Statistical Analysis Plan
Version 1.1, 11 May 2022

Protocol OP-108

Protocol Title: A Randomized, Controlled, Open-Label Phase 3 Study of Melflufen in combination with Daratumumab Compared with Daratumumab in Patients with Relapsed or Relapsed-Refractory Multiple Myeloma

National Clinical Trial number: NCT04649060

Oncopeptides AB

STATISTICAL ANALYSIS PLAN

PROTOCOL OP-108

A Randomized, Controlled, Open-Label Phase 3 Study of Melflufen in combination with Daratumumab Compared with Daratumumab in Patients with Relapsed or Relapsed-Refractory Multiple Myeloma

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1.1	1	Clarification of impact on statistical analysis due to the early termination of the study	Early termination of study

APPROVAL SIGNATURES

STUDY TITLE: A Randomized, Controlled, Open-Label Phase 3 Study of Melflufen in combination with Daratumumab Compared with Daratumumab in Patients with Relapsed or Relapsed-Refractory Multiple Myeloma

PROTOCOL NUMBER: *Version 2.1: Amendment 2, November 25, 2020*

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BPI	brief pain inventory
BPI-SF	brief pain inventory - short form
BR	best response
CA	chromosomal abnormalities
CBR	clinical benefit rate
CI	confidence interval
cm	centimeters
CMH	Cochran-Mantel-Haenszel
CR	complete response
CSR	clinical study report
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
CTX	c-terminal telopeptide
DOR	duration of response
DOCB	duration of clinical benefit
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMD	extramedullary disease
eCRF	electronic case report form
EOT	end of treatment
FAS	full analysis set
FISH	fluorescence *in situ* hybridization
FLC	free light chain
F-U	follow-up
ICH	International Council of Harmonisation
IFE	immunofixation
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
INR	international normalized ratio
IRC	independent review committee
ISS	international staging system
i.v.	intravenously

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
MRD	minimal residual disease
MDSC	myeloid derived suppressor cell
NCA	non-compartmental analysis
NCI	National Cancer Institute
NGS	next generation sequencing
NK	natural killer
NRS	numeric rating scale
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PFS-FU	progression free survival follow-up
PI	proteasome inhibitor
PINP	procollagen I N - terminal propeptide
PK	pharmacokinetics
p.o.	per os/by mouth/orally
PPAS	per protocol analysis set
PR	partial response
PRO	patient reported outcome
PT	preferred term
PVC	peripheral venous catheter
q.d.	Quaque die/ one a day
QoL	quality of life
rHuPH20	recombinant human hyaluronidase PH20
R-ISS	revised international staging system
RANK	receptor activator of nuclear factor-kappa B
RNA	ribonucleic acid
RRMM	relapsed refractory multiple myeloma
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
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

SF	short form
SFLC	serum free light chain
SMQ	Standardized MedDRA Query
SOC	system organ class
SPEP	serum protein electrophoresis
TEAE	treatment-emergent adverse event
TRACP-5b	tartrate-resistant acid phosphatase 5b
TTR	time to response
TTP	time to progression
TTNT	time to new therapy
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
WHO	World Health Organization
WBC	white blood cells

1. EARLY TERMINATION OF STUDY

The study was prematurely terminated by the Sponsor 7 Feb 2022. As a consequence, no formal statistical analyses will be performed, and most activities as described in the SAP will no longer be performed.
An abbreviated CSR will be produced based on updated outputs from DMC, where the details are described in the DMC charter and not necessarily according to the details in this SAP.
No efficacy endpoints will be derived.

2. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis and reporting for the study protocol Version 2.1: Amendment 2, November 25, 2020 entitled; a randomized, controlled, open-label phase 3 study of melflufen in combination with daratumumab compared with daratumumab in patients with relapsed or relapsed-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 of Harmonisation (ICH) guidelines E9 (Statistical Principles for Clinical Trials).
This SAP does not include the description of immunogenicity, PRO, PK and biomarkers analyses.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To show superiority of progression free-survival (PFS) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.

3.2 SECONDARY OBJECTIVES

3.2.1 KEY SECONDARY OBJECTIVES

- To evaluate and compare Overall Response Rate (ORR) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.
- To evaluate and compare Duration of Response (DOR) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.
- To assess the safety and tolerability of melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.

3.2.2 OTHER SECONDARY OBJECTIVES

- To evaluate and compare efficacy endpoints in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone:
  - Best response during the study
  - Clinical benefit rate (CBR)
  - Duration of Clinical Benefit (DOCB)
  - Time to response (TTR)
  - Time to progression (TTP)
  - Time to next treatment (TTNT)
  - Overall survival (OS)

3.3 EXPLORATORY OBJECTIVES

- To assess minimal residual disease (MRD) in patients achieving a complete response (CR) or very good partial response (VGPR) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.
- To evaluate the Progression Free Survival following next line of treatment (PFS-2) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.
- To assess and compare the changes in pain in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.

- To assess and compare responses in patients with extramedullary myeloma (plasmacytomas).
- To assess and compare use of health services and number and duration of hospitalizations in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone, and in patients who crossover and receive treatment with melflufen, daratumumab and dexamethasone.
- To evaluate the melphalan pharmacokinetic (PK) parameters during treatment with melflufen, the impact of covariates on this relationship and the inter-occasion variability in melphalan exposure (Arm A).
- To assess the PK and immunogenicity of subcutaneous daratumumab.
- To evaluate the immunogenicity of recombinant human hyaluronidase PH20 (rHuPH20) following subcutaneous daratumumab administration.
- To assess translational biomarkers that might predict response/non-response to the treatment, aid in monitoring of disease progression as well as improve understanding of mechanism of action.
- To assess and compare functional status and wellbeing based on patient reported outcome (PRO) assessments for patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.
- To evaluate efficacy in patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone after progression on daratumumab:
  - Overall response rate (ORR)
  - Duration of response (DOR)
  - Best response during the study
  - Clinical benefit rate (CBR)
  - Duration of Clinical Benefit (DOCB)
  - Time to response (TTR)
  - Time to progression (TTP)
  - Time to next treatment (TTNT)
  - Overall Survival (OS)
  - Progression free-survival (PFS)

- To assess and compare the changes in pain for patients in Arm B who crossover to treatment with melflufen, dexamethasone and daratumumab.
- To assess and compare functional status and wellbeing based on patient reported outcome (PRO) assessments for patients in Arm B who crossover to treatment with melflufen, dexamethasone and daratumumab.
- To assess the safety and tolerability of melflufen, dexamethasone and daratumumab treatment for patients in Arm B who crossover.

