Protocol OP-108
Version 2.1, 25 November 2020

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

Title Page

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Protocol Number:	OP-108
Compound:	Melflufen
Brief Title:	An Open-label, Phase 3 Study of Melflufen with Daratumumab compared to Daratumumab in patients with RRMM
Study Phase:	Phase 3
Acronym:	**LIGHTHOUSE**
Sponsor Name:	Oncopeptides AB
Legal Registered Address:	Västra Trädgårdsgatan 15 SE-111 53 Stockholm, Sweden
Regulatory Agency Identifying Number(s):	IND: 116362 EudraCT: 2019-002161-36
Clinical Research Organization:	PSI CRO AG Baarerstrasse 113a 6300 Zug, Switzerland
Approval Date:	**Version 1.0: January 29, 2020** **Version 2.0: Amendment 1, September 03, 2020** **Version 2.1: Amendment 2, November 25, 2020**

Signature Page – Sponsor and Lead Investigator

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Protocol Agreement Page - Principal Investigator

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

Protocol Number: OP-108

By signing this protocol acceptance page, I confirm I have read, understood, and agree to conduct the study in accordance with the current protocol.

_____

Name of Study Center

_____

Principal Investigator Name (Printed)

_____ _____

Principal Investigator (Signature) Date

This clinical study was designed and shall be implemented and reported in accordance with the International Conference of Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

Confidential information contained in the clinical study protocol will not be used for any purpose other than the evaluation and conduct of the clinical investigation, unless prior written approval has been obtained from the Sponsor Oncopeptides AB.

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 2 (non-substantial)	25 November 2020
Amendment 1	03 September 2020
Original Protocol	29 January 2020

Overall Rationale for Amendment 1, 03 September 2020:

The overall rationale for Amendment 1 is an update of the study design to 1:1 randomization and increased sample size to 240 patients with 90% power at the request of Competent Authorities.

Also, a crossover opportunity has been added to allow patients with documented disease progression in Arm B to receive melflufen, dexamethasone and daratumumab treatment.

In addition, exclusion criteria related to infections have been updated with information about COVID-19.

Information that the subcutaneous formulation of daratumumab used in the study has been approved by FDA in the US, EMA in Europe and MHRA in UK during 2020 has been added.

Overall Rationale for Amendment 2, 25 November 2020:

Non-substantial amendment due to update of assigned safety CRO from PSI to TFS. SAE reporting email address updated to safety.report@oncopeptides.com.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 2 Introduction	Adding that melphalan flufenamide is referred to as melflufen.	The international nonproprietary name of melflufen is melphalan flufenamide.
1.1 Synopsis 2.1 Study Rationale	Adding that the subcutaneous formulation of daratumumab to be used in the study was approved by FDA in US, by EMA in Europe and MHRA in UK in 2020.	Approval of subcutaneous (s.c.) daratumumab obtained by FDA, EMA and MHRA since protocol version 1.0 was finalised.
1.1 Synopsis 1.2 Schema 2.1 Study Rationale 2.3 Benefit/Risk Assessment 3 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.1 Study Treatment Administered 8.1.3Procedures after active study treatment Appendix 3: Optional crossover for patients in Arm B to treatment with melflufen, dexamethasone and daratumumab	Patients that received daratumumab monotherapy and have confirmed disease progression may receive the melflufen, daratumumab and dexamethasone combination as an optional crossover within the study. Updates are made throughout the protocol in applicable sections. All assessments for the optional crossover are specifically described in Appendix 3: Optional crossover for patients in Arm B to treatment with melflufen, dexamethasone and daratumumab.	Revised study design
1.1 Synopsis 3 Objectives and Endpoints	Clarification of Key secondary objectives. Objectives based on PROs are moved from secondary to exploratory objectives with clarification that endpoints based on PROs are including summary score of EORTC QLQ-C30 and utility index of EQ-5D.	Clarification

1.1 Synopsis 5.1 Inclusion Criteria 5.2 Exclusion Criteria	Exclusion criteria 2: If treated with daratumumab or another anti-CD38 antibody: Refractory to treatment or failure to achieve at least PR as best response Replaced with Inclusion criteria 5: Prior treatment with daratumumab or another anti-CD38 antibody is allowed if the patient has: • Achieved at least PR and is not refractory to previous anti-CD38 antibody treatment • At least 6 months since last dose of anti-CD38 antibody prior to Cycle 1/Day 1 (C1/D1) • Not discontinued anti-CD38 antibody treatment due to related Grade ≥ 3 toxicity	Clarifying patient eligibility for patients previously treated with daratumumab or another anti-CD38 antibody.
1.1 Synopsis 5.1 Inclusion Criteria 5.2 Exclusion Criteria 8.4.7 Laboratory Test Abnormalities	Exclusion criteria 8 updated. Known active infection that is uncontrolled (including symptomatic or asymptomatic COVID-19) or has required intravenous systemic therapy within 14 days of randomization. Patients that has required oral anti-infective treatment within 14 days of randomization should be discussed with the Medical Monitor. Added information in Laboratory Test Abnormalities: A positive COVID-19 (SARS-CoV-2) test should always be considered clinically significant.	Adding clarification that known infection due to COVID-19 is an exclusion criterion.
1.1 Synopsis 6.1.1 Study Regimens and Administration	2:1 randomization changed to 1:1 randomization and number of patients randomized updated from 170 to 240.	Revised study design from 2:1 to 1:1 randomization and 90% power.

1.1 Synopsis	Study Treatment Arm A; Table updated with footnote to correspond to protocol. b) Premedication should be administered to prevent infusion related reactions (see protocol).	Clarification in synopsis.
1.2 Schema	Study Schema updated.	Revised study design.
1.3 Schedule of Activities (SoA) 8.1.3.2 Procedures 8 weeks after last dose of daratumumab 8.1.3.3.1 Progression Free Survival Follow-Up	Pregnancy test added for Woman of Child Bearing Potential at 8 and 12 weeks after last daratumumab dose. The 8 and 12- weeks urine test can be taken at home.	Updated to have monthly pregnancy testing during the same time period as contraception is required.
1.3 Schedule of Activities (SoA) 8.1 Study procedures Table 10-2 Blood and Bone Marrow Volumes 8.10.2 DNA/RNA Sequencing	Blood sample for DNA/RNA sequencing should be collected before dosing at cycle 1, at time of response (CR or VGPR), and at the time of disease progression. Clarification of when samples shall be taken in case of response and disease progression and removed as assessment on Day 8, 15 and 22.	Clarification
1.3 Schedule of Activities (SoA) Table 10-2 Blood and Bone Marrow Volumes	Blood sample for myeloma related bone disease biomarkers should be collected before dosing at Day 1 of all cycles, at the EOT visit and at PFS-FU.	Including samples at PFS-FU independent of disease progression.
1.3 Schedule of Activities (SoA) 8.1 Study procedures	Clarifications of cycle-specific assessments against information described in the protocol body for consistency, including adding separate rows in SoA for subsequent therapy review.	Clarification
1.3 Schedule of Activities (SoA) 4.5.1Study Completion for a patient	Clarification that patient study end date and primary reason for ending study will be collected.	Clarification

1.3 Schedule of Activities (SoA) 6.3.1 Study Drug Administration 8.1.2.3 Procedures Day 8, 15 and 22	If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then Complete Blood Count assessments may be excluded at Day 8 and Day 22.	To limit the number of mandatory visits for the patient during the cause of the study.
2.2 Background	Information on number of patients estimated with myeloma in the US has been updated with figures from 2019. Isatuximab added as an approved drug for the treatment of Multiple Myeloma.	Update with recent information. Recently approved treatment.
2.3 Benefit/Risk Assessment	New table added "Assessment of important potential risk" with important potential risks and mitigation strategy.	Clarification of what the important potential risks that are associated with the study interventions and study procedures.
4.3 Justification for Dose	Reference added to the approved subcutaneous formulation Darzalex FASPRO™.	FDA approval obtained in May 2020.
5.1 Inclusion Criteria 5.2 Exclusion Criteria	See above.	See above.
6.1.1 Study Regimens and Administration	Rewording of footnotes in table regarding pre-medication and dexamethasone administration.	Clarification
6.1.4 Daratumumab Administration (Arm A and B)	Updated that the requirement of patients to remain in the clinic 3 hours after their daratumumab administration is only for the first administration (Cycle 1 Day 1), and then up to investigators discretion for subsequent Cycles.	Most administration related reactions occur following the first injection.
6.1.4.1.2 Post-dose Medications	Adding information about post-dose administration of steroids for daratumumab.	Alignment with prescribing information.

6.2.3.2 Daratumumab Storage	Mandatory filtration has been removed from the protocol and replaced by referring to Pharmacy manual.	Filtration requirements will be described in the Pharmacy Manual.
6.3.1 Study Drug Administration	Adding information that if a patient's tolerability is good in two preceding cycles, Visits at Day 8 and Day 22 do not have to be completed.	To reduce the number of visits for the patient.
6.5.1 Required Concomitant Therapy 6.5.2 Recommended Concomitant Therapy	High risk patients are mandated, to receive pneumocystis prophylaxis.	Alignment with Investigators Brochure.
6.5.3 Prohibited Concomitant Therapy	The use of live vaccines is prohibited during the study and for 90 days after last dose of study treatment. Acetylsalicylic acid, at doses ≥ 1 g per dose or 3 g per day should be avoided due to an increased risk of bleeding in patients receiving dexamethasone.	Update from 30 to 90 days at the request of competent authorities. Alignment with dexamethasone prescribing information.
6.6.3.1 Dose Modifications for Melflufen and Daratumumab	Clarification that patients with neutropenia should be monitored for signs of infection.	Clarification
6.6.3.2 Dose modifications for Dexamethasone (Arm A)	Omeprazole has been replaced with proton pump inhibitors.	Addition
6.6.3.3 Dose Modifications for Daratumumab	Clarified that Infusion Related Reactions is also used as the definition for systemic reactions to daratumumab subcutaneous injections. Added separate information about local reactions after administration.	Clarification
8.1.1 Procedures during screening	Explanation of what myeloma history characteristics to be collected at screening.	Clarification
8.1.2.1 Procedures Day 1	Duplicated information deleted.	Duplicated information within the same section.

8.10.1 Minimal Residual Disease (MRD) assessment	Details on MRD has been added.	Clarification.
8.4.7 Laboratory Test Abnormalities	Removed “Induce clinical signs and symptoms”	Clarification. If there are signs and symptoms these should be reported, not the lab value.
8.11 Immunophenotyping /Immunoprofiling	Clarification of heading to Immunophenotyping/Immunoprofiling. Immunoprofiling sample times corrected against SoA.	Correction and clarification.
9.2 Sample Size Determination	Samples size has been updated based on 1:1 randomization.	Revised study design from 2:1 to 1:1 randomization and 90% power.
9.3 Populations	Clarification of the Per Protocol Analysis set that will be used for sensitivity analysis.	Clarification
9.4 Statistical Analyses	Details added on the statistical analyses. Information added regarding efficacy analyses of the primary and secondary endpoints, multiplicity and pharmacokinetic data. Sub-section added about efficacy analyses of key secondary endpoints. Sub-section added about efficacy analyses of exploratory endpoints. Sub-section added about handling of dropouts and missing data.	Addition of information.
9.5 Interim Analyses	Sub-section about Sample Size Re-estimation has been deleted.	Sample size revised.
9.5.1 Data Monitoring Committee	Added the DMC can recommend continuing the study, with or without modifications, or stop the study based on benefit/risk concerns.	Addition of information.

Table 10-1 Protocol-Required Laboratory Assessments Table 10-2 Blood and Bone Marrow Volumes	Hepatitis B, C and HIV screen only to be taken at screening. Pharmacokinetic, immunogenecity and immunoprofiling tests added to correspond to SoA. Clarification of timepoints as described above.	Correction and clarification.
10.1.3 Informed Consent Process	Patients in Arm B who are eligible to crossover to treatment with melflufen, daratumumab and dexamethasone must sign an IRB/IEC/REB approved informed consent before the new treatment is started.	Revised study design.
Appendix 2: Clinical Laboratory Tests	Central labs corrected with PK and biomarkers against SoA and Table 8-2.	Correction and clarification.
Appendix 3: Optional crossover for patients in Arm B to treatment with melflufen, dexamethasone and daratumumab	Schedule of activities, criteria for initiation of study procedures for patients in Arm B who crossover to treatment with melflufen, dexamethasone and daratumumab.	Addition of information for crossover
Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	COVID-19 reporting added.	Addition of information related to COVID-19.
Appendix 17	Tick box added for 0 at No pain. Space for adding time added.	Correction
11 References	Literature references in the protocol added into the Reference list.	Correction
Signature Page – Sponsor	Change of Sponsor Clinical Operation Directors.	Administrative update.
Protocol	Administrative updates.	Administrative updates.

Changes Amendment 2 (non-substantial)

Section # and Name	**Description of Change**	**Brief Rationale**
Signature Page – Sponsor	Change of Sponsor Clinical Study Physician.	Administrative update.
Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Assigned safety CRO changed from PSI to TFS SAE reporting email address added: safety.report@oncopeptides.com	Safety CRO changed for the study from PSI to TFS
Appendix 5: Contraceptive Guidance and Collection of **Pregnancy Information**	Assigned safety CRO changed from PSI to TFS SAE reporting email address added: safety.report@oncopeptides.com	Safety CRO changed for the study from PSI to TFS
Protocol	Administrative updates and corrected typos.	Administrative updates.

Table of Contents

List of Tables

1. Protocol Summary

1.1. Synopsis

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

Short Title: An Open-label, Phase 3 Study of Melflufen with Daratumumab compared to Daratumumab in patients with RRMM

Rationale:

The outcome of relapsed/refractory multiple myeloma (RRMM) is still unsatisfactory despite recent improvements in treatment. Melphalan flufenamide (hereinafter referred to as melflufen) is a novel peptide-drug conjugate that is rapidly taken up by MM cells due to its high lipophilicity (Chauhan et al 2013, Wikström et al 2017). Once inside the myeloma cell, the activity of melflufen is determined by its immediate cleavage by peptidases into hydrophilic alkylator payloads that are entrapped (Wikström et al 2017, Gullbo et al 2003). Melflufen is 50-fold more potent than melphalan in myeloma cells in vitro due to the increase of intracellular alkylator activity (Chauhan et al 2013, Wikström et al 2017). Daratumumab is a monoclonal antibody targeting CD38 and has shown activity in RRMM as a single agent with limited hematological toxicity (Lokhorst 2014). The combination of melflufen, dexamethasone and intravenous daratumumab is explored in the clinical study OP-104 ANCHOR. Early data has shown promising efficacy and limited non-hematologic toxicity in line with previous experiences of melflufen in earlier studies. The aim of this Phase 3 study (OP-108) is to evaluate the drug combination melflufen, dexamethasone and daratumumab compared to daratumumab monotherapy in patients with RRMM. Daratumumab monotherapy is used as comparator since it is an approved treatment in the intended study population. Patients who received daratumumab monotherapy and have confirmed disease progression may receive the melflufen, daratumumab and dexamethasone combination as an optional treatment within the study. A subcutaneous co-formulation of daratumumab in combination recombinant human hyaluronidase PH20 has been evaluated versus intravenous daratumumab in a Phase 3 trial (Mateos et al 2019). Based on the data from that study (the COLUMBA trial), the subcutaneous formulation of daratumumab was approved in 2020 by FDA in US, EMA in Europe and MHRA in UK and will be used in both treatment arms in study OP-108.

Objectives and Endpoints

The objectives and endpoints for the study are presented in Table 1-1.

Table 1-1 Study objectives and Endpoints

Objectives[a]	Endpoints[a]
Primary:	
To show superiority of progression free-survival (PFS) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	PFS (time from the date of randomization to the date of first documentation of confirmed progressive disease (PD) or death due to any cause).
Key Secondary:	
To evaluate and compare Overall Response Rate (ORR) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	ORR (proportion of patients who achieve a best confirmed response of stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR) or Partial Response (PR)).
To evaluate and compare Duration of Response (DOR) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	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).
To assess the safety and tolerability of melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	Frequency and Grade of treatment emergent adverse events (TEAE).
Other Secondary:	
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)	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).
Exploratory:	
To assess minimal residual disease (MRD) in patients achieving a CR or VGPR in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	Assessment of MRD status by Next Generation sequencing (NGS) in patients who achieve a CR or VGPR.
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.	PFS-2 (defined as time from randomization to progression on next line of treatment or death from any cause, whichever occurs first).
To assess and compare the changes in pain in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	Value and changes in pain, in BPI-SF and Numeric Rating Scale (NRS) for measure of bone pain.
To assess and compare responses in patients with extramedullary myeloma (plasmacytomas).	Response rate (CR and PR) according to International Myeloma Working Group (IMWG) consensus criteria of extramedullary myeloma (plasmacytomas).
To assess and compare use of health services and number and duration of hospitalizations in patient 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.	Number of health services. Number and days of hospitalization.
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).	PK parameters of melphalan at selected time points.
To assess the PK and immunogenicity of subcutaneous daratumumab.	Serum daratumumab concentrations Incidence of antibodies to daratumumab
To evaluate the immunogenicity of recombinant human hyaluronidase (rHuPH20) following subcutaneous daratumumab administration.	Incidence of antibodies to rHuPH20
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.	• 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, PINP, Total RANK, Osteopontin, Osteocalcin, CTX, bone ALP. • Serum levels of cytokines IL-6, IL-10. • Immune profiling in peripheral blood including but not limited to T Reg., MDSC and NK cells.
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.	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.
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)	ORR (proportion of patients who achieve a best confirmed response of stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR) or Partial Response (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).
	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.
	TTR (time from crossover to the date of the first documented confirmed response in a patient who has responded with ≥PR).
	TTP (time from crossover to the date of the first documented confirmed PD).
	TTNT (time from crossover to the date of next anti-myeloma treatment or until death).
	OS (time from crossover until death of any cause)

To assess and compare the changes in pain for patients in Arm B who crossover to treatment with melflufen, dexamethasone and daratumumab.	Value and changes in pain, in BPI-SF and Numeric Rating Scale (NRS) for measure of bone pain.
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.	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.
To assess the safety and tolerability of melflufen, dexamethasone and daratumumab treatment for patients in Arm B who crossover.	Frequency and Grade of treatment emergent adverse events (TEAE).

a) All tumor response and progression-dependent endpoints are assessed by the investigator and an Independent Review Committee (IRC) according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) guidelines (Kumar et al 2016).

Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

1. Male or female, age 18 years or older;
2. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol;
3. A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening;
4. Double refractory to an immunomodulatory drug (IMiD) and a Proteasome Inhibitor (PI) (regardless of the number of prior lines of therapy), **or** have received at least 3 prior lines of therapy including an IMiD and a PI (the definition of refractory includes intolerance to an IMiD/PI after at least two 28-day cycles of therapy);
5. Prior treatment with daratumumab or another anti-CD38 antibody is allowed if the patient has:
    - Achieved at least PR and is not refractory to previous anti-CD38 antibody treatment
    - At least 6 months since last dose of anti-CD38 antibody prior to Cycle 1/Day 1 (C1/D1)
    - Not discontinued anti-CD38 antibody treatment due to related Grade ≥ 3 toxicity
6. Measurable disease defined as any of the following:
    - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
    - ≥ 200 mg/24hr of monoclonal protein in the 24-hour urine collection by electrophoresis (UPEP)
    - Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain (FLC) ratio
7. Life expectancy of ≥ 6 months;

8. ECOG performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the Medical Monitor);
9. Ability to understand the purpose and risks of the study, ability to participate in all the procedures required by the protocol and provide signed and dated informed consent;
10. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470msec;
11. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study treatment administration on Cycle 1 Day 1:
    - Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days (14 days for pegfilgrastim) prior to initiation of study treatment)
    - Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusions during the 10 days prior to initiation of therapy)
    - Hemoglobin ≥ 8.0 g/dL (Red Blood Cell (RBC) transfusions are permitted)
    - Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), except patients diagnosed with Gilbert's syndrome that have been reviewed and approved by the Medical Monitor
    - Aspartate transaminase/Aspartate aminotransferase (AST, also known as Serum Glutamic Oxaloacetic Transaminase (SGOT)) and Alanine transaminase/Alanine aminotransferase (ALT, also known as Serum Glutamic Pyruvic Transaminase (SGPT)) ≤ 3.0 x ULN
    - Renal function: Estimated creatinine clearance by Cockcroft- Gault formula of ≥ 45 mL/min
12. Must have or be willing to have an acceptable central catheter. (Port A cath, peripherally inserted central catheter (PICC) line, or central venous catheter);

13. a) Male patients: Male patient who agrees to use contraception as detailed in this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period.

    b) Female patients**:** A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

    i. Not a woman of childbearing potential (WOCBP) **<u>or</u>**

    ii. A WOCBP who agrees to follow the contraceptive guidance in the protocol during the treatment period and for at least 3 months after the last dose of study treatment.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Primary refractory disease (i.e. never responded with at least MR to any prior therapy);
2. Prior treatment with CD38 CAR-T cell therapy or CD38/CD3 bispecific antibodies;

3. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) less than 50% of predicted normal;
4. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification;
5. Evidence of mucosal and/or internal bleeding or platelet transfusion refractory (platelet count fails to increase by > 10,000 cells/mm^3 after a transfusion of an appropriate dose of platelets);
6. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., heart failure class III or IV according to New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, significant cardiac conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months);
7. Known active infection that is uncontrolled (including symptomatic or asymptomatic COVID-19) or has required intravenous systemic therapy within 14 days of randomization. Patients who has required oral anti-infective treatment within 14 days of randomization should be discussed with the Medical Monitor;
8. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance;
9. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation;
10. Human immunodeficiency virus (HIV) or active hepatitis C viral infection, either known or if detected during screening;
11. Hepatitis B: both active (defined as HBsAg+) or non-active hepatitis B (defined as HBsAg-, Anti-HBs+, Anti-HBc+):
    - Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-).
12. Concurrent known or suspected amyloidosis or plasma cell leukemia;
13. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);
14. Known central nervous system (CNS) or meningeal involvement of myeloma:
15. Any of the following treatments, within the specified timeframe:
    - Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy.
    - The use of live vaccines within 30 days before initiation of therapy.
    - IMiDs, PIs and or corticosteroids within 2 weeks prior to initiation of therapy.
    - Other investigational therapies and monoclonal Antibody (mAb) within 4 weeks of initiation of therapy.
    - Prednisone up to but no more than 10 mg orally quaque die/one a day (q.d.) or its equivalent for symptom management of comorbid conditions is permitted but dose

should be stable for at least 7 days prior to initiation of therapy;

16. Residual side effects to previous therapy > Grade 1 prior to initiation of therapy (alopecia any grade and/or neuropathy Grade 1 without pain are permitted);
17. Prior stem cell transplant (autologous and/or allogenic) within 6 months of initiation of therapy;
18. Prior allogeneic stem cell transplantation with active graft-versus-host-disease;
19. Prior major surgical procedure or radiation therapy within 4 weeks of the initiation of therapy (this does not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy);
20. Known intolerance to the required dose and schedule of steroid therapy, as determined by the investigator;
21. Known hypersensitivity to any of the agents in this study including hyalonuridase
22. Prior treatment with melflufen

Overall Design:

This is an open-label, randomized, international, multicenter Phase 3 trial which will enroll patients with RRMM who are either double refractory to an IMiD and a PI, or had at least 3 prior lines of therapy including exposure to both an IMiD and a PI. Patients will be randomized (1:1) to Arm A or Arm B. For each arm, treatment will be given in 28-day cycles and may be given in an outpatient treatment setting. Patients in Arm B may, after confirmed progressive disease, crossover and receive treatment with melflufen, dexamethasone and daratumumab and continue in the study.

