs.

Analysis flags are to be derived to indicate if the AE is a DLT AE (D), a prior AE (P), a TEAE (T) or a follow-up AE (FU) based on the following definitions:

- Dose-limiting toxicity AEs (D): As indicated on the Adverse Events/Serious Adverse Events eCRF and is only to be assessed for Phase I patients.
- Prior AEs (P): Defined as AEs that started before the first dose of study drug (overall reference start date).
- Treatment-emergent AEs (T): Defined as AEs that started or worsened on or after the first dose of study drug (overall reference start date) up to and including the derived EOT date.
- Follow-up AEs (FU): Defined as AEs that started or worsened after the derived EOT date.

Adverse events (AEs) are to be coded using the MedDRA central coding dictionary, Version 20.0.

Incidence of TEAEs are to be presented by SOC and PT. Uncoded AEs (i.e., AEs with no dictionary coding information available) are only to be presented if applicable using the investigator's Verbatim Term (eCRF) as PT within the text "UNCODED" as SOC. System Organ Classes (SOCs) are to be sorted by total decreasing frequency. Preferred Terms (PTs) are to be sorted by total decreasing frequency within each SOC. If SOCs or PTs have the same total frequency they are to be sorted alphabetically.

For presentation and derivation purposes, the following statistics are defined:

- n: Defined as the number of patients with at least one TEAE in each category. Patients with multiple TEAEs in each category are counted only once in each category.
- m: Defined as the number of mentions (events) in each category, i.e., the actual unique number of events.
- N: Defined as the total number of patients in the relevant analysis set.
- %: Defined as the percentage of patients with at least one TEAE in each category calculated relative to the total number of patients in the relevant analysis set.

By-patient data listings are to include all AEs (i.e., TEAEs and non-TEAEs [AEs that did not start within

the defined treatment period of evaluation]) for the All Patients Screened Analysis set. However, for the by-patient data listing of AEs leading to discontinuation of study drug (melflufen or dexamethasone or both) the output is to be limited to the SAF Analysis Set.

16.1.1. SEVERITY

The severity of AEs is to be described using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Treatment-emergent AEs (TEAEs) starting after the first dose of study drug (overall reference start date) with a missing severity are to be analyzed as a missing category. For AEs not adequately addressed in the CTCAE, Table 3: Toxicity Scale is to be used for grading the severity.

Table 3: Toxicity Scale

Severity	Description
Grade I - Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
Grade II - Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
Grade III - Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
Grade IV - Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable
Grade V - Fatal	Death

16.1.2. RELATIONSHIP

The relationship to study drug, as indicated by the investigator, is classified as:

- Not related.
- Possibly related.
- Definitely related.

A related TEAE is defined as a TEAE for which relationship to ***melflufen*** is indicated as possibly related or definitely related. TEAEs starting after the first dose of study drug (overall reference start date) with a missing relationship are to be analyzed as a missing category.

In addition the following relationships will also be summarized and defined as follows:

- A TEAE related to dexamethasone is defined as a TEAE for which the relationship to

dexamethasone is indicated as possible related or definitely related.

- A TEAE related to melflufen and/or dexamethasone is defined as a TEAE for which the relationship to melflufen is indicated as possible related or definitely related and/or relationship to dexamethasone is indicated as possible related or definitely related.

16.1.3. Action Taken with Study Drug

The action taken with study drug, as indicated by the investigator, is classified as:

- Dose interrupted.
- Dose reduced.
- Dose delayed.
- Dose held.
- Other.

Action taken classified as drug permanently discontinued (melflufen) or dose permanently discontinued (dexamethasone) is to be used to identify and select all AEs leading to discontinuation of study drug.

A summary of treatment-related TEAEs by action taken with melflufen as well as action taken with dexamethasone is also to be presented with a by-group specification indicating the cycle occurrence (refer to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP).

16.1.4. Adverse Events (AEs) Leading to Death

Adverse events (AEs) leading to death are selected as all AEs with an outcome recorded as “Fatal”.

16.1.5. Serious Adverse Events (AEs)

Serious AEs are events judged as “Serious” by the investigator. Serious criteria include the following events:

- Death.
  - Date of death.
  - Primary cause of death.
  - Date of autopsy (if performed).
  - Death certificate (if available).
- Life-threatening.
- Hospitalization or prolongation of existing hospitalization.
  - Date of admission.
  - Date of discharge.