Additional exploratory analyses of endpoints related to pharmacokinetics and HRQoL will be described separately.

4. STUDY DESCRIPTION

4.1 STUDY DESIGN

This is an open-label, randomized, international, multicenter Phase 3 trial which will enroll patients with relapsed or relapsed-refractory multiple myeloma (MM) who are either double refractory to an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI), given alone or in combination or had at least 3 prior lines of therapy including being exposed to both an IMiD and a PI. The patients will be randomized in a 1:1 fashion into either one of two treatment arms, Arm A or Arm B. Patients who receive daratumumab in Arm B and have a confirmed disease progression will have the option to crossover and receive treatment with melflufen, daratumumab and dexamethasone.

4.2 STUDY TREATMENT

Arm A:

In Arm A melflufen i.v. 30 mg will be administered on Day 1 in every 28-day cycle in combination with daratumumab s.c. 1800 mg according to the schedule in Table 1-1.

Table 1-1 Daratumumab Schedule, Arm A

Cycles	Days
1 and 2	1, 8, 15 and 22
3 to 6	1 and 15
7 +	1

Dexamethasone 40 mg p.o. (20 mg p.o. for patients ≥ 75 years) will be given weekly (see Table 1-2).

Table 1-2 Dexamethasone dosing schedule

Dexamethasone dosing on days when melflufen and daratumumab are given		
All Cycles Day 1	patients < 75 years of age	40 mg prior to melflufen administration
	patients ≥ 75 years of age	20 mg prior to melflufen administration
Dexamethasone dosing on days when only daratumumab is given[a]		
Cycle 1 and 2: Days 8, 15 and 22 **Cycle 3 to 6:** Day 15	patients < 75 years of age	40 mg prior to daratumumab administration
	patients ≥ 75 years of age	20 mg prior to daratumumab administration
Dexamethasone dosing on weeks when no other drug is given		
Cycle 3 to 6: Days 8 and 22 **Cycle 7+** Days 8, 15 and 22	patients < 75 years of age	40 mg weekly
	patients ≥ 75 years of age	20 mg weekly

a) Prior to daratumumab administration in Cycle 1, oral dexamethasone may be substituted with i.v. dexamethasone during Cycle 1, at the investigator's discretion, if this is the standard of care of the study center.

Arm B:

In Arm B daratumumab will be given at the dose of 1800 mg s.c. according to the schedule in Table 2-1.

Table 2-1 Daratumumab Schedule, Arm B

Cycles	Days
1 and 2	1, 8, 15 and 22
3 to 6	1 and 15
7 +	1

Patients in Arm B who are confirmed to have disease progression while receiving daratumumab alone may be eligible to crossover and receive treatment with melflufen, dexamethasone and daratumumab, using the daratumumab dosing schedule at the time of disease progression. Once a patient is determined to be eligible, treatment with melflufen, dexamethasone and daratumumab has to start within 56 days from the last dose of daratumumab in Arm B.

4.3 TREATMENT DURATION

Patients in both treatment arms will receive treatment until there is documented PD (Progressive Disease) according to the IMWG-URC (International Myeloma Working Group Uniform Response Criteria) guidelines (Kumar et al. 2016), unacceptable toxicity, the patient/treating physician determines it is not in the patient's best interest to continue, or patient's withdrawal of consent. Confirmed PD (on two consecutive assessments if based on M-protein assessments) should be verified by the Medical Monitor prior to treatment discontinuation. Patients in Arm B with documented PD verified by the Medical Monitor may crossover and receive treatment with melflufen, dexamethasone and daratumumab (using the daratumumab dosing schedule corresponding to the cycle when disease progression occurred). Patients receiving therapy after crossing over will receive treatment until there is documented PD, unacceptable toxicity, the patient/treating physician determines it is not in the patient's best interest to continue, or patient's withdrawal of consent. Confirmed PD should be verified by the Medical Monitor prior to treatment discontinuation.

4.4 INDEPENDENT REVIEW COMMITTEE (IRC)

All response assessments, including PD, will be assessed by an Independent Review Committee (IRC) using the International Myeloma Working Group (IMWG) response criteria. The IRC members will be blinded to all treatment data (including investigator response) and perform their reviews in closed-meeting sessions.

4.5 DATA MONITORING COMMITTEE (DMC)

An independent Data Monitoring Committee (DMC) will perform surveillance of efficacy/safety balance at regular intervals during the study, using unblinded treatment-aggregated data. The scope of work, procedures, roles and responsibilities for the DMC are described in a separate DMC charter. The DMC can recommend continuing the study, with or without modifications, or stop the study based on benefit/risk concerns.

4.6 DOSE MODIFICATIONS

There are no dose reductions for daratumumab. For the other drugs, dose modifications will be implemented for individual patient tolerability according to dose modification guidelines described in Section 6.6 of the protocol. Patients unable to tolerate therapy following implementation of the guidelines will be permanently discontinued, unless in the opinion of the investigator and approved by the Medical Monitor, it is in the patient's best interest to continue therapy. In addition, patients discontinuing either melflufen or daratumumab in Arm A (or patients in Arm B who crossover to treatment with melflufen, dexamethasone and daratumumab), may continue with the remaining 2 study drugs according to the protocol, if in the best interest of the patient and approved by the Medical Monitor.