Arm A:

- Melflufen 30 mg will be given as a 30-minute intravenous (i.v.) infusion.
- Dexamethasone 40 mg weekly will be given per oral (p.o.). Patients ≥ 75 years should receive a reduced dose of dexamethasone (20 mg weekly).
- Daratumumab 1800 mg will be given subcutaneously (s.c.) as a 15 mL injection over 3-5 minutes with premedication for the prophylaxis of infusion reactions.

Arm B:

- Daratumumab 1800 mg will be given subcutaneously as a 15 mL injection over 3-5 minutes with pre-medication for the prophylaxis of infusion reactions. Patients with confirmed disease progression after treatment in Arm B have the option to crossover and receive treatment with melflufen, dexamethasone and daratumumab.

Number of Patients:

240 patients are planned to be randomly assigned to study treatment and the final analysis will take place when 160 patients have experienced a PFS event. 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).

Treatment Groups and Duration:

The following tables summarizes the study drug administration schedule during each 28-day cycle.

Study Treatment Arm A:

Melflufen 30 mg (i.v.)	Daratumumab 1800 mg (s.c.)[a]	Dexamethasone (p.o.)[b]
All cycles: Day 1	**Cycle 1 and 2:** Days 1, 8, 15 and 22 **Cycle 3 to 6:** Days 1 and 15 **Cycle 7+:** Day 1	40 mg weekly for patients < 75 years of age 20 mg weekly for patients ≥75 years of age

a) Pre-medication should be administered to prevent infusion related reactions (see protocol).
b) Prior to melflufen infusion 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 (SoC) of the study center. For additional details on dexamethasone administration see protocol.

Study Treatment Arm B:

Daratumumab 1800 mg (s.c.)[a, b]
Cycle 1 and 2: Days 1, 8, 15 and 22 **Cycle 3 to 6:** Days 1 and 15 **Cycle 7+:** Day 1

a) Pre-medication should be administered to prevent infusion related reactions (see protocol).
b) Patients with confirmed disease progression in Arm B have the option to receive melflufen, dexamethasone and daratumumab (dose and schedule as in Arm A).

Dose modifications of each drug will be implemented for individual patient tolerability according to dose modification guidelines described in the protocol. This also applies to patients doing the crossover in the study. 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.

Treatment duration:

Patients in both treatment arms will receive treatment until there is documented PD according to the IMWG-URC 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.

Study Assessments:

All study visits and assessments are summarized in Schema (see Section **Error! Reference source not found.**) and Schedule of Activities (see Section 1.3). Study visits and assessments to be performed after patients cross over are summarized in a separate Schedule of Activities in Study Protocol Appendix 3.

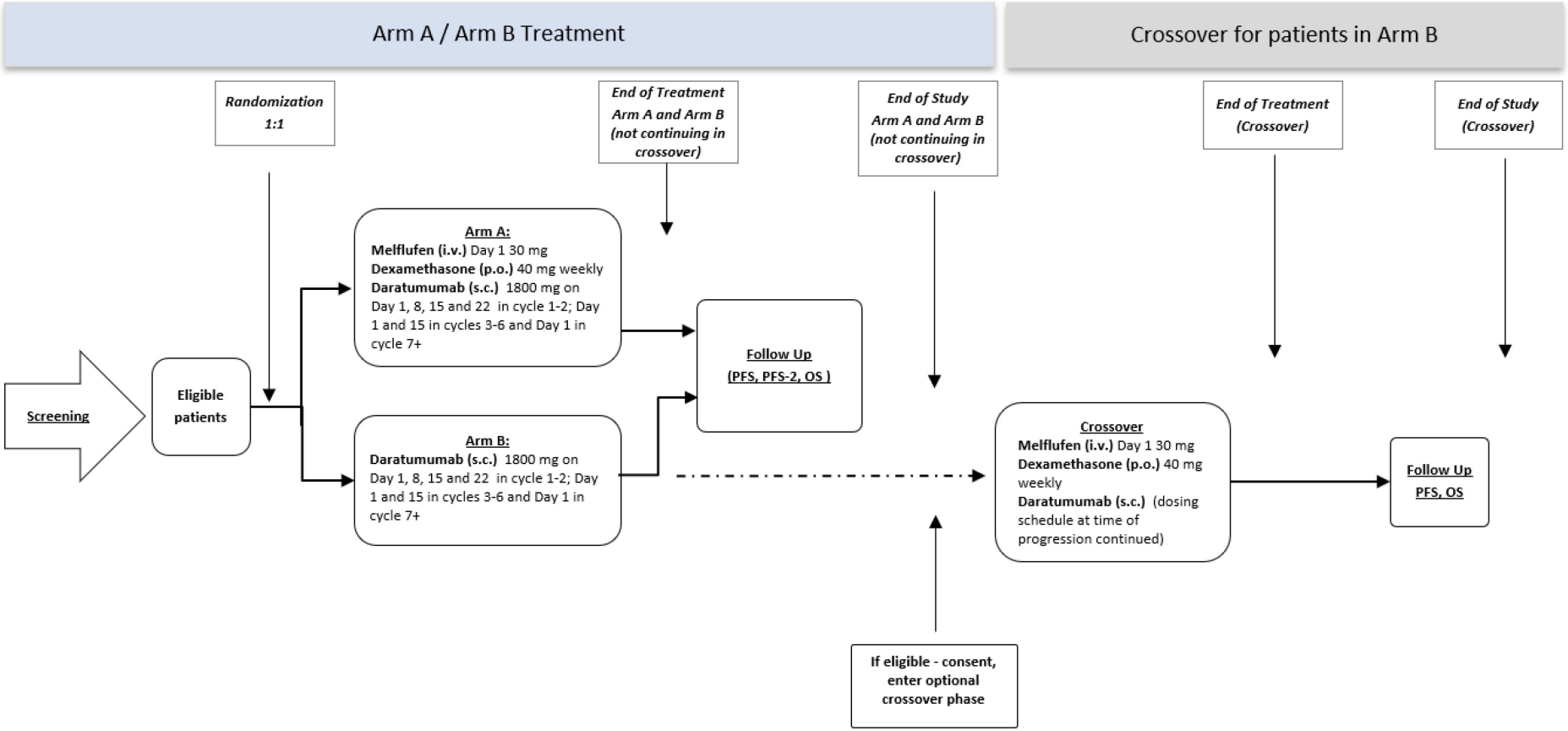
Independent Review Committee:

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

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will perform surveillance of efficacy/safety balance at regular intervals during the study, using unblinded treatment-aggregated data.

1.2. Schema


Arm A / Arm B Treatment
Crossover for patients in Arm B
Randomization 1:1
End of Treatment Arm A and Arm B (not continuing in crossover)
End of Study Arm A and Arm B (not continuing in crossover)
End of Treatment (Crossover)
End of Study (Crossover)
Screening
Eligible patients
Arm A:
Melflufen (i.v.) Day 1 30 mg
Dexamethasone (p.o.) 40 mg weekly
Daratumumab (s.c.) 1800 mg on Day 1, 8, 15 and 22 in cycle 1-2; Day 1 and 15 in cycles 3-6 and Day 1 in cycle 7+
Arm B:
Daratumumab (s.c.) 1800 mg on Day 1, 8, 15 and 22 in cycle 1-2; Day 1 and 15 in cycles 3-6 and Day 1 in cycle 7+
Follow Up (PFS, PFS-2, OS)
Crossover
Melflufen (i.v.) Day 1 30 mg
Dexamethasone (p.o.) 40 mg weekly
Daratumumab (s.c.) (dosing schedule at time of progression continued)
Follow Up PFS, OS
If eligible - consent, enter optional crossover phase

1.3. Schedule of Activities (SoA)

Table 1-2 Schedule of Activities (SoA)

Assessment	**Screening Day -21 to -1**	**Regimen A and B, All Cycles** (except where specified)					**End of Treatment Visit** [dd]	**8 weeks after last dose of daratumu-mab**	**PFS - FU** [ee]	**OS and PFS-2-FU** [ff]	**End of Study**
		Day 1	Day 4 (Cycle 1 and 3) [cc]	Day 8	Day 15	Day 22					
Visit Window		±3 days (except Cycle 1)	±0 days	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Informed consent [a]	X										
Inclusion and exclusion criteria	X										
Medical history and demographics [b]	X										
Myeloma history including characteristics [c]	X										
Physical examination [d]	X	X		(X)	(X)	(X)	X				
Vital signs [e]	X	X		(X)	(X)	(X)	X				
Pulmonary Function Tests	X										

Assessment	**Screening Day -21 to -1**	**Regimen A and B, All Cycles** (except where specified)					**End of Treatment Visit** [dd]	**8 weeks after last dose of daratumu-mab**	**PFS - FU** [ee]	**OS and PFS-2-FU** [ff]	**End of Study**
		Day 1	Day 4 (Cycle 1 and 3) [cc]	Day 8	Day 15	Day 22					
Visit Window		±3 days (except Cycle 1)	±0 days	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
ECOG performance status	X	X					X				
Pregnancy test [f]	X	X					X	X[f]	X [f]		
Urinalysis	X										
M protein assessment (and myeloma response assessment from Cycle 2)[g]	X	X					X		X		
β2-microglobulin	X										
RBC typing and antibody screening [h]	X										
Hematology [i]	X	X		X	X	X	X				
Chemistry [j]	X	X					X		(X)		
Hepatitis B, C and HIV screen	X										

Assessment	**Screening Day -21 to -1**	**Regimen A and B, All Cycles** (except where specified)					**End of Treatment Visit** [dd]	**8 weeks after last dose of daratumu-mab**	**PFS - FU** [ee]	**OS and PFS-2-FU** [ff]	**End of Study**
		Day 1	Day 4 (Cycle 1 and 3) [cc]	Day 8	Day 15	Day 22					
Visit Window		±3 days (except Cycle 1)	±0 days	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Coagulation	X										
Blood sample for DNA/RNA sequencing [k]		X					(X)		(X)		
Blood sample for myeloma related bone disease biomarkers [l]		X					X		X		
Bone marrow aspiration [m]	X	(X)					(X)		(X)		
12- lead Electrocardiogram [n]	X						X				
Chest X-ray [o]	X										
Extramedullary myeloma (plasmacytoma) assessment [p]	X	(X)					(X)		(X)		
Lytic bone lesion assessment: skeletal X-ray or low-dose CT [q]	X	(X)					(X)		(X)		

Assessment	**Screening Day -21 to -1**	**Regimen A and B, All Cycles** (except where specified)					**End of Treatment Visit** [dd]	**8 weeks after last dose of daratumu-mab**	**PFS - FU** [ee]	**OS and PFS-2-FU** [ff]	**End of Study**
		Day 1	Day 4 (Cycle 1 and 3) [cc]	Day 8	Day 15	Day 22					
Visit Window		±3 days (except Cycle 1)	±0 days	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Randomization [r]	X										
Criteria for initiation of therapy/new cycle[s]		X									
PRO assessments (EORTC QLQ-C30 and EQ-5D-3L) [t]		X					X		X		
PRO Pain Assessments (BPI-SF, NRS) [u]		X			(X)		X		X		
Dexamethasone administration and review of patient compliance, **Arm A only**		X		X	X	X					
Melflufen administration, **Arm A only**		X									
Daratumumab administration **Arm A and Arm B** according to treatment schedule		X		(X)	(X)	(X)					

Assessment	**Screening Day -21 to -1**	**Regimen A and B, All Cycles** (except where specified)					**End of Treatment Visit** [dd]	**8 weeks after last dose of daratumu-mab**	**PFS - FU** [ee]	**OS and PFS-2-FU** [ff]	**End of Study**
		Day 1	Day 4 (Cycle 1 and 3) [cc]	Day 8	Day 15	Day 22					
Visit Window		±3 days (except Cycle 1)	±0 days	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Pharmacokinetic samples **melphalan, Arm A only** [v]		X[C1, C2]									
Pharmacokinetic samples daratumumab[w]		X[C1, C3, C7, C12]	X				X	X			
Immunogenicity samples daratumumab [x]		X [C1, C7, C12]					X	X			
Immunogenicity samples rHUPH20 [x]		X[C1, C7, C12]					X	X			
Immunoprofiling samples [y]		X[C1, C6]					X				
Use of health services and hospitalization [z]	X	X					X		X		
Concomitant medications [aa]	X →	→	→	→	→	→	X				

Assessment	**Screening Day -21 to -1**	**Regimen A and B, All Cycles** (except where specified)					**End of Treatment Visit** [dd]	**8 weeks after last dose of daratumu-mab**	**PFS - FU** [ee]	**OS and PFS-2-FU** [ff]	**End of Study**
		Day 1	Day 4 (Cycle 1 and 3) [cc]	Day 8	Day 15	Day 22					
Visit Window		±3 days (except Cycle 1)	±0 days	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
AE monitoring [bb]	X →						X				
Subsequent therapy review [gg]										X	
End of study information [hh]											X

(X) Only if indicated (see footnotes and treatment schedule)

C1 = Cycle 1; C2 = Cycle 2; etc.

a) All patients must sign an (IRB/IEC/REB)-approved ICF within 28 days of randomization and prior to any study related procedures.

b) Medical History including demographics, prior and current medical illness and conditions, prior surgical procedures.

c) MM history including characteristics, date of initial diagnosis, International Staging System (ISS), Revised International Staging System (R-ISS) and cytogenetics at diagnosis (if previously evaluated). ISS and R-ISS stage at screening. Prior surgery, radiation and anticancer therapy, including start and stop dates, documentation of best response, date of progressive disease and relapsed or refractory status.

d) A physical examination, including assessment for extramedullary myeloma will be conducted at screening, Day 1 of each cycle and End of Treatment (EOT) visit. A symptom directed physical examination will be conducted as needed during treatment period.

e) Vital signs including blood pressure, pulse, respiratory rate, temperature will be assessed at screening, at each dosing day before melflufen dose and before and after daratumumab dosing and at EOT visit. Height will be assessed at screening only. Weight will be assessed at screening, Day 1 of each cycle and at EOT visit.

f) All WOCBP must have a negative serum or urine pregnancy test prior to the initiation of therapy at each cycle. Pregnancy test will also be taken at EOT visit, 8 weeks after last dose of daratumumab and at 12 weeks after last dose of daratumumab. The 8 and 12-weeks urine test can be taken at home and

site can contact the patient for follow-up by phone.

g) SPEP, UPEP, serum and urine Immunofixation ((IFE) if SPEP or UPEP are not detectable and to confirm a CR), quantitative immunoglobulins (Igs) and SFLC assay (only required if SPEP and UPEP are not measurable [UPEP is < 200 mg/24 hours and SPEP is < 0.5 g/dL]) are to be conducted at screening, pre-dose Cycle 1 Day 1 and prior to each cycle even if treatment is delayed. Quantitative Igs need to be repeated for patients with IgA or IgD myeloma for all response assessments. In the event treatment is delayed 2 weeks, response assessments are required to be repeated on the day the new cycle starts.
If treatment is discontinued at or beyond ≥ 6 weeks (Day 43) the response assessments should be repeated on the day of the decision (or as soon as possible ≥ 30 days after last dose of study drug) as part of the EOT visit. Daratumumab Interference Reflex Assay (DIRA) test should be conducted in patients with IgG kappa MM with SPEP
   - ≤0.2 g/dl on 2 or more consecutive cycles
     OR
   - at zero, but persistently positive IFE for IgG kappa on 2 or more occasions

h) Interference with cross-matching and red blood cell antibody screening: Type and screen patients prior to starting treatment.

i) Hematology: Complete Blood Count (CBC) with differential, and platelet count should be taken at screening and at Day 1, 8, 15 and 22 of all cycles, prior to initiation of therapy, and at the EOT visit. If melflufen is discontinued and the partner therapy is continued, the schedule of CBC evaluations may be conducted at the investigator's discretion but must at a minimum be performed on Day 1 of each subsequent cycle and before each dose of daratumumab. If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded at Day 8 and Day 22.

j) Chemistry should be taken at screening and at Day 1 of all cycles, at the EOT visit, prior to initiation of therapy. During PFS-FU serum calcium and albumin (corrected calcium) are required if evidence of PD.

k) Blood sample for DNA/RNA sequencing should be collected before dosing at Cycle 1, at time of response (CR or VGPR), and at the time of disease progression.

l) Blood sample for myeloma related bone disease biomarkers should be collected before dosing at Day 1 of all cycles, at the EOT visit and at PFS-FU.

m) Bone marrow aspirate (BMA) to be collected at screening for % plasma cells, morphology, cytogenetics by Interphase Fluorescence In Situ Hybridization (iFISH), and for exploratory biomarker analysis. A repeat sample is required in patients with suspected CR/VGPR to confirm response and for MRD assessment. A BMA sample may be needed to confirm disease progression, if taken, samples will also be used for biomarker analysis See Protocol and Laboratory manual.

n) A 12-lead ECG will be performed at screening and EOT visit. Q-Tc interval to be assessed by Fridericia formula.

o) Chest X-ray is optional if low-dose Computerized Tomography (CT) is performed for skeletal assessment and will only be performed at baseline. If performed within 6 weeks from initiation of therapy, repeat of assessment is only needed if clinically relevant.

p) Known or suspected extramedullary myeloma (plasmacytomas) are to be assessed, with the same method at screening and every 2 cycles up to disease progression.

q) Lytic bone lesion assessment: skeletal X-ray or low-dose CT scan should be performed at screening if previous skeletal survey > 6 weeks from initiation of therapy and when clinically indicated. Limited X-rays may be performed to confirm PD.

r) Treatment cannot begin prior to randomization and must begin ≤ 5 days after randomization. The 5 day window is included in the 21 days screening period, i.e., if treatment starts 5 days after randomization, randomization has to be done latest at day 16 after Screening visit.

s) Evaluate if the treatment should be given, delayed or held. See Protocol for details.

t) EORTC QLQ-C30 and EQ-5D-3L should be completed prior to any procedures on the day of the visit and prior to being told anything related to health; the questionnaires should be administered even if the treatment is not given. See Protocol for details.

u) BPI-SF and NRS for measure of bone pain. The patient should complete the questionnaires prior to any procedures, and prior to dexamethasone dosing, on the day of the visit and prior to being told anything related to health; the questionnaires should be administered even if the treatment is not given. BPI-SF should be completed first and if patient has experienced pain, the NRS for measure of bone pain should be completed. The questionnaires should be submitted to patients at Day 1 and Day 15 of Cycle 1-3. From Cycle 4, the questionnaires should be submitted to patient on Day 1 of each cycle. The questionnaires should also be submitted at the time of EOT visit, at the time of disease progression and at the time of starting a new treatment (Day 1 of new treatment). See Protocol for details.

v) Melphalan pharmacokinetic (PK) samples will be collected in patients in Arm A. Samples will be drawn in connection to the first two melflufen treatment cycles, 5–10 minutes after the end of the melflufen infusion, 1 hour after the end of the melflufen infusion (+/- 5 min window acceptable) and 2-4 hours after the end of the melflufen infusion (as late as possible within the time frame).

w) Daratumumab PK samples will be collected in patients in Arm A and Arm B at pre-dose on Day 1 of Cycle 1, 3, 7, and 12, on Day 4 in Cycles 1 and 3 and at EOT visit and at 8 weeks after the last dose of daratumumab. Not applicable for patients in Arm B after crossover to treatment with melflufen, dexamethasone and daratumumab.

x) Serum samples for immunogenicity (daratumumab and rHuPH20) to be collected in both Arm A and Arm B pre-dose on Day 1 of Cycle 1, 7, and 12 and at EOT visit and at 8 weeks after the last dose of daratumumab. Not applicable for patients in Arm B after crossover to treatment with melflufen, dexamethasone and daratumumab.

y) Whole blood samples will be collected pre-dose on Cycle 1 Day 1, Cycle 6 Day 1 and at the EOT visit.

z) Use of health services and days of hospitalization will be completed by the patient at screening, on Day 1 of each cycle, at time of EOT visit and at follow-up until start of new treatment. To be completed prior to any procedures on the day of the visit and prior to being told anything related to health.

aa) Concomitant medications and procedures: All blood products and medications within 21 days prior to first dose until the EOT visit should be recorded.

bb) SAEs will be collected from signing of the ICF until 30 days after last dose of study treatment or initiation of subsequent therapy whichever occurs first. AEs will be collected from the start of study treatment until 30 days after the last dose of any study drug (melflufen, dexamethasone or daratumumab) or initiation of subsequent therapy whichever occurs first.

cc) Day 4 is a visit for daratumumab PK sampling and will be performed when possible to schedule on weekdays.

dd) EOT visit should be scheduled 30 days after last dose of study treatment or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle). If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug, the EOT visit should occur as close as possible before the first dose of the new drug (this also applies to crossover treatment for patients in Arm B). For patients who are randomized but withdraw from study, for any reason, prior administration of any study drug, the EOT visit should be completed as soon as possible after decision to remove patient from study (including withdrawal of consent to study treatment) has been made. For patients in Arm B who crossover to treatment with melflufen, dexamethasone and daratumumab, the EOT visit could be done at the same day as the initiation visit for the new treatment Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EOT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy.

ee) Schedule the first assessment 4 weeks after the EOT visit. Patients who discontinue therapy for reasons other than disease progression should continue

to have monthly disease assessments done until documented disease progression or initiation of subsequent therapy. Confirmed disease progression requires 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC). The second assessment must be a separate serum and urine sample. If the second consecutive M protein sample can only be obtained after the start of subsequent therapy, it may be used as confirmation of PD.

ff) Following confirmed disease progression or initiation of subsequent therapy, follow-up for PFS-2, overall survival status and second primary malignancies will take place every three months +/- 7 days for at least 24 months.

gg) Subsequent therapy review including regimen (all individual drugs), start and stop dates. If PD has not been confirmed prior to the initiation of subsequent therapy, the reason for the subsequent therapy, best response, and date of disease progression per investigator review.

hh) Patient study end date and primary reason for ending the study will be collected.

2. Introduction

Melphalan flufenamide (hereinafter referred to as melflufen) is a novel peptide-drug conjugate designed for targeted enrichment of alkylating moieties in tumor cells and belongs to a novel class of drugs called peptide-drug conjugates. Once monthly intravenous (iv) melflufen, in combination with weekly dexamethasone, has shown encouraging clinical results in relapsed and refractory multiple myeloma (RRMM) patients (see current Investigator's Brochure (IB) of melflufen for details). Initial promising data from the OP-104 Anchor study established the maximum tolerated dose for testing the combination of melflufen and daratumumab in RRMM patients.

2.1. Study Rationale

The outcome in relapsed/refractory multiple myeloma is still unsatisfactory despite recent improvements in treatment. Thus, new therapeutic options are needed. Melflufen is a peptide-conjugated alkylator that is rapidly taken up by MM cells due to its high lipophilicity (Chauhan et al 2013, Wickström et al 2017). Once inside the myeloma cell, the activity of melflufen is determined by its immediate cleavage by peptidases into hydrophilic alkylator payloads that are entrapped (Wikström et al 2017, Gullbo et al 2003). Melflufen is 50-fold more potent than melphalan in myeloma cells in vitro due to the increase of intracellular alkylator activity (Chauhan et al 2013, Wickström et al 2017). The ongoing clinical study OP-104 ANCHOR evaluates the combination of melflufen, dexamethasone and daratumumab in patients with RRMM previously treated with 1-4 lines of therapy and refractory to an immunomodulatory agent (IMiD) and/or a proteasome inhibitor (PI). Promising efficacy has been shown, with a median ORR of 76% and a median immature progression-free survival (PFS) of 14.3 months (ASH poster #3124 of abstract Ocio et al 2019). Grade 3/4 adverse events were mainly cytopenias with limited non-hematologic toxicity. These results are in line with previous experiences of melflufen in combination with dexamethasone only in earlier clinical studies in RRMM. It is therefore reasonable to confirm the efficacy of this drug combination in a Phase 3 trial in a patient population that reflects the approved indication for daratumumab as monotherapy including an option for patients randomized to daratumumab monotherapy to crossover and receive treatment with melflufen, daratumumab and dexamethasone after documented disease progression. The study will use the subcutaneous formulation of daratumumab, which was approved in 2020 by FDA in US, EMA in Europe and MHRA in UK.

