Protocol Number: OP-104

Official Title: An Open-Label Phase 1/2a Study of the Safety and Efficacy of Melflufen and Dexamethasone in Combination with either Bortezomib or Daratumumab in Patients with Relapsed or Relapsed-Refractory Multiple Myeloma

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Statistical Analysis Plan

Sponsor:	Oncopeptides AB
Protocol No:	OP-104
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1 Approvals

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3 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Oncopeptides Protocol OP-104.

4 Scope

This plan is a living document that will be created during the trial start-up. The SAP will be drafted after final electronic case report forms (eCRF) are available and maintained throughout the lifecycle of the trial. Each version of the SAP will require sign off from the Project Manager and Oncopeptides prior to programming starting or being updated based on an amended version of the SAP.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, adverse events handling and laboratory data

5 Introduction

This SAP should be read in conjunction with the study protocol and eCRF. This version of the plan has been developed using the protocol version 6.1 amendment 7 dated 10 April 2020 and eCRF dated 06 August 2020. Any further changes to the protocol or eCRF may necessitate updates to the SAP.

The SAP is to be developed in two stages. An initial 'Stable' SAP will be created for programming purpose. Versions of the SAP up to initial sponsor approval will be known as stable SAP v0.x.The initial approved SAP will then be called Stable SAP v1.0. The final version of the SAP, known as Final SAP, will be issued for sponsor approval prior to database lock.

5.1 Changes from Protocol and Clarification

Clarification to the efficacy analysis set definition

The definition of the efficacy analysis set from Section 12.3.1.3 of the protocol is "Efficacy evaluable patients are those who receive at least 2 doses of melflufen and ≥ 50% of the partner therapy (excluding dexamethasone) during Cycles 1 and 2, had a baseline disease assessment, and had at least 1 post-baseline disease assessment ≥ 28 days after first dose.".

To clarify the condition regarding the partner therapy, this means that patients must have had at least 50% of the partner therapy across the two first cycles rather than at least 50% within each cycle.

Additional analysis of time to next treatment (TTNT)

In Section 12.5.1.3 of the protocol, TTNT is defined as the time (months) from initiation of therapy to the date of the first documented next treatment. As the protocol does not specify how deaths or those that do not have subsequently therapy will be handled the following two definitions have been added to the SAP:

$TTNT_a$: Duration will be time (months) from the study treatment start to the start of first subsequent therapy (excluding radiotherapy). Patients who have no subsequent therapy will be censored at the earlier of date of death and date of last contact.

$TTNT_b$: Duration will be time (months) from the study treatment start to the start of the first subsequent therapy (excluding radiotherapy) or death. Patients who have no subsequent therapy and do not have a date of death will be censored at the date of last contact.

Formula for Body Surface Area (BSA)

Protocol references BSA DuBois Formula in Appendix J but the formula stated is Mosteller (Mosteller, 1987).This is clarified in the SAP.

6 Study Objectives

6.1 Primary Objectives

6.1.1 Phase 1 Primary Objective

To determine the optimal dose of melflufen, up to a maximum of 40 mg, given every 28 days, in triple drug combination therapy in patients with relapsed or relapsed refractory multiple myeloma (RRMM). Each treatment regimen (Regimen A: melflufen plus bortezomib and dexamethasone and Regimen B: melflufen plus daratumumab and dexamethasone) and dose will be evaluated separately.

6.1.2 Phase 2a Primary Objective

To evaluate the overall response rate (ORR: proportion of patients with ≥ PR) of melflufen, in each combination regimen, at the dose levels and schedules determined in Phase 1 in efficacy evaluable patients as well as in all treated patients. Each treatment regimen and dose level will be evaluated separately.

6.2 Secondary Objectives

- To evaluate the best response including the complete response/stringent complete response (CR/sCR), very good partial response (VGPR), PR and clinical benefit rate (CBR: proportion of patients with ≥ minimal response (MR)), time to response (TTR), duration of response (DOR: PR or better), duration of clinical benefit (CB), progression free survival (PFS) and overall survival (OS) up to a minimum of 2 years in efficacy evaluable as well as all treated patients. International Myeloma Working Group Uniform Response Criteria (IMWG-URC) guidelines will be used (Rajkumar et al, 2011). Each treatment regimen and dose level will be evaluated separately.
- To further explore the safety and tolerability of the combination regimens. Each treatment regimen and dose level will be evaluated separately.

6.3 Exploratory Objectives

- Pharmacokinetics will be evaluated in patients enrolled at selected sites only.
- To evaluate minimal residual disease (MRD) in patients achieving a CR.

7 Study Design

This is an open-label, Phase 1/2a, multicenter study which will enroll patients with relapsed or RRMM to combination regimens of melflufen with currently approved agents. The currently planned combinations include:

- Regimen A: Melflufen plus bortezomib and dexamethasone
- Regimen B: Melflufen plus daratumumab and dexamethasone

Each combination will begin with a Phase 1 component which will follow the standard 3 + 3 Phase 1 design with 3 to 6 patients at each dose level, depending on dose limiting toxicity (DLT) observed in the first cycle of each patient. Patients who discontinue treatment during Cycle 1 for reasons other than study drug related toxicity and/or who are considered non-evaluable for DLT assessment, may be replaced at the discretion of the Data Safety Monitoring Committee (DSMC). Patient recruitment will continue until a full cohort of

safety evaluable patients has been achieved. A DSMC will evaluate all treated patients in each cohort prior to the next dose level decisions.

Up to 3 dose levels of melflufen will be tested: 30 mg, 40 mg, or 20 mg given on Day 1 of every 28-day cycle. Detailed dosing breakdown of each Regimen can be found in protocol Section 4.1.

Other dose levels or schedules of melflufen, daratumumab, bortezomib and dexamethasone may be explored based on tolerability following review and recommendation by the DSMC.

Once the optimal dose of melflufen has been determined for each combination Regimen in Phase 1, approximately 20 additional efficacy evaluable patients will be enrolled in each combination Regimen and treated at this dose in a Phase 2a part of the study. Patients will be assessed for response after each cycle according to the IMWG-URC.

7.1 Dose Escalation Procedure (Phase 1)

The first cohort of patients enrolled in the Phase 1 portion of each Regimen will receive melflufen dose level 1 (melflufen 30 mg). A full safety evaluation will be conducted by a DSMC when the planned number of melflufen safety evaluable patients have completed the first cycle of combination therapy with DLT assessment. The optimal dose of melflufen in combination therapy will be defined as the highest of 20, 30 or 40 mg of melflufen that results in ≤ 1/6 patient with DLT during the first cycle of therapy. The minimum dose of melflufen is 20 mg.

- If no DLT is reported in the first three patients at a dose level, that dose level will be considered safe and three patients will be enrolled at the next dose level.
- If 1/3 patients in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable patients.
- If 2/3 patients in a cohort at a dose level has a DLT, that dose level will not be considered safe and no further dose escalation will take place.
- If there are < 2 patients with a DLT among the expanded cohort of six evaluable patients a cohort of three patients will be enrolled in the next higher dose level.
- If there are 2 or more patients with a DLT among the expanded cohort of six evaluable patients, that dose level will not be considered safe and no further dose escalation will take place.
- If less than 6 patients have been treated in the next lower dose level, additional patients will be entered into this dose level until there are 6 patients treated. If ≤ 1 of these 6 patients encountered DLT, then this dose level will be taken forward to Phase 2a. If 2 or more of the 6 patients encounter DLT, a lower dose will be considered.

7.2 Sample Size Considerations

The Phase 1 sample size will be based on the number of dose levels to be evaluated within each Regimen. It is anticipated that a maximum of 12 patients are enrolled in each Regimen during Phase 1.

Phase 2a sample size will include approximately 20 additional efficacy evaluable patients in order to reach a total of 26 efficacy evaluable patients per Regimen to better describe the efficacy and safety of each combination.

8 Study Endpoints

8.1 Primary Endpoints

8.1.1 Phase 1 Primary Endpoint

The primary endpoint of Phase 1 is to analyze the frequency and grade of AE's occurring at each dose level to be tested during Cycle 1 of therapy. Each treatment Regimen and dose level will be evaluated separately.

8.1.2 Phase 2a Primary Endpoint

The primary endpoint of Phase 2a is the overall response rate (sCR, CR, VGPR, or PR) observed in patients treated at the optimal dose of melflufen in combination therapy according to IMWG-URC. Each treatment Regimen and dose level will be evaluated separately.