5. SAMPLE SIZE AND POWER CALCULATION

The sample size of 200 patients was calculated based on achieving 90% power to observe a statistically significant result for comparing the treatment arms in terms of PFS, using a log-rank test for 2 survival curves and the parameter assumptions presented in Table 3-1. Assuming a dropout rate of approximately 15%, it is anticipated to randomize 120 patients in each treatment arm, to a total number of 240 patients.

The randomization will be stratified by number of previous lines of treatment (<3 prior lines of treatment versus ≥3 prior lines of treatment) and previous treatment with daratumumab or another anti-CD38 antibody (no previous treatment versus previous treatment).

The final analysis will take place when 160 patients have experienced a PFS event.

Table 3-1 Sample Size Determination

Parameter	Assumption
Power	90%
Significance level	5%, two-sided
Hazard Ratio (Arm A / Arm B)	0.60
Distribution of survival curves	Exponential
Method	Lakatos normal approximation
Accrual time	24 months
Follow up time	6 months after last patient randomized
Total study time	18 months
Median PFS for Arm A	6.7 months
Median PFS for Arm B	4.0 months

The assumptions for this sample size estimation are based on preliminary data from an ongoing phase 1/2 study (ANCHOR OP-104) and a pooled analysis of two open-label Phase 1/2 studies of daratumumab monotherapy (IB for melflufen, Usmani et al. 2016).

6. ANALYSIS ENDPOINTS

6.1 PRIMARY ENDPOINTS

- PFS (time from the date of randomization to the date of first documentation of confirmed PD or death due to any cause).

6.2 SECONDARY ENDPOINTS

6.2.1 KEY SECONDARY ENDPOINTS

- ORR (proportion of patients who achieve a best confirmed response of stringent Complete Response (sCR), CR, VGPR or Partial Response (PR)).
- DOR (time from the first evidence of confirmed assessment of sCR, CR, VGPR or PR to first confirmed disease progression, or death due to any cause). DOR is defined only for patients with a confirmed PR or better.
- Frequency and Grade of treatment emergent adverse events (TEAE)

6.2.2 OTHER SECONDARY ENDPOINTS

- Best Response (proportion of patients with sCR, CR, VGPR, PR, Minimal Response (MR), Stable Disease (SD), PD or non-evaluable).
- CBR (the proportion of patients who achieve a best confirmed response of sCR, CR, VGPR, PR or MR).
- 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). DOCB is defined only for patients with a confirmed MR or better.
- TTR (time from randomization to the date of the first documented confirmed response in a patient who has responded with ≥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 or until death)
- OS (time from date of randomization to death due to any cause).

6.3 EXPLORATORY ENDPOINTS

- Assessment of MRD status by Next Generation sequencing (NGS) in patients who achieve a CR or VGPR.
- PFS-2 (defined as time from randomization to progression on next line of treatment or death from any cause, whichever occurs first).
- Value and changes in pain in Brief Pain Inventory – SF (BPI-SF) and Numeric Rating Scale (NRS) for measure of bone pain.
- Response rate (CR and PR) according to IMWG consensus criteria of extramedullary myeloma (plasmacytomas).
- Number of health services.
- Number and days of hospitalization.
- PK parameters of melphalan in selected treatment cycles.
- Serum daratumumab concentrations.
- Incidence of antibodies to daratumumab.
- Incidence of antibodies to rHuPH20.
- DNA/RNA-based drug response biomarkers including but not limited to aminopeptidases and esterases.
- Serum levels of bone reabsorption related proteins including but not limited to TRACP-5b (Tartrate-resistant acid phosphatase 5b), PINP (Procollagen I N-terminal Propeptide), Total RANK, Osteopontin, Osteocalcin, CTX (C-Terminal telopeptide), bone ALP (Alkaline phosphatase).
- Serum levels of cytokines IL-6, IL-10.
- Immune profiling in peripheral blood including but not limited to T Reg. (Regulatory T), MDSC (Myeloid-derived suppressor cell) and NK (Natural killer) cells.
- Value and changes from baseline in EORTC QLQ-C30 summary score, each scale of the EORTC QLQ-C30, EQ-5D utility index, each dimension of the EQ-5D-3L, and the Visual Analogue Scale (VAS) of the EQ-5D-3L.
- ORR (proportion of patients who achieve a best confirmed response of sCR, CR, VGPR or PR after crossover).

- DOR (time from the first evidence of confirmed assessment (after crossover) of sCR, CR, VGPR or PR to first confirmed disease progression, or death due to any cause). DOR is defined only for patients with a confirmed PR or better after crossover.
- Best Response (proportion of patients with sCR, CR, VGPR, PR, Minimal Response (MR), Stable Disease (SD), PD or non-evaluable) after crossover.
- CBR (the proportion of patients who achieve a best confirmed response of sCR, CR, VGPR, PR or MR) after crossover.
- DOCB (time from first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR after crossover to first confirmed disease progression, or to death due to any cause). DOCB is defined only for patients with a confirmed MR or better after crossover.
- TTR (time from crossover to the date of the first documented confirmed response in a patient who has responded with ≥PR after crossover).
- TTP (time from crossover to the date of the first documented confirmed PD after crossover).
- TTNT (time from crossover to the date of next anti-myeloma treatment or until death after crossover).
- OS (time from crossover until death of any cause after crossover).
- Value and changes from crossover in pain, in BPI-SF and NRS for measure of bone pain.
- Value and changes from crossover in EORTC QLQ-C30 summary score, each scale of the EORTC QLQ-C30, EQ-5D utility index, each dimension of the EQ-5D-3L, and the Visual Analogue Scale (VAS) of the EQ-5D-3L after crossover.
- Frequency and Grade of treatment emergent adverse events (TEAE) after crossover.
- PFS (time from crossover to the date of first documentation of confirmed PD or death due to any cause after crossover).