2.2. Background

2.2.1. Multiple Myeloma

Multiple myeloma is a malignancy of differentiated plasma cells that mainly affects older patients, with a median age at onset of 65 to 70 years and a slight male predominance. MM is the second most common hematologic malignancy and 32,270 patients were estimated to be diagnosed with myeloma in the United States in 2019, with a 5-year survival of 52.2% (SEER 2019).

The disease is characterized by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin (usually of the IgG or IgA type or free urinary light chain [paraprotein, M-protein or M-component]). Patients with MM may experience significant decrement to quality of life, including bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia, and compromised renal function (including renal failure) (Jordan et al. 2014). The disease course for MM varies with the disease stage at diagnosis, cytogenetic profile, as well as age and patient comorbidities. Survival in myeloma is significantly variable depending on host factors, tumor burden, biology and response to treatment (Chng et al. 2014). However, the disease remains ultimately fatal.

There are currently 7 classes of approved drugs for the treatment of MM, including steroids (prednisone and dexamethasone), IMiDs (thalidomide, lenalidomide and pomalidomide), PIs (bortezomib, carfilzomib and ixazomib), histone deacetylase inhibitors (panobinostat), conventional chemotherapy (melphalan, cyclophosphamide, doxorubicin), including high dose melphalan with autologous stem-cell transplantation (ASCT), monoclonal antibodies (elotuzumab, daratumumab and isatuximab) and nuclear export inhibitors (selinexor). The selection of treatment in relapsed/refractory multiple myeloma is challenging. The National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2.2019) and a recent overview published in the Mayo Clinic Proceedings (Kumar et al 2016) detail an array of single agent, doublet and triplet combination regimens that can be considered. Patients for whom stem cells were cryopreserved early in the disease course, and who are transplant candidates, may benefit from ASCT as salvage therapy (Cavo et al. 2011). In general, MM patients will receive an average of 4 to 8 different treatment regimens during their life span.

Improvements in therapies have significantly increased the expected life span for these patients, especially for younger patients (Kristinsson et al 2014). However, despite the availability of effective therapies, the optimal combinations and sequencing of these agents with other therapies and with one another is still unclear. Only 20 to 30% of the RRMM patients typically respond to any particular treatment and ultimately patients relapse from all available options. Given the inevitable relapses seen in these patients, new approaches to therapy are clearly still needed.

2.2.2. Melflufen

Melflufen, a first-in-class peptide-drug conjugate, is rapidly taken up by MM cells due to its high lipophilicity (Wickström et al. 2017). Once inside the myeloma cell, melflufen is immediately cleaved by peptidases, leading to entrapment of the hydrophilic alkylator payloads. (Wickström et al 2017, 2010, Gullbo et al 2003).

In primary patient-derived MM tumor cells, melflufen demonstrated approximately 50-100 fold higher efficacy than melphalan, explained by the 50-fold higher intracellular concentration of alkylating moieties achieved after melflufen vs. melphalan exposure in the culture (Chauhan 2013, Ray 2016, Wickström et al. 2017).

Mechanistic studies have shown that melflufen induces rapid, irreversible DNA damage; accumulation of reactive oxygen species and apoptosis associated with mitochondrial dysfunction and release of cytochrome c, activation of caspases and poly adenosine diphosphate (ADP) ribose polymerase cleavage. Moreover, melflufen inhibits angiogenesis and MM cell migration. (Chauhan et al. 2013, Ray et al 2016, Strese et al. 2013).

Importantly, in vitro studies in MM cell lines resistant to dexamethasone, bortezomib, and melphalan have demonstrated melflufen efficacy at same concentrations as observed in the parental, non-resistant cell lines (Chauhan 2013). Likewise, in the *in vivo* efficacy studies with different human tumors, including MM, superior antitumor activity yet seemingly comparable toxicity of melflufen was observed compared to equimolar dosage of melphalan (Wickström et al. 2007, Chauhan et al. 2013).

Melflufen has been evaluated in combination with low dose dexamethasone in patients with relapsed/refractory myeloma in a Phase 1/2 clinical trial (O-12-M1, NCT01897714). The trial established the recommended dose at 40 mg of melflufen every 28 days combined with 40 mg dexamethasone weekly. Based on the 45 patients treated with 40 mg melflufen every 28 days in combination with weekly dexamethasone, the ORR (PR or better) was 31% and the CBR (MR or better) was 49%. The patients had a median of 4 prior lines of therapy, including IMiD, PIs and alkylators. The median PFS was 5.7 months based on 41 events, and the overall survival (OS) was 20.7 months based on 23 events in the 45 patients (Richardson et al, 2017).

There are also ongoing clinical studies in RRMM patients, including a Phase 2 study in patients refractory to pomalidomide and/or daratumumab (OP-106 HORIZON, NCT02963493), a Phase 1/2 study where melflufen and dexamethasone are combined with daratumumab or bortezomib (OP-104 ANCHOR, NCT03481556), and a randomized Phase 3 study (OP-103 OCEAN, NCT03151811) comparing melflufen and dexamethasone to pomalidomide and dexamethasone.

The safety profile of melflufen suggested by preclinical studies is supported by clinical data from the completed O-12-M1 and ongoing clinical trials.

As of 6 February 2019, 263 patients with RRMM had received at least one dose of melflufen.

The most common treatment emergent adverse events (TEAE) in the trials O-12-M1 and OP-106 (HORIZON) were hematological events, such as thrombocytopenia, neutropenia and anemia. This is not unexpected since hematological events are common both as a consequence of the disease of MM and of treatment with alkylators. These events were assessed to be dose-related, reversible and monitorable.

Treatment related Grade 3 and 4 AEs were reported in 37 out of 45 patients (82%) in the O-12-M1 trial. Those related to melflufen and occurring in ≥ 5% of the patients are presented in Table 2-1.

Table 2-1 Summary of melflufen treatment related Grade 3 or 4 AEs in O-12-M1

Summary of Melflufen Treatment Related Grade 3 or 4 AE in ≥ 5% of 45 Patients Dosed with 40 mg Melflufen in combination with weekly dexamethasone in Clinical Trial O-12-M1		
System Organ Class (Preferred Term)	**Patients with Grade 3 or 4 AEs n (%)**	**Patients with Grade 4 AEs n (%)**
Any melflufen treatment-related event	37 (82)	19 (42)
Blood and lymphatic system disorders *Thrombocytopenia* *Neutropenia* *Anemia* *Lymphopenia*	36 (80) 26 (58) 26 (58) 19 (42) 3 (7)	19 (42) 17 (38) 11 (24) 0 (0) 1 (2)

There were no non-hematological Grade 3/4 AEs which were reported in >5% of the patients.

Taken together, clinical and preclinical data support that melflufen delivers a higher anti-tumor activity compared with equimolar administration of the alkylator melphalan but with a similar safety profile.

Please see the IB for melflufen for further information.

2.2.3. Daratumumab

Daratumumab is a first-in-class, human immunoglobulin G1 kappa (IgG1κ) mAb that binds to malignant cells expressing CD38 with high affinity and induces tumor cell death through several immune-mediated mechanisms. Daratumumab was initially approved in RRMM as monotherapy based on results from study GEN501 (Lokhorst et al. 2014, Usmani et al. 2016) and the SIRIUS study (Lonial et al. 2016, Usmani et al. 2016). The combined results showed an overall response rate to daratumumab of 31% in a heavily pretreated population (Usmani et al. 2016). Some of the responses were deep (4.7% of the patients had a CR or better) and durable (median duration of response [PR or better] was 7.6 months). Daratumumab is also approved in RRMM in combination with lenalidomide and dexamethasone (Dimopoulos et al, 2016), or bortezomib and dexamethasone (Palumbo et al. 2016), for the treatment of patients with multiple myeloma who have received at least one prior therapy, and in combination with pomalidomide for patients who have received at least two previous lines of therapy (Chari et al. 2017). In newly diagnosed MM patients considered ineligible for stem cell transplant, daratumumab was studied and subsequently approved in combination with bortezomib, melphalan and dexamethasone (Mateos et al. 2018). These studies reported that the addition of daratumumab to these therapies improved response rates while increased toxicity mainly consisted of daratumumab-related infusion reactions, including when combined with the alkylating agent melphalan, and resulted in approval for daratumumab in these combinations. The Phase 1b PAVO (MMY-1004) study evaluated subcutaneously-administered daratumumab in combination with the recombinant

human hyaluronidase PH20 enzyme (rHuPH20) in patients with relapsed or refractory MM. The safety and PK profile were similar with lower rate of infusion-related reactions compared with the IV formulation (Usmani et al. 2019). This has later been confirmed in the Phase 3 COLUMBA trial that showed non-inferiority in terms of ORR and a lower rate of infusion-related reactions for the subcutaneous formulation (Mateos et al. 2019).

Daratumumab is a targeted immunotherapy directed toward cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. Once binding to CD38 occurs, daratumumab induces cell death through diverse immune-mediated mechanisms (complement-dependent cytotoxicity [CDC], antibody-dependent cell-mediated cytotoxicity [ADCC], antibody dependent cellular phagocytosis [ADCP]), and induction of apoptosis (de Weers 2011, Overdijk 2015.

Translational biomarker studies of Phase 1 and Phase 2 multiple myeloma daratumumab patient samples (GEN501 and MMY2002, respectively) reveal immunomodulatory effects of daratumumab (Krejcik 2016). Daratumumab leads to the elimination of highly immunosuppressive subsets of CD38+ T-regulatory cells (Tregs), CD38+ myeloid derived suppressor cells (MDSCs), and CD38+ B regulatory cells (Bregs). It has also been shown that daratumumab may modulate the enzymatic activity of CD38 and may lead to a reduction in immunosuppressive adenosine levels (Horenstein 2016).

2.2.4. Melflufen and Daratumumab

The safety and efficacy of melflufen in combination with daratumumab and dexamethasone is being evaluated in a Phase 1/2a trial (OP-104 ANCHOR). RRMM patients included in this study have previously received 1-4 previous lines of therapy and must be refractory to an IMiD or a PI or to both. Preliminary data from the 33 patients treated with melflufen 30 mg (n=6) or 40 mg (n=27) in combination with daratumumab and dexamethasone has shown a safety profile consistent with previous trials, with Grade 3/4 treatment-related AEs reported in 27 (82%) patients, and thrombocytopenia (n=21, 64%) and neutropenia (n=20, 61%) being most commonly reported treatment-related AEs. At a data cutoff (8 October 2019) the ORR was 76% in all treated patients and median immature PFS was 14.3 months (ASH poster #3124 of Ocio et al 2019).

2.3. Benefit/Risk Assessment

Although the incorporation of novel agents such as PIs and IMiDs has significantly improved outcomes of patients suffering from multiple myeloma, myeloma is not yet curable and new treatment options are needed. Ongoing trials in RRMM with melflufen and dexamethasone with or without daratumumab has shown promising efficacy. It is therefore reasonable to evaluate whether patients with relapsed-refractory MM may receive benefit from the drug combination of melflufen, dexamethasone and daratumumab in a patient population that reflects the approved indication for daratumumab as monotherapy. The safety profile of melflufen and dexamethasone has been consistent and manageable throughout the trials, with thrombocytopenia and other hematologic toxicity being most frequent.

The prognosis is poor in patients progressing while on treatment with daratumumab (Gandhi et al. 2019), therefore it is feasible to include an option to crossover and receive treatment with the melflufen, daratumumab and dexamethasone.

Important potential risks with the study drugs are presented in Table 2-2. More detailed information about the known and expected benefits and risks of melflufen, dexamethasone and daratumumab can be found in the IBs for melflufen and daratumumab respectively and the Summary of Product Characteristics / US Prescribing Information for dexamethasone.

Table 2-2 Assessment of important Potential Risks

Important Potential Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s)		
Infections	Severely ill MM patients are at increased risk of developing infections and infections are common adverse events with melflufen, dexamethasone and daratumumab. There may be a further increased risk for infections when concomitantly administering all three drugs.	Patients should be monitored for signs of infection as part of SoC and as part of regular follow-up during the clinical study. NCCN guidelines (2020) (see Section 6.5.2) on infectious prophylaxis should be closely followed.
Thrombocytopenia, Neutropenia, and Anemia	Thrombocytopenia, neutropenia, and anemia are known consequences of MM but also common, adverse drug reactions associated with melflufen and daratumumab.	Patients should be monitored as part of SoC and as part of regular follow-up during the clinical study. Careful attention is to be paid to the monitoring of blood counts. General supportive measures, together with appropriate blood and platelet transfusions as well as hematopoietic growth factors should be administered if necessary (see Section 6.5.2).

Severe and/or serious systemic infusion/administration-related reactions, including anaphylactic reaction	Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with daratumumab.	Patients should be observed carefully during daratumumab administrations for systemic administration-related reactions, especially following the first injection. Prophylactic treatment required prior to daratumumab to minimize or to treat administration related reactions can be found in Section 6.1.4.1. Daratumumab should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions, if they occur.
Study Procedures		
Placement of central line, including Port-A-Cath and peripherally inserted central catheter (PICC) line	A central line is needed for the administration of melflufen. Known risks with placement of central lines include pneumothorax, vascular perforation, catheter associated thrombosis, and central line infections.	Central lines will be placed at centers well trained and experienced in the procedure. Patients will be monitored for signs of complications as part of SoC.

3. Objectives and Endpoints

Objectives[a]	Endpoints[a]
Primary:	
To show superiority of progression free-survival (PFS) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	PFS (time from the date of randomization to the date of first documentation of confirmed progressive disease (PD) or death due to any cause).
Key Secondary:	
To evaluate and compare Overall Response Rate (ORR) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	ORR (proportion of patients who achieve a best confirmed response of stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR) or Partial Response (PR)).
To evaluate and compare Duration of Response (DOR)in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	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).
To assess the safety and tolerability of melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	Frequency and Grade of treatment emergent adverse events (TEAE).
Other Secondary:	
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)	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).
Exploratory:	
To assess minimal residual disease (MRD) in patients achieving a CR or VGPR in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	Assessment of MRD status by Next Generation sequencing (NGS) in patients who achieve a CR or VGPR.
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.	PFS-2 (defined as time from randomization to progression on next line of treatment or death from any cause, whichever occurs first).
To assess and compare the changes in pain in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.	Value and changes in pain, in BPI-SF and Numeric Rating Scale (NRS) for measure of bone pain.
To assess and compare responses in patients with extramedullary myeloma (plasmacytomas).	Response rate (CR and PR) according to International Myeloma Working Group (IMWG) consensus criteria of extramedullary myeloma (plasmacytomas).
To assess and compare use of health services and number and duration of hospitalizations in patient 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.	Number of health services. Number and days of hospitalization.
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).	PK parameters of melphalan at selected time points.
To assess the PK and immunogenicity of subcutaneous daratumumab.	Serum daratumumab concentrations.

	Incidence of antibodies to daratumumab.
To evaluate the immunogenicity of recombinant human hyaluronidase (rHuPH20) following subcutaneous daratumumab administration.	Incidence of antibodies to rHuPH20.
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.	• 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, PINP, Total RANK, Osteopontin, Osteocalcin, CTX, bone ALP. • Serum levels of cytokines IL-6, IL-10. • Immune profiling in peripheral blood including but not limited to T Reg., MDSC and NK cells.
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.	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.
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)	ORR (proportion of patients who achieve a best confirmed response of stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR) or Partial Response (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).
	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.
	TTR (time from crossover to the date of the first documented confirmed response in a patient who has responded with ≥PR).
	TTP (time from crossover to the date of the first documented confirmed PD).
	TTNT (time from crossover to the date of next anti-myeloma treatment or until death).
	OS (time from crossover until death of any cause).
To assess and compare the changes in pain for patients in Arm B who crossover to treatment with melflufen, dexamethasone and daratumumab.	Value and changes in pain, in BPI-SF and Numeric Rating Scale (NRS) for measure of bone pain.
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.	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.
To assess the safety and tolerability of melflufen, dexamethasone and daratumumab treatment for patients in Arm B who crossover.	Frequency and Grade of treatment emergent adverse events (TEAE).

a) All tumor response and progression-dependent endpoints are as assessed by the investigator and IRC according to the IMWG-URC guidelines (Kumar et al. 2016).

4. Study Design

4.1. Overall Design

This is an open-label, randomized, international, multicenter Phase 3 trial which will enroll patients with relapsed or relapsed-refractory MM who are either double refractory to an IMiD and a 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 and 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..

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 4-1. dexamethasone 40 mg p.o. (20 mg p.o. for patients ≥ 75 years) will be given weekly (see Section 6.1.3 and Table 6-4).

Pre-medication for the prophylaxis of infusion reactions and post-medication should be administered according to Section 6.1.4.1.

Table 4-1 Daratumumab Schedule, Arm A

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

Arm B:

In Arm B daratumumab will be given at the dose of 1800 mg s.c. according to the schedule in Table 4-2. Pre-medication for the prophylaxis of infusion reactions and post-medication should be administered according to Section 6.1.4.1.

Table 4-2 Daratumumab Schedule, Arm B

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

a) Patients with confirmed disease progression in Arm B have the option to receive melflufen, dexamethasone and daratumumab (dose and schedule as in Arm A).

4.1.1. Treatment duration

Patients in both treatment arms will receive treatment until any of the following events is reached. This also applies for patients in Arm B who crossover and receive treatment with melflufen, daratumumab and dexamethasone:

- there is documented PD according to the IMWG-URC guidelines (Kumar et al.2016 to be confirmed on two consecutive assessments (if PD due to increase in M-protein), and verified by the Medical Monitor prior to treatment discontinuation, see Appendix 8. to be confirmed on two consecutive assessments (if PD due to increase in M-protein), and verified by the Medical Monitor prior to treatment discontinuation, see Appendix 8.
- unacceptable toxicity.
- the patient/treating physician determines it is not in the patient's best interest to continue.
- patient's withdrawal of consent.

4.2. Scientific Rationale for Study Design

In the Phase 1/2 trial (OP-104 ANCHOR) investigating melflufen and dexamethasone with either bortezomib or daratumumab, the melflufen+dexamethasone+daratumumab combination in patients previously treated with an IMiD and a PI and refractory or intolerant to an IMiD, PI, or both, has demonstrated a safety profile consistent with data in previous studies evaluating melflufen and dexamethasone. In the daratumumab-containing regimen, Grade 3/4 AEs have been mainly hematological, including thrombocytopenia (64%) and neutropenia (61%) in the 33 included patients. Promising efficacy has been demonstrated with an ORR of 76% and a median immature PFS of 14.3 months (ASH poster #3124 of abstract Ocio et al 2019).

Although the incorporation of novel agents such as PIs and IMiDs has significantly improved outcomes of patients suffering from multiple myeloma, myeloma is not yet curable and new treatment options are needed, especially for patients who have progressed during therapies containing PIs and/or IMiDs. Melflufen has a unique mechanism of delivering an alkylating payload to MM cells. Given the demonstrated efficacy of melflufen and dexamethasone and promising early results in the clinical study OP-104 ANCHOR, melflufen is an appropriate candidate for confirmation of efficacy and safety in a triple-drug combination. The study is intended to support a regulatory submission for a marketing authorization of melflufen in combination with daratumumab and dexamethasone in a patient population where daratumumab as monotherapy is approved and is considered a reasonable treatment option (NCCN Guidelines v 2 2020). The poor prognosis in patients refractory to daratumumab (Gandhi et al. 2019) and the demonstrated activity of melflufen in daratumumab-refractory patients (Richardson et al. 2019) makes it reasonable to include a crossover option with melflufen, daratumumab and dexamethasone for patients in the daratumumab arm with documented disease progression.

The assumptions regarding sample size are described in Section 9.2.

4.3. Justification for Dose

The dosing schedule of melflufen 40 mg i.v. in combination with dexamethasone was previously established in the Phase 1/2 trial O-12-M1 and has subsequently been used in the Phase 2 trials OP-106 HORIZON and OP-107 BRIDGE as well as in the Phase 3 OP-103 OCEAN trial.

The dosing schedule of melflufen, dexamethasone and daratumumab is based on emerging data from the Phase 1/2a OP-104 ANCHOR trial in RRMM in which two dose levels of melflufen are evaluated: 30 and 40 mg. In this study, the recommended Phase 2 dose of melflufen was determined to be 40 mg i.v. on day 1 in a 28-day cycle in combination with daratumumab 16 mg/kg i.v. and dexamethasone 40 mg weekly (20 mg for patients ≥ 75 years). The ORR at the 30 mg and 40 mg dose levels were similar, 83% and 74% respectively. However, at the 40 mg dose level more frequent dose reductions were needed to manage thrombocytopenias, resulting in a similar dose intensity (cumulative dose) as the lower 30 mg level. The benefit-risk profile was therefore considered more favorable for the 30 mg melflufen dose level in this combination, and this dose was chosen for the proposed Phase 3 study.

The recommended dose for subcutaneous daratumumab is 1800 mg daratumumab (and 30,000 units hyaluronidase) when administered as monotherapy or in combinations with other agents including PIs and IMiDs, with appropriate pre- and post-medications (Darzalex FASPRO™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use see US prescribing information and Summary of Product Characteristics (SmPC)). In the COLUMBA trial the subcutaneous formulation of daratumumab at a fixed dose demonstrated non-inferiority compared to i.v. daratumumab in terms of ORR, with less infusion-related reactions (Mateos et al. 2019).

4.4. End of Treatment Definition

A patient is considered to have completed study treatment when all study drugs (melflufen, dexamethasone and daratumumab) are discontinued for any reason.

4.5. End of Study Definition

4.5.1. Study Completion for a patient

A patient is considered to have completed the study if he/she has completed all visits for the study including follow up visits for time to next anti-myeloma treatment, PFS-2 and overall survival.

A patient is also considered to end the study when they withdraw from the study for any reason prior to completion.

Patient study end date and primary reason for ending study will be collected.

4.5.2. Study Definition

The end of the study is defined as the date when the last patient completes the last study visit (which may be a follow-up visit), or the date the Sponsor determines to terminate the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Patients in this study will have a diagnosis of MM, be double refractory to an IMiD and a PI or have received at least 3 prior lines of therapy including at least one IMiD and one PI, and must meet all entry criteria defined in Sections 5.1 and 5.2 below.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

1. Male or female, age 18 years or older;
2. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol;
3. A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening;
4. Double refractory to an IMiD and a PI (regardless of the number of prior lines of therapy), **or** have received at least 3 prior lines of therapy including an IMiD and a PI (the definition of refractory includes intolerance to an IMiD/PI after at least two 28-day cycles of therapy);
5. Prior treatment with daratumumab or another anti-CD38 antibody is allowed if the patient has:
    - Achieved at least PR and is not refractory to previous anti-CD38 antibody treatment
    - At least 6 months since last dose of anti-CD38 antibody prior to Cycle 1/Day 1 (C1/D1)
    - Not discontinued anti-CD38 antibody treatment due to related Grade ≥ 3 toxicity
6. Measurable disease defined as any of the following:
    - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
    - ≥ 200 mg/24hr of monoclonal protein in the 24-hour urine collection by electrophoresis (UPEP)
    - Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain (FLC) ratio
7. Life expectancy of ≥ 6 months;
8. ECOG performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the Medical Monitor);
9. Ability to understand the purpose and risks of the study, ability to participate in all the

procedures required by the protocol and provide signed and dated informed consent;

10. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (Q-TcF) interval of ≤ 470 msec;
11. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study treatment administration on Cycle 1 Day 1:
    - Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days (14 days for pegfilgrastim) prior to initiation of study treatment)
    - Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusions during the 10 days prior to initiation of therapy)
    - Hemoglobin ≥ 8.0 g/dL (RBC transfusions are permitted)
    - Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), except patients diagnosed with Gilbert's syndrome that have been reviewed and approved by the Medical Monitor
    - AST (also known as SGOT) and ALT (also known as SGPT) ≤ 3.0 x ULN
    - Renal function: Estimated creatinine clearance by Cockcroft- Gault formula of ≥ 45 mL/min
12. Must have or be willing to have an acceptable central catheter. (Port A cath, peripherally inserted central catheter (PICC) line, or central venous catheter);

a) Male patients: Male patient that agrees to use contraception as detailed in

13. Appendix 5 of this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period.

Female patients: A female patient is eligible to participate if she is not pregnant (see

b) Appendix 5), not breastfeeding, and at least one of the following conditions applies:

Not a woman of childbearing potential (WOCBP) as defined in

i. Appendix 5 **or**

A WOCBP who agrees to follow the contraceptive guidance in

ii. Appendix 5 during the treatment period and for at least 3 months after the last dose of study treatment.

