Statistical Analysis Plan
Version 2.2, 24 January 2022

Protocol OP-109

Protocol Title: A randomized, two-period, cross-over, Phase 2 study, comparing the pharmacokinetics, and assessing safety and tolerability of peripheral and central intravenous administration of melflufen in patients with relapsed and refractory multiple myeloma.

National Clinical Trial number: NCT04412707

Oncopeptides AB

STATISTICAL ANALYSIS PLAN

PROTOCOL OP-109

A randomized, two-period, cross-over, Phase 2 study, comparing the pharmacokinetics, and assessing safety and tolerability of peripheral and central intravenous administration of melflufen in patients with relapsed and refractory multiple myeloma

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DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
1.0	26 June 2020
2.0	17 May 2021
2.1	14 July 2021
2.2	24 January 2022

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
2.0	Signature page	The names of PSI project manager, OP study statistician and OP study physician were updated	To reflect the changes in the study team on both PSI and OP sides
	Introduction	The referenced protocol version changed to the version 2.2 (10 March 2021)	To refer to the latest protocol version
	3.1. Study Design	Figure 1. “Study Design” was updated following the corresponding update in the protocol	For compliance with the latest protocol version
	6. Analysis Populations	For the safety analysis set the clarification regarding the analysis by sequence arms added	To avoid any ambiguity
	7.1. General Conventions and Statistical Considerations	a) Additional details added to better reflect the general way of summaries presentation. b) Additional clarifications added regarding the assignment of measurements to particular injection type happened just prior to the shift to the other injection type	To improve comprehensibility and avoid ambiguity
	7.2. Definition of Baseline, Study Visits and Visit	Baseline definitions were updated, including the reference to the latest	To improve comprehensibility and avoid ambiguity

	Windows	measurement prior to the dexamethasone/melflufen start date	
	7.3. Handling of Missing Data	For missing start day and month case the additional clarification for the case with incomplete end date added	To make sure that all possible scenarios are covered
	7.4. Patient Disposition	a) added number and percentage of patients randomized and never treated b) added COVID-19 related discontinuations c) number of patients died removed	a) client request b) to assess COVID-19 impact on discontinuation c) there is a separate summary dedicated to Deaths
	7.5. Protocol Deviations	Added that major protocol deviations are supposed to be analyzed not only by deviation type, but also by relationship to COVID-19	To assess COVID-19 impact on major protocol deviations
	7.6.2. Medical History and Current Medical Conditions	MedDRA version has been updated to 24 or higher	To reflect the actual MedDRA version used
	7.6.3. Multiple Myeloma Disease History	Additional details on derivation of the next variables were added: bone marrow plasma cells (%), cytogenetics abnormalities at study entry, bone lesion assessments	To make sure that all data collection peculiarities are taken into account for analysis
	7.6.4. Prior MM Therapies	Definitions of frontline transplant, time from frontline transplant to relapse, double and triple class refractoriness, as well refractoriness to the prior therapy line were updated	To reflect the current sponsor's view on that
	7.6.5. Prior and Concomitant Medication	a) WHODD version updated to 1 March 2021 b) the first and last dose refer to the earliest of dexamethasone and melflufen and the latest of dexamethasone and melflufen respectively, instead of referring to melflufen only	a) to reflect the actual WHODD version used b) to reflect the revised approach considering the combination of drugs rather than melflufen alone
	7.7.1. Response	Clarifications that best overall	To improve comprehensibility

	Rates	confirmed response includes only assessment collected prior to the new therapy initiation and that confirmed PD to be identified as per separate rule than confirmed sCR-SD responses	and avoid ambiguity
	7.7.2. Time to Event Parameters	a) Footnotes to the Tables 2 and 3 were added b) derivation formulae added for various parameters	a) following sponsor's request b) to improve comprehensibility and avoid ambiguity
	7.7.3. Efficacy Assessments	Statement re replacement of missing central assessments with unscheduled local ones added	To address updated eCRF design and data collection process
	7.8.1. Exposure to Study Treatment	Dose delay due to COVID-19 analysis added	To assess the impact of COVID-19 on dose delay
	7.8.2. Local Reactions	Clarification added that for the VIP Score there is an exception to the rule specified 7.1 regarding the assignment of measurements to particular injection type happened just prior to the shift to the other injection type	To avoid ambiguity
	7.8.3. Adverse Events	a) the way of presentation changed to by sequence arms b) MedDRA version has been updated to 24 or higher c) the first and last dose refer to the earliest of dexamethasone and melflufen and the latest of dexamethasone and melflufen respectively, instead of referring to melflufen only d) Dexamethasone related summaries were added to the list e) the definition updated for Thrombocytopenia, Neutropenia, Anemia grouped adverse events categories. The new categories added: myelodysplastic syndrome,	a), d), e) following sponsor's request for consistency with the other studies b) To reflect the actual MedDRA version used c) to reflect the revised approach considering the combination of drugs rather than melflufen alone f) to improve comprehensibility and avoid ambiguity

		second primary malignancies, infective pneumonia f) clarification added that for by cycle presentation maximum toxicity grade should be identified separately within each cycle	
	7.8.4. Laboratory Data	a) the way of presentation changed to by sequence arms b) clarification added that only local assessments are used for the summaries c) clarification added that for by cycle presentation the worst grade should be identified separately within each cycle d) eGFR added to the list of parameters for which toxicity grade should be presented	a) following discussions with the sponsor regarding the most appropriate way of presentation, considering cross-over design b) and c) to improve comprehensibility and avoid ambiguity d) to reflect the data properly
	7.8.5. Vital Signs	The way of presentation changed to by sequence arms	following discussions with the sponsor regarding the most appropriate way of presentation, considering cross-over design
	7.8.7. 12-Lead Electrocardiogram (ECG)	The way of presentation changed to by sequence arms	following discussions with the sponsor regarding the most appropriate way of presentation, considering cross-over design
	7.9.2. Treatment Satisfaction and Quality of Life	Clarifications regarding way of presentation were added	following discussions with the sponsor regarding the most appropriate way of presentation, considering cross-over design
	7.10.2. ECOG	Section updated	For consistency with the other studies
	9. Deviations from Analysis as Described in the Protocol	Deviations to the protocol regarding way of presentation by sequence arm added	To document existing deviation to the protocol
2.1	7.8.3. Adverse Events	The statement that only deaths occurred prior to the subsequent therapy are to be presented in the summary of	The client decided to consider all deaths happened for summary of deaths and not only those happened

		deaths was removed	prior to subsequent therapy
2.2	Signature page	The name of the OP Head of Clinical Pharmacology and the name of the OP study physician as well as the name of PSI Medical Writer were updated	To reflect the changes in the study team on the OP and PSI sides
	7.5 Protocol Deviations	Clarification added that for the Overall column all major protocol deviations are presented, regardless if they happened within treatment period or not	To fix the way of presentation used for the interim analysis and provide a summarization of all available major protocol deviations data
	7.6.5. Prior and Concomitant Medications	The word “Haemapoetic” was replaced with “Haematopoietic”	To fix the spelling
	7.7.2 Time to Event Parameters Table 3 Conventions for Censoring for TTP	Death mentioning was removed from the first censoring rule	Death is not treated as an event for the time to progression analysis
	7.7.3 Efficacy Assessments	Serum and Urine immunofixation central lab data excluded from summaries presentation, will only be presented in the listings	Removed from summaries presentation as only measured at screening and at some specific conditions
	7.7.3 Efficacy Assessments	The part regarding replacement of missing central results with available local results was removed	Myeloma specific laboratory data were supposed to be collected centrally as per the protocol. There was a very small amount of such data collected locally, which were collected as Unscheduled results and could not be presented within a summary by time points