7. ANALYSIS POPULATIONS

Analysis Population	Description
Enrolled Population Set	Includes all screened patients, i.e. patients having completed assessments and procedures during screening as outlined in Section 8.1.1 of the protocol. The Enrolled Population Set will

	include randomized patients and non- randomized patients (defined as screening failures) and will be used for summaries of disposition.
Full Analysis Set (FAS)	Includes all patients who are randomized. Analyses will be performed according to the treatment assigned at randomization. The primary endpoint and all secondary efficacy endpoints will be based on FAS.
Safety Analysis Set	Includes all patients in the FAS with at least one exposure to any study drug. Analyses will be performed according to the treatment actually received.
Pharmacokinetic Analysis Set	Includes all patients in FAS who received at least 1 dose of daratumumab or for melflufen includes all patients in FAS who received at least 1 dose of melflufen and have 3 samples with measurable concentrations in at least one treatment cycle. Analyses will be performed according to the treatment actually received.
Per Protocol Analysis Set	The Per Protocol Analysis Set includes all patients in the FAS who have received at least 1 dose of study medication. Patients who have important protocol deviations, related to critical eligibility criteria, the assessment of efficacy or the safety of the patient who could significantly impact the interpretation of study result, will be excluded from the PPAS. These major protocol deviations include: • Eligibility criteria not fulfilled • Patient received incorrect study drug • Absence of post-baseline MM response assessments The final list of major deviations will be made during the blinded data review meeting prior to final database lock. The PPAS will be used for sensitivity analyses of selected efficacy variables. Analyses will be performed according to the treatment actually received.
QoL Analysis Set	All patients who received at least 1 dose of melflufen or Daratumumab, respectively, and have evaluable changes in QoL parameters. Analyses will be performed according to the treatment actually received.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All analyses will be performed using SAS (statistical analysis software) version 9.4 or higher. Descriptive statistics for continuous variables will include the number of patients with non-missing data (n), arithmetic mean, standard deviation (SD), median, minimum and maximum. Summary statistics for categorical variables will contain count and percentage based on the number of patients in the selected analysis population. Percentages will be presented to one decimal, except for zero and one hundred percent, which will be presented as 0% and 100%. 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 variables for which information is missing, without a percentage.
By default the data collected in the electronic case report form (eCRF) and by external vendors will be used for analysis unless it is specified that additional derivation is required.

Demographics and efficacy analyses will be repeated for the following subgroups:

- Patients with <3 prior lines of treatment and ≥3 prior lines of treatment, respectively
- Patient double-refractory to an IMiD and PI or not, respectively
- Patients previously treated with anti-CD38 antibody or not, respectively
- Patients with extramedullary disease

In case of mis-stratification the actual value from the CRF, and not the IWRS value, will be used for statistical analyses (e.g., for subgroup analysis, Cox models, Cochran-Mantel-Haenszel (CMH) test, etc.)

8.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

Where assessments are made 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. Where assessments are not performed on the first treatment day, screening or last available observation prior to the first dose of study drug will be considered as baseline. Refer to the protocol for the study visits-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 will be excluded from all summaries by time point. Unscheduled assessments will be considered when deriving myeloma response parameters as described in Section 7.7 and for analysis of laboratory parameters by worst toxicity grade as specified in Section 7.8.3 of this SAP. All unscheduled assessments will be presented in the respective listings.

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

8.3 HANDLING OF MISSING DATA

Missing data will not be estimated or carried forward for any of the other summaries or analyses not mentioned in this section. 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 adverse event (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.
- 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.
Adverse events with a missing relationship will be 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.
Adverse events with a missing severity will be 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.

8.4 PATIENT DISPOSITION

Disposition summary will be based on the Enrolled Population Set and presented by treatment arms and overall. Disposition data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately, where applicable.

The disposition of patients includes:

- Number (%) of patients randomized
- Number (%) of treated patients
- Number (%) of patients in the FAS, PPAS, Safety, PK and QoL Analysis Sets
- Number (%) of patients permanently discontinued from the treatment along with the primary reasons for permanent treatment discontinuation
- Number (%) of patients in PFS follow-up (F-U), PFS-2 F-U and OS F-U
- Number (%) of patients discontinued from the study and reasons for study discontinuation

Treatment discontinuations due to AEs specific to COVID-19 will also be presented separately.

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

8.5 PROTOCOL DEVIATIONS

Major protocol deviations will be summarized by deviation type for the FAS and presented by treatment arms and overall. Protocol deviations data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately. All protocol deviations will also be provided in a listing.

8.6 PATIENT CHARACTERISTICS

8.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

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

- 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
- Hepatitis and HIV screening, including: hepatitis B surface antigen (HBsAg), anti-hepatitis B core antibody (Anti-HBc), anti-hepatitis B surface antibody (Anti-HBs), anti-HCV antibody, anti-HIV1/2 antibody/antigen

Baseline and demographics characteristics will also be repeated by subgroups:

- Patients with <3 prior lines of treatment and ≥3 prior lines of treatment, respectively
- Patient double-refractory to an IMiD and PI or not, respectively
- Patients previously treated with anti-CD38 antibody or not, respectively
- Patients with extramedullary disease

Data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately.

A listing will be provided for patient's demographic and baseline characteristics.

Separate listings will be provided for hepatitis and HIV screening, patient childbearing potential and ECOG results.