8.2 Secondary Endpoints

The secondary endpoints for Phase 1 and 2a are:

- Best response during the study (sCR, CR, VGPR, PR, MR, stable disease [SD], PD or non-evaluable)
- Clinical benefit rate (CBR)
- Time to progression (TTP)
- Time to response (TTR)
- Time to next treatment (TTNT)
- Duration of response (DOR)
- Duration of clinical benefit (DCR)
- Progression free survival (PFS)
- Overall survival (OS)
- Frequency and maximum grade of AE's (according to CTCAE v4.03)
- Laboratory abnormalities

8.3 Exploratory Endpoints

- PK parameters of melphalan at selected time-points
- The rate of minimal residual disease (MRD) negative or positive status for patients achieving a complete response (CR)

8.4 Demographics and Baseline Disease Characteristics

Baseline disease characteristics will be obtained from the 'Multiple Myeloma at Study Entry' eCRF page.

Time since initial diagnosis (years) will be calculated as: (Date of first dose of the first study treatment administered - Date of diagnosis + 1)/365.25.

Date of initial multiple myeloma diagnosis will be taken from the 'Multiple Myeloma History at Diagnosis' from the eCRF page.

Body surface area (BSA) will be calculated for each patient using the following formula (Mosteller, 1987):

$$\textbf{BSA} = \sqrt{\frac{Height\,(cm) \times Weight\,(kg)}{3600}}$$

OR

$$\textbf{BSA} = \sqrt{\frac{Height\,(in) \times Weight\,(lbs)}{3131}}$$

Height and weight collected at screening will be used.

Both international staging system (ISS) as collected on the eCRF and derived ISS will be summarized.

ISS will be derived from serum β2-microglobulin and albumin at baseline using the following rules (Palumbo et al , 2015):

ISS Stage	**Criteria**
Stage I	Serum β2-microglobulin<3.5 mg/L and serum albumin ≥ 35 g/L.
Stage II	Not ISS stage I or III
Stage III	Serum β2-microglobulin≥5.5 mg/L
Unknown	If β2-microglobulin and albumin is missing. If β2-microglobulin<3.5 mg/L and albumin is missing. If β2-microglobulin is missing.
Not Done	If β2-microglobulin and albumin is specified as 'Not Done'. If β2-microglobulin<3.5 mg/L and albumin is 'Not Done'. If β2-microglobulin is 'Not Done'.

Both revised international staging system (R-ISS) as collected on the eCRF and derived R-ISS will be summarized.

R-ISS will be derived from ISS stage, cytogenetic abnormalities and Lactate Dehydrogenase (LDH) at baseline using the following rules (Palumbo et al, 2015)):

R-ISS Stage	**Criteria**
R-I	ISS stage I and standard risk cytogenetic* abnormality by iFISH and normal LDH. Normal LDH is defined as < ULN (upper limit of normal)
R-II	Not R-ISS stage I of III
R-III	ISS stage III and either high risk cytogenetic* abnormality by FISH or high LDH. High LDH is defined as >ULN.
Unknown	If ISS stage is 'Unknown'. If ISS stage III and cytogenetic abnormalities='standard risk' and LDH is missing. If ISS stage III and cytogenetic abnormalities= 'Unknown' and LDH is normal. If ISS stage I and either cytogenetic abnormality='Unknown' or LDH is missing.
Not Done	If ISS stage is 'Not Done'. If ISS stage III and cytogenetic abnormalities='standard risk' and LDH is 'Not Done'. If ISS stage III and cytogenetic abnormalities= 'Not Done' and LDH is normal.

R-ISS Stage	Criteria
	If ISS stage I and either cytogenetic abnormality= 'Not Done' or LDH is 'Not Done'.

*In derivation of R-ISS Stage, only FISH del(17p), t(4;14), t(4 ;14) (p16 ;q32), t(14;16) and t(14 ;16) (q32 ;q23) will be considered as high risk cytogenetic abnormalities. Similarly for this derivation, FISH (t(14;20), t(14 ;20) (q32 ;q11) ,gain1q(+1q), gain (1q21) and hypodiploidy will be considered as standard risk abnormalities.

High-risk and standard-risk cytogenetic abnormality is defined as the following (Sonneveld et al, 2016)

High-risk	Standard-risk
FISH: t(4;14), t(4 ;14) (p16 ;q32), t(14;16), t(14 ;16) (q32 ;q23), t(14;20), t(14 ;20) (q32 ;q11),del(17p),gain1q(+1q), gain (1q21) and hypodiploidy.	All others including: FISH: t (11;14), t (6;14)
Karyotype: del (13) or del (13q)	

8.5 Monoclonal Protein Spike

Monoclonal protein spike (M-protein) is assessed from serum and urine protein electrophoresis test (SPEP/UPEP), and/or serum free light chain (sFLC). The second serum electrophoresis M-protein will also be considered when determining measurable SPEP.

Measurable M-protein at screening and baseline are defined as follows:

- Measurable SPEP is defined as M-protein ≥ 0.5 g/dL.
- Measurable UPEP is defined as M-protein ≥ 200 mg/day.
- Measurable sFLC is defined as involved FLC (Serum Kappa FLC or Lambda Kappa FLC) ≥ 100 mg/L with abnormal Serum Kappa/Lambda ratio (defined as values outside 0.26-1.65).

8.6 Prior Treatment for Multiple Myeloma

Prior treatment for multiple myeloma will be recorded on the Prior Systemic Cancer Therapy (Medications) and Prior Systemic Cancer Therapy (Lines of Therapy) pages of the eCRF.

All medications will be coded using version DDE B3 Mar_2019 or later of the World Health Organization (WHO) Drug Dictionary (DD).

Prior agents within regimens will be summarized using WHO DD Standardized Drug Groupings (SDG):

- Proteasome inhibitors (PI) is defined as WHO DD SDG 'Antineoplastic proteasome inhibitors'
- Immunomodulatory drugs (IMiD) is defined as WHO DD SDG 'Antineoplastic thalidomide analogues'
- Anti-CD38 monoclonal antibodies (mAb) is defined as WHO DD SDG 'Antineoplastic CD38 antigen inhibitors'
- Other mAb are defined as WHO DD SDG 'Monoclonal antibodies – antineoplastic' excluding SDG 'Antineoplastic CD38 antigen inhibitors'
- Alkylators is defined as WHO DD SDG 'Antineoplastic alkylating drugs'
- Other antineoplastic drugs for the treatment of multiple myeloma will be referred to as 'Other'

Any experimental or investigational drugs that are not covered by WHO DD SDG will be reviewed manually and classified as one of the above therapeutic drug classes if applicable. Classifications will be documented as part of the database lock procedures and further described in the Clinical Study Report.

High-dose melphalan is defined as those that have had a transplant and melphalan given on the same line of therapy, with melphalan given within a week prior to the transplant and reason for medication being stopped is 'Finished course of therapy' or 'Other' .

Refractory myeloma is defined as disease that is nonresponsive while on therapy or progresses on or within 60 days of last therapy, where the last therapy is defined as the last dose of the last line of therapy (Anderson et al, 2008). Nonresponsive disease is defined as failure to achieve MR or better as the best response to a line of therapy.

Refractory to a single agent (excluding Dexamethasone [identified using preferred term of 'Dexamethasone']) within a regimen will be determined by comparing the date of relapse/PD (as captured on the 'Multiple Myeloma History – Prior Systemic Cancer Therapy (Lines of Therapy)' eCRF page) to the start and stop date of an agent. If this is on or after the first administration date of the agent and within 60 days of the last administration date, then the patient should be considered refractory to the agent. In addition, if the patient stops taking the agent due to progressive disease, the patient will be considered refractory. Start and stop dates for particular agents as well as reasons for stopping are captured on the 'Multiple Myeloma History - Prior Systemic Cancer Therapy (Medications) eCRF page. If a patient achieves SD or PD as the best response to a line of therapy, the patient would be considered refractory to all agents in that line (excluding 'Dexamethasone'). Refractory statuses will be presented for drug classes as listed in bullets above, for individual agents within the classes, and furthermore the fraction of double-refractory (refractory to at least 1 PI and at least 1 IMiD in any line of therapy or within the same line of therapy) will be presented.

8.7 Extent of Exposure

8.7.1 Overall Exposure

Overall treatment duration time (weeks) = ((last dose date – first dose date) +1)/7

where the last dose date is the greatest of:

- Last dose of Melflufen + 28
- Last dose of Bortezomib
- Last dose of Dexamethasone
- Last dose of Daratumumab

The number of treated cycles is calculated as the sum of the cycles where a patient has received at least one dose of any study drug during the 28 days of that cycle.