APPROVAL SIGNATURES

STUDY TITLE: A randomized, two-period, cross-over, Phase 2 study, comparing the pharmacokinetics, and assessing safety and tolerability of peripheral and central intravenous administration of melflufen in patients with relapsed and refractory multiple myeloma

PROTOCOL NUMBER: *OP-109*

SAP Final 2.2, 24 January 2022

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under curve
$AUC_{(0-\infty)}$	area under the concentration-time profile from 0 hours to infinity
$AUC_{(0-t)}$	area under the concentration-time profile from 0 hours to the last measurable concentration
BMA	bone marrow aspiration
CBC	complete blood count
CBR	clinical benefit rate
COVID-19	coronavirus disease of 2019
CI	confidence interval
cm	centimeters
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
CV%	coefficient of variation
CVC	central venous catheter
DOCB	duration of clinical benefit
DOR	duration of response
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMD	extramedullary disease
EOT	end of treatment
FAS	full analysis set
FISH	fluorescence *in situ* hybridization
FLC	free light chain
GMR	geometric mean ratio
ICH	International Council for Harmonisation
IFE	immunofixation
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria

ISS	International Staging System
i.v.	intravenous
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
mAb	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
MRI	magnetic resonance imaging
NCA	non-compartmental analysis
NCI	National Cancer Institute
NRS	numerical rating scale
ORR	overall response rate
PD	progressive disease
PFS	progression free survival
PFS-FU	progression free survival follow-up
PI	proteasome inhibitor
PK	pharmacokinetic(s)
p.o.	per os/by mouth/orally
PR	partial response
PT	preferred Term
PVC	peripheral venous catheter
q.d.	Quaque die/ one a day
QOL	quality of life
R-ISS	revised international staging system
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
S-Cr	serum creatinine
SD	standard deviation; stable disease (depending on context)
SDG	standardized drug groupings
SDTM	study data tabulation model
SFLC	serum free light chain
SMQ	standardized MedDRA query
SOC	system organ class
SPEP	serum protein electrophoresis
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
TTP	time to progression
TTR	time to response
ULN	upper limit of the normal range

UPEP	urine protein electrophoresis
US	United States
VAS	visual analogue scale
VGPR	very good partial response
VIP	visual infusion phlebitis
WBC	white blood cells
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis and reporting for the study protocol OP-109 v.2.2 (10 March 2021) entitled; A randomized, two-period, cross-over, phase 2 study, comparing the pharmacokinetics, and assessing safety and tolerability of peripheral and central intravenous (i.v.) administration of melflufen in patients with relapsed and refractory multiple myeloma. The purpose of the plan is to outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry. If the protocol is amended, this SAP will be revised as required.

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

This SAP does not include the description of biomarkers analysis.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To evaluate and compare the pharmacokinetic (PK) variables maximum observed concentration (C_{max}), area under the concentration-time profile from 0 hours to the last measurable concentration ($AUC_{(0-t)}$) and area under the concentration-time profile from 0 hours to infinity ($AUC_{(0-\infty)}$) of melphalan after central and peripheral i.v. infusion of melflufen
- To assess the local tolerability of peripheral i.v. administration of melflufen

2.2 SECONDARY OBJECTIVES

- To evaluate and compare the PK variables C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of melflufen and desethyl-melflufen, and to evaluate the elimination half-life ($t_{½}$) for melflufen, melphalan and desethyl-melflufen after central and peripheral i.v. infusion of melflufen
- To assess safety and general tolerability of melflufen

- To evaluate efficacy:

- Best response during the study
- Overall response rate (ORR)
- Clinical benefit rate (CBR)
- Duration of response (DOR)
- Duration of Clinical Benefit (DOCB)
- Time to response (TTR)
- Time to progression (TTP)
- Time to next treatment (TTNT)
- Progression Free Survival (PFS)

2.3 EXPLORATORY OBJECTIVES

- To assess translational biomarkers that might predict effects of the treatment, aid in monitoring of disease progression as well as improve understanding of mechanism of action
- To assess and compare patient satisfaction and preference, nurse convenience and preference after central and peripheral i.v. administration of melflufen
- To assess Quality of Life (QoL) based on Patient Reported Outcome (PRO)
- To assess use of health services and days of hospitalization

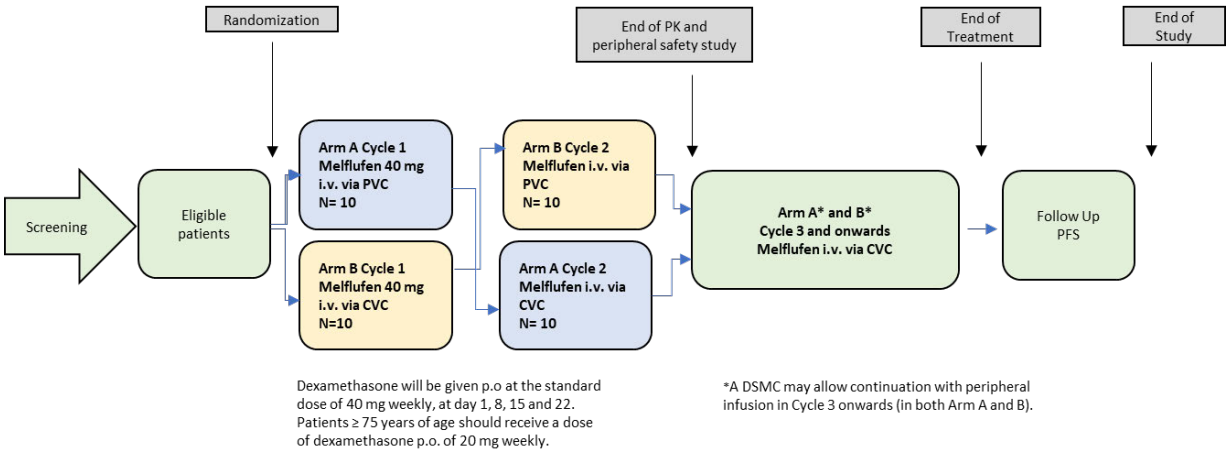
3. STUDY DESCRIPTION

3.1 STUDY DESIGN

This is a randomized, two-period, cross-over Phase 2 study, comparing PK, and assessing safety, tolerability and efficacy of peripheral and central i.v. administration of melflufen in patients with relapsed and refractory multiple myeloma (RRMM). It is an international study, enrolling patients in the United States (US) and Europe. The study will enroll patients following at least 2 lines of prior therapy.

Patients will be randomized (1:1) to Arm A or Arm B (see Figure 1). For each arm, treatment will be given in 28-day cycles and may be given in an outpatient treatment setting. PK samples will be collected at Day 1 of Cycles 1 and 2.

Figure 1. Study Design



3.2 STUDY TREATMENT

Arm A:

- At Cycle 1, melflufen 40 mg will be administered as a 30-minute infusion via a peripheral venous catheter (PVC). From Cycle 2 and onwards melflufen will be administered as a 30-minute infusion via a central catheter*.
- Dexamethasone will be given p.o. at the standard dose of 40 mg weekly, at days 1, 8, 15 and 22. Patients ≥ 75 years of age should receive a dose of dexamethasone p.o. of 20 mg weekly.