8.6.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Medical history will be summarized by Medical Dictionary of Regulatory Activities (MedDRA)

(version 23.0 or higher), System Organ Class (SOC) and preferred term (PT) using number (n) and percentage (%) of patients having at least one occurrence of a disease for the FAS by treatment arms and overall. Medical history data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately. A listing will be provided for patient medical history.

8.6.3 MULTIPLE MYELOMA DISEASE HISTORY

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

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

The following disease characteristics at screening will be summarized descriptively for the FAS:

- Stage of disease (ISS and R-ISS)
- Heavy chain and light chain subtypes
- Evidence of lytic bone lesions
- Evidence of EMD
- EMD subtype split
- Disease status (relapsed/relapsed-refractory)
- Time since diagnosis in years (calculated as [date of first dose of study drug – 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 drug– date of most recent relapse/progression+1]/30.4375)
- Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), kappa/lambda values
- Bone marrow plasma cells (%) as values and by categories (<30%, 30 - <60%, ≥60%)
- 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 (<25, 25 - <50, 50 - <75, 75 - <LLN)
- Absolute neutrophil count (ANC) (10^9/L) as values and categories (<0.5, 0.5-<1.0, 1.0 – 1.5, and >1.5)
- Hemoglobin (g/L) as values and categories (<65, 65 - <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
- Creatinine clearance (ml/min) as values 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 4.

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

Data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately.

Table 4: 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 by 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
Lactase 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 high LDH

A separate summary dedicated to fluorescence in situ hybridization (FISH) cytogenetics investigations at diagnosis and screening 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;q 23), t(14,20), t(14,20)(q32,q11).
- Not high-risk consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk.
- Unknown consists of patients for whom the FISH procedure was not done or unevaluable.

The same analysis as for FISH will also be presented for cytogenetics investigations performed by karyotyping.

Bone lesion assessments at screening will be analyzed descriptively with the number and percentage of patients. The following information will be presented: number and percentage of patients for whom skeletal survey or low dose CT scan was performed, method of skeletal

survey, result of exam, and bone lesion locations. The same information will be presented for the other imaging procedures.
Listings will be provided for patient MM history.

8.6.4 PRIOR MM THERAPIES

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

- Number and percentage of patients who had a frontline transplant (transplant as a component of the first line of therapy). This can be a single or tandem transplant. Planned tandem autologous or tandem autologous-allogeneic transplants are considered as one line of therapy.
- 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 tandem autologous-allogeneic transplants are considered as one line of therapy.
- Frontline transplant type (allogeneic or autologous)
- 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 in years (as continuous variable as well as per categories < 1 year, ≥1 year – <1.5 years, ≥1.5 years – ≤2 years, >2 years)
- 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)

- Number and percentage of patients who received an IMiD, PI, and anti-CD38 mAb (triple-class)
- Number and percentage of patients that are double class refractory to at least one prior line (refractory to at least one PI and one IMiD)
- Number and percentage of patients with prior radiotherapy

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

- IMiD is defined as WHO DD 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 multiple myeloma will be referred to as 'Other. These 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.

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

8.6.5 PRIOR AND CONCOMITANT MEDICATION

All concomitant medications will be coded using the WHO Drug Dictionary (WHODD) dated 01 March 2020 or higher.

A medication is considered prior if stopped before the date of the first study drug (Melflufen, Daratumumab or Dexamethasone) dose. Concomitant medications are defined as medications with a start date or end date on or after the date of first study drug dose and start date before the date of the last study drug dose + 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 treatment arms and overall.
Concomitant medication data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately. The definition of concomitant medications stays the same as for the main part of the study but with first and last study drug doses referring to the first and last study doses during crossover part of the study.
Patients may have more than one medication per ATC class and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. The summaries will be ordered by descending frequency of ATC class and preferred name within each ATC class in the total group. Prior medications will be presented separately in the same way.
Separate summaries will be provided for the number and percentage of patients with the following medication categories: "Haemapoetic growth factors" (WHO DD SDG "Colony stimulating factors") and "Transfusions" (including the following PTs: "Platelets", "Erythrocytes", "Red blood cells").
A listing of prior and concomitant medications will be provided.

8.7 EFFICACY ENDPOINTS AND ANALYSIS

All efficacy analyses will be produced for the FAS by treatment arms and overall. Efficacy data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately. The primary efficacy endpoint will also be presented for the PPAS as sensitivity analysis.
All tumor response and progression-depended objectives will be assessed by investigators according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Kumar et al.2016).
All the efficacy analyses will be repeated for the following subgroups:

- Patients with <3 prior lines of treatment and ≥3 prior lines of treatment, respectively
- Patient double-refractory to an IMiD and PI or not, respectively
- Refractory to an alkylator (yes, no)
- Patients previously treated with anti-CD38 antibody or not, respectively

- Patients with extramedullary disease at baseline (yes, no) as a whole group and separated per paraskeletal vs soft tissue EMD
- Age
  - <65, ≥65 years
  - <75, ≥75 years
- Sex (male, female)
- ISS at baseline (I, II or III)
- R-ISS at baseline (R-I, R-II or R-III)
- Prior autologous stem cell transplant (yes, no)
- Maximum plasma cell involvement (%) at baseline, as assessed with bone marrow assessment (<30, 30 - <60, ≥60)
- Baseline creatinine clearance (ml/min) (<45, 45 - < 60, 60 - < 90, ≥90)
- Baseline LDH (<1.5×ULN, ≥1.5×ULN)
- Baseline albumin (g/L) (<35, ≥35)
- Cytogenetic risk groups as determined by FISH (standard risk, high risk, unknown)

The respective subgroup variables will be excluded from the Cox models and CMH tests.

8.7.1 PRIMARY ENDPOINT

The primary endpoint PFS is defined as the duration in months from the date of randomization until first documentation of confirmed disease progression as assessed by IRC or death due to any cause, whichever occurs first. PFS time, in months, is calculated as (PFS date – date of randomization +1)/30.4375.