If a data-cut is being applied to analysis, then if last dose of Melflufen + 28 days > data-cut-off date then the last dose of melflufen is equal to data cut-off date.

The follow-up from Cycle 1, Day 1 to data-cut off with be calculated as (date of study end – date of Cycle 1, day 1 visit) + 1 for patients who ended the study before data-cut off. For patients that are still ongoing in the study the follow-up from Cycle 1, Day 1 will be calculated as (date of cut-off – date of Cycle 1, day 1 visit) + 1.

8.7.2 Melflufen Exposure

Melflufen will be administered intravenously as a 30-minute infusion on Day 1 of every 28-day cycle.

Time on melflufen in weeks is defined as (date of last dose + 28 days – date of first dose + 1)/7.

Total cumulative dose (mg) of melflufen is defined as sum of actual doses administered over time.

Planned dose of melflufen at a cycle is calculated as the starting melflufen dose assigned to the patient.

The total melflufen planned dose is calculated as the starting melflufen dose assigned to the patients * the number of treated cycles.

Duration of Infusion (mins) = infusion end time – infusion start time.

Average duration of infusion (mins) = sum of durations of infusions (mins)/number of infusions.

Average dose of melflufen (mg/week) = total melflufen cumulative dose administered (mg)/time on melflufen (weeks).

Relative dose intensity of melflufen (%) = total melflufen cumulative dose administered (mg)/total melflufen planned dose (mg) * 100.

Relative dose intensity based on average weekly dose (%) = average dose of melflufen (mg)/ planned dose (mg) * 100, where planned dose is either 20, 30 or 40 mg per 4 weeks = 5, 7.5 or 10 mg/week.

Relative dose intensity by cycle (%) = total melflufen dose administered in each cycle/planned dose in each cycle * 100.

8.7.3 Bortezomib Exposure

In Regimen A, bortezomib 1.3mg/m^2 is will be administered twice weekly on Days 1, 4, 8 and 11 of each 28-day cycle. Exposure to bortezomib will be defined as the following:

Time on bortezomib in weeks is defined as (date of last dose – date of first dose + 1)/7.

Total bortezomib cumulative dose is calculated as the sum of bortezomib dose administered during the study.

Planned dose (mg) in a cycle is calculated as 4 doses * 1.3mg/m^2 * baseline BSA (m^2)

The total number of treated cycles is calculated as the sum of the number of cycles where a patient has received at least one dose of bortezomib during the 28 days of that cycle.

The total bortezomib planned dose (mg) is calculated as 4 doses per cycle * 1.3 mg/m^2 * baseline BSA (m^2) * number of treated cycles.

Relative dose intensity (%) is calculated as the total cumulative dose administered (mg)/total planned dose (mg) * 100.

Relative dose intensity by cycle (%) = total cumulative dose administered in each cycle(mg)/ total planned dose in that cycle (mg) * 100.

8.7.4 Dexamethasone Exposure

In Regimen A, dexamethasone 20 mg orally (p.o.) (12 mg for ≥ 75 years of age) will be given on Days 1, 4, 8, 11, and 40 mg (20 mg for patients ≥ 75 years of age) on Days 15 and 22 of each 28-day cycle.

In Regimen B dexamethasone 40 mg p.o (20 mg p.o, for patients ≥ 75 years of age) will be given weekly.

Exposure to dexamethasone will be defined as the following:

Time on dexamethasone in weeks is defined as (date of last dose – date of first dose + 1)/7.

Total dexamethasone cumulative dose is calculated as the sum of dexamethasone dose administered during the study.

The total number of treated cycles is calculated as the sum of the number of cycles where a patient has received at least one dose of dexamethasone during the 28 days of that cycle.

The total dexamethasone planned dose for Regimen A is calculated as ((4 doses per cycle * 20 mg or 12mg, depending on age) + (2 doses per cycle * 40mg or 20mg, depending on age)) * number of treated cycles.

The total dexamethasone planned dose for Regimen B is calculated as ((4 doses per cycle * 40mg or 20mg, depending on age) * number of treated cycles.

Relative dose intensity (%) is calculated as the total cumulative dose administered (mg)/total planned dose (mg) * 100.

Relative dose intensity by cycle (%) = total cumulative dose administered in each cycle/total planned dose in that cycle * 100.

8.7.5 Daratumumab Exposure

In Regimen B daratumumab 16mg/kg will be given weekly for 8 doses, every 2 weeks for 8 doses and then every 4 weeks. See table below for schedule of daratumumab dosing:

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

*Due to prolonged infusions time of the first dose of daratumumab, the Cycle 1 infusion of daratumumab will be given on Day 2 of Cycle 1.

Exposure to daratumumab will be defined as the following:

Time on daratumumab in weeks is defined as (date of last dose – date of first dose + 1)/7.

Total daratumumab cumulative dose is calculated as the sum of daratumumab dose administered during the study.

The total number of treated cycles is calculated as the sum of the number of cycles where a patient has received at least one dose of daratumumab during the 28 days of that cycle.

The total daratumumab planned dose (mg) is calculated as 4 doses per cycle * 16mg/kg * baseline weight (kg) * (number of treated cycles from Cycle 1 to 2) + 2 doses per cycle * 16mg/kg * baseline weight (kg) * (number of treated cycles from Cycles 3 to 6) + 16mg/kg * baseline weight (kg) * (number of treated cycles after Cycle 7).

e.g. if patient discontinues at Cycle 3 then total daratumumab planned dose = 2 * 4 * 16mg/kg * baseline weight (kg), if patient discontinues at Cycle 6 then 8 * 16mg/kg+3 * 2 * 16mg/kg * baseline weight (kg).

Relative dose intensity (%) is calculated as the total cumulative dose administered (mg)/total planned dose (mg) * 100.

Relative dose intensity by cycle (%) = total cumulative dose administered in each cycle/ total planned dose in each cycle* 100.

8.8 Efficacy Endpoints

All tumor response and progression-dependent endpoints are as assessed by the investigator according to the IMWG-URC (Rajkumar et al, 2011).

8.8.1 Best confirmed response

At each efficacy assessment visit, the investigator records the myeloma response according to the IMWG Uniform Response Criteria on the Myeloma Response Assessment eCRF. Possible responses ordered from best to worst are sCR, CR, VGPR, PR, MR, SD or PD. Response can also be recorded as Not Evaluable or Unknown. MRD negativity/positivity are subcategories of sCR and CR. The 'Not Evaluable' category will include patients that do not have sufficient evaluations to assess response according to the IMWG-URC and therefore have a missing best response.

For response categories (sCR, CR, VGPR, PR, MR and SD), the best confirmed response will be the best response recorded by the investigator after the patient received the first dose of melflufen until PD or start of subsequent treatment. All response categories must be confirmed at a consecutive assessment. A response as good as or better than the first response constitutes confirmation of the first response. Two consecutive visits should also confirm the lesser of the pair e.g. if a patient has consecutive visit of VGPR then PR, PR will be confirmed with unconfirmed response of VGPR. A missing/NE response following an initial response will not invalidate confirmation of that response (e.g. CR-NE-CR will still be considered a confirmed CR. More than one NE visit (e.g. CR-NE-NE-CR), however, will preclude the initial response from being confirmed. In case there are unscheduled assessments between two planned visits the unscheduled visit evaluation should not impact the classification of response unless it shows PD. PD also requires confirmation at 2 consecutive assessments before the institution of any new therapy, unless the progression is due to plasmacytoma in which case, only one assessment is needed. This is determined by response of 'Yes' to the questions 'Was there any evidence of a new bone lesion or new extramedullary plasmacytomas?' or 'Was there any evidence of progression or existing bone lesions or extramedullary plasmacytomas?'. All response categories and SD also require no known evidence of progressive or new bone lesions or progressive or new plasmacytoma. Progressive or new plasmacytoma will be ascertained from the Extramedullary Plasmacytoma Evaluation eCRF page.

The table below describes possible best responses and confirmation patterns:

Pattern	Best Confirmed Response	Best Unconfirmed Response
CR-sCR	CR	sCR
CR-NE-CR	CR	CR
CR-NE-NE-CR	Missing	CR
PR-PR	PR	PR
MR-sCR	MR	sCR
PR-NE-CR	PR	CR
PR-NE-PR	PR	PR
VGPR-PR	PR	VGPR
PR-VGPR	PR	VGPR
SD-SD-PD	SD	SD

8.8.2 Overall Response Rate

The overall response rate is the proportion of patients who achieve a best confirmed response of sCR, CR, VGPR, or PR.