Arm B:

- At Cycle 1, melflufen 40 mg will be given as a 30-minute infusion via a central catheter. At Cycle 2, melflufen will be administered as a 30-minute infusion via a PVC. From Cycle 3 and onwards melflufen will be administered as a 30-minute infusion via a central venous catheter (CVC)*.
- Dexamethasone will be given p.o. at the standard dose of 40 mg weekly, at days 1, 8, 15 and 22. Patients ≥ 75 years of age should receive a dose of dexamethasone p.o. of 20 mg weekly.

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

* After 6 patients have received peripheral infusion with adequate PK data, a Data Safety Monitoring Committee (DSMC) will assess the safety and tolerability of received peripheral infusion. The DSMC may then allow continuation with peripheral infusion in Cycle 3 and onwards (in both Arm A and B) to further study local tolerability with repeat peripheral infusions. The investigator in agreement with the patient will determine whether continued treatment will use peripheral or central administration.

3.3 DATA AND SAFETY MONITORING COMMITTEE

An independent DSMC will perform surveillance of efficacy/safety balance at regular intervals and on an as needed basis during the study to safeguard the interest of study patients. The DSMC will consist of the lead investigator, Sponsor representative(s), the contract research organization (CRO) global medical monitor and headed by an independent chairperson. All activities and processes surrounding the DSMC will be outlined in the DSMC Charter.

The DSMC will assess the benefit/risk profile of the study. All reported grade 3-4 treatment-related non-hematological adverse events (AEs), all local toxicities at the peripheral injection site as well as all serious adverse events (SAEs), as well as efficacy and PK data will be presented to the DSMC.

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

After 6 patients have received 2 cycles of 40 mg melflufen, one cycle via peripheral infusion and one cycle via central infusion with adequate PK data, the DSMC will assess the safety and tolerability of received infusions. The DSMC may then allow continuation with the peripheral infusion in Cycle 3 onwards (in both Arm A and B) to further study local toxicity with repeat peripheral infusions. The investigator, in agreement with the patient, will determine whether continued treatment will use peripheral or central administration.

If no major safety signals have been reported, recruitment may continue during preparations for the DSMC meeting.

Following a DSMC evaluation of data from at least 20 PK - evaluable patients, with an observation period of at least 28 days from the second dose of melflufen, the main PK and safety and tolerability study may be concluded.

A patient is considered to have completed the PK study when administered two 40 mg doses of melflufen with PK sampling, one PK sampling series following peripheral administration and one PK sampling series following central administration and that the sampling series are sufficient to evaluate all PK parameters. Patients in both arm A and B will receive treatment until there is documented progressive disease (PD) according to International Myeloma Working Group Uniform Response Criteria (IMWG-URC) guidelines, unacceptable toxicity, the patient/treating physician determines it is not in the patient´s best interest to continue, or patient´s withdrawal of consent.

4. SAMPLE SIZE AND POWER CALCULATION

Evaluation of combined data for the melflufen studies O-12-M1, OP-103, OP-104 and OP-107 on patients with multiple myeloma (MM) has demonstrated a relationship between melphalan systemic exposure and the lowest (nadir) levels of neutrophils and thrombocytes in treatment cycle 1. The incidence of grade 3 and grade 4 events increased in parallel with the melphalan AUC values. For melflufen and desethyl-melflufen no corresponding relationship has been found. Melphalan AUC has therefore been selected as the main PK parameter for which similarity between central and peripheral melflufen administration should be assessed.

The within-patient variability in melphalan PK parameters after melflufen administration has been evaluated in study OP-103 from data for the first two treatment cycles in 59 patients. The within-patient standard deviations (SD) in log scale were C_{max}: 0.251, AUC: 0.248 and AUC_{inf}: 0.217. Based on a geometric mean ratio peripheral vs. central of 0.95, a 90% confidence interval (CI) for the ratio of geometric means within bioequivalence limits of 0.8 and 1.25, and 80% power, a sample size of 20 patients (10 per sequence) is required assuming a within-patient variability for period differences (in log scale) of 0.29.

Approximately 25 patients will be enrolled to achieve 20 PK- and local tolerance-evaluable patients.

5. ANALYSIS ENDPOINTS

5.1 PRIMARY ENDPOINTS

PK:

- C_{max} of melphalan
- $AUC_{(0-t)}$ of melphalan
- $AUC_{(0-\infty)}$ of melphalan

Safety:

- Frequency and severity of local reactions including phlebitis at infusion site after peripheral i.v. administration

5.2 SECONDARY ENDPOINTS

PK:

- Cmax of melflufen and desethyl-melflufen
- AUC(0-t) of melflufen and desethyl-melflufen
- AUC(0-∞) of melflufen and desethyl-melflufen
- Elimination half-life t½ of melflufen, melphalan and desethyl-melflufen

Safety:

- Frequency and Grade of Treatment emergent Adverse Events (TEAEs)

Efficacy:

- Best Response (stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD) or PD
- ORR (including CR/sCR, VGPR and PR)
- CBR proportion of patients with ≥ MR as best response
- DOR (time from the first confirmed response of sCR, CR, VGPR or PR to first confirmed disease progression, or death due to any cause)
- DOCB (time from first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause)

- TTR (time from randomization to the date of the first documented confirmed response in a patient that has responded with ≥ PR (sCR, CR, VCPR or PR))
- TTP (time from the date of randomization to the date of the first documented confirmed PD)
- TTNT (time from randomization to the date of next anti-myeloma treatment)
- PFS (time from the date of randomization to the date of first documentation of confirmed PD or death due to any cause)

Exploratory:

- DNA, RNA and protein-based drug response biomarkers including but not limited to aminopeptidases and esterases
- Value in each scale assessed by patients
- Value in each scale assessed by nurses
- EQ-5D-5L:
  - Value and changes from baseline in Visual Analogue Scale (VAS) and EQ-index
  - Number of patients by category and dimension
- Number of health services
- Number and days of hospitalization

6. ANALYSIS POPULATIONS

Full analysis set

All patients who are randomized. Patients will be analyzed according to the treatment assigned at randomization. All efficacy endpoints will be performed using the full analysis set (FAS).

Safety Set

All patients randomly assigned to study treatment that receive at least a partial dose of study treatment (melflufen and/or dexamethasone). Patients will be analyzed according to the treatment/administration route (peripheral or central) they actually received. For the safety analysis by sequence arms the planned sequence arms as randomized will be used. All safety endpoints will be performed using the safety analysis set.

PK Set

All patients that have received at least two melflufen doses of 40 mg and have sufficient PK samples taken at Cycle 1 and 2 for determination of all PK variables. One PK sampling series

following peripheral administration and one PK sampling series following central administration. Patients with a dose reduction in Cycle 2 are not evaluable for PK.