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Primary refractory disease (i.e. never responded with at least MR to any prior therapy);
2. Prior treatment with CD38 CAR-T cell therapy or CD38/CD3 bispecific antibodies;
3. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) less than 50% of predicted normal;
4. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification;
5. Evidence of mucosal and/or internal bleeding or platelet transfusion refractory (platelet count fails to increase by > 10,000 cells/mm^3 after a transfusion of an appropriate dose of platelets);
6. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., heart failure class III or IV according to New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, significant cardiac conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months);
7. Known active infection that is uncontrolled (including symptomatic or asymptomatic COVID-19) or has required intravenous systemic therapy within 14 days of randomization. Patients who has required oral anti-infective treatment within 14 days of randomization should be discussed with the Medical Monitor;
8. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance;
9. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation;
10. Human immunodeficiency virus or active hepatitis C viral infection, either known or if detected during screening;
11. Hepatitis B: both active (defined as HBsAg+) or non-active hepatitis B (defined as HBsAg-, Anti-HBs+, Anti-HBc+):
    - Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-).
12. Concurrent known or suspected amyloidosis or plasma cell leukemia;
13. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);
14. Known CNS or meningeal involvement of myeloma:
15. Any of the following treatments, within the specified timeframe:

- Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy.
- The use of live vaccines within 30 days before initiation of therapy.
- IMiDs, PIs and or corticosteroids within 2 weeks prior to initiation of therapy.
- Other investigational therapies and mAb within 4 weeks of initiation of therapy.
- Prednisone up to but no more than 10 mg orally q.d. or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to initiation of therapy;

16. Residual side effects to previous therapy > Grade 1 prior to initiation of therapy (alopecia any grade and/or neuropathy Grade 1 without pain are permitted);
17. Prior stem cell transplant (autologous and/or allogenic) within 6 months of initiation of therapy;
18. Prior allogeneic stem cell transplantation with active graft-versus-host-disease;
19. Prior major surgical procedure or radiation therapy within 4 weeks of the initiation of therapy (this does not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy);
20. Known intolerance to the required dose and schedule of steroid therapy, as determined by the investigator;
21. Known hypersensitivity to any of the agents in this study including hyalonuridase
22. Prior treatment with melflufen

5.3. Lifestyle considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently eligible to be randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if appropriate and in consultation and approval of the Medical Monitor.

5.5. Population Diversity

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of these patient factors in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Investigators are encouraged to recruit a diverse population.

6. Study Intervention

Study intervention is defined as treatment with melflufen, dexamethasone and daratumumab in Arm A and daratumumab in Arm B. Both treatments are intended to be administered to a study patient according to the study protocol.

Treatment will be given in 28-day cycles and may be given in an outpatient setting.

6.1. Study Treatment Administered

See Table 6-1 for an overview of the study drugs and their respective characteristics.

Table 6-1 Study Drugs

Study Drug Name:	**Melflufen**	**Daratumumab**	**Dexamethasone**
Pharmaceutical form:	Powder for solution for infusion	Solution for injection	Tablet
Unit dose strength(s)/	20 mg	16 mL of solution which includes 120 mg/mL of daratumumab, in combination with rHuPH20 [2000 U/mL]	4 mg
Dosage:	30 mg	1800 mg	40 mg (20 mg for patients ≥75 years)
Route of Administration	Intravenous (i.v.) via central catheter	Subcutaneous (s.c.)	Oral (p.o.)[a]

Study Drug Name:	Melflufen	Daratumumab	Dexamethasone
Packaging and Labeling	melflufen powder for solution for infusion is filled in 50 mL glass vials with grey rubber stoppers and flip-off seals. The vials will be delivered in boxes containing enough vials for several administrations. Each vial and box will be labeled as required per country requirement.	daratumumab (s.c) is supplied as a single use, sterile, liquid product in a glass vial closed with a stopper and aluminum seal with a gray plastic flip off cap. Each vial and box will be labeled as required per country requirement.	dexamethasone (p.o.) will be supplied by Oncopeptides AB to all countries except the USA. There are 20 tablets in each package. Where supplied, it will be labeled as required per country requirement.
Storage conditions	Refrigerated 2°C – 8°C (36°F–46°F) Protected from light	Refrigerated 2°C – 8°C (36°F–46°F) Protected from light	Ambient 15°C–25°C (59°F–77°F)
Further information	Investigator's Brochure and Pharmacy Manual	Investigator's Brochure and Pharmacy Manual	Summary of Product Characteristics (SmPC) or Prescribing Information, as well as Pharmacy Manual

a) For patients in Arm A: Oral dexamethasone may be substituted with i.v. dexamethasone in cycle 1, at the investigator's discretion if this is the standard of care of the study center.

6.1.1. Study Regimens and Administration

Patients will be randomized (1:1) to Arm A (melflufen+dexamethasone+daratumumab) or Arm B (daratumumab). Treatment will be given in cycles and may be given in an outpatient treatment setting. Each cycle is 28 days.

Arm A:

- Melflufen 30 mg will be given as a 30-minute i.v. infusion.
- Dexamethasone 40 mg weekly will be given p.o. Patients ≥75 years old should receive a reduced dose of dexamethasone (20 mg weekly).
- Daratumumab 1800 mg will be given s.c. as a 15 mL injection over 3-5 minutes with pre-medication for the prophylaxis of infusion reactions.

Arm B:

- Daratumumab 1800 mg will be given s.c. as a 15 mL injection over 3-5 minutes with pre-medication for the prophylaxis of infusion reactions. Patients with confirmed disease progression in Arm B have the option to crossover to treatment with melflufen, dexamethasone and daratumumab (dose and schedule as in Arm A).

Table 6-2 and Table 6-3 summarize the study drug administration schedule during each 28-day cycle.

Table 6-2 Study Treatment Arm A

Melflufen dose (i.v.)	Daratumumab dose (s.c.)[a]	Dexamethasone dose[b] (p.o.)[c]
All cycles: Day 1	**Cycle 1 and 2:** Days 1, 8, 15 and 22 **Cycle 3 to 6:** Days 1 and 15 **Cycle 7+:** Day 1	40 mg weekly for patients < 75 years 20 mg weekly for patient ≥ 75 years

a) Pre-medication should be administered to prevent infusion/administration related reactions (see Section 6.1.4.1)
b) For additional details on dexamethasone administration see Section 6.1.3.
c) Prior to melflufen infusion 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.

Table 6-3 Study Treatment Arm B

Daratumumab dose[a] [b](s.c.)
Cycle 1 and 2: Days 1, 8, 15 and 22 **Cycle 3 to 6:** Days 1 and 15 **Cycle 7+:** Day 1

a) Pre-medication should be administered to prevent infusion related reactions (see Section 6.1.4.1).
b) Patients with confirmed disease progression in Arm B have the option to crossover and receive melflufen, dexamethasone and daratumumab (dose and schedule as in Arm A).

6.1.2. Melflufen Administration (Arm A)

Prophylactic treatment with anti-emetic drug(s) prior to melflufen administration is recommended. Subsequent anti-emetic drugs against delayed emesis should be administered at

the discretion of the investigator. Concomitant medication shall be documented in the concomitant medication page in the electronic case report form (eCRF).

On days when melflufen and daratumumab are scheduled on the same day melflufen should be administered first.

Melflufen should be administered as a 30-minute i.v. infusion through a central catheter (Port A Cath, PICC line or central venous catheter), which should be inserted according to standard local practice. All patients must have an acceptable central catheter for infusion prior to the initiation of the first dose of melflufen.

Before infusion:

- Document vital signs prior to start of infusion.
- Prepare the central catheter by flushing with approximately 20 mL of 0.9% sodium chloride .

Infusion:

- The melflufen should be administered as a 30-minute intravenous infusion.
- Record start and stop time for infusion.

After infusion:

- First, flush the central catheter with approximately 20 mL of 0.9% sodium chloride. Then follow with additional flushing as per institutional guidelines if necessary.

The planned and actual administered dose, as well as the start and stop time for the infusion, should be documented in the source documents and on the appropriate eCRF page. See Section 6.2 for preparation, handling, storage and accountability. Refer to the Pharmacy Manual for details on melflufen preparation and administration.

6.1.3. Dexamethasone Administration (Arm A)

Dexamethasone 40 mg p.o. (20 mg p.o. for patients ≥ 75 years) will be given weekly for all patients in Arm A. Dexamethasone should always be administered prior to melflufen when both melflufen and daratumumab is given (i.e. on Day 1 of each cycle).

Additional steroids may be given as needed to prevent or treat hypersensitivity reactions at the investigator's discretion and as per the Standard of Care (SoC) for the site. Table 6-4 outlines the dexamethasone doses and schedule for administration.

Table 6-4 Dexamethasone dosing schedule

Dexamethasone dosing on days when melflufen and daratumumab are given[a]		
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.

6.1.4. Daratumumab Administration (Arm A and B)

Daratumumab will be given at the dose of 1800 mg daratumumab (in combination with rHuPH20 [2000 U/mL]) administered s.c. by manual push [15 mL] over 3-5 minutes at alternating left/right abdominal sites. Pre- and post-medications should be administered for the prophylaxis of infusion/related reactions (see Section 6.1.4.1). Vital signs should be measured pre-dose and post-dose on all dosing days. Patients shall remain in the clinic 3 hours after their first daratumumab administration (Cycle 1 Day 1) and up to investigator's discretion for following Cycles.

6.1.4.1. Daratumumab Pre-dose and Post-dose Medications

6.1.4.1.1. Pre-dose Medications

In an effort to prevent administration related reactions, all patients will receive the following medications 1 to 3 hours prior to each daratumumab administration (1 hour prior to study drug administration is preferred):

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg i.v. or p.o.
- An antihistamine: diphenhydramine 25-50 mg i.v. or p.o., or equivalent. Avoid i.v. use of promethazine.
- Corticosteroids (long acting or intermediate-acting)
    - Arm A (melflufen, dexamethasone and daratumumab):

Dexamethasone is a part of the background regimen and will serve as the steroid for premedication. No additional corticosteroid pre-medication is needed

- Arm B (daratumumab):

Dexamethasone 20 mg (or equivalent corticosteroid) i.v. or p.o. Following the second injection, the dose of the corticosteroid may be reduced to dexamethasone 12 mg i.v. or p.o,.

For patients in Arm B who receive melflufen, dexamethasone and daratumumab treatment after crossover, no additional corticosteroid pre-medication is needed.

- Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg p.o., or equivalent) is optional on Cycle 1 Day 1 and can be administered up to 24 hours before administration as per investigator's discretion.

If necessary, all p.o. pre-dose medications may be administered outside of the clinic on the day of administration, provided they are taken within 3 hours before administration.

6.1.4.1.2. Post-dose Medications

Administer the following post-dose medications:

- Arm A (melflufen, dexamethasone and daratumumab):

Consider administering dexamethasone at a dose of less than or equal to 4 mg orally beginning of the day after administration of daratumumab.

- Arm B (daratumumab):

Administer dexamethasone 4 mg (or equivalent corticosteroid) orally for 2 days, starting the day after the administration of daratumumab.

If the patient does not experience a major systemic administration-related reaction after the first 3 doses of daratumumab, consider discontinuing the administration of corticosteroids (except the background regimen-specific corticosteroid).

For patients with a higher risk of respiratory complications (e.g., patients with mild asthma or patients with COPD who have an FEV1<80% at screening or developed FEV1 <80% during the study without any medical history) the following post-dose medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (e.g., inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with COPD)

Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after patients are released from the hospital/clinic. If an at-risk patient experiences no major administration-related reactions, then these post-dose medications may be waived after 4 doses at the investigator's discretion.

Any post-dose medication will be administered after the administration has completed.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.
2. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, i.e. receipt reconciliation, and final disposition record. Drug accountability will be reviewed by the CRO monitor during site visits and at the completion of the study. A copy of the drug destruction policy and the completed drug log should be provided to the CRO monitor upon request.
4. At study close-out, and as appropriate during the study, all unused study drug packaging and any associated supplies should be discarded according to the site drug destruction policy following review and approval of the site CRO monitor. A copy of the drug destruction policy and the completed drug accountability log should be provided to the CRO monitor.
5. Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.2.1. Melflufen

6.2.1.1. Melflufen Packaging and Labeling

Melflufen is formulated as a sterile lyophilized powder for solution for infusion (containing melflufen and the excipient sucrose). The drug product, melflufen powder for solution for infusion, is filled in 50 mL glass vials with grey rubber stoppers and flip-off seals. Each vial contains 20 mg of melflufen. These will be delivered in paper boxes containing enough vials for several administrations.

Please refer to the Pharmacy Manual for further details on packaging and labeling.

6.2.1.2. Melflufen Storage

Melflufen must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the temperature log should be checked, and notice given to supplier of the condition of the shipment. Melflufen shall be stored at 2°C – 8°C (36°F–46°F) (refrigerated) protected from light.

6.2.1.3. Melflufen Supply

Melflufen will be provided by Oncopeptides AB.

6.2.1.4. Melflufen Special Handling

Melflufen is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling melflufen solutions. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices.

6.2.1.5. Melflufen Drug Preparation

Note: Refer to the Pharmacy Manual for detailed instruction for reconstitution and dilution of melflufen in preparation for infusion. A well-coordinated plan between the pharmacy and treatment room is recommended.

- Melflufen is administered i.v. through a central catheter, which should be inserted according to standard local practice. All patients must have an acceptable catheter for infusion (Port A Cath, PICC line or CVC).
- Melflufen degrades in solution. It is very important to adhere to the timelines for preparation that are outlined in the Pharmacy Manual. This requires very good coordination between staff at the pharmacy and the patient treatment area. Careful attention and documentation of the preparation procedures and time frames are required.
- Melflufen is reconstituted in 40 mL 5% glucose infusion solution per 20 mg vial of melflufen. The reconstituted melflufen is diluted to 250 mL in 0.9% sodium chloride infusion solution and should be refrigerated immediately, see Pharmacy Manual for detailed instructions.

6.2.2. Dexamethasone

6.2.2.1. Dexamethasone Packaging and Labeling

Dexamethasone (p.o.) will be supplied as a 4 mg tablet with 20 tablets in each package by Oncopeptides AB to all countries except the USA. Where supplied, it will be labeled as required per country requirement. No additional labeling is required for the use of commercial dexamethasone in the USA.

6.2.2.2. Dexamethasone Storage

Dexamethasone is to be stored at controlled room temperature. Consult the package insert or SmPC for dexamethasone for additional storage and usage instructions. Upon receipt, the temperature log should be checked, and notice given to supplier of the condition of the shipment.

6.2.2.3. Dexamethasone Supply

Oral dexamethasone will be supplied by Oncopeptides AB to sites located outside the USA. USA sites will use commercially available dexamethasone supplies.

6.2.3. Daratumumab

6.2.3.1. Daratumumab Packaging and Labeling

Daratumumab is a colorless to yellow, preservative-free solution for injection. Each single use drug product vial contains approximately 16 mL of solution which includes 120 mg/mL of daratumumab. Daratumumab will be labeled for investigational use according to local regulations.

6.2.3.2. Daratumumab Storage

Store the drug product vial in a refrigerator at 2°C – 8°C (36°F–46°F). Protect from light during refrigerated storage. Protection from light is not needed during dose preparation of administration. Do not freeze or shake the drug product vial or prepared drug syringe. This product contains no preservative. Upon receipt, the temperature log should be checked, and notice given to supplier of the condition of the shipment. Please refer to the Pharmacy Manual for specifications.

Do not store any unused portion of the injection solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

6.2.3.3. Daratumumab Supply

Daratumumab will be supplied by Oncopeptides AB.

Please refer to the Pharmacy Manual for complete details on drug supply and ordering procedures.

6.2.3.4. Daratumumab Drug Preparation

Daratumumab drug product vials should be stored at 2°C – 8°C (36°F–46°F) and protected from light. The drug product vials should be kept in original carton until assigned for use. Drug product vials should not be frozen or shaken.

Remove drug product vial from the 2°C – 8°C (36°F–46°F) storage and equilibrate at room temperature for at least 30 minutes (from the time the vial is removed from 2°C – 8°C (36°F–46°F) storage until preparation of a syringe. The vial must not be stored at room temperature and room light for more than 24 hours including equilibration time before first vial puncture.

NOTE: The maximum allowable time at room temperature and room light from puncturing the vial to administering the syringe contents to the patient is 4 hours.

Refer to the Pharmacy Manual for detailed instructions for preparation and requirements for administration.

6.3. Measures to Minimize Bias

6.3.1. Study Drug Administration

The study drug administration is more frequent in treatment arm A, i.e. dexamethasone dosing on weeks when no other drug is given, see Table 6-4. There is a potential risk that these additional visits may not be attended for pragmatic and logistic reasons. In addition, patients who have not required any dose modification or delays, G-CSF and transfusions during the last two cycles may skip visits at Day 8 and Day 22, and it is possible that this may be more common for patients in treatment Arm B. This may introduce bias in reporting of data. Special attention will therefore be given to frequency of visits not attended during data review and final analysis.

A potential bias may also be introduced from varying frequency and degree of drug interruptions due to adverse events, as a result of differences between treatment arms regarding expected adverse events. This may lead to varying intensity of drug exposure as well as unbalanced timing of assessments between treatment arms. Special attention will therefore be given to this potential bias during data review and final analysis.

6.3.2. Randomization

Patients will be randomly assigned to study treatment through an Interactive Web Response System (IWRS) system. This provides automated confirmation of assignments and documentation. It also assures inventory management and real-time reporting of study enrollment status.

The randomization will be stratified to minimize bias in endpoints due to differences in baseline characteristics between the investigational arm and the control arm. 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).

6.3.3. Data Access Plan

This is a randomized controlled study where the open-label treatment allocation is unblinded for investigators and other personnel involved in monitoring and data validation. To minimize the potential bias from review and processing of unblinded data, the access to data will be restricted to varying degrees by study roles. Access to data and processes for data management reports are specified in a separate Data Access Plan.

6.3.4. Medical Monitoring Plan

Patients' eligibility will be verified by the Medical Monitor before randomization to assure consistency and documentation of medical judgements related to the eligibility criteria. Processes pertaining to this activity are described in a separate Medical Monitoring Plan.

6.3.5. Data Monitoring Committee

Safety and tolerability will be reviewed during the study by an independent Data Monitoring Committee (DMC) as described in Section 9.5.1.

6.3.6. Independent Review Committee

All response assessments will be done by investigators based on IMWG guidelines. These guidelines will ensure consistency of response assessments across patients and sites. As a sensitivity analysis, an Independent Review Committee (IRC) will also evaluate the response assessments as described in Section 9.5.2.

6.4. Study Treatment Compliance

Compliance with melflufen and daratumumab will be assured by administration of the study treatment under the supervision of the investigator or his/her designee and should be documented in the study drug administration and accountability records. Compliance with dexamethasone (in Arm A) will be verified by accountability, patient inquiry and documented in the source documents and eCRF, as well as in a patient diary.

6.5. Concomitant Therapy

Any blood products, medications and vaccines (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving within 21 days prior to the initiation of therapy or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Required Concomitant Therapy

- **Anti-viral prophylaxis**

  It is required that patients receive prophylaxis against herpes zoster using oral acyclovir (400 mg twice daily) or valacyclovir (500 mg twice daily) or equivalent antiviral therapy per institutional guidelines and at the discretion of the site investigator, unless the patient develops a hypersensitivity to the agents.
  Reactivation of Hepatitis B: See Section 6.6.3, regarding management of patients at risk for, or diagnosed with, reactivation of hepatitis B.

- **Contraceptive measures**

Males and females of child-bearing potential shall be required to use effective contraceptive methods (or abstinence) prior to initiation of study drug, while on therapy and for 3 months after the last dose of study drug. The best method should be determined in consultation with the Investigator. See

Appendix 5.

- **Pneumocystis prophylaxis**

  All patients are recommended, and high risk patients are mandated, to receive pneumocystis prophylaxis, see Section 6.5.2.

6.5.2. Recommended Concomitant Therapy

- Pneumocystis prophylaxis:

  All patients are recommended, and high risk patients are mandated, to receive pneumocystis prophylaxis concomitant treatment according to the National Comprehensive Cancer Network (NCCN) or institutional guidelines: http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

  - Trimethoprim/sulfamethoxazole – Prophylaxis: single or double strength daily or double strength 3 times per week. The dose and administration schedule may require adjustment for renal insufficiency.
  - Patients who are found to be intolerant of pneumocystis prophylaxis while on study may continue on study at the discretion of the investigator. Alternative pneumocystis prophylaxis regimens should be considered

- Antimicrobial prophylaxis:

  - For patients with history of cytomegalovirus (CMV) infection that required treatment, prophylactic treatment per NCCN or institutional guidelines is recommended. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
  - Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period per NCCN or institutional guidelines. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

- Thrombocytopenia and neutropenia are known consequences of MM but also the most common expected AEs associated with melflufen. Careful attention is to be paid to the monitoring of blood counts. General supportive measures, together with appropriate blood and platelet transfusions and hematopoietic growth factors should be administered if necessary. It is recommended, at the investigator's discretion, that platelet transfusion should be avoided within ≤ 5 days of the next dose in order to assess endogenous platelet recovery and avoid the possibility of excessive myelosuppression (Excluding Cycle 1, Day 1 which adheres to the guidelines in Section 6.6.1.1 for use of growth factors and platelet transfusions prior to the first dose of therapy).
- Prophylactic treatment with anti-emetic(s) prior to melflufen administration is recommended. Subsequent anti-emetic drugs against emesis should be administered at the discretion of the investigator.

- Prophylactic treatment required prior to daratumumab to minimize or to treat infusion related reactions can be found in Section 6.1.4.1.
- Patients should receive full supportive care while on study at the investigator's discretion, including red blood cell transfusions, anti-emetics, anti-diarrheals and analgesics etc.
- Bisphosphonate therapy i.v. or p.o. should be administered if indicated in accordance with institutional guidelines.
- Other prophylactic treatment for patient related concomitant conditions or risks may be considered.