8.8.3 Clinical Benefit Rate

The clinical benefit rate is the proportion of patients who achieve a best confirmed response of sCR, CR, VGPR, PR or MR.

8.8.4 Unconfirmed Responses

Best unconfirmed responses will be derived, as per the rules described in Section 8.8.1 without the requirements for response confirmation at consecutive visits (this involves taking into consideration all responses from first dose until start of subsequent therapy or PD). Unconfirmed ORR and CBR will be derived based on best unconfirmed responses.

8.8.5 Progression Free Survival

Progression free survival is defined as the time in months from date of initiation of therapy to the earlier of confirmed disease progression or death due to any cause. Patients with unconfirmed PD as the final response assessment will use the date of latest PD assessment as the date of progression. Patients without confirmed disease progression, without progression as the last assessment, or death will be censored on the date of their last evaluable myeloma response assessment, prior to initiation of subsequent therapy.

8.8.6 Duration of Overall Response

The duration of overall response is defined as the time in months from first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. Patients with unconfirmed PD as the final response assessment will use the date of latest PD assessment as the date of progression. DOR is defined only for patients with a confirmed PR or better. Patients without confirmed disease progression, without progression as the last assessment, or death, will be censored on the date of their last evaluable myeloma response assessment, prior to initiation of subsequent therapy.

8.8.7 Duration of Clinical Benefit

The duration of clinical benefit is the time in months from the first evidence of confirmed assessment of sCR, CR, VGPR, PR or MR to the date to first confirmed disease progression, or death due to any cause. Patients with unconfirmed PD as the final response assessment will use the date of latest PD assessment as the date of progression. Duration of clinical benefit is only defined for patients with a confirmed MR or better. Patients without confirmed disease progression without progression as the last assessment, or death, will be censored on the date of their last evaluable myeloma response assessment, prior to initiation of subsequent therapy.

8.8.8 Time to Response

The time to response is the time in months from first dose of therapy to first documented confirmed response. Only patients with confirmed response (sCR, CR, VGPR or PR) are considered for this endpoint.

8.8.9 Time to Progression

The time to progression is defined as the time in months from initiation of therapy to the date of the first documented confirmed progression. Patients with unconfirmed PD as the final response assessment will use the date of latest PD assessment as the date of progression. Patients without confirmed disease progression, without progression as the last assessment, will be censored on the date of their last evaluable myeloma response assessment or their date of death (whichever occurs sooner), prior to the start of subsequent therapy.

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.

8.8.10 Overall Survival

Overall survival is the time in months from date of initiation of therapy to death due to any cause. Patients still alive at the end-of -study, or lost to follow-up, will be censored at the last day known alive.

8.8.11 Time to Next Treatment

Analyses of Time to next treatment (TTNT) will use two alternative definitions, referred to as $TTNT_a$ and $TTNT_b$.

$TTNT_a$: Duration will be time (months) from the study treatment start to the start of first subsequent therapy (excluding radiotherapy). Patients who have no subsequent therapy will be censored at the earlier of date of death and date of last contact.

$TTNT_b$: Duration will be time (months) from the study treatment start to the start of the first subsequent therapy (excluding radiotherapy) or death. Patients who have no subsequent therapy and do not have a date of death will be censored at the date of last contact.

8.8.12 Pharmacokinetic Analysis

PK parameters will be calculated and provided by the Sponsor using Non-Compartmental Analysis (NCA) and the software [redacted] or later ([redacted] The derivation of PK parameters is done by the Pharmacokineticist. The following PK parameters will be assessed for melphalan:

- Maximum observed concentration (C_{max})

  Maximum plasma concentration (Cmax) is defined as the maximum observed drug concentration observed in plasma over all PK sample concentrations. It will be obtained from the **Cmax** parameter calculated by [redacted] If there is no measurable concentration in the subject's PK profile, then Cmax will be missing for that subject. Cmax will be reported in units of ng/mL.

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

  AUC(0-∞) 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-∞) will be obtained from the **AUCINF_obs** parameter calculated by [redacted].

- Elimination half-life

  The apparent terminal elimination half-life (t½) is defined as the time required for the drug concentration to decrease by a factor of one-half in the terminal phase. t½ can be estimated as ln(2) / Ke, Ke referring to terminal phase elimination rate constant of the apparent log-linear decrease as defined by 3 data points. It will be obtained from the **HL_Lambda_z** parameter calculated by [redacted]. t1/2 will be reported in units of min.

PK samples will be collected in patients from both Regimens, at selected sites only. Three plasma samples for determination of melphalan concentrations will be drawn in each of the first two melflufen treatment cycles, 10–15 minutes after the end of infusion, 1 hour after the end of infusion and the third sample 2 to 4 hours after the end of infusion (as late as possible within the time frame). For Regimen B, the third sample will be taken after the daratumumab infusion in cycle 2.

A requirement for a profile to be evaluable is that all 3 samples have measurable concentrations and that concentrations are strictly decreasing over time. 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.

The following statistics will be derived for C_{max}, $AUC_{(0-\infty)}$ and Elimination half-life:

Geometric mean = exp (arithmetic mean of the log-transformed data)

Geometric standard deviation = exp(standard deviation for log transformed data)

Geometric CV%= sqrt (exp(variance for log transformed data) - 1)) * 100

8.9 Adverse Events

An AE is any untoward medical occurrence in a study patient administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the patient begins study therapy is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

8.9.1 Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) will be defined as any AE that started on or after the first day of study treatment, whichever treatment is administered first, and within 30 days of the last administration of study treatment or before start of subsequent anticancer treatment (whichever occurs first) or that worsen on or after the first day of study treatment.

8.9.2 Relationship to Study Drugs

AEs will be rated as ‘unrelated’, ‘possibly related’ or ‘probably related’ to each study drug, by the investigator. AEs with missing relationship for one of the drugs will be considered as having a ‘missing’ relationship to that study drug. AEs that are categorized as ‘possibly related’ or ‘probably related’ to melflufen will be considered as ‘melflufen-related’ AEs. The same rule applies to each study drug (bortezomib, daratumumab and dexamethasone).

8.9.3 Adverse Events Leading to Dose Modification

An AE can lead to a change in drug/dose administrations (drug interrupted; dose reduced) of each of the study drugs. An AE leading to dose modification of melflufen is defined as an AE with ‘Action taken with melflufen’ recorded as ‘Drug interrupted’ or ‘Dose reduced’. The same rule applies to each study drug and respective action taken variable (bortezomib, daratumumab and dexamethasone). Dose modification to any study drug is defined as an AE that has led to a change in drug/dose administration of any of melflufen, bortezomib, daratumumab and dexamethasone.

8.9.4 Adverse Events Leading to Permanent Discontinuation of Study Drug

An AE that leads to permanent discontinuation of study drug, is defined as an AE with ‘action taken with any study drug’ of ‘Drug withdrawn’.

8.9.5 Adverse Event Severity

AE severity will be rated using the CTCAE (Version 4.03) toxicity grade as ‘Grade 1-mild, ‘Grade 2-moderate’, ‘Grade 3-severe’, ‘Grade 4-life threatening’ or ‘Grade 5-Death’ by the investigator.

8.9.6 Grouped Adverse Events

Adverse events will be grouped as follows:

- Neutropenia (grouped) – preferred terms (PT) ‘Neutropenia’, ‘Neutrophil count decreased’ or ‘Neutropenia worsening’;
- Thrombocytopenia (grouped) – PTs ‘Thrombocytopenia’ or ‘Platelet count decreased’ or ‘Thrombocytopenia worsening’;
- 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’};

- Secondary primary malignancies: Standardized MedDRA Query (SMQ){'Malignant or unspecified tumors'[200000]} + Myelodysplastic syndromes [10028536] (HLT), excluding: Plasma cell neoplasms [1003522] (HLGT).

8.9.7 Adverse Event Infections

Infections will be identified through the following SOC: Infections and infestations

8.9.8 COVID-19 related Adverse Events

COVID-19 AEs will be identified through the following PTs: Asymptomatic COVID-19, COVID-19, SARS-coV-2 test, , SARS-CoV-2 test positive, COVID-19 immunization, COVID-19 pneumonia, COVID-19 prophylaxis, COVID-19 treatment, SARS-CoV-2 test false negative, Suspected COVID-19.