Duration of hospitalization is to be calculated as follows:

- Hospitalization duration (days) = (<Date of hospital discharge> – <date of hospital admission>) + 1. Only if date of hospital discharge is not missing (i.e., ongoing).

- Persistent or significant disability/incapacity.
- Congenital abnormality/birth defect.
- Medically significant.
- Other/Specification (eCRF).

16.1.6. Adverse Events (AEs) Leading to Discontinuation of Study Drug

Adverse events (AEs) leading to permanent discontinuation of study drug are to be identified and selected based on the action taken with melflufen being drug permanently discontinued and/or the action taken with dexamethasone being dose permanently discontinued. The incidence of TEAEs leading to discontinuation of study drug is to be presented by:

- Melflufen (IV).
- Dexamethasone.
- Melflufen (IV) and Dexamethasone, i.e., patient discontinued both study drugs.

16.1.7. Adverse Events (AEs) Leading to Discontinuation of Study

Adverse events (AEs) leading to discontinuation of study are to be identified based on the response to the question "Did the AE cause the subject to discontinue from the study?"

16.1.8. Adverse Events (AEs) Meeting Dose-Limiting Toxicity (DLT) Criteria

Adverse events (AEs) meeting DLT criteria are only to be assessed for Phase I patients during Cycle 1. Dose-limiting toxicity AEs are to be identified and selected based on the response to the question "Is this adverse event a DLT?"

16.1.9. All Treatment-emergent AEs (TEAEs)

Based on the aforementioned definitions, three overview summaries are to be provided including TEAEs, treatment-related (melflufen) TEAEs and TEAEs of special interest. The following are to be presented for the overview summaries:

- Any TEAE.
- Treatment-emergent AEs leading to death.
- Serious TEAEs.
- Treatment-emergent AEs leading to discontinuation of melflufen and/or dexamethasone.
- Treatment-emergent AEs leading to discontinuation of study.

- Treatment-emergent AEs leading to dose reduction of melflufen and/or dexamethasone.
- Dose-limiting toxicity TEAEs.
- Treatment-emergent AEs by relationship to melflufen.
- Grade ≥ III treatment-emergent AEs by relationship to melflufen.
- Serious treatment-emergent AEs by relationship to melflufen.
- Treatment-emergent AEs by relationship to dexamethasone.
- Grade ≥ III treatment-emergent AEs by relationship to dexamethasone.
- Serious treatment-emergent AEs by relationship to dexamethasone.
- Treatment-emergent AEs by relationship to melflufen and/or dexamethasone.
- Grade ≥ III treatment-emergent AEs by relationship to melflufen and/or dexamethasone.
- Serious treatment-emergent AEs by relationship to melflufen and/or dexamethasone.
- Treatment-emergent AEs by severity.
- Treatment-emergent AEs by worst severity.
- Treatment-emergent AEs of special interest. Refer to Section 16.2 Adverse Events (AEs) of Special Interest of this SAP.
- Treatment-emergent AEs by action taken.
- Treatment-emergent AEs leading to action taken with melflufen.
- Treatment-emergent AEs leading to action taken with dexamethasone.

16.1.10. TIME TO ONSET OF TREATMENT-EMERGENT AES (TEAES)

The median time to onset (including 25th and 75th percentiles) of Grade III (severe) and/or Grade IV (life-threatening) neutropenia and thrombocytopenia TEAEs is to be calculated using the Kaplan-Meier statistics. Similar code as described in Section 15.3.1 Secondary Efficacy Variables and Derivations of this SAP is to be applied. Patients with no Grade III or Grade IV neutropenia and thrombocytopenia TEAEs are to be censored at the time of the derived EOT date.

16.1.11. DERIVATIONS

Time to onset of Grade III (severe) and/or Grade IV (life-threatening) TEAEs (per patient per event) is to be calculated using the following formula:

- Time to onset of Grade III or Grade IV TEAEs (months) [per event] = (<date of first Grade III or Grade IV TEAE [per event]> - <date of first dose of study drug>)/365.25 × 12.

- Only to be presented for the SAF Analysis Set. The overall reference start date is referenced as the date of first dose of study drug in the time to onset calculation for Grade III or Grade IV TEAEs up to and including the derived EOT date.

16.2. ADVERSE EVENTS (AEs) OF SPECIAL INTEREST

Adverse events (AEs) of special interest include neutropenia and thrombocytopenia events based respectively on PT Code [10029354] and [10043554] and are to be presented for the All Patients Screened Analysis Set in the by-patient data listing.