7. ANALYTICAL PLAN AND STATISTICAL METHODS

7.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All analyses will be performed using SAS statistical analysis software (SAS, SAS/GRAPH and SAS/STAT; version 9.4 or higher of SAS for Windows [SAS Institute Inc.; Cary, NC, USA]).
Descriptive statistics for continuous variables will include the number of patients with non-missing data (n), arithmetic mean, SD, median, minimum and maximum. Summary statistics for categorical variables will contain count and percentage based on the number of patients in the selected analysis population. Percentages will be presented to one decimal, except for zero and one hundred percent, which will be presented as 0% and 100%.
For descriptive statistics of continuous variables, the accuracy of the minimum and maximum should match the original data; for the mean and median one more decimal point in addition to the original data will be presented, and for SD two more decimal points in addition to the original data will be presented. For the derived variables (e.g. time since diagnosis) minimum and maximum will be presented with one decimal after point; mean, median and SD decimals will be applied following the rule above.
Presented decimal places should however not be greater than 4.
Denominators for percentages will be based on the number of patients with non-missing data in the population used in each column, for the summaries presented by time points the denominator will be the number of patients with non-missing data at each time-point. A “missing” category will be included for any parameter for which information is missing, without a percentage.
Formal statistical analysis will only be conducted for selected PK endpoints. Other endpoints will primarily be presented using descriptive statistics.
By default the data collected in the electronic case report form (eCRF) and by external vendors will be used for analysis unless it is specified that additional derivation is required.

In general demographics, disposition, historical and efficacy summaries will be presented by sequence groups (i.e. A and B) and total unless otherwise specified; safety tables will be presented

either by combined groups (i.e. administration route: PVC and CVC) and total or sequence groups and total as specified in the specific sections of this SAP below.

For the presentation by combined groups the assessments that happen prior to the shift to the new injection type are all linked to the previous type of injection, including also the measurements that happen just prior to the injection at the day of the new injection, the exception is the analysis of visual infusion phlebitis (VIP) scores where both pre-infusion and post-infusion assessments are linked to PVC injection type at cycles where PVC infusion is performed.

7.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

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

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

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

For any events before the first dose date, study day is calculated as: event date – date of first administration of study treatment. As such, one day before first dose date was study day -1.

Because unscheduled assessments are not associated with any scheduled time point, they are excluded from all summaries by time point. Unscheduled assessments will be considered when deriving myeloma response parameters as described in the Section 7.7. and for analysis of laboratory parameters by worst toxicity grade as specified in the Section 7.8.4. of this SAP. All unscheduled assessments will be presented in the respective listings.

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

will be applied.

7.3 HANDLING OF MISSING DATA

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

- Start dates (e.g., AE onset date or start date of medication, date of diagnosis, date of relapse). For missing start day only - day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation, unless there is a complete end date which is earlier.
- For missing start day and month - day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation, unless there is a complete end date which is earlier (or incomplete end date with month earlier than month of the date being used for calculation, when year is the same).
- Stop dates (e.g., AE resolution date or stop date of medication). For missing stop day only - day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).

- For missing stop day and month - day and month will be imputed as the last day of the year (i.e., 31 December).

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

In case of incomplete date of relapse, for the purpose of calculation of the time since most recent relapse the rules mentioned above for the partial start date will be used. However, for the purpose of calculation of time since frontline transplant to relapse and derivation of refractory status the simplified approach of assigning first day of a month in case of missing day and 1 January in case

of missing month and day will be used.

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

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

AEs with missing severity are considered severe (grade 3) for purposes of summaries. Imputed relationship and severity will not be included in the listings.

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

7.4 PATIENT DISPOSITION

Disposition summary will be based on the FAS and presented by sequence treatment arms.

The disposition of patients includes:

- The number and percentage of treated patients
- The number and percent of randomized but never treated patients
- Number (%) of patients in Safety and PK sets
- Number (%) of patients permanently discontinued from the treatment along with the primary reasons for permanent treatment discontinuation. The numbers above will also be presented separately for the type of administration (PVC or CVC) during which the discontinuation occurred
- Number (%) of patients in PFS follow-up
- Number (%) of patients discontinued from the study and reasons for study discontinuation

Treatment discontinuations due to AE specific to coronavirus disease of 2019 (COVID-19) or other pandemic-related reasons will be presented separately.

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

7.5 PROTOCOL DEVIATIONS

Major protocol deviations will be summarized by deviation type and relationship to COVID-19

for the FAS by combined treatment arms and Overall. Overall column includes all the major protocol deviations, including those that happened on Screening and Follow-Up period, while combined treatment arm columns include only those that happened during the treatment period and could be linked to the particular administration type.

All protocol deviations will also be provided in a listing.

7.6 PATIENT CHARACTERISTICS

7.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

The following demographic and baseline characteristics will be summarized descriptively for the FAS by sequence treatment arms:

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

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

7.6.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Medical history will be summarized by Medical Dictionary of Regulatory Activities (MedDRA) (version 24.0 or higher), System Organ Class (SOC) and preferred term (PT) using number (n) and percentage (%) of patients having at least one occurrence of a disease for FAS by sequence treatment arms. A listing will be provided for patient medical history.

7.6.3 MULTIPLE MYELOMA DISEASE HISTORY

The following disease characteristics at diagnosis will be summarized descriptively for the FAS by sequence treatment arms:

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

The following disease characteristics at baseline/study entry will be summarized descriptively for the FAS by sequence treatment arms:

- Stage of disease (ISS and R-ISS)
- Heavy chain and light chain subtypes
- Evidence of lytic bone disease
- Evidence of EMD
- Time since diagnosis in years (calculated as [date of first dose of study drugs (the earliest of melflufen and dexamethasone first dose) – date of diagnosis+1]/365.25). Partial dates will be imputed according to the section 7.3 of this SAP
- Time since most recent relapse/progression in months (calculated as [date of first dose of study drugs (the earliest of melflufen and dexamethasone first dose) – date of most recent relapse/progression+1]/30.4375)
- Baseline serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), kappa/lambda values
- Baseline maximum bone marrow plasma cells (%) as values and by categories (<30%, 30 - <60%, ≥60%) (Note: The maximum bone marrow plasma cells involvement will be defined as the highest value amongst any of the available baseline test results from the following local bone marrow lab parameters: clonal plasma cells (%) (immature plasma cells/total cells) and plasma cells (%) (plasma cells ratio)).
- Baseline laboratory assessments
  - β2 microglobulin (mg/L) as values and categories (< 3.5, 3.5 – 5.5 and > 5.5)
  - Platelet count (10^9/L) as values and categories (<75, ≥75 - ≤ 100, >100 - ≤ 150, >150)
  - ANC (10^9/L) as values and categories (<1.0, 1.0 – 1.5, and >1.5)
  - Hemoglobin (g/L) as values and categories (<80, 80 – 100, >100)
  - Lactate dehydrogenase (LDH) (u/L) as values and categories (<1.5xULN and ≥1.5xULN)
  - Albumin (g/L) as values and categories (<35, ≥35)
  - Creatinine

- estimated glomerular filtration rate (eGFR) (mL/min/1.73m2) and categories (<45, ≥45 - <60, ≥60 - <90, ≥90)
- Corrected calcium

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

ISS will be derived from screening serum β2 microglobulin and albumin. This derived ISS will in turn be used with screening serum lactate dehydrogenase (LDH) and high-risk cytogenetics at study entry as defined by the R-ISS guidelines to derive R-ISS. Derived ISS and R-ISS will be referred as "Derived ISS" and "Derived R-ISS" respectively.

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

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

A separate summary dedicated to fluorescence in situ hybridization (FISH) cytogenetics investigations at diagnosis and study entry will be presented, including the number and percentage of patients having particular types of cytogenetic abnormalities. Cytogenetics abnormalities will also be pooled by risk level (high-risk, standard-risk and Unknown).