Additional PTs will be added as per MedDRA up-versioning. This list will be finalized prior to database lock.

8.10 Lab Toxicity

Grade 3 or 4 ANC count will be identified using the following rules :

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
ANC (Low)	<LLN - 1.5 x 10^9/L	<1.5 - 1.0 x 10^9/L	<1.0 - 0.5 x 10^9/L	<0.5 x 10^9/L

Onset of Grade 3 or 4 ANC is the date of the lab test assessment. Date of resolution is defined as when the Grade has decreased to 2 or lower based on laboratory data.

8.11 Baseline and Change from Baseline

Unless otherwise specified, baseline will be defined as the latest assessment taken prior to the first dose of the study drug.

Change from Baseline is defined as:

Observed result at nominal time point – observed result at baseline.

8.12 Visit Windows

For the assessments scheduled (all cycles expect for Cycle 1, Day 1) a +/- 3-day window is permitted in accordance with the protocol.

If any assessment for a scheduled visit falls outside of the pre-specified windows, it will nevertheless be included for the analyses of that visit. Data from assessments made at the end of trial visit will be assigned to the end-of-treatment visit. If more than 1 value is available for a given visit, the worst value will be used for summaries by visit, and all data will be listed.

Extra, unscheduled assessments (e.g. laboratory data or vital signs) will not be considered at individual visit analyses, but will be included in assessments which span the entire period (e.g. worst case, potentially clinically important etc.). Unscheduled assessments will be labelled as 'Unscheduled' in listings. In the event multiple protocol-specified assessments are reported within the same visit window the value reported for the scheduled visit should be used in summaries by timepoint, and if this value is missing or unknown the earliest reported value of scheduled and unscheduled assessments within the visit window should be used.

8.13 Handling of Dropouts and Missing Data

Missing data will not be estimated or carried forward for any of the summaries or analysis except for time to event variables. Censoring rules for time to event variables are covered in Section 14.2.1.

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 an AE is treatment-emergent), the date will be imputed as described below for adverse events and diagnosis.

Handling of Partial or Missing Dates

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.
- 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.
- Completely missing dates – AEs will be set to the first study drug administration date and concomitant medications will be set to the first study drug administration. Other entirely missing dates will not be imputed.

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).
- For completely missing stop dates, the date of the data cut-off/database lock will be imputed.

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g. MAR2011, 2009). No other imputation of missing data will be performed.

9 Analysis Sets

9.1 Dose Limiting Toxicity Analysis Set

The DLT analysis set includes all patients in Phase 1 that complete Cycle 1 of therapy or are discontinued due to a DLT event defined in Protocol Sections 6.6.1 and 6.6.2. The DLT analysis set will be used for the evaluation of the MTD in Phase 1. Patients that have been replaced in the original assigned cohort will not be included in the DLT analysis set.

Patients will be summarized according to the treatment regimen and actual dose level received.

9.2 Safety Analysis Set

The safety analysis set includes all patients that have received at least one dose (or partial dose) of melflufen, dexamethasone, or partner therapy (bortezomib or daratumumab).

The safety analysis set will be the primary population for the summaries of all efficacy, exposure and safety data.

Patients will be summarized according to the treatment regimen and actual dose received.

9.3 Efficacy Analysis Set

The efficacy analysis set is a subset of the safety analysis set and includes:

- all patients who receive at least 2 doses of melflufen and ≥50% (on average as opposed to within each cycle) of the partner therapy (bortezomib or daratumumab) during Cycles 1 and 2,
- have a baseline disease assessment,
- and have at least 1 post-baseline disease assessment ≥28 days after first dose.

The efficacy analysis set includes all patients enrolled into Phase 2a and the patients from Phase 1 that received the dose that was carried forward for the Phase 2a portion of the study. The efficacy analysis set is to be used as supportive analysis for the ORR, CBR and DOR.

Patients will be summarized according to the treatment regimen and actual dose level received.

10 Interim Analyses

10.1 Phase 1

A Data safety monitoring committee (DSMC) will be convened for this study and will primarily act to safeguard the interests of study patients, assess safety and efficacy data, and for monitoring the overall conduct of the study. The committee will consist of Oncopeptides AB Study Physician, the Global Lead Investigator, the CRO Medical Monitor and will be chaired by an independent multiple myeloma expert. At the end of each cohort, the committee will meet and evaluate all the current safety data and make decisions regarding dose escalation or cohort expansion in the Phase 1 component of the study. The committee will also determine when the optimal dose has been reached and make recommendations on the Phase 2a dose and schedule. The DSMC may provide recommendations for stopping or continuing the study or for alternate dose and schedule of a given Regimen after review of the data. The DSMC may also make recommendations related to the selection, recruitment, and retention of patients, their management and the procedures for data management and quality control. Additional details regarding the DSMC may be found in the DSMC Charter.

10.2 Phase 2a

The DSMC will meet regularly to assess the benefit/risk profile in the Phase 2a portion of the study. All reported Grade 3-4 treatment-related non-hematological AEs, as well as all serious adverse events (SAEs), and any treatment-related deaths due to hematologic or non-hematologic AEs will then be presented to the DSMC. If the DSMC considers the AE patterns differ from the Reference Safety Information for the individual drugs in the combination (see Protocol Section 12.5.2), the DSMC may recommend additional safety monitoring or stopping further recruitment. Please see the DSMC charter for further information regarding the stopping rules.

11 Data Review

Before each delivery, data management will make every reasonable effort to collect and clean critical data as much as possible. Please refer to the data transfer plan for a definition of critical data.

Oncopeptides will implement an independent review of the myeloma response assessment and progression assessments performed by the investigator. This review process is described in a separate document.

11.1 Data Handling and Transfer

External data to be used for all deliveries will be transferred as per the related data transfer agreements. Please refer to the data management plan for further details.

12 Statistical Methods

Statistical analyses will be performed using SAS® Version 9.4 or higher.

Each treatment regimen and dose level will be evaluated separately. Statistical analysis will be reported using summary tables, inferential analysis, figures and data listings.

For data which are presented in months, a conversion factor of 30.4375 days will be used.

For data which are presented in years, a conversion factor of 365.25 days will be used.

The following conventions for presentation of data will be used:

Categorical variables:

- Categorical variables will be summarized using number of observations and percentages. The denominator for percentage will be the number of patients in the population with data available (n) unless otherwise stated. Missing categories may be added as appropriate.
- Percentages will be presented to one decimal place and will not be presented for zero counts. 100% will be presented without decimals.

Continuous variables:

- The number of patients with non-missing data (n), mean, median, minimum, and maximum will be summarized. The minimum and maximum will be summarized with the same number of decimal places as the value collected; mean and median will be presented to one more decimal place than the value collected. Standard deviation will be presented to two more decimal places.

  Individual patient data recorded on the eCRFs and any derived data will be presented by treatment regimen and patient in data listings.

  All TFLs will be based on the actual treatment that a patient has received.

12.1 Subject Analysis Sets

Number and percentage of patients in the safety analysis set, DLT analysis set, efficacy analysis set will be summarized. The denominator will be the number of patients in the safety analysis set.

12.2 Subject Disposition

Subject disposition data will be summarized by dose level and regimen.

The number and percentage of patients treated and ongoing in the study will be presented. Furthermore, patients alive and dead up-to the data-cutoff will be presented. Percentages will be based on the number of patients treated.

An additional summary of number and percentage of patients who completed and discontinued from the study, and discontinued treatment, together with a breakdown of the corresponding reasons for discontinuation of treatment and discontinuation of study as recorded on the ‘Disposition-End-of-Study’ and ‘Disposition-End-of-Treatment’ eCRF pages will be presented. This summary will be provided for the safety analysis set. Patients that have discontinued the study will be provided in a listing.

12.3 Protocol Deviations

Per PRA processes, protocol deviations will be entered into system of record (CTMS). The study team and Sponsor will conduct on-going reviews of the deviation data and the resulting set of evaluable subjects throughout the study; adjusting the deviation criteria as seems appropriate. The evaluable subjects must be finalized prior to database lock.

The Protocol Deviation Guidance Document defined all important protocol deviations and specified how a protocol deviation should be coded.

A protocol deviation listing of subjects in the safety analysis set will be provided.

A separate listing for protocol deviations related to the COVID-19 identified through search of 'COVID' at the beginning of the deviation text will be provided.