In addition to the incidence of TEAEs of special interest an overview of TEAEs of special interest in combination with neutrophil and platelet laboratory data as well as hematopoietic growth factor and standardized transfusion administration is to be presented. With reference to Section 6.3 Cycle Length, Cycle Assignment, and Cycle Completion of this SAP, the combined presentation by cycle occurrence is to include:

- The number (n) of patients treated in a cycle.
- The number (n) of patients with at least one TEAE/Neutropenia.
  - Grade 1 to Grade 4 (based on worst grade per cycle).
    - Including the number of mentions in each category (events).
  - Duration (days) per grade.
    - Based on the actual number of mentions per grade.
- The number (n) of patients with at least one TEAE/Thrombocytopenia.
  - Grade 1 to Grade 4 (based on worst grade per cycle).
    - Including the number of mentions in each category (events).
  - Duration (days) per grade.
    - Based on the actual number of mentions per grade.
- The number (n) of patients with at least one laboratory/hematology assessment:
  - Neutrophils abs (decreased).
    - Common Terminology Criteria for Adverse Events (CTCAE) Grade 0 to Grade 4, and ≥ Grade 3.
  - Platelets abs (decreased).
    - Common Terminology Criteria for Adverse Events (CTCAE) Grade 0 to Grade 4, and ≥ Grade 3.
  - The number (n) of patients with at least one hematopoietic growth factor.
    - Filgrastim.
    - Neupogen.
    - …
  - The number (n) of patients with at least one standardized transfusion type.
    - Platelet transfusion.
    - Red blood cell transfusion.

- …

Percentage (%) calculations are as follows:

- For the number (n) of patients with at least one TEAE, percentage (%) is to be calculated relative to the total number of patients treated per individual cycle.
- For the number (n) of patients with at least one laboratory/hematology assessment, percentage (%) is to be calculated relative to the total number of patients treated per individual cycle with at least one assessment following study drug administration on Cycle x Day 1.
- For the number (n) of patients with at least one hematopoietic growth factor or standardized transfusion, percentage (%) is to be calculated relative to the total number of patients treated per individual cycle with at least one administration following melflufen administration on Cycle x Day 1.

Patients with a normal result (i.e., a result not complying with the CTCAE grade for the laboratory/hematology assessments) are to be assigned a Grade 0 severity. The summarized output is to be repeated for the following by-group variable:

- Overall.
- Melflufen dose reduced.
- Melflufen dose reduction.
  - For this by-group variable, the total number of patients in the relevant analysis set (N) is to present a subset of the number of patients in the Safety Analysis Set, i.e., the number of patients with at least one melflufen dose reduction across all cycles. Dose reduction is based on the action taken with melflufen.
- Melflufen dose interrupted.
  - Similarly this by-group variable is to present a subset of the number of patients in the Safety Analysis Set, i.e., the number of patients with at least one melflufen dose interruption across all cycles. Dose interruption is based on the action taken with melflufen.

The laboratory/hematology assessments of special interest, hematopoietic growth factors, and standardized transfusions are to be presented in a by-patient figure for the SAF Analysis Set. Melflufen administration and potential dose modifications are also to be included in this figure. Neutrophils abs (decreased) and platelets abs (decreased) of CTCAE Grade 3 and/or 4 are to be highlighted in the presentation.

16.2.1.1. DERIVATIONS

Treatment-emergent AE duration (days) is calculated as follows:

- Treatment-emergent AE duration (days) = (<Stop date> - <start date of the event>) + 1.

Patients experiencing an ongoing TEAE (i.e., no stop date is available) are to be censored at the timepoint of the subsequent laboratory assessment that adheres to the cycle initiation criteria (Section 3.1 General Description of this SAP) or EOT. Default summary statistics to be presented for

TEAE duration per grade include all mentions (events) at that particular grade.

16.3. LABORATORY EVALUATIONS

Safety laboratory data as captured on the Local Laboratory/Complete Blood Count, Local Laboratory/Serum Chemistry, Local Laboratory/Coagulation, and Local Laboratory/Urinalysis eCRFs are to be presented. Complete blood count (i.e., hematology), serum chemistry, coagulation, and urinalysis (pH being the only quantitative urinalysis variable) data are only to be obtained from local laboratories. Laboratory system/category, variable and SI are presented in Appendix 5 International System of Units (SI) of this SAP.