High-risk is defined in case the following abnormalities were found: deletion (17p), gain 1q (+1q), gain (1q21); t (4;14), t(4;14) (p16;q32), t (14;16), t (14;16) (q32;q23), t(14;20), t(14;20) (q32;q11). Standard-risk consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk. Standard-risk category will only be presented at diagnosis.
Unknown: consists of patients for whom the FISH procedure was not done or unevaluable.
Bone lesion assessments at screening will be analyzed descriptively with the number and percent of patients, including number and percent of patients for whom skeletal X-Ray or low dose CT scan was performed, method of skeletal survey, result of exam (in case multiple results are available patients are counted only for the result of exam based on the most severity case in the order of 'Abnormal – clinically significant', 'Abnormal – not clinically significant', 'Normal'), bone lesions locations, the same information will be presented for the other imaging procedures.
Listings will be provided for MM history.

7.6.4 PRIOR MM THERAPIES

The following information related to prior MM therapies will be summarized for the FAS by sequence treatment arms:

- Number and percentage of patients who had a transplant
- Number of patients who had a salvage transplant (defined as any transplant where the patient has already had 1 or more transplants in earlier lines). Planned tandem autologous or autologous-allogeneic are considered as one transplant
- Frontline transplant type (allogeneic or autologous). Frontline transplant is the first transplant per patient irrespective in which therapy line it was applied. The number and percentage of patients having frontline transplant per prior therapy line will be presented
- Number and percentage of patients with the tandem transplant
- Number and percentage of patients with at least one prior autologous transplant, and number and percentage of patients with at least two prior autologous transplants
- Number of prior autologous transplants
- Time from frontline transplant to relapse (the earliest relapse following frontline transplant, not necessarily after the prior therapy line when frontline transplant occurred) in years (as

continuous variable as well as per categories < 1 year, ≥1 year – <1.5 years, ≥1.5 years – ≤2 years, >2 years) . Calculated as [date of relapse – date of frontline transplant+1]/365.25)

- Number of prior systemic therapy lines
- Best response to the last prior line of therapy
- Refractory status to last prior line of therapy
- Number and percentage of patients with any prior therapy lines (as well as during the last therapy) including: immunomodulatory drugs (IMiD's), proteasome inhibitors (PI's), alkylators, anti-CD38 monoclonal antibodies (mAb), other mAb and others
- The number and percentage of patients refractory to at least one prior line of therapy (as well as to last prior therapy line) mentioned in the point above
- Number and percentage of patients who received an IMiD and PI (double-class) in any of the prior therapy lines
- Number and percentage of patients who received an IMiD, PI, and anti-CD38 mAb (triple-class) in any of the prior therapy lines
- Number and percentage of patients that are double class refractory (refractory to at least one PI and one IMiD happened in any of the prior therapy lines and not necessarily in one therapy line)
- Number and percentage of patients that are triple-class refractory (refractory to at least one PI, at least one IMiD and at least one Anti-CD38 mAb happened in any of the prior therapy lines and not necessarily in one therapy line) or triple intolerant (if the patient discontinued at least one PI, at least one IMiD and at least one Anti-CD38 mAb due to toxicity in any of the prior therapy lines and not necessarily in one therapy line , and did not receive a drug in the same therapeutic drug class again prior to entering the current study)
- Number and percentage of patients with prior radiotherapy.

The next lists of drugs are associated with each drug class:

- IMiD is defined as World Health Organization Drug Dictionary (WHODD) Standardized Drug Groupings (SDG) "Antineoplastic thalidomide analogues".
- PI is defined as SDG "Antineoplastic proteasome inhibitors".
- Alkylators is defined as SDG "Antineoplastic alkylating drugs".
- Anti-CD38 mAb is defined as SDG "Antineoplastic CD38 antigen inhibitors".

- Other mAb is defined as SDG "Monoclonal antibodies – antineoplastics" excluding SDG "Antineoplastic CD38 antigen inhibitors".
- Other antineoplastic drugs for the treatment of MM will be referred to as 'Other". Will be identified by manual review of the drugs not included into the categories above.

Refractory is defined as non-response disease (achieving SD or PD as the best response) while on therapy, or reason for termination was PD, or relapse/progression within 60 days after stop date of treatment.

Patient considered refractory to the therapy line if refractory to any of the prior therapies within the prior therapy line, whereas a patient is deemed as non-refractory to a therapy line in case of non-refractory to all of agents in the therapy line. Otherwise, a patient's refractory status to the therapy line will be considered unknown.

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

7.6.5 PRIOR AND CONCOMITANT MEDICATION

All concomitant medications will be coded using the WHODD dated 01 March 2021 or higher.

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

The number and percentage of patients with at least one concomitant medication will be summarized by the Anatomical Therapeutic Chemical (ATC) class (ATC 2 and ATC 4) and preferred name. Summaries will be presented by FAS by sequence treatment arms. Patients may have more than one medication per ATC class and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. The summaries will be ordered by descending frequency of ATC class and preferred name within each ATC class in the total group. Prior medications will be presented separately in the same way.

Concomitant medication is assigned to the particular cycle if taken between the date of the study drugs (the earliest of melflufen/dexamethasone) administration at particular cycle and date of study drugs administration in subsequent cycle. If patient discontinued somewhere in between the cycles

concomitant medication is assigned to the cycle in which the discontinuation has happened.
Separate summaries will be provided for the number and percentage of patients with the following medication categories: "Haematopoietic growth factors" (WHODD SDG "Colony stimulating factors") and "Transfusions" (including next PTs: "Platelets", "Erythrocytes", "Red blood cells").
A listing of prior and concomitant medications will be provided.

7.7 EFFICACY ENDPOINTS AND ANALYSIS

All efficacy analyses will be produced on the FAS and Safety analysis set by sequence treatment arms.
All tumor response and progression-depended objectives are assessed by investigators according to the IMWG-URC (Kumar et al.2016).

7.7.1 RESPONSE RATES

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

Best Overall Confirmed Response

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

Confirmed response: Two consecutive assessments with the same response result made at any time. In case at the second consecutive assessment (made at any time) the response is higher than the previous one then confirmed response (linked to the first assessment visit) will be the first one (e.g., PR – VGPR consecutive pair will lead to a PR confirmed response at the first visit). In case the second consecutive response is lower than the first one then confirmed response (linked to the first assessment visit) will be the second one (e.g. CR-VGPR consecutive pair will lead to a VGPR

confirmed response at the first visit).

This rule for confirmed response above is only applicable to sCR-SD responses; confirmed PD is treated separately as two consecutive PD assessments.

Best Unconfirmed Response

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

ORR

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

CBR

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

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

7.7.2 TIME TO EVENT PARAMETERS

PFS

PFS is defined as the time from the date of randomization to the date of first documentation of confirmed PD or death due to any cause, whichever occurs first. PFS time, in months, is calculated as (PFS date – date of randomization +1)/30.4375.

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

Table 2. Conventions for PFS date derivation and censoring

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

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

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

DOR

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

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

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

DOCB

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

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

TTR

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

TTP

TTP is defined as time in months from randomization to the date of the first documented confirmed progression. TTP will be censored and summarized using the same method as for PFS, but not considering death in the censoring rules, see Table 3 below.
TTP will be derived as (TTP date – randomization date +1)/30.4375.