12.4 Demographic and Baseline Disease Characteristics

12.4.1 Demographics

Descriptive statistics will be produced for demographic baseline characteristics by dose level and regimen. Age (years), Age group (<65, ≥65-75 and >75 years), height (cm), weight (kg), and BSA (m^2) will be summarized as continuous data. Gender (male, female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other), and ethnicity (Hispanic or Latino, Not Hispanic or Latino) will be summarized as the number and percentage of patients in each category. Summaries will be provided for the safety analysis set.

12.4.2 Baseline Disease Characteristics

The following variables obtained from the 'Multiple Myeloma Status at Study Entry' eCRF page, will be summarized descriptively by dose level and regimen:

- ISS stage at study entry
- R-ISS stage at study entry
- Derived ISS at study entry
- Derived R-ISS at study entry
- Type of measurable disease at study entry
- SPEP, UPEP, Serum Kappa/Lambda values at study entry
- Current disease status (Relapsed, Relapsed-refractory) determined by the investigator
- Evidence of lytic bone disease at study entry
- Evidence of extramedullary disease at study entry
- Light chain subtype (kappa, lambda, biclonal, unknown)
- Heavy chain subtype at diagnosis (IgG, IgA, IgD, IgE, IgM, None)
- Time since initial diagnosis (years)
- Time since most recent relapse/progression (months)

Other Baseline characteristics that will be summarized are:

- Albumin (<35 g/L and ≥35 g/L)
- Baseline LDH (<1.5 x ULN and ≥1.5 x ULN)
- Creatinine Clearance <45 mL/min, ≥45 – 60 mL/min, ≥60 – 90 mL/min, ≥90 mL/min)
- Beta 2 Microglobulin (<3.5 mg/L, ≥3.5 - 5.5 mg/L, >5.5 mg/L)
- Platelets (<75, ≥75-100 10^9 /L, >100- 150 10^9/L, >150 10^9/L)
- Hemoglobin (<80, ≥80 - 100 g/L and >100 g/L)
- ANC (<1.0 10^9/L, ≥1.0-1.5 10^9 /L, and >1.5 10^9 /L)
- ECOG (0, 1, 2, 3, 4)

The information collected on the 'Multiple Myeloma Status at Diagnosis' eCRF page will be presented in a similar way in a separate table.

The following variables for the bone marrow assessments, obtained from the 'Cytogenetic Abnormalities at Study Entry – FISH' and 'Cytogenetic Abnormalities at Study Entry - Karyotype' eCRF pages, will be summarized descriptively by dose level and regimen:

- Was Cytogenetics performed by FISH at study entry? [Yes, No, Unknown] (from the 'Multiple Myeloma Status at Study Entry' eCRF page)
- Cytogenetics performed by FISH Abnormalities at study entry [t(4; 14), t(4;14) (p16;q32) etc…]
- Cytogenetics identified by FISH (High-risk, Standard risk, Unknown);- High-risk group: consist of subjects that have cytogenetics performed by FISH at study entry, where abnormalities have been found as such: genetic subtype t(4; 14), t(14:16), have deletion 17p, presence of gain 1q, t(14;20) or presence of hypodiploidy.
  - Standard-risk group: consists of subjects that have cytogenetics performed by FISH at study entry were abnormalities selected are not high-risk features.
  - Unknown risk group: consists of subjects with procedure being not done or failed. Cytogenetics performed is 'No' or 'Unknown'.
- Was Cytogenetics performed by Karyotype at study entry? [Yes, No, Unknown] (from the 'Multiple Myeloma Status at Study Entry' eCRF page)
- Cytogenetics performed by Karyotype Abnormalities at study entry [t(4; 14), t(4;14) (p16;q32) etc]
- Cytogenetics identified by Karyotype (High-risk, Standard risk, Unknown);
  - High-risk group: consist of subjects that have cytogenetics performed by Karyotype at study entry, were abnormalities have been found as such: consists of subjects who have presence of del(13)
  - Standard risk group: consists of subjects that have cytogenetics performed by Karyotype who have absence of del(13)
  - Unknown risk group: consists of subjects with procedure being not done or failed. Cytogenetics performed is 'No' or 'Unknown'
- Cytogenetics identified by FISH and Karyotype (High-risk, Standard risk, Unknown);
  - High-risk group: Consists of patients with at least 1 of any of the high-risk factors by either FISH or Karyotype
  - Standard-risk group: Both procedures performed but none of the high-risk features are present.
  - Unknown risk group: Both procedures were not done or failed, or only one was performed and the results did not indicate the patient was high-risk.
- Multi-high risk identified by FISH and Karyotype
  - High risk patients are identified as for the combined group in the previous bullet but at least 2 of the identifiers were met.
- Bone marrow Plasma Cell Involvement (%) [descriptive statistics]

The information collected on the 'Cytogenetic Abnormalities at Diagnosis – FISH' and 'Cytogenetic Abnormalities at Diagnosis – Karyotype' eCRF pages will be presented in a similar way in a separate table.

All summaries will be provided for the safety analysis set.

All demographic and baseline disease characteristic data will be provided in a listing.

12.4.3 Prior Treatment for Multiple Myeloma

Prior medications are coded using version WHODrug DDE B3 Mar_2019 or later.

The following information will be summarized by dose level and regimen for the safety analysis set:

- Number and percentage of patients with at least one transplant (Autologous and Allogeneic)
- Number and percentage of patients with a tandem transplant [Yes, (Autologous-Autologous, Allogeneic-Allogeneic, Autologous-Allogeneic, Allogeneic-Autologous), No]

- Time from frontline transplant to relapse (continuous and categorical [<1 year, ≥1 year - <1.5 years, ≥1.5 years - <2 years, ≥2 years]
- Number and percentage of patients with a salvage transplant (defined as any transplant where the patient has already had 1 or more transplants in earlier lines (planned tandem or double transplants are considered one transplant))
- Type of salvage transplant (Autologous and Allogeneic)
- Number and percentage of patients with a tandem transplant as part of salvage transplant [Yes, (Autologous-Autologous, Allogeneic-Allogeneic, Autologous-Allogeneic, Allogeneic-Autologous), No];
- Number of prior regimens (continuous and categorical [1,2,3,4,>4])
- Best response to last prior regimen
- Refractory status to last prior regimen
- Number and percentage of patients with a prior regimen that has an agent in the categories defined in Section 8.6
- Number and percentage of patients with an agent in the categories defined in Section 8.6, in most recent prior regimen
- Patients refractory to any prior agent
- Patients refractory to agent in at least one prior regimen
- Patients refractory to agent in last prior regimen
- Patients double refractory (refractory to both Proteasome inhibitors and Immunomodulatory drugs)

12.4.4 Medical and Surgical History

Medical and surgical history will be coded according to MedDRA dictionary version 23.0 or later. Summaries will be presented by dose level, regimen, SOC and PT for the safety analysis set.

12.4.5 Prior and Concomitant Medications

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from version March 2019 of WHO DD version or later.

The medication data will be summarized descriptively for the safety analysis set, by study dose level, regimen, ATC level 2, ATC level 4 and preferred term.

Medications with a stop date before the first date of study medication will be considered prior medications. Medications with start date or stop date on or after the first date of study medication and the start date is before the date of the last dose + 30 days, or are ongoing at the time of first dose, will be considered concomitant medications. The prior and concomitant medications will be summarized separately. For handling of partial dates, please refer to Section 8.13.

12.4.6 Concomitant Procedures

Medications identified as procedures via the question ‘Is this a procedure?’ will be classified using the version 23.0 or later of the MedDRA dictionary.

These will be presented in a separate listing.

13 Treatments

13.1.1 Extent of Study Drug Exposure

13.1.1.1 Exposure to Melflufen, Bortezomib, Dexamethasone and Daratumumab

Exposure will be based on the safety analysis set.

The overall treatment duration as defined in Section 8.7.1 along with the number of cycles that any study drug was taken and the number of patients taking any study drug in each cycle will be presented descriptively by dose level and regimen. In addition, the extent of exposure of melflufen, bortezomib, dexamethasone and daratumumab separately will be presented by dose level and regimen.

The median follow-up time from Cycle 1, Day 1 to data cut-off or end of study will also be presented in months as per derivation in Section 8.7.1.

The extent to exposure of melflufen, bortezomib, dexamethasone and daratumumab will be characterized by:

- Total cumulative dose administered (mg) (continuous)
- Time on treatment (weeks) (continuous)
- Relative dose intensity (%) (continuous)
- Relative dose intensity by cycle (%) (continuous)
- Average relative dose intensity for melflufen (%) (continuous)
- Total number of treated cycles (continuous and categorical)
- Average dose of melflufen (mg/week) (continuous)
- Average duration of infusion of melflufen (min) (continuous)
- Total planned dose (mg) (continuous)

Frequency counts and percentages will be presented for the length of delay (relative to the last cycle) for each cycle and for each drug.