With reference to Appendix 5 International System of Units (SI) of this SAP, a derived "Neutrophils abs" variable is to be created based on the two Local Laboratory/Complete Blood Count eCRF variables "Neutrophils" and "Absolute Neutrophil Count". Depending on which of the two eCRF variables contain data (or the most accurate data pertaining to decimal precision), CCI Biostatistics is to create a derived variable for purposes of the analysis and presentation of output.

The following variables are to be presented for all quantitative laboratory assessments in by-patient data listings:

- Visit (containing cycles and cycle days).
- Date of assessment.
- Result.
- Common Terminology Criteria for Adverse Events (CTCAE) grade.
- Reference range.
- Investigator's judgment as indicated on the eCRF.

With the exception of CTCAE grade and reference range, the above variables are also to be presented for qualitative urinalysis assessments. Pregnancy assessments as indicated on the Local Laboratory/Pregnancy Test eCRF are also to be presented in a by-patient data listing. Refer to Section 6.2 Derived Timepoints and Section 6.4 Baseline of this SAP for the definitions of Baseline and derived EOT, respectively.

A change in the following serum chemistry variables based on the shift from Baseline CTCAE grade to the worst post-baseline CTCAE grade (LOCF assessment up to and including the derived EOT date) (refer to Section 16.3.2 Common Terminology Criteria for Adverse Events (CTCAE) Grading for Laboratory Data of this SAP) is to be presented:

- Glucose (mmol/L). No CTCAE for non-fasting glucose levels.
- Corrected calcium (mmol/L). Common Terminology Criteria for Adverse Events (CTCAE) includes hypercalcemia and hypocalcemia.
- Alkaline phosphatase (IU/L).

- Alanine aminotransferase (IU/L).
- Aspartate aminotransferase (IU/L).
- Total bilirubin (µmol/L). Blood bilirubin as per CTCAE terminology.
- Creatinine (µmol/L).
- Creatinine clearance (mL/min).

Percentage (%) of patients in each category is calculated relative to the total number of patients in the relevant analysis set, with assessments available at Baseline and at least one post-baseline assessment up to and including the derived EOT date (LOCF assessment up to and including the derived EOT date). If more than one disorder exists per the CTCAE criteria, the relevant disorder is presented as a by-variable (e.g., Glucose (mmol/L)/Hyperglycemia). The available CTCAE criteria are detailed in Appendix 3 Common Terminology Criteria for Adverse Events (CTCAE) of this SAP for the relevant variables.

For quantitative laboratory assessments, default summary statistics are to be presented for:

- Observed result at visit (Baseline and derived EOT [LOCF]).
- Change from Baseline (CFB) at derived EOT (LOCF) (refer to Section 6.9 Common Calculations of this SAP).

All assessments (scheduled or unscheduled) are to be presented in the by-patient data listings.

16.3.1. Laboratory Reference Ranges and Clinically significant Criteria

Quantitative laboratory assessments are to be compared with the relevant laboratory reference range in SI units and classified as:

- Low (L): Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High (H): Above the upper limit of the laboratory reference range.

Quantitative laboratory results reported as "< x", i.e., below the lower limit of quantification (BLQ), or "> x", i.e., above the upper limit of quantification (ULQ), are to be converted to x for the purpose of quantitative summaries, but are to be presented as recorded, i.e., as "< x" or "> x" in the by-patient data listings.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), laboratory assessments are also to be assessed as judged by the investigator as follows:

- Normal.
- Abnormal, not clinically significant (ANCS).
- Abnormal, clinically significant (ACS).

16.3.2. Common Terminology Criteria for Adverse Events (CTCAE) Grading for Laboratory Data

The laboratory results are to be graded using the CTCAE, Version 4.03. The worst CTCAE post-baseline result (highest grade) up to and including derived EOT (LOCF) is to be flagged for each patient per relevant laboratory variable as judged by the investigator is to be classified as:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- (*)Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
- (**)Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

(*) Instrumental ADL: Preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

(**) Self-care ADL: Bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Patients with a result not complying with the CTCAE grades for a given laboratory assessment are to be assigned with a Grade 0 severity.

In addition, box plots are to be presented for platelets abs, neutrophils abs, and hemoglobin over time for the SAF Analysis Set.