Table 3. Conventions for Censoring for TTP

Situation	Date of Progression or Censoring	Outcome
No post-baseline disease assessments	Date of randomization	Censored
New anticancer therapy started before documentation of PD	Date of last disease assessment prior to start of new anticancer therapy	Censored
PD immediately after more than 1 consecutively missed disease assessment visit*	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
No PD documentation	Date of last disease assessment	Censored
PD between planned disease assessments	first disease assessment showing PD	Progressed

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

TTNT

TTNT in months will be calculated as time in months from the date of randomization to the start of next line of therapy (excluding radiotherapy). Patients who have no post study myeloma therapy will be censored at the earlier of date of death and date of last contact. TTNT will be summarized using the Kaplan-Meier (K-M) method.

TTNT will be derived as (TTNT date – randomization date +1)/30.4375.

An alternative definition will also be used:
TTNT in months will be calculated from the date of randomization to the start of next line of therapy (excluding radiotherapy) or death. Patients who have no post study myeloma therapy and do not have a date of death will be censored at the date of last contact.

7.7.3 Efficacy Assessments

Myeloma specific laboratory tests results, including SPEP, UPEP, and serum free light chain (SFLC) will be summarized descriptively by assessment visit.

Central laboratory myeloma specific assessment to be used for the summaries.

All the myeloma specific laboratory tests results and other efficacy assessments (i.e. extramedullary plasmacytoma assessment) will be presented in the listings. A separate listing for bone marrow aspirate will be presented.

7.8 Safety Endpoints and Analysis

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

7.8.1 Exposure to Study Treatment

Exposure analysis will be based on the Safety analysis set by sequence treatment arms.

Duration of melflufen treatment in weeks is defined as (date of last dose – date of first dose + 29 days) divided by 7.
If a patient discontinued from treatment and the end of treatment (EOT) visit happened prior to 29 days after last dose, then the duration of melflufen is defined as (date of EOT – date of first dose +1) divided by 7.
If a patient died prior to 29 days after last dose, then the duration of melflufen is defined as (date of death – date of first dose +1) divided by 7.
Duration of dexamethasone treatment in weeks is defined as (date of last dose – date of first dose + 1) divided by 7.
Overall duration of treatment with study drug in weeks is defined as the longest duration of dexamethasone and melflufen treatment.

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

Dose modification information will be summarized descriptively for any drug and then also separately for melflufen and dexamethasone. The number of patients with drug modifications due to AEs will be presented based on the AE eCRF page and the number of patients with each action by frequency will be presented based on the melflufen/dexamethasone administration eCRF page. The number of patients with any drug modification will also be presented by cycle.
A dose delay is defined as a consecutive dose of melflufen administered on day 33 or later following a preceding dose of melflufen (day at the moment of melflufen administration is defined as a difference between Cycle X Day 1 (CXD1) date and C(X-1)D1 date +1). Dose delays will be

categorized as delays in weeks as 1 (day 33 to 39), 2 (day 40 to 46), 3 (day 47 to 53), 4 (day 54 to 60), and >4 weeks (day 61 or later) for each cycle.

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

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

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

7.8.2 LOCAL REACTIONS. PRIMARY SAFETY ENDPOINT

Peripheral infusion related reactions summaries will be presented based on the Safety analysis set by combined PVC treatment arm overall and by cycle.

The number and percentage of patients experiencing at least one local infusion related reaction after peripheral i.v. administration will be presented. Local infusion related reactions will be presented by SOC and PT and also separately by SOC, PT and maximum toxicity grade overall and by cycle. The same rules for analysis as specified in section 7.8.3. Adverse Events section are applicable here.

Local infusion related reactions will be identified from all infusion related reactions using the list of applicable preferred terms (PT), based on selected PTs of the High Level Term (HLT) “Infusion site reactions” and also standardized MedDRA queries (SMQ) “Hypersensitivity” and "Extravasation events (injections, infusions and implants)", the list will be finalized prior to the database lock following manual review of the respective data.

A separate summary will present the number and percentage of patients with particular VIP scores by visit and time point. For VIP scores analysis both pre-infusion and post-infusion assessments are linked to PVC injection type at cycles where PVC infusion is performed.

A listing showing all the infusion related reactions details will be presented. A separate listing will be presented for the VIP Scores.

7.8.3 ADVERSE EVENTS

All AE summaries will be presented based on the Safety analysis set by sequence treatment arms

and total, overall and by cycle unless otherwise specified.

All AEs will be coded using the MedDRA (version 24.0 or higher), for toxicity assessment the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 5.0 AE will be used. The summaries of AEs will be based on TEAEs.

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

An overall summary of TEAEs will be presented. It will include the number and percentage of patients (as well as total event count) with at least one TEAE, patients with at least one grade 3, grade 4 and grade 3/4 TEAE, patients with at least one serious TEAE, and patients with TEAEs leading to death.

The overall summary will include the treatment related TEAEs analyzed separately in three ways: treatment related TEAEs (melflufen and/or dexamethasone related, melflufen related TEAEs, and dexamethasone related TEAEs). It will include the number and percentage of patients (as well as total event count) with related TEAEs; patients with related grade 3, grade 4 and grade 3/4 TEAEs; patients with related serious TEAEs; and patients with related TEAEs leading to death. In addition the number and percentage of patients with TEAEs leading to dose reduction, dose delay and dose discontinuation will be presented separately for overall treatment (melflufen and/or dexamethasone), melflufen and dexamethasone.

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

- TEAEs
- Non-serious TEAEs
- Treatment related (related to melflufen and/or dexamethasone) TEAEs
- Melflufen related TEAEs
- Dexamethasone related TEAEs
- Serious TEAEs
- Treatment related serious TEAEs

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

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

- Thrombocytopenia (SMQ "Haematopoietic thrombocytopenia" – Broad scope)
- Neutropenia (PTs: "Neutropenia", "Neutrophil count decreased", "Febrile neutropenia", "Neutropenic sepsis", "Neutropenic infection", "Cyclic neutropenia", "Band neutrophil count decreased", "Band neutrophil percentage decreased", "Neutrophil percentage decreased", "Agranulocytosis", "Granulocyte count decreased", "Granulocytopenia)
- Anemia (SMQ "Haematopoietic erythropenia" – Broad Scope)
- Myelodysplastic syndrome (PTs: "5q minus syndrome", "Chronic myelomonocytic leukemia", "Myelodysplastic syndrome", "Myelodysplastic syndrome transformation", "Myelodysplastic syndrome unclassifiable", "Refractory anemia with an excess of blasts", "Refractory anemia with ringed sideroblasts","Refractory cytopenia with multilineage dysplasia", "Refractory cytopenia with unilineage dysplasia", "Sideroblastic anemia")
- Second primary malignancies ((SMQ "Malignant or unspecified tumours" and HLT "Myelodysplastic syndromes"), excluding HLGT "Plasma cell neoplasms")
- Febrile neutropenia (PT "Febrile neutropenia")
- Infections (SOC "Infections and infestations")

- Infective pneumonia – broad scope (SMQ "Infective pneumonia")
- Infective pneumonia – narrow scope (SMQ "Infective pneumonia" – Narrow terms)
- Hemorrhage (SMQ "Haemorrhages" – Narrow terms)
- Thrombocytopenia concomitant to hemorrhage: Hemorrhage with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 thrombocytopenia. Grade 3/4 thrombocytopenia resolution date is to be identified based on the laboratory data as a first day when thrombocytopenia assessment is grade 2 or lower (grade ≤ 2 for toxicity "Platelet count decreased").
- Neutropenia concomitant to infection: Infection with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 neutropenia. Grade 3/4 neutropenia resolution date is to be identified based on the laboratory data as a first day when neutropenia assessment is grade 2 or lower (grade ≤ 2 for toxicity "Neutrophil count decreased").