Extent of exposure will be provided in a separate listing.

13.1.2 Dose Modification

The action taken on melflufen, daratumumab, bortezomib and dexamethasone (No action taken, dose reduced, dose held, dose delayed, permanently discontinued, other) will be summarized overall (all (any) study drug/all cycles), overall and by cycle for each treatment. This will be presented by dose and regimen.

A separate, similar summary will be presented showing only modifications for when the reason for action taken is AE.

A summary of modifications due to COVID-19, identified through search of ‘COVID’ in the reason for action taken ‘Other – specify’ text field on the eCRF.

14 Efficacy Analyses

Efficacy data will be summarized by dose level and regimen, for patients in the efficacy analysis set and by dose level and regimen for the safety analysis set (as specified).

14.1 Primary Endpoint

Phase 2a

The primary endpoint of Phase 2a is the overall response rate (sCR, CR, VGPR, PR) observed in patients treated at the optimal dose of melflufen in combination therapy according to IMWG -URC in the efficacy analysis set.

A summary of the confirmed best overall response (sCR, CR, VGPR, PR, MR, SD, PD, NE) as determined by the investigator according to the IMWG-URC (Rajkumar et al, 2011) will be presented without analysis. The ORR will also be presented. The exact binomial 95% confidence interval (CI) for ORR as well as for the separate best response categories of sCR, CR, VGPR and PR will be calculated for each treatment regimen and dose level.

This analysis will be presented for patients in the efficacy analysis set and repeated for the safety analysis set.
The above analysis will be repeated based on the best unconfirmed response, as determined by the investigator.

A listing for myeloma response assessment will be provided.

14.1.1 Sensitivity Analysis – Primary Endpoint

In order to assess the impact of COVID-19 pandemic the following additional analysis will be conducted for the safety analysis set by dose level and regimen:

1) For patients who have an AE of COVID-19, only response assessments up to the start date of the COVID-19 AE will be included.
2) Unconfirmed responses on or after the date of WHO declared COVID-19 as a pandemic (11th March 2020) will be evaluated as confirmed until WHO declare it to be over.

14.2 Secondary Endpoints

14.2.1 Progression Free Survival

PFS is measured from the date of initiation of therapy to the date of documented disease progression or death. PFS will be right-censored according to the following conventions:

Situation	Date of Progression or Censoring	Outcome
No post baseline disease assessments, except in the case of death	Date of initiation of therapy	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
Alive and without PD documentation	Date of last disease assessment	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
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

These conventions are based on the May 2007 Food and Drug Administration (FDA) Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics'. (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071590.pdf)

The number of PFS events, the number of censored events and the reasons for censoring will be presented by dose level and regimen and the distribution of PFS will be summarized and plotted for each dose level and regimen using the Kaplan-Meier (K-M) method. The median PFS along with the first and third quartiles will be estimated for each treatment dose and regimen from the 25th, 50th and 75th percentiles of the

corresponding K-M estimates. The 95% CIs for median PFS along with the quartiles will be constructed using the method of Brookmeyer (Brookmeyer & Crowley, 1982)(. Duration of follow-up for PFS will be summarized according to the K-M estimate of potential follow-up also termed “reverse Kaplan-Meier” (Schemper & Smith, 1996).

This analysis will be presented for the safety analysis set and repeated for the efficacy analysis set. A listing of progression free survival times will be provided.

14.2.1.1 Sensitivity Analysis – Progression Free Survival

In order to evaluate the effect of the COVID-19 pandemic the following sensitivity analysis will be performed based on the safety analysis set.

Regional restrictions due to the COVID-19 pandemic may have caused delays in response assessments regardless of whether a patient contracted COVID-19. The following three sensitivity analyses with modified censoring conventions will be performed on the analysis of PFS to assess the impact of delays in myeloma response assessments.

Sensitivity analysis 1- >2 Consecutively Missed Myeloma Response Assessments

Situation	Date of Progression or Censoring	Outcome
No post baseline disease assessments, except in the case of death	Date of initiation of therapy	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 2 consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
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

Sensitivity analysis 2->3 Consecutively Missed Myeloma Response Assessments

Situation	Date of Progression or Censoring	Outcome
No post baseline disease assessments, except in the case of death	Date of initiation of therapy	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 3 consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
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

Sensitivity analysis 3- Discontinued Study due to COVID-19

Situation	Date of Progression or Censoring	Outcome
No post baseline disease assessments, except in the case of death	Date of initiation of therapy	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
Alive and without PD documentation	Date of last disease assessment	Censored
Unconfirmed PD as the final response assessment and no record of COVID-19 related study discontinuation	Date of latest PD assessment	Progressed
Patient discontinued study due to COVID-19 with an unconfirmed PD as the final response assessment	Date of study discontinuation	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

To further assess the impact of patients who contracted or potentially contracted COVID-19, the following censoring conventions will be applied for additional sensitivity analysis.

Sensitivity analysis 4- COVID-19 Fatal Adverse Event

Situation	Date of Progression or Censoring	Outcome
No post baseline disease assessments, except in the case of death	Date of initiation of therapy	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
Alive and without PD documentation	Date of last disease assessment	Censored
COVID-19 fatal adverse event (identified using the criteria specified in Section 8.9.8)	AE start date	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
Death (other than COVID-19 fatal adverse events) or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death (other than COVID-19 fatal adverse events) before first disease assessment	Date of death	Progressed

Sensitivity analysis 5- COVID-19 Adverse Event

Situation	Date of Progression or Censoring	Outcome
No post baseline disease assessments, except in the case of death	Date of initiation of therapy	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
Alive and without PD documentation	Date of last disease assessment	Censored
COVID-19 adverse event prior to PD (identified using the criteria specified in Section 8.9.8)	Date of AE start date	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
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

14.2.2 Other Efficacy Endpoints

DOR will be calculated for patients who achieve a confirmed response of PR of better. Dates of progression or censoring will be determined as described for the analysis of PFS in Section 14.2.1. Distribution of DOR will be summarized for each regimen and dose level using the Kaplan-Meier method as described for the analysis of PFS.

The same COVID-19 pandemic-related sensitivity analysis described for PFS will also be performed for DOR using the safety analysis set.

DCB will be calculated for patients who achieve a confirmed response of MR or better. Dates of progression or censoring will be determined as described for the analysis of PFS in Section 14.2.1. Distribution of DCB will be summarized for each regimen and dose level using the Kaplan-Meier method as described for the analysis of PFS.

OS is defined as time (months) from the date of initiation of therapy to date of death due to any cause. Patients who are alive will be censored at the last follow-up visit. The analysis of OS will be performed by the Kaplan-Meier method as for PFS.

Sensitivity analysis 4 and 5 which refer to patients who contracted or potentially contracted COVID-19 adverse events will also be applied to OS for the safety analysis set. Patients with COVID-19 fatal adverse event will be censored as date of AE start date. Those with COVID-19 adverse events prior to PD will be censored to date of AE start date.

A summary of the CBR will be presented without analysis. The exact binomial 95% CI for CBR will be calculated for each treatment regimen and dose level. This analysis will be repeated based on the best unconfirmed response, as determined by the investigator.

TTP and TTNT, will be summarized using the same methods as for PFS. TTR will be summarized descriptively.

All secondary endpoints will be summarized primarily using the safety analysis set and ORR, DOR and CBR will be repeated using the efficacy analysis set.

Additional exploratory sub-analysis may be conducted to identify sub populations that may benefit from therapy or to clearly define the safety profile and efficacy more clearly and/or to correlate biomarkers with clinical outcomes.

14.3 Exploratory Endpoints

14.3.1 Minimal Residual Disease

The number and rate of positive and negative MRD evaluations will be summarized without analysis for patients who achieve a CR for each treatment regimen and dose level separately.

To evaluate the diagnostic value of bone marrow aspirate in the detection of negative MRD, sensitivity assessments are conducted. For patients with negative MRD, the following bone marrow test parameters from the same assessment will be presented in the listing: Plasma cells (%).

14.3.2 Pharmacokinetics (PK)

All PK parameters provided by the PK program for melphalan are listed in Table *1*: PK Parameters to be calculated. The derivation of PK parameters is done by the Pharmacokineticist. All parameters will be presented in a listing in minimum.