Disease progression is defined according to IMWG-URC as PD or death due to any cause, whichever occurs first. PFS will be right-censored according to conventions adapted from the FDA Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics and the FDA Guidance for Industry, Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics.

PFS will be right-censored for patients who meet one of the following conventions (the ones with Outcome=Censored) described in Table 5 below:

Table 5. 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 primary statistical analysis of PFS will be performed using a Log-rank test stratified by the randomization stratification factors. The Cox proportional hazard will be used to estimate the hazard ratio for melflufen+dexamethasone+daratumumab versus daratumumab and its 95% confidence interval (CI). Ties will be handled using the Efron methodology.
The distribution of PFS will be summarized using Kaplan-Meier method. The median PFS will be estimated for each treatment arm as the 50th percentile of the corresponding Kaplan-Meier estimates. The 25% and 75% quantiles will also be presented. 95% CI will be based on the

log(-log(survival)) distribution.

Superiority will be demonstrated if the p-value from the statistical test is lower than 0.05 (i.e., the upper limit of the 95 % confidence interval for the hazard ratio is <1). All statistical tests will be two-sided, and have a null hypothesis of no difference between treatment arms for the applicable endpoint. See Section 7.7.5 for a description of multiplicity adjustments.

The following sensitivity analyses for PFS have been added:

- PFS as assessed by investigators
- Unstratified log-rank test and unstratified Cox model
- New anticancer therapy treated as an event
- New anticancer therapy not treated as an event or a censoring event
- Death or PD immediately after more than one consecutively missed disease assessment visit will be treated as an event
- Analysis based on scheduled assessment dates instead of actual assessment dates (i.e. progression dates recorded between scheduled visit dates will be assigned the next scheduled tumor assessment date as the date of progression)

8.7.2 KEY SECONDARY EFFICACY ENDPOINTS

There are two key secondary efficacy endpoints:

- ORR
- DOR

The analysis of the key secondary efficacy endpoints will be performed using statistical methods with multiplicity control described in Section 7.7.5.

8.7.2.1 RESPONSE RATES

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 IRC.

ORR will be presented together with two-sided 95% exact binomial confidence intervals based

on the Clopper-Pearson method. The treatment groups will be compared using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

Confirmed response: Two consecutive assessments with the same response result made at any time. If the second consecutive assessment (made at any time) the response is higher than the previous one, then the 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). If the second consecutive response is lower than the first one, then the 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 is only applicable to sCR-SD responses; confirmed PD is treated separately.
All the details of myeloma response assessment will be presented in a listing.

8.7.2.2 TIME TO EVENT PARAMETERS

DOR

DOR is defined as the time in months from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR (as assessed by IRC) to first confirmed disease progression according to the IMWG-URC (as assessed by IRC) or to death due to any cause. DOR is defined only for patients with a confirmed PR or better. DOR is to be censored using the same rules as for PFS. DOR will be derived as (DOR date – date of first documented confirmed response (≥PR) + 1)/30.4375.

DOR analysis will be performed using Kaplan-Meier method. The median time to event will be estimated for each treatment arm from the 50th percentile of the corresponding Kaplan-Meier estimates. 95% confidence intervals will be based on the log(-log(survival)) distribution.

The stratified log-rank test and the Cox model will be applied in the same way as for the primary PFS analysis.

8.7.3 OTHER SECONDARY EFFICACY ENDPOINTS

8.7.3.1 RESPONSE RATES

Response rates (Best response and CBR) and other dichotomous parameters will be presented together with 95% exact binomial confidence intervals based on the Clopper-Pearson method. The treatment groups will be compared using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

Best Overall Confirmed Response

The best overall confirmed response during the study, including PFS-FU response assessments, (sCR, CR, VGPR, PR, MR, SD, PD, or non-evaluable) as assessed by the IRC according to IMWG-URC, will be summarized descriptively.

Best Unconfirmed Response

The best IRC assessed response achieved on study, including PFS-FU response assessments. This response may not be confirmed by a consecutive assessment.

CBR

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

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

Concordance analysis

The concordance between the IRC assessment and the investigator's assessment of progression will be summarized descriptively with frequency tables displaying best overall confirmed response, cross-classified by rater.

Sensitivity analyses have been added for the key secondary endpoints (ORR and DOR) as assessed by investigators.

8.7.3.2 TIME TO EVENT PARAMETERS

Time-to-event analyses (DOCB, TTP, TTNT and OS) will be performed using Kaplan-Meier method. The median time to event will be estimated for each treatment arm from the 50th percentile of the corresponding Kaplan-Meier estimates. 95% confidence intervals will be based on the log(-log(survival)) distribution.

The stratified log-rank test and the Cox model will be applied in the same way as for the primary PFS analysis.

DOCB

DOCB will be calculated as time in months from the first evidence of confirmed IRC assessment of sCR, CR, VGPR, PR or MR to first confirmed disease progression, or to death due to any cause. DOCB is defined only for patients with a confirmed MR or better. DOCB is to be censored using the same rules as for PFS.
DOCB will be derived as (DOCB date – date of first documented confirmed response (≥MR) + 1)/30.4375.

TTP

TTP is defined as time in months from randomization to the date of the first documented confirmed progression as assessed by IRC. TTP will be derived as (TTP date – randomization date +1)/30.4375.
TTP will be right-censored for patients who meet one of the following conventions described in Table 6 below:

Table 6. Conventions for TTP 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	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

Time to next treatment (TTNT) in months will be calculated from the date of randomization to the start of the 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.

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 as time in months from the date of randomization to the start of the 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 derived as (TTNT date – randomization date +1)/30.4375.