6.5.3. Prohibited Concomitant Therapy

- Concurrent therapy with any approved or investigative anticancer therapeutic drug with activity against MM, including alpha interferon and/or chronic use of clarithromycin, is not allowed.
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) > prednisone 10 mg/day (or its equivalent) are not permitted. However, steroids required for the treatment of daratumumab infusion related reactions are permitted. Topical and inhaled corticosteroids are permitted.
- Other investigative agents should not be used during the study.
- Radiation therapy, unless only to a limited area for bone pain to a pre-existing lesion – this may be considered in consultation with and approval by the Medical Monitor.
- The use of live vaccines is prohibited during the study and for 90 days after last dose of study treatment.
- Thrombopoietin receptor agonists are not permitted. Platelet transfusions are allowed in case of thrombocytopenia.
- The prophylactic use of Granulocyte-colony stimulating factor (G-CSF) and platelet transfusions are not permitted to render the patient eligible for trial participation except as described within the inclusion criteria Section 5.1.
- Acetylsalicylic acid, at doses ≥ 1 g per dose or 3 g per day should be avoided due to an increased risk of bleeding in patients receiving dexamethasone.

6.6. Dose Modification

Dose modifications are permitted during the study according to guidelines described below.

- Toxicity should be assessed using the common terminology criteria for adverse events (CTCAE) version 5.0 (See Appendix 7).
- All dose modifications should be based on the worst preceding toxicity.
- Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly.

- Dose modification of one agent and not the others is appropriate if toxicity is related primarily to one of the agents.
- No dose escalations are permitted in any given patient once a dose level has been reduced.
- Dose modifications different from those stated in the protocol should only be made in consultation with the Medical Monitor or Sponsor; unless required for immediate patient safety.
- Administration of the study treatment should be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the investigator, warrants discontinuation.
- All interruptions or changes to study treatment administration must be recorded in the eCRF.
- In case of dose reduction of any study therapy, the dose should not be re-escalated to the higher dose once the AE resolves.

6.6.1. Criteria for initiation of therapy

6.6.1.1. Day 1, Cycle 1

Prior to initiation of therapy, patients must continue to meet eligibility criteria including ECOG performance status of ≤ 2 and the Cycle 1 Day 1 laboratory results must also meet the entry criteria as follows:

- ANC ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] of initiation of therapy).
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusion during the previous 10 days to initiation of therapy). Thrombopoietin receptor agonists are not permitted, see Section 6.5.3.
- Hemoglobin ≥ 8.0 g/dL (RBC transfusions are permitted).
- Total Bilirubin ≤ 1.5 x upper limit of normal, except patients diagnosed with Gilbert's syndrome that have been reviewed and approved by the Medical Monitor.
- AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN
- Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min (Appendix 13).

Criteria for initiation of a crossover in Arm B after confirmed disease progression have been specified in Appendix 3.

6.6.1.2. Day 1, Subsequent cycles

- ANC must be ≥ 1,000 cell/mm^3 (1.0 x10^9/L). For administration of growth factors see Section 6.5.2.
- All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except peripheral neuropathy Grade 1 without pain, alopecia and fatigue ≤ Grade 2).

- Absence of daratumumab IRR that require discontinuation (Grade 4 or Grade 3 on three occurrences in the previous cycle see Section 6.6.3.3.1.
- Platelet count:
    - Arm A (melflufen, dexamethasone and daratumumab): Platelet count must be ≥ 50,000 cell/mm^3 (50.0 x 10^9/L) (platelet transfusions not recommended within ≤ 5 days of dosing (see Section 6.5.2). For patients in Arm A that have discontinued melflufen but remain on daratumumab and dexamethasone the platelet count must be ≥ 25,000 cell/mm^3 (25.0 x 10^9/L)
    - Arm B (daratumumab): Platelet count must be ≥ 25,000 cell/mm^3 (25.0 x 10^9/L) (platelet transfusions not recommended within ≤ 5 days of dosing (see Section 6.5.2).

If these criteria are not met on the scheduled Day 1, the new cycle should be held, and patients should be re-evaluated weekly. Refer to Section 6.6.3 for guidelines on dose modification due to drug related toxicity.

The maximum amount of time for which study therapy may be held due to drug related toxicity is 28 days from a scheduled Day 1 (Day 57). If study treatment is not administered for more than 28 days due to drug related toxicity the patient will be removed from the study treatment and enter follow up phase. If the patient was clearly benefiting from therapy, the patient may be able to continue treatment at the Investigator's discretion and in consultation with the Medical Monitor, after resolution of the AE. This also applies to the patients who crossover.

6.6.2. Dose Reduction Steps

6.6.2.1. Dose Reduction Steps for Melflufen

Dose modifications of melflufen for drug related toxicity are permitted. Multiple dose reductions are permitted however, the lowest dose permitted is 10 mg (see (Table 6-5). If a patient is unable to tolerate the lowest dose of melflufen due to drug related toxicity the patient must be withdrawn from treatment. No dose increases after previous dose reductions are allowed. Prior to each cycle of melflufen the criteria for initiation of therapy must be met (see Section 6.6.1). Patients who discontinue treatment with melflufen in Arm A for any reason may continue treatment with daratumumab and dexamethasone. In the event that melflufen is discontinued and the partner therapy is continued, the schedule of CBC and platelet evaluations may be conducted at the investigator's discretion but must at a minimum be performed Day 1 of each subsequent cycle and before each dose of daratumumab.

Table 6-5 Dose Reduction Steps for Melflufen

Starting dose	Dose reduction Step - 1	Dose reduction Step – 2	Dose reduction Step – 3
30 mg	20 mg	15 mg	10 mg

6.6.2.2. Dose Reduction Steps for Dexamethasone

Table 6-6 outlines the dose reduction steps for dexamethasone. Dose reductions of dexamethasone other than those listed in Table 6-6 or discontinuation may be considered in consultation with the Medical Monitor. Table 6-8 outlines the dose modification guidelines for toxicity related to dexamethasone.

Table 6-6 Dose Reduction Steps for Dexamethasone

Starting dose	Dose reduction Step - 1	Dose reduction Step - 2
40 mg	20 mg	12 mg
20 mg	12 mg	4 mg

6.6.2.3. Dose Reduction Steps for Daratumumab

There are no dose reduction steps for daratumumab. A patient who discontinues treatment with daratumumab due to AEs, except from hematologic toxicity, in Arm A may continue treatment with melflufen and dexamethasone, after consultation with Medical Monitor.

6.6.3. Dose Modifications Based on Toxicity

6.6.3.1. Dose Modifications for Melflufen and Daratumumab

Melflufen is a potent myelosuppressive agent, and it is essential that careful attention be paid to the monitoring of blood counts. General supportive measures, together with appropriate red blood cell and platelet transfusions and hematological growth factors, should be instituted if necessary. It is recommended, at the investigator's discretion, that platelet transfusion should be avoided within 5 days of the next dose of melflufen in order to assess endogenous platelet recovery and avoid the possibility of excessive myelosuppression. Table 6-7 outlines the dose modification for toxicity related to melflufen and daratumumab.

Patients with neutropenia should be monitored for signs of infection as described in section 6.5.2

Patients who discontinue treatment for a study related AE including abnormal laboratory value must be followed as described in Section 8.1.3.

Table 6-7 Dose Modification for Toxicity Related to Melflufen and Daratumumab

Toxicity	Cycle Day	Action with Melflufen	Action with Daratumumab
Hematologic Toxicity – Supportive therapy with platelets and growth factors is permitted according to the guidelines in Section 6.5.			
ANC <1000 mm^3 (<1.0 x 10^9 /L) Platelet count <50,000 mm^3 (<50.0 x 10^9 /L)	Day 1	Hold, evaluate weekly and resume therapy when criteria for initiation of a new cycle are met (Section 6.6.1)	Hold, evaluate weekly and resume therapy when criteria for initiation of a new cycle are met For patients in Arm B and patients in Arm A that have discontinued melflufen, dosing may continue if platelets are >25,000 mm^3 (>25.0 x 10^9 /L) (Section 6.6.1).
		First occurrence - if resolved in ≤ 14 days same dose may be resumed. Dose reduction or delay may be considered.	No dose reduction of daratumumab is permitted.
		If resolved in > 14 days or a subsequent occurrence, dose reduction is required.	
ANC < 500 mm^3 (0.5 x 10^9/L) Platelet count <25,000 mm^3 (<25.0 x 10^9 /L)	Day 8, 15 or 22 (see Section 6.1.4) for daratumumab schedule)	Not applicable	Hold until resolved to ≤ Grade 2 within the cycle (see Section 6.1.4) for daratumumab schedule)
Non-hematologic Toxicity			
Reactivation of HBV	Any Day		Hold until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with

			concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.
Grade 3 drug related non-hematologic toxicity	Day 1	Hold, evaluate weekly[a] and resume therapy when criteria for initiation of a new cycle are met (see Section 6.6.1). Reduce dose if attributed to melflufen[c]	Hold and evaluate with next scheduled administration. Resume therapy within the cycle if resolved to ≤ Grade 1 or baseline or hold for remainder of cycle and resume therapy when criteria for initiation of a new cycle are met (see Section 6.6.1).
Grade 3 drug related non-hematologic toxicity	Any day during a cycle	If attributed to melflufen, reduce by one dose level when criteria for a new cycle are met[b]	No dose reduction is permitted, refer to Section 6.6.3.3.1 for management of infusion-related reactions
Grade 4 drug related non-hematologic toxicity	Any day	Discontinue therapy	Discontinue therapy

a) If cycle prolongation of more than 28 days (beyond Day 57) is needed, study treatment is to be discontinued unless in the investigator's opinion the patient is benefitting from therapy. Continuation must be discussed with the Medical Monitor on a case by case basis.

b) A dose reduction may not be required if: the toxicity can be managed with appropriate therapy or the risk of recurrence may be reduced by the use of appropriate prophylactic therapy (e.g. anti-emetics and anti-diarrheals for nausea, vomiting and diarrhea) AND/OR the toxicity was transient and/or does not warrant a dose reduction in the opinion of the investigator in consultation with the Medical Monitor (headache, abnormal laboratory value, fatigue). This must be discussed with the Medical Monitor on a case by case basis.

c) Alternate dose modification may be considered in discussion with the Medical Monitor. Continued dosing with or without dose reduction of melflufen may be considered after contact with the Medical Monitor in case of non-study drug related cycle prolongations (for example: influenza).

6.6.3.2. Dose modifications for Dexamethasone (Arm A)

Dose modifications for dexamethasone are permitted. If a patient is unable to tolerate dexamethasone due to dexamethasone related toxicity, dexamethasone may be further reduced or

discontinued following consultation with the Medical Monitor. In the event of a cycle delay, unrelated to dexamethasone toxicity, dexamethasone may be continued weekly at the investigator's discretion.

Table 6-8 Dose Modification for Toxicity Related to Dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with Histamine 2 receptor (H2) blockers, sucralfate, or proton pump inhibitors (PPIs) . If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or PPIs. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed. Decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose by another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration ≥ Grade 3 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness ≥ Grade 3 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

Alternate dose modification may be considered in discussion with the Medical Monitor.

6.6.3.3. Dose Modifications for Daratumumab

There are no dose reductions for daratumumab.

6.6.3.3.1. Management of Infusion Related Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with subcutaneous daratumumab. To be consistent with the IB for daratumumab as well as available prescribing information, the definition Infusion-related reactions (IRRs) is used for systemic reactions related to daratumumab administration, also when daratumumab is given as an injection over time in this protocol and not as an infusion. Patients should be observed carefully during daratumumab administrations for systemic administration-related reactions, especially following the first and second injections. Daratumumab should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions if they occur.

If an IRR develops during daratumumab administration, the administration should be temporarily interrupted. Patients who experience AEs during daratumumab administration should be treated for their symptoms. Patients should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, patients may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab should be discontinued.The most common local reaction after daratumumab administration has been injection site erythema. Monitor for local reaction and consider symptomatic management.

Infusion-related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR to be related to administration of study treatment, then the daratumumab administration should be interrupted. When the patient’s condition is stable, daratumumab administration may be restarted at the investigator's discretion.

If the patient experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the patient must be permanently discontinued from daratumumab treatment.

Infusion-related Reactions of Grade 3 or Higher

For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped, and the patient must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator's discretion.

If the intensity of the AE returns to Grade 3 after restart of the daratumumab administration, then the patient must be permanently discontinued from daratumumab treatment.

For IRR AEs that are Grade 4, the daratumumab administration must be stopped, and the patient permanently discontinued from daratumumab treatment.

Recurrent Infusion-related Reactions

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the patient must be permanently discontinued from daratumumab treatment.

6.6.3.3.2. Daratumumab precautions

Daratumumab binds to CD38 on RBCs and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that the patient has received daratumumab according to local requirements. Type and screen RBC prior to starting daratumumab, see Section 8.1.1.

6.7. Intervention after the End of the Study

There is no planned intervention following the end of the study.

7. Discontinuation of Study Intervention and Patient Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

Patients may be withdrawn from study treatment if any of the following occur:

- His/her own request at any time.
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Any of the events outlined in Section 4.1.1 Treatment duration
- Requiring other anticancer therapeutic drug, corticosteroids for non-malignant conditions, other investigative agent, live vaccine, or dialysis, as further detailed in Section 6.5.3.
- Confirmed pregnancy.
- Lost to follow-up.
- An incidence or a seriousness of SAEs in this study or other studies indicating a potential danger for the patient's health caused by the study treatment.

In the event of patient withdrawal from study treatment the reason(s) for withdrawal of study treatment and the date at which the decision is made should be documented. Safety monitoring and follow-up assessments should continue as appropriate according to the study schedule, unless the patient has withdrawn consent for study participation.

As for any other reason to discontinue treatment, the patient can still continue in follow up (unless consent has been withdrawn for study participation and not only for treatment).

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Patient Discontinuation/Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent, if allowed as per local regulations.
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- The reason(s) for withdrawal of study participation and the date at which the decision is made should be documented.

7.3. Lost to Follow Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Study procedures and their timing for patients who crossover are summarized in the SoA in Appendix 3. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Study procedures

8.1.1. Procedures during screening

Potential patients will be contacted to determine their interest in participating in this study. All patients must sign and date an IRB/IEC/REB approved informed consent form within 28 days of enrollment and prior to any study related procedure and enrollment. After providing written informed consent, the patients will be evaluated for eligibility by screening tests and conformity to study inclusion and exclusion criteria.

Once a patient is determined to be eligible for screening and satisfy all initial inclusion and exclusion criteria (Sections 5.1 and 5.2), screening procedures will be performed as listed below. If at any point during screening, a finding disqualifies the patient from study participation, no further screening tests will be performed.

The screening visit will occur within 21 days before randomization and treatment must begin ≤ 5 days after randomization but not before. The following assessments will be performed at the screening visit:

- Demographics
    - Date of birth, age, gender, race and ethnicity
- Medical history, including the following:
    - Prior and current medical illness and conditions
    - Prior surgical procedures
- Myeloma history including
    - Characteristics (including heavy chain or light chain subtype, evidence of EMD

or lytic bone lesions)
    - Date of initial diagnosis
    - ISS and R-ISS stage and cytogenetics at diagnosis (if previously evaluated)
    - ISS and R-ISS stage at time of screening
    - All prior myeloma treatment, also including surgery and/or radiation, documenting:
        - start and stop dates
        - assessment of best response
        - date of progressive disease and relapsed or refractory status
- Physical examination, including assessment for extramedullary myeloma. Baseline symptoms and residual toxicity from previous therapy, including neuropathy.
- Vital signs including height, weight, blood pressure, pulse, respiratory rate and temperature.
- ECOG performance status
- Pregnancy test, only for WOCBP
- RBC typing and antibody screening; Inform blood banks that the patient will receive daratumumab, according to local practice. See Section 6.6.3.3.2.
- 12- lead electrocardiogram (ECG); Q-Tc interval to be assessed by Fridericia formula
- Blood tests;
    - Hematology: CBC with differential and platelet count
    - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), creatinine, estimated creatinine clearance (by Cockcroft-Gault Formula), glucose (fasting), ALT (SGPT), AST (SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH).
    - Coagulation: Prothrombin time (PT), international normalized ratio (INR).
    - β2-microglobulin
- M protein assessments, see Section 8.2.1.
- Hepatitis B screening: HBsAg, Anti-HBs, Anti-HBc
- Hepatitis C screening: Anti-HCV
- HIV screening: Anti-HIV1/2 and HIV1/2 antigen
- Pulmonary function test: spirometry
- Urinalysis
- Bone marrow aspiration; The aspirate will be used for the following assays and should be divided into aliquots with the below priority order. Refer to Laboratory Manual for additional information.
    1. % plasma cells and morphology (smear)
    2. The rest of the aspirate should be divided into aliquots in the following order:
        i. 1 mL for possible MRD assessment (first draw)
        ii. 4 mL for cytogenetics by interphase Fluorescence In-Situ Hybridization (iFISH), karyotyping and DNA/RNA sequencing.
- Review prior/concomitant medications
- Extramedullary myeloma assessment. If imaging is used the method must provide bidimensional measurements with same method to be used throughout the study.

- Chest X-ray (optional if low-dose CT is performed for skeletal assessment). If performed within 6 weeks from initiation of therapy, repeat only needed if clinically indicated.
- Skeletal X-ray or low-dose CT scan; required if previous assessment is > 6 weeks from initiation of therapy.
- Inclusion/Exclusions criteria review
- Use of health services and hospitalization
- SAE monitoring

The Investigator will review each patient's screening data and document the patient's acceptability for study participation. The patient may be enrolled upon approval by the Medical Monitor.

For patients who fail screening, the Investigator will record demographics and reason for screen fail, eligibility criteria and any SAE in the appropriate sections of the eCRF and note the reason for exclusion. These documents and the patient's signed informed consent form will be retained in the study files.

8.1.2. Procedures during study treatment, all cycles

The following procedures will be performed during active study treatment at the times specified. All procedures are applicable at all cycles unless otherwise specified.

8.1.2.1. Procedures Day 1

- Criteria for initiation of therapy should be fulfilled, see Section 6.6.1.
- PRO assessments (EORTC QLQ-C30 and EQ-5D-3L), prior to any study visit activities (tests, examination or treatment). The questionnaires should be administered even if the treatment is not given, see Section 8.12.
- PRO pain assessments (BPI-SF and NRS for measure of bone pain), prior to study visit activities (tests, examination or treatment). BPI-SF should be completed first and if patient has experienced pain, the NRS for measure of bone pain should be completed. The questionnaires should be administered even if the treatment is not given, see Section 8.12.
- Physical examination; including assessment for extramedullary myeloma. Plasmacytomas that can be followed by physical examination should also be evaluated at each cycle with measurements documented in the source documents.
- Vital signs, including blood pressure, pulse, respiratory rate, temperature, should be assessed before melflufen dose as well as before and after daratumumab dosing. Weight should be assessed prior to melflufen dose.
- ECOG performance status
- Pregnancy test; only for WOCBP
- Blood tests:
    - Hematology: CBC with differential and platelet count
    - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), serum creatinine, estimated creatinine clearance (by Cockcroft-Gault Formula), glucose (non-fasting), ALT (SGPT), AST (SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH).

  - Blood sample for DNA/RNA sequencing should be collected before dosing at Cycle 1 day 1 and at the time of response (CR or VGPR) and at the time of disease progression.
  - Blood sample for myeloma related bone disease biomarkers should be collected before dosing.

    See Laboratory Manual for additional information.

- Bone marrow aspiration; at the time of CR/VGPR and if needed to confirm disease progression, the below samples should be obtained in the following order and sent to the central laboratory for analysis. See Laboratory Manual for additional information.
  1. % plasma cells and morphology including immunohistochemistry
  2. 3 mL for MRD assessment (not applicable in case of suspected PD)
  3. DNA/RNA sequencing
- Concomitant medications review
- M-protein assessments described in Section 8.2.1 is planned pre-dose Day 1 of each cycle (day 29 of prior cycle) and with assessment of myeloma response from Cycle 2. If treatment is delayed, an assessment should still be made at day 29 and should be repeated prior to next cycle if the delay is 2 weeks or longer, and to confirm any response or PD.
- Extramedullary myeloma assessment; Known or suspected plasmacytomas should be assessed, using the same method as at screening, every 2 cycles up to disease progression.
- Skeletal X-ray or low-dose CT scan; as clinically indicated.
- Administration of study treatment; see Section 6.1.
- Pharmacokinetic blood samples for melphalan; for patients in Arm A, cycle 1 and 2 only (see Section 8.6.1).
- Pre-dose pharmacokinetic blood samples for daratumumab for patients in Arm A and Arm B, cycle 1, 3, 7 and 12.
- Pre-dose serum samples for immunogenicity (daratumumab) for patients in Arm A and Arm B, cycle 1, 7 and 12.
- Pre-dose serum samples for immunogenicity (rHuPH20) for patients in Arm A and Arm B, cycle 1, 7 and 12.
- Pre-dose whole blood samples for immunoprofiling at Cycle 1 and Cycle 6.
- Use of health services and hospitalization
- AE monitoring

8.1.2.2. Procedures Day 4 (Cycle 1 and 3)

Pharmacokinetic blood samples for daratumumab for patients in both Arm A and B (Cycle 1 and 3 only) when possible to schedule on weekdays.

8.1.2.3. Procedures Day 8, 15 and 22

- If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then Day 8 and Day 22 visits do not have to be completed. Pain assessments (BPI-SF and NRS for measure of bone pain), prior to any study visit activities (tests, examination or treatment) on Day 15 of cycles 1-3. BPI-SF should be completed first and if patient has experienced pain, the NRS for

measure of bone pain should be completed. The questionnaires should be administered even if the treatment is not given.

- Physical examination: symptom directed as needed during treatment.
- Vital signs; including blood pressure, pulse, respiratory rate, temperature, to be assessed before and after each daratumumab administration (see Section 6.1.4 for daratumumab administration schedule).
- Blood tests:
    - Hematology: CBC with differential and platelet count. If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then Complete Blood Count assessments may be excluded at Day 8 and Day 22.
- See Laboratory manual for additional information. Concomitant medications review
- Administration of study treatment, see Section 6.1.
- AE monitoring

8.1.2.4. Procedures if melflufen is discontinued

If melflufen is discontinued and the partner therapy is continued, the schedule of assessments should continue as outlined in the SoA, Section 8.1.2 and 8.1.3. The schedule of CBC and platelet evaluations may be conducted at the investigator's discretion but must at a minimum be performed on Day 1 of each subsequent cycle and before each dose of daratumumab. Patients who discontinue melflufen and continue to be treated with the other drugs in the Regimen should also be followed for response, PFS, PFS-2 and OS.

8.1.3. Procedures after active study treatment

Patient will be treated until progressive disease (confirmed PD should be verified by Medical Monitor prior to discontinuation of therapy), unacceptable toxicity, consent withdrawal, or if the patient/treating physician determines it is not in the patient's best interest to continue. Patients in Arm B with documented disease progression may have the option to crossover and receive treatment with melflufen, dexamethasone and daratumumab.

An EOT visit will be scheduled within 30 days of the last dose of study drug. Patients that discontinue therapy for reasons other than disease progression will enter PFS follow-up. Patients who discontinue therapy for disease progression in Arm A will enter PFS-2 follow-up. Once disease progression has occurred, patients will enter the OS follow-up. Patient in Arm B will enter OS follow-up directly after confirmed disease progression in PFS follow-up. Patients in Arm B who are eligible for the crossover may have a combined EOT/initiation of crossover visit within 28 days of the last daratumumab dose in Arm B. Refer to SoA in Appendix 3 for details.

Patients with Grade 3 or 4 thrombocytopenia or neutropenia should be followed until resolution to ≤ Grade 2 or start of subsequent therapy. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, not expected to resolve or the patient is lost to follow-up (as defined in Section 7.3).

Patients who withdrew consent for treatment will continue to be followed for disease progression and/or survival unless they explicitly withdraw consent for these procedures.

Refer to Section 8.1.3 and SoA for complete details of the EOT and Follow-up assessments

required at each time point.

8.1.3.1. Procedures at End of Treatment Visit

EOT visit should be scheduled 30 days (accepted time window ±3 days) after last dose of study treatment or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle). For patients who are randomized but withdraw from study, for any reason, prior administration of any study drug the EOT visit should be completed as soon as possible after decision to remove patient from study (including withdrawal of consent to study treatment) has been made.