Table 1: 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

Phoenix WinNonLin ID	Unit	Parameter code	CDISC submission value
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 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.

Descriptive statistics for drug concentrations by time point and PK variables will be provided for melphalan by cycle, dose and regimen. For C_{max}, $AUC_{(0-\infty)}$, and t½ arithmetic mean ± standard deviation, geometric mean with coefficient of variation, median with minimum and maximum will be given. Other PK parameters will provided in a listing.

A mean value graph (with arithmetic means) by cycle, dose and regimen will be generated for melphalan concentrations in plasma from all subjects based on planned time (min) relative to start of melflufen infusion.

15 Safety Analyses

All safety results will be presented for the safety analysis set and by actual treatment. No formal statistical analysis will be performed for the safety endpoints. Safety endpoints will be presented by dose level and regimen.

15.1 Adverse Events

All AEs will be coded to a primary system organ class (SOC) and preferred term (PT) using MedDRA version 23.0 dictionary or later.

An overall summary of TEAEs will be provided showing the number and percentage of patients for the following:

- Any TEAEs
- Any Grade 3 or Higher TEAEs
- Any treatment-related TEAEs (relationship to any treatment and relationship to individual treatments)
- Any TEAEs in Phase 1
- Any TEAEs in Phase 2
- Any Grade 3 or Higher treatment-related TEAEs
- Any serious TEAEs
- Any non-serious TEAEs
- Any treatment-related serious TEAEs
- Any TEAE leading to discontinuation of study treatment
- Any COVID-19 TEAE leading to discontinuation of study treatment
- Any TEAE leading to modification (reduction or interruption) of study treatment
- Any TEAEs leading to Death
- Grouped terms for neutropenia, thrombocytopenia, myelodysplastic syndrome and secondary primary malignancies as defined in Section 8.9.6
- Any grade 3 or 4 grouped terms for neutropenia, thrombocytopenia, myelodysplastic syndrome and secondary primary malignancies as defined in Section 8.9.6

The number and percentage of patients who experience at least one TEAE will be summarized by SOC and PT for the following types of events:

- Any TEAE
- Any TEAEs in Phase 1
- Any TEAEs in Phase 2
- Any TEAE by maximum CTCAE Grade (Grade 1- Grade 5)
- Any treatment-related (overall, melflufen, daratumumab, bortezomib and dexamethasone) TEAE
- Any treatment-related (overall, melflufen, daratumumab, bortezomib and dexamethasone) by maximum CTCAE Grade (Grade 1-Grade 5)
- Any treatment-emergent SAE
- Any treatment-emergent non-SAE

- Any treatment-related (overall, melflufen, daratumumab, bortezomib and dexamethasone) treatment-emergent SAE
- Any TEAE resulting in dose modification of study drug (drug interrupted, dose reduced) (any, melflufen, daratumumab, bortezomib, and dexamethasone)
- Any TEAE leading to permanent discontinuation of study drug

A patient reporting the same AE more than once will be counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination. For such cases, the maximum CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. Treatment-related AEs, defined as AEs with a relationship of possibly or probably related to any study drug, will be summarized in the same way. The number and percent of patients who experience a grouped AE will be summarized for each treatment regimen and dose level.

All AEs will be listed.

In all AE summaries data will be ordered by decreasing frequency in the overall population by SOC and PT within SOC.

For all summaries of treatment-related and dose modification, each study drug (melflufen, daratumumab, bortezomib and dexamethasone) will be presented separately and overall.

Furthermore, infections with an onset date within +/- 7 days of the onset and/or resolution date of Grade 3 or 4 ANC, will be summarized by SOC and PT. A listing will also be provided.

An additional summary of all deaths (based on the Patient Death eCRF page) will be presented, regardless of treatment emergence. Summaries will include death prior to first dose (based on the safety analysis set), deaths that occurred ≤30 and >30 days after last dose of study treatment, deaths ≤60 days after first dose (early deaths), related/non-related deaths to study drug and primary cause of death. Overall counts will be provided, and events will also be presented by SOC and PT.

A corresponding listing of deaths will be provided.

Furthermore, the number of subjects diagnosed with a second primary malignancy in overall survival follow-up will be presented (based on the Overall Survival eCRF page).

15.1.1 Laboratory Data

All clinical laboratory parameters will be converted to consistent units according to the International System of Units (SI) before summarization and the baseline measurement will be the last measurement taken prior to first study drug administration.

Shift tables will be presented based on CTCAE criteria, using Grade 1 – Grade 4 as well as Grade 0 indicating no abnormality. For some laboratory parameters, deviations from the normal range in both directions (either above or below) are of interest; these parameters are shown in Table 2: Direction of abnormality of lab parameters. In such cases, the parameter will be summarized by direction of abnormality.

Table 2: Direction of abnormality of lab parameters

Category	Parameter	Direction of Worst Value
Hematology	Hemoglobin	Decrease
	Leukocytes	Increase and Decrease
	Neutrophils	Decrease
	Platelets	Decrease
	Lymphocytes	Increase and Decrease
Chemistry	ALT	Increase
	AST	Increase

Category	Parameter	Direction of Worst Value
	Albumin	Decrease
	Alkaline phosphatase	Increase
	Calcium	Increase and Decrease
	Creatinine	Increase
	Glucose	Increase and Decrease
	Magnesium	Decrease
	Phosphate	Decrease
	Potassium	Increase and Decrease
	Sodium	Increase and Decrease
	Bilirubin	Increase

- Numeric parameters: Actual values and change from baseline for each parameter will be summarized with descriptive statistics by visit, including a separate summary for the last on-treatment measurement.
- Categorical laboratory parameters: The distribution of the categories will be summarized by visit.
- Parameters for which there are NCI-CTCAE Grades defined: The shift from baseline to the worst grade on-treatment will be presented.
- Neutrophils and Platelets will be presented by maximum CTCAE toxicity grade (Grade 1-Grade 5) and cycle (1,2,3,4,5 etc.).
- Number of Grade ≥ 3 Neutrophils and Platelets events by cycle will be presented.

Myeloma-Specific lab tests, Hepatitis B, Urinalysis, Bone marrow aspirate and biopsy results and change from baseline will be listed

15.1.2 Vital Signs and Body Surface Area

All vital sign data will be listed for the safety analysis set. Parameters include: Body surface area (m^2), Diastolic blood pressure (DBP) (mmHg), Height (cm), Pulse rate (beats/min), Respiratory rate (breaths/min), Systolic blood pressure (SBP) (mmHg), Temperature (C) and Weight (kg).

15.1.3 Physical Examinations, ECGs, and Other Observations Related to Safety

Listings will also be provided for the following safety assessments using the safety analysis set:

- Pregnancy test summary
- Electrocardiogram (ECG)
- Complete physical examination
- Direct physical examination
- ECOG results
- Chest X-ray
- Pulmonary function testing

Results from the extramedullary plasmacytoma evaluation and the bone lesion assessment will be listed.

16 Validation

[redacted] goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

17 References

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ATC	Anatomic therapeutic classification
BSA	Body surface area
CBR	Clinical benefit rate
CRF/eCRF	Case report form/electronic case report form
CR	Complete response
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation
DD	Drug dictionary
DIRA	Daratumumab interference reflex assay
DLT	Dose limiting toxicity
DOR	Duration of response
DSMC	Data safety monitoring committee
ECG	Electrocardiogram
HLT	Higher level term
IMiD	Immunomodulatory drug
IMWG-URC	International myeloma working group uniform response criteria
ISS	International staging system
IVRS	Interactive voice response system
i.v.	Intravenously
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
MedDRA	Medical dictionary for regulatory activities
MM	Multiple myeloma
MR	Minimal response
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NCI	National cancer institute
ORR	Best objective response
OS	Overall survival
PD	Progressive disease

PFS	Progression free survival
PI	Proteasome inhibitors
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
R-ISS	Revised international staging system
RRMM	Relapsed refractory multiple myeloma
SAE	Serious adverse event
SAP	Statistical analysis plan
sCR	Stringent complete response
SD	Stable disease
SDG	Standardized drug groupings
sFLC	Serum free light chain
SI	International system of units
SOC	System organ class
SPEP	Serum protein electrophoresis
TEAE	Treatment emergent adverse event
TTNT	Time to next treatment
TTP	Time to progression
TTR	Time to response
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WHO	World health organization

Appendix 2 Tables, Figures, Listings, and Supportive SAS Output Appendices

The TOC and TFL shells will be provided in a separate document.