OS

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

TTR

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

8.7.4 EXPLORATORY EFFICACY ENDPOINTS

PFS-2

PFS-2 is defined as time from randomization to progression as assessed by IRC on the next line of treatment or death from any cause, whichever occurs first. Patients with no progression or death will be censored on the date of last disease assessment after the next line of treatment started.

PFS-2 time, in months, will be calculated as (PFS-2 date – date of randomization +1)/30.4375.

PFS-2 will be presented and analyzed similarly to PFS.

PFS-2 will be performed using Kaplan-Meier method. The median time to event will be estimated for each treatment arm from the 50th percentile of the corresponding Kaplan-Meier estimates. 95% confidence intervals will be based on the log(-log(survival)) distribution. The stratified log-rank test and the Cox model will be applied for PFS-2 the same way as for the primary PFS analysis.

MRD Status

The number and percentage of patients with particular MRD status will be summarized for patients achieving CR or VGPR response (as their best response as assessed by IRC) by treatment arm. For patients having multiple MRD results the worst result will be used (the order

is non-evaluable; negative; positive, where positive is worst).

The number and percentage of patients with MRD or not in patients achieving CR or VGPR will be presented.

Response Rate in Patients with Extramedullary Myeloma

The response rate in patients with extramedullary myeloma (present at screening) will be estimated as the proportion of patients who achieve a confirmed response of CR and PR as their best response, as assessed by the IRC, and have extramedullary myeloma present at screening.

Crossover Analyses

To evaluate efficacy in patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone after disease progression on daratumumab, the response rate (ORR, Best Response (BR) and CBR) and time to event (DOR, DOCB, TTR, TTP, TTNT and OS) will be presented descriptively with 95% confidence intervals. Time to event will be calculated from date of first treatment after crossover.

8.7.5 MULTIPLICITY

For the primary and the key secondary efficacy analyses, the overall 2-sided level of significance will be alpha = 0.05. The hypothesis testing of key secondary endpoints will be conducted using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary efficacy endpoint comparison is statistically significant at an alpha level of 0.05. If this comparison is not statistically significant, then the comparison of key secondary efficacy endpoints will be considered nominal, descriptive and exploratory.

First, the superiority of PFS in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone will be tested at an alpha level of 0.05. If the primary endpoint is statistically significant, the following key secondary endpoint will be tested in this fixed order at an alpha level of 0.05:

- Overall Response Rate (ORR) in patients treated with melflufen and dexamethasone in

combination with daratumumab compared to daratumumab alone.

If this key secondary endpoint above is statistically significant then the following key secondary endpoint will be tested at an alpha level of 0.05:

- Duration of Response (DOR) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.

8.7.6 Other Efficacy Assessments

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

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.

8.8 Safety Endpoints and Analysis

All analyses of safety will be based on the Safety Analysis Set and presented by treatment arms and overall, unless otherwise specified for specific analysis. Safety data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately.

8.8.1 Exposure to Study Treatment

Exposure analysis will be based on the Safety Analysis Set and presented by treatment arms. Study treatment administration, including duration of exposure, total dose, dose modifications will be summarized for each group separately.

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 meflufen 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 meflufen 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.
Duration of daratumumab treatment in weeks is defined as (date of last dose – date of first dose + 1) divided by 7.
For treatment Arm A, overall duration of treatment with study drug in weeks is defined as the longest duration of dexamethasone, daratumumab and melflufen treatment.

The duration of study treatment exposure will be summarized descriptively and presented for overall treatment duration (Arm A only) and also separately for melflufen, dexamethasone and daratumumab and will include the following: treatment duration in weeks, number of cycles received (and also number of doses for dexamethasone and daratumumab), cumulative dose (in mg) of study drug received per patient, average dose of study drug (mg/week for melflufen, dexamethasone and daratumumab), and the total number and percentage of patients receiving a dose per cycle (for overall treatment (Arm A only) and 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 derivation holds for dexamethasone and daratumumab.

Dose modification information will be summarized descriptively for any drug and then also separately for melflufen, dexamethasone and daratumumab. The number of patients with drug modifications due to AEs will be presented based on the AE eCRF page, number of patients with each action by frequency will be presented based on the melflufen, dexamethasone and daratumumab administration eCRF pages. 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 the 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 dose delay due to COVID-19 pandemic will be summarized.

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

8.8.2 ADVERSE EVENTS

All AE summaries will be presented based on the Safety Analysis Set and presented by treatment arms and overall. AE data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately.

All AEs will be coded using the MedDRA (version 23.0 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 (Treatment Emergent Adverse Events).
TEAEs are defined as AEs that start on or after the first day study treatment (melflufen, daratumumab, or dexamethasone) is administered and within 30 days of the last administration of study treatment or before the start of a subsequent anticancer treatment (whichever occurs first) or that worsen on or after the first day of study treatment. The definition of TEAEs used for the crossover part of the study stays the same as for the main part of the study but with first and last study drug doses referring to the first and last study drug doses during crossover part of the study.
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; patients with TEAEs leading to discontinuation; and patients with TEAEs leading to death.
The overall summary will include the treatment related TEAEs analyzed separately in four ways: treatment related TEAEs (melflufen and/or dexamethasone and/or daratumumab-related – presented for Arm A and daratumumab-related - presented for Arm B), melflufen related TEAEs, dexamethasone-related TEAEs, and daratumumab-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 held and dose discontinuation will be presented separately for overall treatment (meflufen and/or dexamethasone and/or daratumumab – presented for Arm A and daratumumab-related – presented for Arm B) and melflufen.