If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug, the EOT visit should occur as close as possible before the first dose of the new drug. For patients in Arm B who are eligible to crossover, the EOT visit should occur as soon as possible after confirmed disease progression and it may be combined with the initiation of the crossover visit (see SoA Appendix 3 for more details).

Patients progressing while on treatment, require 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC). The confirmed PD should be verified by the Medical Monitor prior to discontinuation of treatment. The second assessment must be a separate serum and urine sample. (If the second consecutive M protein sample can only be obtained after the start of subsequent therapy, it may be used as confirmation of PD). Patients in Arm B need to have the second assessment obtained before start of crossover.

- PRO assessments (EORTC QLQ-C30 and EQ-5D-3L), prior to any examination/procedure. If the EOT is for a reason other than PD, the assessments should be continued, on any on-site visit, each month until PD and/or start of new anti-myeloma treatment.
- PRO pain assessments (BPI-SF and NRS for measure of bone pain), prior to any examination/procedure. BPI-SF should be completed first and if patient has experienced pain, the NRS for measure of bone pain should be completed. If the EOT is for a reason other than PD, the assessments should be continued, on any on-site visit, each month until PD and/or start of new anti-myeloma treatment.
- Physical examination; including and assessment for extramedullary myeloma.
- Vital signs; including weight, blood pressure, pulse, respiratory rate and temperature.
- ECOG performance status.
- Pregnancy test; only for WOCBP.
- 12-lead ECG, Q-Tc interval to be assessed by Fridericia formula.
- Blood tests;
    - Hematology: CBC with differential and platelet count.
    - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), serum creatinine, estimated creatinine clearance) (by Cockcroft-Gault Formula), glucose (non-fasting), ALT (SGPT), AST (SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH).
- Blood sample for DNA/RNA sequencing should be collected in case of disease progression or response (CR or VGPR).
- Blood sample for myeloma related bone disease biomarkers should be collected in case of disease progression.

- Bone marrow samples to be taken if needed to confirm disease progression. See Laboratory Manual for additional information.
- M protein and myeloma response assessments, see Section 8.2.1
- Extramedullary myeloma assessment; known or suspected plasmacytomas should be assessed until disease progression.
- Skeletal X-ray or low dose CT scan; as clinically indicated.
- Concomitant medications review
- AE monitoring; Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EOT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, not expected to resolve or the patient is lost to follow-up (as defined in Section 7.3).
- Pharmacokinetic blood samples for daratumumab
- Serum samples for immunogenicity (daratumumab)
- Serum samples for immunogenicity (rHuPH20).
- Whole blood samples for immunoprofiling.
- Use of health services and hospitalization

8.1.3.2. Procedures 8 weeks after last dose of daratumumab

- Pharmacokinetic blood samples for daratumumab.
- Serum samples for immunogenicity (daratumumab).
- Serum samples for immunogenicity (rHuPH20).
- Pregnancy test; only for WOCBP.
- Instruct WOCBP to do a urine pregnancy test at home 12 weeks after last dose of daratumumab.

These samples are not required for patients in Arm B who enter the crossover.

8.1.3.3. Procedures during follow up

8.1.3.3.1. Progression Free Survival Follow-Up

- PRO assessments (EORTC QLQ-C30 and EQ-5D-3L), should be completed monthly on any on-site follow-up visit until PD and/or start of new anti-myeloma treatment. If PD and start of next treatment occur at the same time, only one assessment is required at that time. If the new treatment starts during OS follow-up, an additional assessment must be completed at that time.
- PRO pain assessments (BPI-SF and NRS for measure of bone pain), monthly on any on-site follow-up visit until PD and/or start of new anti-myeloma treatment. If PD and start of next treatment occur at the same time, only one assessment is required at that time. If the new treatment starts during OS follow-up, an additional assessment must be completed at that time. BPI-SF should be completed first and if patient has experienced pain, the NRS for measure of bone pain should be completed.
- Blood sample for DNA/RNA sequencing should be collected at time of response (CR or VGPR) and at the time of disease progression.

- Blood sample for myeloma related bone disease biomarkers should be collected at PFS-FU. See Laboratory manual for additional information
- Bone marrow samples to be taken if needed to confirm disease progression.
- Extramedullary myeloma assessment; Known or suspected plasmacytomas should be assessed every 2 months until disease progression.
- Skeletal X-ray or low dose CT scan; as clinically indicated.
- M protein and myeloma response assessment;
    - Monthly until confirmed disease progression or initiation of next anti-myeloma treatment, for patients who discontinue study treatment for reasons other than disease progression.
    - Confirmed disease progression requires 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC). The second assessment must be a separate serum and urine sample. If the second consecutive M protein sample only can be obtained after the start of subsequent therapy, it may be used as confirmation of PD.
    - The first assessment should be performed 4 weeks after the EOT visit. Serum calcium, albumin (corrected calcium) required if this is the presenting symptom of disease progression.
    - When disease progression has been confirmed, the patients will enter PFS-2 follow up.
- Second primary malignancies follow-up.
- For WOCBP: Collect and record any result of a urine pregnancy home test performed 12 weeks after last dose of daratumumab on the following PFS-FU if not done separately by phone.
- Use of health services and hospitalization

8.1.3.3.2. Procedures during PFS-2 follow up

Following documented disease progression on the study treatment, the patients will be followed for progression on the next line of treatment and secondary primary malignancies every 3 months +/-7days. Patients in Arm B with confirmed disease progression who continue and crossover to treatment with melflufen, daratumumab and dexamethasone will not be followed for PFS-2.

During the follow up the below assessments should be recorded:

- Subsequent therapy review;
    - Regimen (all individual drugs)
    - Start and stop dates
    - If PD has not been confirmed prior to the initiation of subsequent therapy, the reason for the subsequent therapy should be documented.
    - Best response
    - Date of disease progression per investigator review.
- Second primary malignancies follow-up.

8.1.3.3.3. Procedures during Overall Survival follow-up

Following PFS, patients will be contacted every 3 months +/- 7 days for OS for 24 months. Follow-up may be completed by phone, email, site visit or other method of contact. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable.

PFS-2 and OS will be captured every 3 months until median PFS-2 has been reached, or a minimum of 24 months. Following 24 months, annual follow up of OS might be conducted and information can then be captured outside the eCRF, and as an addendum to the study report.

8.2. Efficacy Assessments

Time points for all efficacy assessments are provided in Section 8.1.

8.2.1. Response Assessments

Samples for response assessments should be sent to the central laboratory for analysis, except where specified, see also central Laboratory Manual for instructions.

- M protein assessments:
  - FLC levels (kappa/lambda) including dFLC (difference between involved FLC and uninvolved FLC) and FLC ratio (involved FLC/uninvolved FLC).
    - FLC assessment is not required in the presence of measurable SPEP and/or UPEP (SPEP ≥ 0.5 g/dL and/or UPEP ≥ 200 mg/24 hours).
    - FLC is required to confirm sCR, regardless of type of measurable disease.
  - Electrophoresis
    - SPEP
    - UPEP
  - Immunofixation (IFE)
    - Serum immunofixation;
      - To be performed at baseline and at any time when M protein by SPEP becomes non-detectable to confirm CR.
      - Quantitative immunoglobulins should be included for patients with IgA and IgD myeloma.
    - Urine immunofixation
      - To be performed at baseline and at any time when M protein by UPEP becomes not detectable to confirm CR.
  - Daratumumab Immunofixation reflex Assay (DIRA) test, for patients with IgG kappa MM with M-protein assessment by SPEP.
    - ≤0.2 g/dL on 2 or more consecutive cycles.

    or
    - Not detectable M-protein, but persistently positive IFE for IgG kappa on 2 or more occasions.

    N.B. As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive due to daratumumab.

- Serum calcium (corrected calcium to be performed at local laboratory).
- Bone Marrow Aspirate: In patients with suspected CR or VGPR to confirm response and for MRD assessment, by next generation sequencing (NGS) .

8.2.2. Skeletal X-rays and low-dose CT scans

Skeletal survey includes lateral radiograph of the skull, and anterioposterior views of femur and humeri anterioposterior, and lateral views of the spine, and anterioposterior views of the pelvis and ribs. Low-dose CT scan may be used in addition to or in place of conventional X-ray with the same technique to be used with each evaluation. Limited X-rays may be performed as clinically indicated to confirm PD.

8.2.3. Extramedullary Myeloma (plasmacytoma) Assessment

Known or suspected extramedullary myeloma (plasmacytomas) are to be assessed at screening, every 2 cycles and every 2 months during PFS-follow- up to disease progression.

- Method(s) of evaluation should be able to provide bidimensional measurements and must be defined at baseline (for lesions present at screening); methods may include, CT scan or MRI physical examination or photography. Once the method is selected, extramedullary myeloma lesions should be evaluated with the same method throughout the trial.
- Lesions will be assessed according to IMWG-URC guidelines (Kumar et al 2016). Other lesions, including visceral lesions should be evaluated by CT, scan or MRI as appropriate.
- For skin lesions, only measurable lesions with a caliper should be reported.
- Lesions that are evaluable but not measurable should be reported. These lesions should disappear completely in case of CR or increase in size in order to be reported as cause for disease progression.

8.3. Safety Assessments

Time points for all safety assessments are provided in Section 8.1, SoA and in Appendix 3 for patients in Arm B doing the crossover.

8.3.1. Physical Examinations

A physical examination, including assessment for extramedullary myeloma will be conducted at screening, Day 1 of each cycle and at the EOT visit. A symptom directed physical examination will be conducted as needed during treatment period. Plasmacytomas that can be followed by physical examination are to be evaluated on Day 1 of each cycle. The timing of the assessment is described in Section 8.1.

The outcome of the assessments will be recorded as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”. Clinically significant findings prior to first dose of study drug will be documented as Medical History. Clinically significant findings after screening will be documented as AE/SAEs. An asymptomatic abnormal physical examination finding should only be reported as an AE if it is clinically significant or if it fulfils the criteria for an SAE. If an abnormal physical examination finding is associated with

clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated physical examination finding should be considered additional information.

8.3.2. Vital Signs

Vital signs will be measured, at the timepoint specified in Section 8.1 and SoA, will include height, weight, temperature, systolic and diastolic blood pressure, pulse and respiratory rate.

The outcome of the assessments will be recorded as "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant". An asymptomatic abnormal vital sign finding should only be reported as an AE if it is clinically significant, or if it fulfils the criteria for an SAE. Vital sign abnormalities should only be reported using one event term. For example – a high blood pressure recording (systolic blood pressure of 180 mm Hg) and hypertension, *both* should not be used to record the AE. If an abnormal vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated vital sign result should be considered additional information.

8.3.3. Electrocardiograms

12-lead ECGs will be taken as outlined in Section 8.1 in supine position, after the patient has been lying down for at least three minutes. Q-Tc interval should be assessed by Fridericia formula. The Investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant".

An asymptomatic abnormal ECG finding should only be reported as an AE if it is clinically significant or if it fulfils the criteria for an SAE. ECG abnormalities should only be reported using one event term. For example, an ECG recording of a rapid heart rate (a PR interval of 120 ms) and tachycardia, *both* should not be used to record the AE.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and Section 8.1 and SoA for the timing and frequency. All protocol-required laboratory safety assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA. For patients in Arm B who continue and crossover to treatment with melflufen, daratumumab and dexamethasone, see SoA in Appendix 3.

A screening test may need to be repeated just prior to randomization if the initial value was trending downward, not reached nadir from last dose of prior therapy or based on clinical presentation (this may be done at the Investigator's discretion or upon request of the Medical Monitor). Patients are required to have all laboratory evaluations completed at the study center during Cycle 1. Starting at Cycle 2, the evaluations may be done at the study center laboratory or other local laboratory as long as the results are reviewed by the study center within 24 hours and toxicity assessment is completed. Exceptions may be made only in consultation with the Medical Monitor.

The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The

laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are defined in Section 8.4.7.

All protocol specified laboratory assessments performed in addition to protocol specified time points must be recorded in the eCRF.

Other laboratory values from non-protocol specified laboratory assessments considered clinically significant by the investigator, as defined in Section 8.4.7 or supportive of understanding the patient's condition related to an AE or SAE must be recorded in the eCRF. See Section 8.4.7.1 for additional laboratory reporting guidelines.

8.3.4.1. Hepatitis and HIV assessments

Hepatitis B, Hepatitis C and HIV assessments are required at screening. Patients with Hepatitis B both active (defined as HBsAg+) and non-active (HBsAg-, Anti-HBs+, Anti-HBc+), active Hepatitis C or HIV infections are excluded.

8.3.5. Medical History and Myeloma history including characteristics

A complete medical history will include evaluation for past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, metabolic, lymphatic, hematologic, immunologic, dermatologic, psychiatric, and genitourinary disorders, medical-, surgical- and radiation history, and review of any other diseases or disorders.

8.3.6. Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of required, recommended and prohibited medications are found in Section 6.5.

8.3.7. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 6) will be assessed at screening, at Cycle 1 Day 1, prior to administration of study treatment and at the EOT visit.

8.3.8. Health Services and Hospitalizations

Number of health services, and number and days of hospitalizations will be assessed from screening, on Day 1 of each cycle, at time of EOT visit and at follow up until start of new treatment.

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF) until 30 days after the last administration of any study drug. In patients not receiving any study drug, every SAE occurring until date of documentation of screen failure OR date of documentation of EOT must be reported.

All AEs will be collected from the first dose of study drug until 30 days after the last study drug administration.

AEs, including SAEs, attributable to subsequent therapy should not be recorded.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not on the AE section, unless it is an SAE.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of information being available.

Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EOT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, not expected to resolve or the patient is lost to follow-up (as defined in Section 7.3). In addition to this, Investigators are not obligated to actively seek information regarding new AEs, including SAEs, after the EOT visit. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AEs, including SAEs, and the procedures for completing and transmitting SAE reports are provided in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.2. Method of Detecting AEs

Care will be taken not to introduce bias when detecting AEs, including SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs, including SAEs

After the initial AE/SAE, the investigator is required to proactively follow each patient at subsequent visits/contacts. Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EOT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, not expected to resolve or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor or designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an Individual Case Safety Report, safety line listing or any other specific safety information from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Details of all pregnancies, that occur after the start of treatment until 3 months after last dose of study drug administration, in female patients and female partners of male patients will be collected.

If a pregnancy is reported, the investigator should inform the Sponsor or designee within 24 hours from learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered as SAEs.

8.4.6. Fatal Events

Death is an outcome of a serious adverse event and not a serious adverse event in itself. When death is an outcome, the event(s) resulting in death should be reported (e.g., “pulmonary embolism” with a fatal outcome). The appropriate diagnosis or term should be recorded and assigned severity Grade 5;

In instances of death due to “Disease Progression” the cause of death should be indicated as the event or condition resulting in death to the extent possible (e.g., “respiratory failure” due to progressive MM);

Deaths that occur later than 30 days after the last study drug administration should be reported as SAEs only if assessed as related to the study treatment.

8.4.7. Laboratory Test Abnormalities

Laboratory abnormalities are usually not recorded as AEs; however clinically significant laboratory abnormalities must be recorded as AEs (or serious AEs) if they meet the definition of an AE (or serious AE) as described in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Clinically significant laboratory abnormalities are those that:

- Require concomitant therapy
- Require medical intervention
- Require change in study treatment
- Investigator considers clinically significant for any reason

The Investigator will record the grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition. Laboratory AEs should be recorded using only one event term per event such as thrombocytopenia for low platelet count but not as both (thrombocytopenia and low platelet count).

A positive COVID-19 (SARS-CoV-2) test should always be considered clinically significant. Reporting of COVID-19 infections is described in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. Additional Laboratory Reporting Guidelines

Extra attention should be given to reporting all Grade 3 and 4 platelet and neutrophil counts. They must be:

- Collected and reported during the study period and the EOT visit;
- Ongoing Grade 3 and 4 platelet and ANC values at the time of the EOT visit are to be followed until resolution (≤ Grade 2), or stabilization, or initiation of a subsequent therapy;
- All ANC and platelet counts collected during the treatment period and until the EOT visit, i.e. both those collected at protocol specified time points and any additional time points (unscheduled assessments), must be reported in the eCRF and if applicable also as an AE/SAE;
- All ANC and platelet counts associated with an SAE regardless of the nature of the event, must be reported in the details of the SAE report;
- Supportive care such as platelet transfusions and G-CSF given for an AE or prophylactic reasons must be reported in the eCRF and if applicable also in the SAE report.
  Other laboratory values from non-protocol specified laboratory assessments considered clinically significant by the investigator, as defined in Section 8.4.7 or support understanding the patient's condition related to an AE or SAE must be recorded in the eCRF.

8.5. Treatment of Overdose

For this study, any dose of melflufen greater than 30 mg per cycle (including 30 mg administered < 28 days [+/-3day window]) will be considered an overdose.

The ponsor recommends supportive treatment with close observation of CBC in particular to platelets and neutrophil count in case of an overdose. Prophylactic measures and/or treatment of thrombocytopenia or neutropenia should be considered in the event of an overdose. Refer to concomitant therapy Section 6.5 for further guidance on antimicrobial prophylaxis in the case of severe neutropenia.

In the case of an overdose of daratumumab or dexamethasone, please refer to the IB, Product information and SmPC, respectively for guidance.

In the event of an overdose (melflufen, dexamethasone or daratumumab), the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities until they no longer can be detected systemically (return to ≤ Grade 3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6. Pharmacokinetic assessments

8.6.1. Pharmacokinetic assessment melphalan

PK samples will be collected in patients in Arm A. Three plasma samples for determination of melphalan concentrations will be drawn in each of the first two melflufen treatment cycles (Cycle 1 and 2), at the following time points according to Table 8-1:

Table 8-1 PK sampling timepoints melphalan

	Cycle 1 and 2
Sample 1, timepoint	5-10 minutes after the end of melflufen infusion
Sample 2, timepoint	1 hour after the end of melflufen infusion (+/- 5 min window allowed)
Sample 3 timepoint	2-4 hours after the end of melflufen infusion (as late as possible within the time frame)

All PK samples must be drawn peripherally and **not** from the central catheter. Refer to the Laboratory Manual for details on sample collection and processing.

8.6.2. Pharmacokinetic assessment daratumumab

All PK samples must be drawn peripherally and **not** from the central catheter. Refer to the Laboratory Manual for details on sample collection and processing.

Daratumumab PK samples will be collected in patients in Arm A and Arm B at pre-dose on Day 1 of Cycle 1, 3, 7, and 12, on Day 4 in Cycles 1 and 3 and at End of treatment visit and at 8 weeks after the last dose of daratumumab. Daratumumab PK samples will not be collected in patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone after they have initiated their new treatment regimen.

8.7. Immunogenicity

8.7.1. Immunogenicity of Daratumumab

Serum samples to be collected in both treatment arms at pre-dose on Day 1 of Cycle 1, 7, and 12, at the EOT and at visit 8 weeks after the last dose of daratumumab. It will be the same blood draw as for daratumumab PK. Daratumumab immunogenicity samples will not be collected in patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone after they have initiated their new treatment regimen.

Refer to the Laboratory Manual for details on sample collection and processing.

8.7.2. Immunogenicity of Recombinant Human Hyaluronidase

Plasma for rHuPH20 immunogenicity will be collected in both treatment arms at pre-dose on Day 1 of Cycles 1, 7, and 12, at the EOT and at visit 8 weeks after the last dose of daratumumab. Plasma for rHuPH20 immunogenicity will not be collected in patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone after they have initiated their new treatment regimen.

Refer to the Laboratory Manual for details on sample collection and processing.

8.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9. Genetics

Cytogenetic characterization of MM by karyotyping and iFISH and biomarker analysis (MRD assessment and DNA/RNA sequencing) described in Appendix 2Appendix 2Appendix 2 are planned to be conducted. No other genetic analysis will be performed as part of this study.

8.10. Biomarkers

Collection of samples for biomarker research is a part of the study and the following samples are required and will be collected from all patients in this study as specified in the SoA and in Table 8-2. Samples are planned to be tested to identify biomarkers that predict the treatment outcome and detect patient subgroups that are likely to respond to the study drug(s). Analysis such as outlined in Table 8-2 and Sections 8.10.1, 8.10.2 and 8.10.3 are planned but may not be conducted if deemed as obsolete during later stages of the study; other exploratory analyses may be added based on emerging new findings.

Table 8-2 Summary of biomarker assessments

Marker	Tissue	Timepoint	Method	Purpose of analysis
Minimal Residual Disease (MRD)	Bone Marrow	- Screening - At the time of response (CR and VGPR)	Next Generation Sequencing	Indicator of clinical outcomes and response to therapy.
Novel biomarkers including expression of aminopeptidases/esterases	Bone Marrow	- Screening - At the time of response (CR and VGPR) - At the time of disease progression	DNA/RNA sequencing	Identify novel biomarkers that may predict response.
	Blood	- Pre-dose, Cycle 1 day 1. - At the time of response (CR and VGPR) - At the time of disease progression	Circulating tumor cells DNA/RNA sequencing	
Biomarkers for myeloma-related bone disease: TRACP-5b Total RANK PINP Osteopontin Osteocalcin IL-6 IL-10 CTX Bone ALP	Blood (serum)	- Pre-dose, Day 1 of all cycles - End of treatment visit - During PFS-FU	ELISA	Surveillance of therapy effects on bone disease progression.
Immunoprofiling	Blood	-Pre-dose Cycle 1 Day 1 - Cycle 6 Day 1 - End of treatment visit	ELISA/flow cytometry	Identify biomarkers of biologic activity of the therapy in specific subpopulations of immune cells.

Samples may be stored for a maximum of 5 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to study treatment.

8.10.1. Minimal Residual Disease (MRD) assessment

Minimal Residual Disease (MRD) refers to the number of malignant cells that remain in a patient during and following treatment. It is a reliable indicator of clinical outcomes and response to myeloma therapies (Kumar et al 2016). To follow the minimal residual disease in the treated patients, a diagnostic assay is used which utilizes next generation sequencing (NGS) to identify frequency and distribution of clonal sequences consistent with a malignant cell population in the bone marrow samples. MRD will be determined by detection and tracking of clonal rearrangement of immunoglobulin heavy chain variable region (IGH FR1/FR2, FR3, and IGK) using most up to date Illumina platform at the time of the analysis with currently verified minimum sensitivity of 10^{-5} and achievable sensitivity of 10^{-6}.

Bone marrow aspirate, 1 mL, should be taken at screening and 3 mL at response (CR and VGPR) and sent to the central laboratory for analysis. Refer to the Laboratory Manual for complete details on sample collection, processing, storage and shipping.

8.10.2. DNA/RNA Sequencing

Sequencing studies are planned to be conducted using next generation sequencing. This will enable the evaluation of changes in DNA/transcriptome profiles that may correlate with biological response to the treatment (Jang et al. 2019). Aminopeptidases/esterases expression levels will be investigated in order to find correlations with observed response, in addition, it may be possible to identify novel biomarkers associated with response or disease progression.

Due to possible challenges in obtaining an adequate amount of bone marrow aspirate for DNA/RNA analysis, an alternative experimental approach is taken utilizing single-cell RNA sequencing of circulating tumor cells, though minimally-invasive alternative, for monitoring tumor burden and response to treatment (Bustoros et al. 2017).

For this approach 10 mL of blood will be collected and sent to the central laboratory for analysis, at the following timepoints (see Laboratory Manual for details):

- Pre-dose, Cycle 1 Day 1
- At the time of response (CR or VGPR)
- At the time of disease progression (at EOT Visit or during PFS follow-up)

Bone marrow aspirate and blood samples will not be used for other reasons than the identification of novel biomarkers by sequencing analysis. Samples may be stored for up to 5 years.