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

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

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

1) within a given SOC
2) within a given SOC and PT combination or MedDRA SMQ

The maximum CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. For by cycle presentation the maximum toxicity grade will be identified separately within each cycle.

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

considered a TEAE unless the end date is prior to the date of the first dose of study drug (the earliest of melflufen and dexamethasone start date).

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

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

7.8.4 LABORATORY DATA

Laboratory data will be summarized for Safety analysis set by sequence treatment arms.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units on Study Data Tabulation Model (SDTM) level. Only local laboratory data will be used for the summaries, however both local and central results will be presented in the listings.

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

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

Shift tables for the change in CTCAE grade (with separate parts for decreased and increased grades) will be constructed for hematology and chemistry laboratory parameters, which have corresponding CTCAE grades to tabulate changes in NCI CTCAE (version 5.0) from baseline to worst post-baseline on study (up to and including EOT visit) CTCAE grade. Number of patients with grade 3 or higher toxicity will be summarized as counts and percentages by cycle. A separate listing of all laboratory results corresponding to grade 3 or 4 will be provided.

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

- Hematology

  - Hemoglobin (increase , decrease)
  - Platelets (decrease)
  - White blood cells (WBC) (increase, decrease)
  - Absolute neutrophil count (ANC) (decrease)
  - Lymphocyte count (increase, decrease)
- Serum Chemistry
  - Alanine aminotransferase (ALT) (increase)
  - Aspartate aminotransferase (AST) (increase)
  - Alkaline phosphatase (increase)
  - Total bilirubin (increase)
  - Creatinine (increase)
  - Calcium (increase, decrease)
  - Glucose (increase, decrease)
  - Albumin (decrease)
  - Uric Acid/Urate (increase)
  - Magnesium (increase, decrease)
  - Phosphorus/Phosphate (increase , decrease)
  - Potassium (increase, decrease)
  - Sodium (increase, decrease)
  - eGFR (decrease)

For hemoglobin, ANC and platelet counts, CTCAE grade shift tables will also be additionally presented by cycles. For by cycle presentation the worst grade is calculated within each cycle. Time from the date of the melflufen dose until the date of grade 3, grade 4 and grade 3/4 onset in particular cycle will be presented for each cycle for ANC and platelets. Time to onset of grade 3, grade 4 and grade 3/4 for ANC and platelets will also be presented overall (duration in days from the treatment start until the date of grade 3, grade 4 and grade 3/4 respectively).

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

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

7.8.5 VITAL SIGNS

Vital signs will be summarized for the Safety analysis set by sequence treatment arms.
Results and change from baseline to post-baseline time-points for weight, blood pressure, pulse, respiratory rate and temperature will be presented.

7.8.6 PHYSICAL EXAMINATION

Physical examination will only be listed without a summary.

7.8.7 12-LEAD ELECTROCARDIOGRAM (ECG)

ECG data will be summarized for Safety analysis set by sequence treatment arms.
ECG data (heart rate, PR interval, QRS interval, QT interval, QTc-Fridericia (QTcF) interval, RR interval) will be summarized using descriptive statistics, changes from baseline to EOT visit will also be evaluated.
Shift tables from baseline (Normal/Abnormal-clinically significant/Abnormal – not clinically significant) to each visit will be summarized for ECG interpretation data.
All ECG data collected will be presented in the listing.

7.9 EXPLORATORY ENDPOINTS AND ANALYSIS

7.9.1 BIOMARKERS

DNA and RNA-based drug response biomarkers including but not limited to aminopeptidases and esterases. The population will be presented separately from the main clinical study report (CSR) and will be managed by the sponsor.

7.9.2 TREATMENT SATISFACTION AND QUALITY OF LIFE (QOL)

Treatment satisfaction and QOL will be analyzed for Safety analysis either by sequence or combined treatment arms as specified in this section below.

Patient satisfaction and preference, nurse convenience and preference

An 11-point numerical rating scale (NRS) will be used to measure patient treatment satisfaction after central and peripheral i.v. administration of melflufen. The scale ranges from 0-10,

where "0" represents no satisfaction, and "10" represents very satisfied. For patient satisfaction and preference scales, the number and percentage of patients having particular score assigned to a particular question will be presented by combined treatment arms by cycle. The results will also be analyzed by means of numeric descriptive statistics (n, mean, SD, median and etc.).

An 11-point NRS will be used to measure nurse convenience to administer treatment. The scale ranges from 0-10, where "0" represents not convenient at all, and "10" represents very convenient. For nurse convenience and preference scales, the number and percentage of nurses having particular score assigned to a particular question will be presented by combined treatment arms by cycle. The results will also be analyzed by means of numeric descriptive statistics (n, mean, SD, median and etc.).

A separate summary by sequence group and overall will present the number and percentage of patients and nurses who preferred PVC or CVC route of administration. Also a cross-tabulation summary presenting the number and percentage of nurses and patients who had the same or different preferences will be created.

EQ-5D-5L

EQ-5D-5L questionnaire consists of two parts – the EQ-5D-5L descriptive system and the EQ VAS and will be presented by sequence treatment arms.
For EQ-5D-5L descriptive system the number and percentage of patients for each score within the dimension will be presented. Shift table from baseline to post-baseline assessments will be used for analysis of results changes.
EQ VAS will be analyzed by means of descriptive statistics and change from baseline.
In addition, the EQ Index will be identified at each time point comparing health state to US value set and analyzed the same as EQ VAS.

Use of health services and hospitalization

The number of health services used and the number of days of hospitalization will be summarized by means of descriptive statistics by sequence treatment arms.

7.10 OTHER ENDPOINTS AND ANALYSIS

7.10.1 PHARMACOKINETICS

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

- C_{max}

  C_{max} is defined as the maximum observed drug concentration observed in plasma over all PK sample concentrations. It will be obtained from the C_{max} parameter calculated by WinNonlin®. If there is no measurable concentration in the subject's PK profile, then C_{max} will be missing for that subject. C_{max} will be reported in units of ng/mL.

- Time of maximum concentration (T_{max})

  Time of maximum plasma concentration (T_{max}) is defined as the time at which the C_{max} occurs. It will be obtained from the T_{max} parameter calculated by WinNonlin®. If there is no measurable C_{max} in the subject's PK profile, then T_{max} will be missing for that subject. T_{max} will be reported in minutes.

- $AUC_{(0-t)}$

  $AUC_{(0-t)}$ is defined as the area under the concentration-time curve from dosing (time 0) to the time of the last measured concentration. $AUC_{(0-t)}$ will be estimated using the Linear Up Log Down calculation method and obtained from the AUClast parameter calculated by WinNonlin®.

- $AUC_{(0-\infty)}$

  $AUC_{(0-\infty)}$ is defined as the total area under the concentration-time curve from start of infusion (time 0) to the limit as the end time becomes arbitrarily large. $AUC_{(0-\infty)}$ will be obtained from the AUCINF_obs parameter calculated by WinNonlin®.

- t½

The apparent t½ is defined as the time required for the drug concentration to decrease by a factor of one-half in the terminal phase. t½ will be estimated as ln(2) / Ke, Ke referring to terminal phase elimination rate constant of the apparent log-linear decrease as defined by at least 3 data points. It will be obtained from the HL_Lambda_z parameter calculated by WinNonlin®. $t_{1/2}$ will be reported in minutes.