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
- Treatment related (related to melflufen and/or dexamethasone and/or daratumumab presented for Arm A and daratumumab-related presented for Arm B) AEs
- Melflufen related TEAEs
- Dexamethasone related TEAEs
- Daratumumab related TEAEs
- Serious TEAEs
- Non-Serious TEAEs
- Treatment related serious TEAEs
- Melflufen related serious TEAEs
- Dexamethasone related serious TEAEs
- Daratumumab related serious TEAEs
- TEAEs by CTCAE toxicity grade
- Treatment related TEAEs by CTCAE toxicity grade

- Melflufen related TEAEs by CTCAE toxicity grade
- Dexamethasone related TEAEs by CTCAE toxicity grade
- Daratumumab 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
- Daratumumab related serious TEAEs by CTCAE toxicity grade
- TEAEs resulting in any treatment modification (hold, reduction, delay, interruption and discontinuation) for each study drug and separately for each modification

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

- Thrombocytopenia (PTs: "Thrombocytopenia", "Platelet count decreased")
- Treatment related thrombocytopenia
- Melflufen related thrombocytopenia
- Dexamethasone related thrombocytopenia
- Daratumumab related thrombocytopenia
- Neutropenia (PTs: "Neutropenia", "Neutrophil count decreased")
- Treatment related neutropenia
- Melflufen related neutropenia
- Dexamethasone related neutropenia
- Daratumumab related neutropenia
- Anemia (SMQ "Haematopoietic erythropenia" (BROAD))
- Treatment related anemia
- Melflufen related anemia
- Dexamethasone related anemia
- Daratumumab related anemia
- Febrile neutropenia (PT "Febrile neutropenia")
- Infections (SOC "Infections and infestations")
- Hemorrhage (SMQ "Haemorrhage terms, excluding laboratory 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 separate summaries for all by SOC, PT and all by SOC, PT, CTCAE toxicity grade analyses.

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

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

A separate summary will present the number and percentage of patients who died during the study treatment period (from the first dose of melflufen (daratumumab for Arm B) up to 30 days after last dose of melflufen (daratumumab for Arm B)) and during follow-up (more than 30 days after last melflufen dose (daratumumab for arm B)) along with the reasons for the deaths, as well as the number of patients who died within 60 days after the first melflufen dose (daratumumab for Arm B). Deaths of patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately.

Listings will be provided for patients experiencing AEs, SAEs, AEs resulting in drug withdrawal

and events with fatal outcome.

8.8.3 LABORATORY DATA

Laboratory data will be summarized for the Safety Analysis Set and presented by treatment arms and overall. Laboratory data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units on Study Data Tabulation Model (SDTM) level. Hematology, chemistry and coagulation 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 and plots 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 is a 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 aminotrasferase (ALT) (increase)

  - Aspartate aminotrasnferase (AST) (increase)
  - Alkaline phosphatase (increase)
  - Total bilirubin (increase)
  - Creatinine (increase)
  - Corrected 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)
- Coagulation
  - International normalized ratio (INR)

For hemoglobin, ANC and platelet counts, CTCAE grade shift tables will also be presented by cycles. Time from the date of the melflufen dose and time from the date of the daratumumab dose in a particular cycle until the date of grade 3, grade 4 and grade 3/4 onset/offset will be presented for each cycle for ANC and platelets. Time to onset and time to offset (resolved to grade 2 or below) 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.

8.8.4 VITAL SIGNS

Vital signs will be summarized for the Safety Analysis Set and presented by treatment arms and overall. Vital signs data for patients in Arm B who crossover to treatment with melflufen,

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

8.8.5 PHYSICAL EXAMINATION

Physical examination results will only be listed without a summary.

8.8.6 12-LEAD ELECTROCARDIOGRAM (ECG)

ECG data will be summarized for the Safety Analysis Set and presented by treatment arms and overall. ECG data for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone will be summarized separately.
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 (excluding the EOT crossover visit) will be summarized for ECG interpretation data.
All ECG data collected will be presented in the listing.

8.9 EXPLORATORY ENDPOINTS AND ANALYSIS

8.9.1 PATIENT REPORTED OUTCOME (PRO)

PRO analyses will be described in a separate analysis plan.

8.9.2 PHARMACOKINETICS

PK analysis will be described in a separate analysis plan.

8.9.3 ECOG

ECOG performance status will be summarized as counts and percentages using shift tables of baseline versus worst performance status during study by treatment arm and overall. The number of patients with improvement 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.

8.9.4 BIOMARKERS

Biomarker exploratory analyses will be described and presented separately from the main clinical study report (CSR) and will be managed by the sponsor.

8.9.5 IMMUNOGENECITY

Immunogenicity analyses of daratumumab and rHUPH20 will be described and presented separately from the main clinical study report (CSR) and will be managed by the sponsor.

9. INTERIM ANALYSES

No interim analyses will be performed.

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

Response assessments by the IRC will be used for the primary analyses while the investigator assessments of response will be used for the sensitivity analysis. The study protocol, Version 2.1, Amendment 2 (November 25, 2020) states that the IRC will evaluate response assessments as sensitivity analysis.

PFS has been explicitly added as an exploratory objective with a corresponding endpoint for patients in Arm B who crossover. It was missed in the objectives section of the protocol but was included elsewhere in the protocol.

TTR will be analyzed descriptively instead of with the Kaplan-Meier method.

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or higher.

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 in the bottom left corner 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 the table/listing will appear bottom left corner 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.

The list of tables, listings and figures (TFLs), and the shells for unique tables and listings are provided in a separate Mock-Up TFLs document.

12. REFERENCES

Lonial S, Weiss B, Usmani S, et al. Daratumumab Monotherapy in Patients with Treatment-Refractory Multiple Myeloma (SIRIUS): An Open-Label, Randomised, Phase 2 Trial. The Lancet 2016; 387 (10027): 1551–1560.

Kumar S, Paiva B, Andersson K et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016; 17; e328-46

Usmani SZ Weiss BM., Plesner T., et al. Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma. Blood, 2016; 128(1):38-44