8.10.3. Biomarkers for myeloma-related bone disease

Biomarkers that reflect the activity of the cell types in the bone marrow microenvironment contributing to myeloma-related bone disease are suitable for surveillance of response, treatment effects, and disease progression (Bhutani et al. 2015).

Biomarkers planned to be analyzed, all previously reported increased in myeloma patients and correlated with the extent of bone disease, include:

- TRACP-5b
- PINP
- Total RANK
- Osteopontin
- Osteocalcin
- IL-6/IL-10
- CTX/bone ALP ratio

A blood sample, 7.5 mL, for serum isolation will be collected, and sent to the central laboratory for analysis, at the following timepoint (see Laboratory Manual for details):

- Day 1 of all treatment cycles
- EOT Visit
- PFS-FU Visits

Biomarkers will be measured in undiluted serum using a validated enzyme-linked immunosorbent assay (ELISA) according to the standard manufacturer's protocols. Serum samples will not be used for other reasons than to evaluate the performance of the biomarkers in the prediction of therapy response. Samples may be stored for up to 5 years.

8.11. Immunophenotyping/Immunoprofiling

The goal of the biomarker analysis is to evaluate the pharmacodynamics and aid in evaluating the drug-clinical response relationship.

Evaluation of blood biomarkers may provide evidence for biomarkers of biologic activity of melfulfen+daratumumab in patients with MM. Flow cytometry will be performed to immunophenotype T-cells and to characterize changes in CD38+ Tregs and CD38+ MDSCs in response to treatment. These cells have been shown to express CD38 and can be depleted by daratumumab in patients with multiple myeloma (Krejcik 2016) and play a role in daratumumab's mechanism of action.

Serum samples for immunoprofiling will be collected in both treatment arms pre-dose on Day 1 of Cycle 1, Day 1 of Cycle 6, and at the EOT visit.

8.12. Patient Reported Outcome assessments

Patient reported outcome assessments include EORTC QLQ-C30, EQ-5D-3L, BPI-SF, NRS for measure of bone pain and use of health services and hospitalization. The patient should complete the questionnaires prior to any procedures on the day of the visit and prior to any study visit activities (tests, examination or treatment). The questionnaires should be administered even if the treatment is not given. If the patient wishes to have the questions read out loud and then answer orally, and the study personnel write the answers on the questionnaires, this is acceptable.

For pain assessment the BPI-SF should be completed first and only if the patient confirms pain has been experienced, the NRS for measure of bone pain should be completed. The NRS for measure of bone pain is a non-validated questionnaire about experienced muscle pain and bone pain.

Table 8-3 Timepoints for patient reported outcome assessments

Timepoint	**EORTC QLQ-C30** **EQ-5D-3L**	**BPI-SF**	**NRS for measure of bone pain** (in case patient indicated pain in BPI-SF)	**Health services and hospitalization**
Screening				X
Day 1, All cycles	X	X	X	X
Day 15, Cycle 1-3		X	X	
End of treatment visit	X	X	X	X
Follow Up until Start of new Treatment	X	X	X	X
Crossover **(Refer to SoA 10.3)**	X	X	X	X

If PD/EOT and start of next anti-myeloma treatment occur at the same time, only one assessment is required at that time. If the EOT is for a reason other than PD, the assessments should be continued, on any on-site visit, each month until PD and/or start of new treatment. If the new treatment starts during OS follow-up an additional assessment must be completed at that time. See Section 8.1.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective with this study is to show superiority of PFS in patients treated with melflufen and dexamethasone in combination with daratumumab (Arm A) compared to daratumumab alone (Arm B). 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 9.4.5 for a description of multiplicity adjustments.

9.2. Sample Size Determination

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 two survival curves and the parameter assumptions presented in Table 9-1

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) 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 9-1 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).

9.3. Populations

For purposes of analysis, the following populations are defined:

Analysis Population	Description
Enrolled Population	Includes all screened patients, i.e. patients having completed assessments and procedures during screening as outlined in Section 8.1.1. The Enrolled population 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 melflufan 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. The PPAS will be used for sensitivity analyses of selected efficacy variables as described later in the SAP. 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.

9.4. Statistical Analyses

The statistical analyses outlined in this section will be further described in the Statistical Analysis Plan (SAP). Statistical analyses will be performed using programming in SAS® version 9.4 or higher, and will be presented as summary tables, figures, and data listings.

For continuous variables, the number of patients with non-missing data (n), mean, standard deviation, median, minimum, and maximum will be summarized. For discrete data, the frequency and percent distribution will be summarized. Graphical methods will be used, as appropriate, to illustrate study endpoints. Individual patient data recorded on the eCRFs and any derived data will be presented by group and patient in data listings.

9.4.1. Efficacy Analyses of the 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. 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.

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% CI.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. 95% CI will be based on the log(-log(survival)) distribution.

9.4.2. Efficacy Analyses of Key Secondary Endpoints

The analysis of the key secondary efficacy endpoints will be performed using statistical methods with multiple control describe in section 9.4.5

There are two key secondary endpoints:

1. ORR (proportion of patients who achieve a best confirmed response of stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR) or Partial Response (PR)).
2. 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).

ORR 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. DOR 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.

9.4.3. Efficacy Analyses of other Secondary Endpoints

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.

Time-to-event analyses (DOCB, TTR, 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.

9.4.4. Efficacy Analyses of Exploratory Endpoints

Response rates (CR and PR) 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 factors.

Time-to-event analyses (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. Stratified log-rank test will be applied for PFS-2 the same way as for the primary PFS analysis.

The number and percentage of patients with MDR or not in patient achieve CR or better will be presented.

For EQ-5D-3L the number and percentage of patients for each score within the dimension will be presented, including shift table from baseline to post-baseline assessments.

Changes in parameters for QoL (QLQ-C30 summary score, each scale of the EORTC QLQ-C30, EQ-5D-3L utility index, each dimension of the EQ-5D-3L, EQ-5D-3L VAS, BPI-SF and NRS) will be analyzed using repeated-measures mixed-models. Changes in QoL parameters will be dependent variables, treatment arm will be fixed effect, and treatment cycle will be repeated effect. QoL parameters and additional fixed effects will be further described in the SAP.

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 and CBR) and time to event (DOR, DOCB, TTR, TTP, TTNT and OS)) will be presented descriptively with 95 % confidence interval. Time to event will be calculated from date of first treatment after crossover.

9.4.5. 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 0.05. If this comparison is not statistically significant, then the comparison of key secondary efficacy endpoints will be considered nominal, descriptive and exploratory. The full procedure will be described in the SAP.

9.4.6. Analyses of Pharmacokinetic Data

PK parameters for melphalan will be derived using non-compartmental analysis in Phoenix WinNonLin®.Statistical analysis of pharmacokinetic (PK) parameters will be performed of the parameters maximum observed concentration, Area under the concentration versus time curve from 0 h to infinity and elimination half-life dependent variables. Results will be described using descriptive statistics and correlations analyses with patient factors.

PK parameters for daratumumab will be analyzed descriptively.

9.4.7. Safety Analyses

Study treatment administration, including duration of exposure, total dose, dose modifications and all AE reporting will be summarized for each group separately, and also separately for patients in Arm B who crossover to treatment with melflufen, daratumumab and dexamethasone.

Each reported AE term will be mapped to a preferred term (PT) and a system organ class (SOC) using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The summaries of adverse events (AEs) will be based on TEAEs. TEAEs are defined as AEs that start on or after the first day of study treatment is administered 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.

The number (%) of patients experiencing TEAEs will be summarized by MedDRA SOC and PT. The denominator for the percentage will be based on the number of patients in the Safety analysis set. 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 will be summarized in the same way.

Summaries of TEAEs and treatment-related AEs will be provided according to maximum toxicity grade. Grade 3 or higher TEAEs and treatment-related AEs, serious AEs, and TEAEs resulting in permanent discontinuation of study treatment will be provided.

Grade 3 and 4 thrombocytopenia and neutropenia will be evaluated to determine their frequency, duration, relationship to treatment and associated significant AEs.

Actual value and change from baseline for all hematology, serum chemistry, and coagulation parameters will be summarized at each scheduled visit. Selected laboratory test results will be assigned toxicity grades using CTCAE 5.0. Shift tables assessing the toxicity grade at baseline versus worst toxicity recorded on study will be presented. A listing of all Grade 3 or higher laboratory values will be provided.

Actual value and change from baseline for vital sign results, including weight, blood pressure, pulse, and temperature, will be summarized at each scheduled visit. Any clinically significant values will be reported by the investigator as AEs.

9.4.8. Other Analyses

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

Biomarker exploratory analyses will be described and presented separately from the main clinical study report (CSR). The following subgroups will be analyzed separately:

- 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

9.4.9. Handling of dropouts and missing data

The SAP will describe how dropouts and missing data impact the calculation of the time to event variables. Missing data will not be estimated or carried forward for any of the other summaries or analyses. If only a partial date is available and is required for a calculation (e.g. time since diagnosis, determination of whether a medication is concomitant or an AE is treatment-emergent), the date will be imputed. Details of methods of imputation will be provided in the SAP.

9.5. Interim Analyses

No interim analyses will be performed.

9.5.1. Data Monitoring Committee

Safety and tolerability will be reviewed regularly during the study. This review will be done by an independent Data Monitoring Committee (DMC), and will be based on aggregate data summaries where the randomized treatment allocation is disclosed. Access to this data will be restricted to the members of DMC. Scope of work, procedures, roles and responsibilities for the DMC is described in a separate DMC charter to ensure independence and minimize potential bias in the evaluation of unblinded data. The DMC can recommend continuing the study, with or without modifications, or stop the study based on benefit/risk concerns.

9.5.2. Independent Review Committee

All response assessments, including PD will be assessed by an Independent Review Committee (IRC) using the IMWG response criteria. The IRC members will be blinded to all treatment data (including investigator response) and perform their reviews in closed-meeting sessions. The IRC members will be provided with patient-level data summaries where treatment is blinded. Scope of work, procedures, roles and responsibilities for the IRC is described in a separate IRC Charter to ensure independence.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and melflufen by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patient must be informed that their participation is voluntary. Patient or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

All patients must sign an (IRB/IEC/REB)-approved informed consent form within 28 days of enrollment and prior to any study related procedures. A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

Patients in Arm B who are eligible to crossover to treatment with melflufen, daratumumab and dexamethasone must sign an IRB/IEC/REB approved informed consent before the new treatment is started.

10.1.4. Data Protection

Patient will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Oncopeptides AB assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

The completed original eCRF is the sole property of the Sponsor and should not be made available in any form to third parties (except to authorized representatives of appropriate regulatory authorities) without written permission from the Sponsor.

10.1.6. Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic CRF (eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The data collection tool for the study will be a validated, internet based, electronic data capture system (EDC) software system called RAVE.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Risk identification and evaluation will be conducted on an ongoing basis by the Sponsor and CRO, as these are key to managing and mitigating risks.

10.1.7. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Definition of what constitutes source data can be found in the site-specific Source Data Location List.

10.1.8. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and if applicable a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is a reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, clinical trial agreement, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- The results of this study will be published and potentially be presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publications of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- The investigators agree to submit any subsequent manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1will be performed.
- Investigators must document their review of each laboratory report.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Please refer to the Laboratory Manual for details on sample collection, processing and shipment.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- During the study, blood and bone marrow will be drawn at the study visits. Limited volumes will be taken at each single occasion. Approximate, maximum volume per sample type and study visit have been listed in Table 10-2. See Section 8.1 for sample collection timepoints.

Table 10-1 Protocol-Required Laboratory Assessments

Laboratory	Laboratory Assessment	Parameters

Local Laboratory	Hematology	• Platelet Count
		• Red Blood Cell (RBC), Erythrocytes Count
		  ○ Hemoglobin
		  ○ Hematocrit
		• RBC, Erythrocytes Indices:
		  ○ Mean Corpuscular Volume (MCV)
		  ○ Mean Corpuscular Hemoglobin (MCH)
		  ○ % Reticulocytes
		• White blood Cell (WBC), Leukocytes count with Differential:
		  ○ Neutrophils
		  ○ Lymphocytes
		  ○ Monocytes
		  ○ Eosinophils
		  ○ Basophils

Laboratory	Laboratory Assessment	Parameters	
	Clinical Chemistry	• Alanine Aminotransferase (ALT) also known as Serum Glutamic-Pyruvic Transaminase (SGPT) • Albumin • Alkaline Phosphatase (ALP) • Aspartate Aminotransferase (AST), also known as Serum Glutamic-Oxaloacetic Transaminase (SGOT) • Blood Urea Nitrogen (BUN) or Urea • Calcium • Chloride • Creatinine (in serum) • Creatinine Clearance (by Cockcroft-Gault formula) • Glucose (fasting at baseline) • Lactase Dehydrogenase (LDH) • Magnesium • Phosphate • Potassium • Sodium • Total Bilirubin • Total Protein • Uric Acid	
Local Laboratory	Blood type and screen	Interference with cross-matching	Prior to daratumumab administration.
		Red Blood Cell Antibody screening	
	Hepatitis B/C and HIV screen	Hepatitis B surface Antigen	
		Anti - Hepatitis B core Antigen	
		Anti - Hepatitis B surface Antigen	
		Anti-HCV antibody	
		Anti-HIV1/2 antibody/antigen	
	Pregnancy test	Serum or urine human Chorionic Gonadotropin (hCG) pregnancy test	
	Coagulation	• Prothrombin Time (PT)	

Laboratory	Laboratory Assessment	Parameters	
		• International Normalized Ratio (INR)	
	Urinalysis	Specific gravity	
		pH	By dipstick.
		Glucose	
		Protein	
		Blood	
		Ketones	
		Microscopic examination	If blood or protein is abnormal.
Central Laboratory	Other blood tests	β2-microglobulin	
	M-protein assessment - 24 hr urine sample	Urine Protein Electrophoresis (UPEP)	
		Urine Immunofixation (U-IFE);	At screening and if UPEP are not detectable and to confirm CR.
	M-protein assessment - Serum	Serum Protein Electrophoresis (SPEP)	
		Serum Immunofixation (S-IFE)	At screening and if SPEP are not detectable and to confirm CR.
		Free Light Chain (SFLC) • Kappa • Lambda • Ratio	
		DIRA	For patients with IgG kappa multiple myeloma with an SPEP: - ≤0.2 g/dL on 2 or more consecutive cycles **or** - No detectable M-protein, but persistently positive IFE for IgG kappa on 2 or more occasions
		Quantitative Immunoglobulins • IgA • IgD • IgE • IgG	- To be repeated at Day 1 in all cycles for IgA and IgD myeloma.

Laboratory	Laboratory Assessment	Parameters	
		• IgM	
	Bone Marrow tests	% plasma cells	
		Cytogenetics	By karyotyping and interphase Fluorescence In-Situ Hybridization (iFISH). Mandatory iFISH probes include t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q).
		Morphology	
		MRD	By Next Generation Sequencing.
		DNA/RNA Sequencing	
	Pharmacokinetic blood test melphalan		For patients in Arm A (not applicable after crossover).
	Pharmacokinetic blood test daratumumab and daratumumab immunogenicity		For patients in Arm A and Arm B (not applicable after crossover).
	rHUPH20 immunogenicity blood test		For patients in Arm A and Arm B (not applicable after crossover).
	Immunoprofiling samples whole blood		For patients in Arm A and Arm B (not applicable after crossover).
	Biomarker blood test	Biomarkers for myeloma-related bone disease • TRACP-5b • Total RANK • Osteopontin • Osteocalcin • IL-6/IL-10 • CTX/bone ALP ratio • PINP	For patients in Arm A and Arm B (not applicable after crossover).

Laboratory	Laboratory Assessment	Parameters	
		DNA/RNA Sequencing	Circulating tumor cells and/or sequencing of the circulating free tumor DNA.

Table 10-2 Blood and Bone Marrow Volumes

Assessment	**Screening Days -21 to -1**	**Regimen A and B, All Cycles (except where specified)**					**End of Treatment**	**8 weeks after last dose of daratumumab**	**PFS-FU**	**OS and PFS2-FU**
		Day 1	Day 4	Day 8	Day 15	Day 22				
Pregnancy test, WOCBP only	X	X					X	X	X	
RBC typing and antibody screening	X									
Hematology	X	X		(X)	X	(X)	X			
Coagulation	X									
DNA/RNA sequencing in blood		X					(X)		(X)	
Biomarkers for myeloma related bone disease in blood		X					X		X	
Chemistry	X	X					X		(X)	
Hepatitis B, C and HIV screen	X									
Bone marrow aspiration	X	(X)					(X)		(X)	
M protein assessment	X[a]	X					X		X	
Pharmacokinetic samples melphalan, Arm A only		(X)								

Assessment	**Screening Days -21 to -1**	**Regimen A and B, All Cycles (except where specified)**					**End of Treatment**	**8 weeks after last dose of daratumumab**	**PFS-FU**	**OS and PFS2-FU**
		Day 1	Day 4	Day 8	Day 15	Day 22				
Pharmacokinetic samples daratumumab		(X)	(X)				X	X		
Immunogenicity samples daratumumab		(X)					X	X		
Immunogenicity samples rHUPH20		(X)					X	X		
Immunoprofiling samples whole blood		(X)					X			
Approximate Blood Volume per visit (mL)	**50**	**75**	**5**	**15**	**15**	**15**	**75**	**10**	**30**	**15**
Approximate Bone Marrow Volume per visit (mL)	**10**	**(10)**					**(10)**		**(10)**	

(X) if indicated
a) Including β2 Microglobulin

10.3. Appendix 3: Optional crossover for patients in Arm B to treatment with melflufen, dexamethasone and daratumumab

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.

Study Treatment after crossover:**Melflufen 30 mg (i.v.)**	**Daratumumab 1800 mg (s.c.)[b, c]**	**Dexamethasone (p.o.)[a]**
All cycles: Day 1	**Dosing Schedule at time of disease progression to be continued:** **If Cycle 1 and 2:** Days 1, 8, 15 and 22 **If Cycle 3 to 6:** Days 1 and 15 **If Cycle 7+:** Day 1	40 mg weekly for patients < 75 years of age 20 mg weekly for patients ≥75 years of age

a) For additional details on dexamethasone administration see Section 6.1.3.

b) Premedication should be administered to prevent infusion/administration related reactions (see Section 6.1.4.1.1).

c) Post-medication may be administrated to minimize administration related reactions according to Section 6.1.4.1.2.

10.3.1. Criteria for initiation of treatment following crossover

Prior to initiation of treatment with melflufen, dexamethasone and daratumumab, patients who crossover must continue to meet eligibility criteria and the entry criteria as follows:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol;
2. Confirmed progressive disease. There should be a documented PD according to the IMWG-URC guidelines (Kumar et al.2016) to be confirmed on two consecutive assessments (if PD due to increase in M-protein), and verified by the Medical Monitor prior to treatment discontinuation, see Appendix 8.
3. Adequate organ function with the following laboratory results during initiation visit/EOT Arm B (within 28 days) and immediately before study treatment administration on Cycle 1 Day 1 following crossover:
   - ANC ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L)

- Platelet count ≥ 50,000 cells/ mm^3 (50 x 10^9/L) (without transfusion during the previous 5 days to initiation of therapy). Thrombopoietin receptor agonists are not permitted, see Section 6.5.3.

4. For patients who crossover, treatment with melflufen, dexamethasone and daratumumab must be started within 56 days from the last daratumumab dose in Arm B.
5. All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except peripheral neuropathy Grade 1 without pain, alopecia and fatigue ≤ Grade 2).

6. a) Male patients: Male patient who agrees to use contraception as detailed in this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period.

   b) Female patients: A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
   i. Not a woman of childbearing potential (WOCBP) **or**
   ii. A WOCBP who agrees to follow the contraceptive guidance in the protocol during the treatment period and for at least 3 months after the last dose of study treatment.

10.3.2. Criteria Day 1, Subsequent cycles

- ANC must be ≥ 1,000 cell/mm^3 (1.0 x10^9/L). For administration of growth factors, see Section 6.6.1.2.
- All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except peripheral neuropathy Grade 1 without pain, alopecia and fatigue ≤ Grade 2).
- Absence of daratumumab IRR that require discontinuation (Grade 4 or Grade 3 on three occurrences in the previous cycle, see Section 6.6.3.3.1).
- Platelet count:
  - Platelet count must be ≥ 50,000 cell/mm^3 (50.0 x 10^9/L) (platelet transfusions not recommended within ≤ 5 days of dosing (see Section 6.5.2). For patients who have discontinued melflufen but remain on daratumumab and dexamethasone the platelet count must be ≥ 25,000 cell/mm^3 (25.0 x 10^9/L).

If these criteria are not met on the scheduled Day 1, the new cycle should be held, and patients should be re-evaluated weekly. Refer to Section 6.6.3 for guidelines on dose modification due to drug related toxicity.

The maximum amount of time for which study treatment may be held due to drug related toxicity is 28 days from a scheduled Day 1 (Day 57). If study treatment is not administered for more than 28 days due to drug related toxicity, the patient will be removed from the study treatment and enter follow up phase. If the patient was clearly benefiting from treatment, the patient may be

able to continue treatment at the Investigator's discretion and in consultation with the Medical Monitor, after resolution of the AE.

10.3.3. Dose Modification and Reduction Steps

Dose reduction steps for melflufen and dexamethasone are outlined in Section 6.6.2.
There are no dose reduction steps for daratumumab.
Dose modifications for toxicity and management of infusion related reactions are outlined in Section 6.6.3.

10.3.4. Study Procedures

Patients in Arm B with confirmed disease progression may receive melflufen, dexamethasone and daratumumab treatment if they are willing and eligible per criteria listed in 10.3.1. All patients who crossover must sign and date an IRB/IEC/REB approved informed consent form within 28 days of initiating treatment with melflufen, dexamethasone and daratumumab and prior to any study related procedure. After providing written informed consent, the patients will be evaluated for eligibility.

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.

10.3.4.1. Crossover initiation visit

The EOT visit after completion of Arm B treatment could be combined with the crossover initiation visit and should be performed within 28 days of last dose of daratumumab. The following assessments will be performed in addition to those completed during the EOT visit:

- Sign and date an IRB/IEC/REB approved informed consent form for the crossover.
- Evaluate criteria per Section 5.1 if patient is eligible for initiation of melflufen and dexamethasone treatment in addition to the current daratumumab dosing schedule.
- β2-microglobulin
- Concomitant medications review
- AE monitoring

10.3.4.2. Procedures Day 1 during crossover

The following study procedures will be performed during active study treatment at the times specified. All study procedures are applicable at all cycles unless otherwise specified.

- Criteria for initiation of therapy should be fulfilled, see Section 6.6.1.
- PRO assessments (EORTC QLQ-C30 and EQ-5D-3L), prior to any study visit activities (tests, examination or treatment). The questionnaires should be administered even if the treatment is not given, see Section 8.12.
- PRO pain assessments (BPI-SF and NRS for measure of bone pain), prior to study visit activities (tests, examination or treatment). BPI-SF should be completed first and if patient has experienced pain, the NRS for measure of bone pain should be completed. The questionnaires should be administered even if the treatment is not given, see Section 8.12.