16.3.3. Textbook Ranges for Laboratory Data

The laboratory results are to be xxx as indicated in Table 5: Standardization of Temperature.

Table 4: Textbook Reference Ranges

White blood cell differential	Percentage reference range
Basophils	0% to 2%
Eosinophils	0% to 4%
Lymphocytes	20% to 44%
Monocytes	2% to 9%
Neutrophils	50% to 70%
Neutrophil-Individual Bands	2% to 6%

Source: Harmening, DM 2009, Clinical Hematology and Fundamentals of Hemostasis, 5th Edition.

16.4. ELECTROCARDIOGRAM (ECG) EVALUATIONS

The corrected QT interval using Fridericia's formula (QTcF) (msec), as indicated on the 12-lead ECG eCRF, is the only 12-lead ECG parameter that is to be reported for the study.

The QTcF interval (msec) as judged by the investigator is to be classified as:

- Normal.
- Abnormal, not clinically significant (ANCS).
- Abnormal, clinically significant (ACS).

Default summary statistics are to be presented for the QTcF variable:

- Observed result at visit (Baseline and derived EOT [LOCF]).
- Change from Baseline (CFB) at derived EOT (LOCF).

All assessments (scheduled or unscheduled) are to be presented in the by-patient data listing.

16.4.1. ELECTROCARDIOGRAM (ECG) ABNORMALITY AS PER SPECIFIED CRITERIA

Abnormal QTcF intervals (msec) are to be identified in accordance with the following predefined abnormal criteria for inclusion in the by-patient data listing:

- Absolute values for QTcF are to be classified as:
  - > 450 msec.
  - > 470 msec.
  - > 480 msec.
  - > 500 msec.

The aforementioned categories are not mutually exclusive and a result can therefore fall into more than one category simultaneously.

- Change from Baseline (CFB) for QTcF is to be classified as:
  - > 30 msec increase from Baseline.
  - > 60 msec increase from Baseline.

If one of the timepoints required for the calculation is not available, no CFB is to be presented.

16.5. VITAL SIGNS

From Cycle 1 Day 1 onwards vital signs assessments are to be performed pre- and post-melflufen infusion. Default summary statistics are to be presented for vital signs assessments for:

- Observed result at visit (Baseline and derived EOT [LOCF]).
- Change from Baseline (CFB) at derived EOT (LOCF).

All assessments (scheduled or unscheduled) are to be presented in the by-patient data listing. The following vital signs variables are to be presented:

- Systolic blood pressure (mmHg).
- Diastolic blood pressure (mmHg).
- Pulse rate (bpm).
- Respiratory rate (breaths/min).
- Standardized body temperature (°C).
- Weight (kg).
- Height (cm). Only recorded at Screening. Not to be included in the summaries, but only to be presented in the by-patient data listing.

16.5.1. Derivations

Body temperature is to be standardized to oral body temperature as indicated in Table 5: Standardization of Temperature.

Table 5: Standardization of Temperature

Temperature method	Standardized to oral body temperature
Oral	No adjustment
Rectal	-(0.3°C to 0.6°C)
Axillary (arm pit)	+(0.3°C to 0.6°C)
Tympanic (ear)	-(0.3°C to 0.6°C)

Standardized intervals based on current research.

16.6. Physical Examination

Any abnormal physical examination finding is to be presented in a by-patient data listing. Clinical significance as judged by the investigator and as indicated on the Physical Examination, Screening, Physical Examination, or Symptom Directed Physical Examination eCRFs is to be presented.

16.7. Other Safety Assessments

16.7.1. Eastern Cooperative Oncology Group (ECOG) Performance

Eastern Cooperative Oncology Group (ECOG) Performance data as indicated on the ECOG Performance Status eCRF is to be presented in a by-patient data listing. The ECOG grades comprise

Grade 1 (normal) to Grade 5 (death).

The worst post-baseline performance grade (highest grade) up to and including derived EOT (LOCF) is to be flagged for each patient.

A change in the performance grade based on the shift from Baseline CTCAE grade to the worst post-baseline CTCAE grade up to and including derived EOT (LOCF) is to be presented.

Percentage (%) of patients in each category is calculated relative to the total number of patients in the relevant analysis set, with assessments available at Baseline and at least one post-baseline assessment up to and including derived EOT (LOCF).

17. DATA NOT SUMMARIZED OR PRESENTED

Not applicable.

18. REFERENCES

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