Blood samples for PK analysis, i.e. melflufen, desethyl-melflufen and melphalan concentrations in plasma, will be collected at the following time points:

Table 4. PK sampling schedule

	Cycle 1 and Cycle 2
During melflufen infusion	Sample 1: 5 minutes Sample 2: 10 minutes Sample 3: 15 minutes Sample 4: 20 minutes Sample 5: 25 minutes Sample 6: 30 minutes -immediately before end of infusion
After end of melflufen infusion	Sample 7: 5 minutes Sample 8: 10 minutes Sample 9: 15 minutes Sample 10: 30 minutes Sample 11: 60 minutes Sample 12: 120 minutes Sample 13: 240 minutes

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

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

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

Table 5. PK parameters to be calculated

Phoenix WinNonLin ID	Unit	Parameter code	CDISC submission value
Rsq		R2	R Squared
Rsq_adjusted		R2ADJ	R Squared Adjusted
Corr_XY		CORRXY	Correlation Between TimeX and Log ConcY
No_points_lambda_z		LAMZNPT	Number of Points for Lambda z
Lambda_z	min	LAMZ	Lambda z
Lambda_z_int	ng/mL	LAMZINT	Lambda z Intercept
Lambda_z_lower	min	LAMZLL	Lambda z Lower Limit
Lambda_z_upper	min	LAMZUL	Lambda z Upper Limit
Lambda_z_span	min	LAMZSPN	Lambda z Span
*HL_Lambda_z	min	LAMZHL	Half-Life Lambda z
*Tmax	min	TMAX	Time of CMAX
*Cmax	ng/mL	CMAX	Max Conc
Cmax_D	ng/mL/mg	CMAXD	Max Conc Norm by Dose
Tlast	min	TLST	Time of Last Nonzero Conc
Clast	ng/mL	CLST	Last Nonzero Conc
Clast_pred	ng/mL	CLSTP	Last Nonzero Conc Pred
*AUClast	min*ng/mL	AUCLST	AUC to Last Nonzero Conc
AUClast_D	min*ng/mL	AUCLSTD	AUC to Last Nonzero Conc Norm by Dose
AUCall	min*ng/mL	AUCALL	AUC All
*AUCINF_obs	min*ng/mL	AUCIFO	AUC Infinity Obs
AUCINF_D_obs	min*ng/mL/mg	AUCIFOD	AUC Infinity Obs Norm by Dose
AUC_%Extrap_obs	%	AUCPEO	AUC %Extrapolation Obs
Vss_obs	L	VSSO	Vol Dist Steady State Obs
Vz_obs	L	VZO	Vz Obs
Cl_obs	L/min	CLO	Total CL Obs
AUCINF_pred	min*ng/mL	AUCIFP	AUC Infinity Pred
AUCINF_D_pred	min*ng/mL/mg	AUCIFPD	AUC Infinity Pred Norm by Dose
AUC_%Extrap_pred	%	AUCPEP	AUC %Extrapolation Pred
Vss_pred	L	VSSP	Vol Dist Steady State Pred
Vz_pred	L	VZP	Vz Pred
Cl_pred	L/min	CLP	Total CL Pred
AUMClast	min*min*ng/mL	AUMCLST	AUMC to Last Nonzero Conc
AUMCINF_obs	min*min*ng/mL	AUMCIFO	AUMC Infinity Obs
AUMC_%Extrap_obs	%	AUMCPEO	AUMC % Extrapolation Obs

AUMCINF_pred	min*min*ng/mL	AUMCIFP	AUMC Infinity Pred
AUMC_%Extrap_pred	%	AUMCPEP	AUMC % Extrapolation Pred
MRTlast	min	MRTIVLST	MRT Intravasc to Last Nonzero Conc
MRTINF_obs	min	MRTIVIFO	MRT Intravasc Infinity Obs
MRTINF_pred	min	MRTIVIFP	MRT Intravasc Infinity Pred

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

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

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

Statistical methods

Descriptive statistics for drug concentrations by time point and PK variables will be provided for melflufen, melphalan and desethyl-melflufen by route of administration. For Cmax, Tmax, AUC(0-t), AUC(0-∞), and t½ arithmetic mean ± SD, geometric mean with coefficient of variation (CV%), median with minimum and maximum will be given by route of administration. Other PK parameters will be provided in a listing.

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

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

where SD is the arithmetic standard deviation.

A mean value graph (with arithmetic means) by administration route will be generated for melflufen, melphalan and desethyl-melflufen concentrations in plasma from all subjects based on planned time (min) relative to start of melflufen infusion. Individual line plots for concentrations will also be created.

Formal statistical analysis will for each compound be performed on the PK parameters AUC (0-t),

$AUC_{(0-\infty)}$ and C_{max} to assess relative plasma exposure. The PK parameters will undergo a logarithmic transformation and will be analyzed using a linear mixed effects model which will include terms for period, sequence and site of infusion (administration route: PVC or CVC) as fixed effects and subject nested within sequence as a random effect. Adjusted geometric mean ratios (GMRs) and 90% CIs for the adjusted GMRs for the comparisons between central and peripheral administration will be provided.

The following SAS code will be used for the analyses (variable names to be updated accordingly):

```
proc mixed data= datasetname;
     class sequence period trt subject;
     model logAVAL=sequence period trt /   ddfm=kenwardroger;
     random subject(sequence);
     estimate 'CVC vs PVC' trt 1 -1 / cl alpha=0.1;
 ods output estimates=est;
run;
```

where trt refers to administration route (PVC or CVC).

GMR with 90% CI is calculated as the exp(estimate of trt comparison in log scale).

A 90% CI of the GMR outside 0.8-1.25 is assessed to be a clinically meaningful difference for melphalan Cmax and AUC. No corresponding criteria will be applied for melflufen or desethyl-melflufen as data from clinical studies show no relationship between their PK parameters and indicators of bone marrow toxicity.

7.10.2 ECOG

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

8. INTERIM ANALYSIS

When the PK and peripheral safety study are completed, an interim CSR will be written. The interim analyses will include at least 20 patients who have received two melflufen doses of 40 mg, have an observation period of 28 days after the second dose and at least one peripheral i.v. infusion.

The objective of the interim CSR will be to evaluate if a peripheral i.v. infusion of melflufen can be introduced in other trials, as an alternative to central i.v. infusion. The interim analysis will include PK analysis described in the Section 7.10.1 of this SAP and safety analysis described in the Section 7.8 of this SAP. Due to the short duration of treatment, efficacy endpoints will not be included in the interim CSR.

9. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

As per the protocol all safety analyses are supposed to be presented by administration group. However during SAP development discussions presentation by sequence arms was found more relevant for most of the safety analyses as providing sufficient information and avoiding confusion in analysis and interpretation due to treatment shifts.

10. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.
The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.
In the top left portion of each table/listing, the protocol number will be presented. On the next line a table/listing number followed by the title of the table/listing and population information will be displayed. Horizontal lines will appear after the column heading of the table/listing. Footnotes will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The SAS program name will appear bottom left in a string and the page number will appear on the bottom right corner of each table/listing. The date and time of creation of table/listing will appear bottom left under to the SAS program name line.
Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format, for example, 07MAY2002.
Shells for unique tables and listings are provided in a separate Mock-Up TFLs document.

11. REFERENCES

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