- Physical examination; including assessment for extramedullary myeloma. Plasmacytomas that can be followed by physical examination should also be evaluated each cycle with measurements documented in the source documents.
- Vital signs, including blood pressure, pulse, respiratory rate, temperature, should be assessed before melflufen dose as well as before and after daratumumab dosing. Weight should be assessed prior to melflufen dose.
- ECOG performance status
- Pregnancy test; only for WOCBP
- Blood tests:
    - Hematology: CBC with differential and platelet count.
    - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), serum creatinine, estimated creatinine clearance (by Cockcroft-Gault Formula), glucose (non-fasting), ALT (SGPT), AST (SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH).
- Bone marrow aspiration; at the time of CR/VGPR, the below samples should be obtained in the following order and sent to the central laboratory for analysis. See Laboratory Manual for additional information.
    1. % plasma cells and morphology including immunohistochemistry
    2. 3 mL for MRD assessment
    3. DNA/RNA sequencing
- Concomitant medications review
- M-protein assessments described in Section 8.2.1 is planned pre-dose Day 1 of each cycle (day 29 of prior cycle) and with assessment of myeloma response from Cycle 2. If treatment is delayed, an assessment should still be made at day 29 and should be repeated prior to next cycle if the delay is 2 weeks or longer, and to confirm any response or PD.
- Extramedullary myeloma assessment; Known or suspected plasmacytomas should be assessed, using the same method as at screening, every 2 cycles up to disease progression.
- Skeletal X-ray or low-dose CT scan; as clinically indicated.
- Administration of study treatment; see Section 6.1.
- Use of health services and hospitalization
- AE monitoring

10.3.4.3. Procedures Day 8, 15 and 22 visits

If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then Day 8 and Day 22 will not be required for the respective cycle.

- Physical examination: symptom directed as needed during treatment.
- Vital signs; including blood pressure, pulse, respiratory rate, temperature, to be assessed before and after each daratumumab infusion (see Section 6.1.4 for daratumumab administration schedule).
- Blood tests:

  - Hematology: CBC with differential and platelet count. If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then Complete Blood Count assessments may be excluded at Day 8 and Day 22.
- Concomitant medications review
- Administration of study treatment, see Section 6.1.
- AE monitoring

10.3.4.4. Procedures after active study treatment

Patients will be treated until progressive disease (confirmed PD should be verified by Medical Monitor prior to discontinuation of therapy), unacceptable toxicity, consent withdrawal, or if the patient/treating physician determines it is not in the patient's best interest to continue.

An EOT visit will be scheduled within 30 days of the last dose of study drug. Patients who discontinue therapy for reasons other than disease progression will enter PFS follow-up. Patients who discontinue therapy for disease progression will enter the OS follow-up.

Patients with Grade 3 or 4 thrombocytopenia or neutropenia should be followed until resolution to ≤ Grade 2 or start of subsequent therapy. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, not expected to resolve or the patient is lost to follow-up (as defined in Section 7.3).

Patients who withdrew consent for treatment will continue to be followed for disease progression and/or survival unless they explicitly withdraw consent for these procedures.

10.3.4.5. Procedures at End of Treatment Visit

EOT visit should be scheduled 30 days (accepted time window ±3 days) after last dose of study treatment or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle). For patients who are randomized but withdraw from study, for any reason, prior administration of any study drug, the EOT visit should be completed as soon as possible after decision to remove the patient from study (including withdrawal of consent to study treatment) has been made.

If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug, the EOT visit should occur as close as possible before the first dose of the new drug.

Patients progressing while on treatment, require 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC). The confirmed PD should be verified by the Medical Monitor prior to discontinuation of treatment. The second assessment must be a separate serum and urine sample. (If the second consecutive M protein sample can only be obtained after the start of subsequent therapy, it may be used as confirmation of PD).

- PRO assessments (EORTC QLQ-C30 and EQ-5D-3L), prior to any examination/procedure. If the EOT is for a reason other than PD, the assessments should be continued, on any on-site visit, each month until PD and/or start of new anti-myeloma treatment.
- PRO pain assessments (BPI-SF and NRS for measure of bone pain), prior to any examination/procedure. BPI-SF should be completed first and if patient has experienced

pain, the NRS for measure of bone pain should be completed. If the EOT is for a reason other than PD, the assessments should be continued, on any on-site visit, each month until PD and/or start of new anti-myeloma treatment.

- Physical examination; including and assessment for extramedullary myeloma.
- Vital signs; including weight, blood pressure, pulse, respiratory rate and temperature.
- ECOG performance status.
- Pregnancy test; only for WOCBP
- 12-lead ECG, Q-Tc interval to be assessed by Fridericia formula.
- Blood tests;
    - Hematology: CBC with differential and platelet count.
    - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), serum creatinine, estimated creatinine clearance) (by Cockcroft-Gault Formula), glucose (non-fasting), ALT (SGPT), AST (SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH).
    - Blood sample for DNA/RNA sequencing.

  See Laboratory Manual for additional information.
- M protein and myeloma response assessments, see Section 8.2.1.
- Bone marrow aspirate (BMA) should be collected to confirm CR/VGPR or if needed to document PD
- Extramedullary myeloma assessment; known or suspected plasmacytomas should be assessed until disease progression.
- Skeletal X-ray or low dose CT scan; as clinically indicated.
- Concomitant medications review.
- AE monitoring; Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EOT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, not expected to resolve or the patient is lost to follow-up (as defined in Section 7.3).
- Use of health services and hospitalization.

10.3.4.6. Procedures during Progression Free Survival follow-up in crossover

During the follow up, the below assessments should be recorded:

- PRO assessments (EORTC QLQ-C30 and EQ-5D-3L), should be completed monthly on any on-site follow-up visit until PD and/or start of new anti-myeloma treatment. If PD and start of next treatment occur at the same time, only one assessment is required at that time. If the new treatment starts during OS follow-up, an additional assessment must be completed at that time.
- PRO pain assessments (BPI-SF and NRS for measure of bone pain), should be completed monthly on any on-site follow-up visit until PD and/or start of new anti-myeloma treatment. If PD and start of next treatment occur at the same time, only one assessment is required at that time. If the new treatment starts during OS follow-up, an additional assessment must be completed at that time. BPI-SF should be completed first and if patient has experienced pain,

the NRS for measure of bone pain should be completed.
- Blood sample for DNA/RNA sequencing should be collected in case of disease progression. See Laboratory manual for additional information.
- Bone marrow aspirate (BMA) should be collected to confirm CR/VGPR or if needed to document PD
- Extramedullary myeloma assessment; Known or suspected plasmacytomas should be assessed every 2 months until disease progression.
- Skeletal X-ray or low dose CT scan; as clinically indicated.
- M protein and myeloma response assessment;
    - Monthly until confirmed disease progression or initiation of next anti-myeloma treatment, for patients who discontinue study treatment for reasons other than disease progression.
    - Confirmed disease progression requires 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC). The second assessment must be a separate serum and urine sample. If the second consecutive M protein sample can only be obtained after the start of subsequent therapy, it may be used as confirmation of PD.
    - The first assessment should be performed 4 weeks after the EOT visit. Serum calcium, albumin (corrected calcium) required if this is the presenting symptom of disease progression.
- Second primary malignancies follow-up.
- For WOCBP: Collect and record any result of a pregnancy home test performed at 8 and 12 weeks after last dose of daratumumab on the following PFS-FU if not done separately by phone. The 8 and 12-weeks pregnancy test can be taken at home, and site can contact the patient for follow-up by phone.
- Use of health services and hospitalization.

10.3.4.7. Procedures during Overall Survival follow-up in crossover

Following PFS, patients will be contacted every 3 months +/- 7 days for OS for 24 months. Follow-up may be completed by phone, email, site visit or other method of contact. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable.

- Subsequent therapy review;
    - Regimen (all individual drugs)
    - Start dates
    - If PD has not been confirmed prior to the initiation of subsequent therapy, the reason for the subsequent therapy should be documented.

OS will be captured every 3 months until a minimum of 24 months. Following 24 months, annual follow up of OS might be conducted, and information can then be captured outside the eCRF and as an addendum to the study report.

Table 10-3 **Schedule of Activities (SoA) Crossover Arm B**

Assessment Crossover	**Crossover initiation visit** **Day** **(-28 to -1**	**Regimen Crossover, All Cycles** (except where specified)				**End of Treatment Visit** [r]	**PFS - FU** [w]	**OS** [s]	**End of Study**
		Day 1	Day 8	Day 15	Day 22				
Visit Window		±3 days (except Cycle 1)	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Informed consent [a]	X								
Criteria for initiation of melflufen, daratumumab and dexamethasone treatment[b]	X								
Physical examination [c]		X	(X)	(X)	(X)	X			
Vital signs [d]		X	(X)	(X)	(X)	X			
ECOG performance status		X				X			
Pregnancy test [e]		X				X	X		
M protein assessment (and myeloma response assessment from Cycle 2) [f]		X				X	X		

Assessment Crossover	**Crossover initiation visit** **Day** **(-28 to -1**	**Regimen Crossover, All Cycles** (except where specified)				**End of Treatment Visit [r]**	**PFS - FU [w]**	**OS [s]**	**End of Study**
		Day 1	Day 8	Day 15	Day 22				
Visit Window		±3 days (except Cycle 1)	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
β2-microglobulin	X								
Hematology [g]		X	X	X	X	X			
Chemistry [h]		X				X	(X)		
Blood sample for DNA/RNA sequencing [t]						(X)	(X)		
Bone marrow aspiration [i]		(X)				(X)	(X)		
12- lead Electrocardiogram [j]						X			
Extramedullary myeloma (plasmacytoma) assessment [k]	X (only if not done at EOT)	(X)				(X)	(X)		
Lytic bone lesion assessment: skeletal X-ray or low-dose CT [l]	X (only if not done at EOT)	(X)				(X)	(X)		

Assessment Crossover	**Crossover initiation visit** **Day** **(-28 to -1**	**Regimen Crossover, All Cycles** (except where specified)				**End of Treatment Visit** [r]	**PFS - FU** [w]	**OS** [s]	**End of Study**
		Day 1	Day 8	Day 15	Day 22				
Visit Window		±3 days (except Cycle 1)	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Criteria for initiation of therapy/new cycle [m]		X							
PRO assessments (EORTC QLQ-C30 and EQ-5D-3L) [u]		X				X	X		
PRO Pain Assessments (BPI-SF, NRS) [x]		X				X	X		
Dexamethasone administration and review of patient compliance		X	X	X	X				
Melflufen administration		X							
Daratumumab administration according to treatment schedule		X	(X)	(X)	(X)				
Use of health services and hospitalization [v]		X				X	X		

Assessment Crossover	**Crossover initiation visit** **Day** **(-28 to -1**	**Regimen Crossover, All Cycles** (except where specified)				**End of Treatment Visit [r]**	**PFS - FU [w]**	**OS [s]**	**End of Study**
		Day 1	Day 8	Day 15	Day 22				
Visit Window		±3 days (except Cycle 1)	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Concomitant medications [n]	X→					→X			
AE monitoring [o]	X→					→X			
Subsequent therapy review [p]							X	X	
End of study information [q]									X

(X) Only if indicated (see footnotes and treatment schedule).

a) All patients who crossover must sign an (IRB/IEC/REB)-approved ICF within 28 days of initiation of treatment with melflufen, dexamethasone and daratumumab and prior to any study related procedures.

b) Patients are eligible to crossover if all the criteria specified in section 10.3.1 of Appendix 3 apply.

c) A physical examination, including assessment for extramedullary myeloma will be conducted at the crossover initiation visit/ End of Treatment (EOT) visit. A symptom directed physical examination will be conducted as needed during treatment period.

d) Vital signs including blood pressure, pulse, respiratory rate, temperature will be assessed at each dosing day before melflufen dose and before and after daratumumab dosing and at EOT visit. Weight will be assessed at Day 1 of each cycle and at EOT visit.

e) All WOCBP must have a negative serum urine pregnancy test prior to the initiation of therapy at each cycle. Pregnancy test also be taken at EOT visit, 8 weeks after last dose of daratumumab and at 12 weeks after last dose of daratumumab. The 8 and 12-weeks urine test can be taken at home, and site can contact the patient for follow-up by phone.

f) SPEP, UPEP, serum and urine Immunofixation ((IFE) if SPEP or UPEP are not detectable and to confirm a CR), quantitative immunoglobulins (Igs) and SFLC assay (only required if SPEP and UPEP are not measurable [UPEP is < 200 mg/24 hours and SPEP is < 0.5 g/dL]) are to be conducted at initiation, pre-dose Cycle 1 Day 1 and prior to each cycle even if treatment is delayed. Quantitative Igs need to be repeated for patients with IgA or IgD myeloma for all response assessments. In the event treatment is delayed 2 weeks, response assessments are required to be repeated on the day the new cycle starts. If treatment is discontinued at or beyond ≥ 6 weeks (Day 43) the response assessments should be repeated on the day of the decision (or as soon as possible ≥ 30 days after last dose of study drug) as part of the EOT visit. Daratumumab Interference Reflex Assay (DIRA) test should be conducted in patients with IgG kappa MM with SPEP
   - ≤0.2 g/dl on 2 or more consecutive cycles
   - OR
   - at zero, but persistently positive IFE for IgG kappa on 2 or more occasions

g) Hematology: Complete Blood Count (CBC) with differential, and platelet count should be taken at each dosing day of all cycles, prior to initiation of therapy, and at the EOT visit. If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded at Day 8 and Day 22.

h) Chemistry should be taken at Day 1 of all cycles, at the EOT visit, prior to initiation of therapy. During PFS-FU serum calcium and albumin (corrected calcium) are required if evidence of PD.

i) Bone marrow aspirate (BMA) should be collected to confirm CR/VGPR or if needed to document PD. See Protocol and Laboratory manual.

j) A 12-lead ECG will be performed at initiation/EOT Arm B and at end of treatment of the crossover. Q-Tc interval to be assessed by Fridericia formula.

k) Known or suspected extramedullary myeloma (plasmacytomas) are to be assessed, with the same method at EOT of Arm B or at the crossover initiation visit if not done at EOT visit, and every 2 cycles up to disease progression.

l) Lytic bone lesion assessment: skeletal X-ray or low-dose CT scan should be performed when clinically indicated. Limited X-rays may be performed to confirm PD.

m) Evaluate if the treatment should be given, delayed, or held. See Protocol Section 6.6.1 and 10.3.2.

n) Concomitant medications and procedures: All blood products and medications within 21 days prior to first dose in Arm B until the EOT visit (end of crossover) should be recorded.

o) SAEs will be collected from signing of the ICF in the main study until 30 days after last dose of study treatment or initiation of subsequent therapy whichever occurs first. AEs will be collected from the start of study treatment until 30 days after the last dose of any study drug (melflufen, dexamethasone or daratumumab) or initiation of subsequent therapy whichever occurs first.

p) Subsequent therapy review including regimen (all individual drugs), start and stop dates. If PD has not been confirmed prior to the initiation of subsequent therapy, the reason for the subsequent therapy, best response, and date of disease progression per investigator review.

q) Patient study end date and primary reason for ending study will be collected.

r) EOT visit should be scheduled 30 days after last dose of study treatment or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle). If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug, the EOT visit should occur as close as possible before the first dose of the new drug.

s) Following confirmed disease progression or initiation of subsequent therapy, follow-up for overall survival status and second primary malignancies will take place every three months +/- 7 days for at least 24 months.

t) Blood sample for DNA/RNA sequencing should be collected at the time of disease progression.

u) EORTC QLQ-C30 and EQ-5D-3L should be completed prior to any procedures on the day of the visit and prior to being told anything related to health; the questionnaires should be administered even if the treatment is not given. See Protocol for details.

v) Use of health services and days of hospitalization will be completed by the patient on Day 1 of each cycle, at time of EOT visit and at follow-up until start of new treatment. To be completed prior to any procedures on the day of the visit and prior to being told anything related to health.

w) Schedule the first PFS assessment 4 weeks after the EOT visit. Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until documented disease progression or initiation of subsequent therapy. See Section 10.3.4.6.

x) BPI-SF and NRS for measure of bone pain. The patient should complete the questionnaires prior to any procedures, and prior to dexamethasone dosing, on the day of the visit and prior to being told anything related to health; the questionnaires should be administered even if the treatment is not given. BPI-SF should be completed first and if patient has experienced pain, the NRS for measure of bone pain should be completed. The questionnaires should be submitted to patients at Day 1 of each cycle. The questionnaires should also be submitted at the time of EOT visit, at the time of disease progression and at the time of starting a new treatment (day 1 of new treatment).

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events <u>Meeting</u> the AE Definition
• Any clinical significant laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be a SAE even if serious conditions are met.

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the assigned safety CRO, TFS, in lieu of completion of the SAE form and AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the assigned safety CRO. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the assigned safety CRO.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The investigator will make an assessment of severity/intensity for each AE and SAE reported during the study. Whenever possible, the CTCAE version 5.0 should be used to describe the event and for assessing the severity of AEs. Any events representing a change in the CTCAE Grade need to be reported on the AE eCRF. This includes any abnormal laboratory values that the investigator considers clinically significant see Section 8.4.7.

For AEs not adequately addressed in the CTCAE, the following severity grading should be used.

Severity	Description
Grade 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
Grade 2 – Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
Grade 4 - Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
Grade 5 – Fatal	Death

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (for melflufen and daratumumab) and Product Information/SmPCs (for Dexamethasone), in his/her assessment.

- Causality should be assessed using the following categories:

Causality	Description
Unrelated	Clinical event with an incompatible time relationship to investigational agent administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the investigational agent;
Possibly related:	Clinical event with a reasonable time relationship to investigational agent administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals;
Probably related	Clinical event with plausible time relationship to investigational agent administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- The investigator must appraise all abnormal laboratory results for their clinical significance. Only if an abnormal laboratory result is considered clinically significant, should it be reported as a treatment emergent adverse event. (See Section 8.4.7).
- There may be situations in which a SAE has occurred, and the investigator has minimal information to include in the initial report to the assigned Safety CRO. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the assigned Safety CRO.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the

assigned safety CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the assigned safety CRO within 24 hours of receipt of the information.

SAE Reporting to assigned Safety CRO, TFS; via Paper SAE reporting form

- Facsimile or email transmission of the SAE paper reporting form is the preferred method to transmit this information to the assigned Safety CRO via email to safety.report@oncopeptides.com or facsimile (local fax numbers are provided in the Investigator Site File)
- In rare circumstances and in the absence of facsimile or email equipment, notification of the CRA or Medical Monitor by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SAE report completion instruction in the Investigator Site File.

COVID-19 reporting

Positive COVID-19 tests are considered clinically significant and must always be reported as a separate AE.

AE verbatim: 'COVID-19 Test Positive'

Start date: Date the positive COVID-19 test was taken

Stop date: Date the subsequent negative COVID-19 test was taken.

COVID-19 related AEs shall be reported like any other non-serious or serious AE, i.e. as specific as possible.

If an AE is due to COVID-19, the verbatim shall start with 'COVID-19', e.g. "COVID-19 related pneumonia", "COVID-19 related renal failure".

Conclusion COVID-19 reporting:

Symptomatic COVID-19 shall be reported as two separate AEs:

One AE for the COVID-19 related event

One AE for the positive COVID-19 test ('COVID-19 Test Positive')

Asymptomatic COVID-19 (no clinical signs and symptoms and a positive COVID-19 test) shall be reported as two separate AEs:

One AE for the COVID-19 related event ('Asymptomatic COVID-19 infection')

One AE for the positive COVID-19 test ('COVID-19 Test Positive')

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are **not considered WOCBP**

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Lack of menses as a result of chemotherapy does not constitute menopausal status.

Contraception Guidance:

Male patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following from the start of the first dose of study drug until 3 months after the last dose of study drug,

- Are abstinent from penile vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10-4 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the treatment and for 3 months after last dose of study drug.

In addition, male patients must refrain from donating sperm for the duration of the treatment and for 3 months after last dose of study drug.

It is not known if melflufen may cause permanent sterility. Therefore, male patients may wish to consider cryo-preservation of semen before initiating therapy with melflufen.

Female patients

Female patients of childbearing potential are eligible to participate if they, from the start of the first dose of study drug until 3 months after the last dose of study drug, agree to use a highly effective method of contraception consistently and correctly as described in Table 10-4.

Table 10-4 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 3 months after the last dose of study treatment.

Pregnancy Testing:

- WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.
- Additional pregnancy testing is required on Day 1 of each cycle during the treatment period and at the End of Treatment visit and as required locally.
- Pregnancy testing should also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing should be performed at the local laboratory.

Collection of Pregnancy Information:

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported on the study specific Pregnancy reporting form. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE, considered reasonably related to the study treatment by the investigator, will be reported to the Sponsor or designee as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study patients , he or she may learn of an SAE through spontaneous reporting.

Male patients with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is receiving melflufen and for 3 months after the last dose of study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours from learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and the child will be forwarded to the Sponsor or designee. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female patients who become pregnant

- The investigator will collect pregnancy information on any female patient who becomes pregnant after start of study drug and until 3 months after last dose of study drug. Information will be recorded on the appropriate form and submitted to the Sponsor or

designee within 24 hours from learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Any female patient who becomes pregnant while on study drug will discontinue study treatment.

Pregnancy Reporting to assigned Safety CRO, TFS; via Paper Pregnancy Reporting Form
• Facsimile or email transmission of the Pregnancy paper Reporting Form is the preferred method to transmit this information to the assigned Safety CRO via email to safety.report@oncopeptides.com or facsimile (local fax numbers are provided in the Investigator Site File) • In rare circumstances and in the absence of facsimile or email equipment, notification of the CRA or Medical Monitor by telephone is acceptable with a copy of the Pregnancy data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Pregnancy CRF pages within the designated reporting time frames. • Contacts for Pregnancy reporting can be found in Pregnancy report completion instruction available in the Investigator Site File.

10.6. Appendix 6: Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	Description
0	Normal activity, fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but fully ambulatory, restricted in physically strenuous but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

10.7. Appendix 7: NCI CTCAE Version 5.0

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) v5.0. Publish Date: (v5.0: Nov 27, 2017)

- https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/
- https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

10.8. Appendix 8: IMWG Uniform Response Criteria

Response	IMWG criteria (Kumar et al., 2016)
Stringent Complete Response (sCR)	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
Complete Response (CR)	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis **or** • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hours. • In patients with only FLC disease, > 90% decrease in the difference between involved and uninvolved FLC levels is required.
Partial Response (PR)	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥ 90% or to < 200 mg/24 hours. • If the serum and urine M-protein are unmeasurable, a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30%. • In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal Response (MR)	• ≥25% but < 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50 – 89%, which still exceeds 200 mg/24 hours. • In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required.

EBMT Criteria	• No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response).
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease.
Progressive Disease (PD)	- Increase of > 25% from lowest response value in any one of the following: Serum M-protein (the absolute increase must be > 0.5 g/dL) and/or - Urine M-protein (the absolute increase must be > 200 mg/24 hours) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL. • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%). • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

All response categories require two consecutive assessments made at any time before the institution of any new therapy; all response categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not to be confirmed. For progressive disease, serum M-protein increases of ≥ 1 g/dL are sufficient to define relapse if starting M-protein is ≥ 5 g/dL.

IMWG clarification for coding PD: The 25% increase refers to M-protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

Daratumumab interference with determination of complete response

Daratumumab is a human IgG kappa mAb that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein. As daratumumab is a

monoclonal IgG kappa antibody, the SPEP and IFE can be positive for daratumumab. For patients with IgG kappa multiple myeloma with an SPEP at or below 0.2 g/dL on 2 or more consecutive cycles, or zero, but persistently positive IFE for IgG kappa on 2 or more occasions, the DIRA test must be completed.

10.9. Appendix 9: Line of Therapy Definition

According to the IMWG Consensus panel 1 on uniform reporting criteria in clinical trials (Rajkumar, 2011, Rajkumar 2015), a line of therapy consists of at least 1 or more cycles of a planned treatment regimen. This may consist of single-agent or combination therapy or a sequence of treatments administered in a planned manner. For example, a planned induction, followed by ASCT followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course is modified to include other treatment agents as a result of disease progression, relapse or toxicity or when a planned period of observation is interrupted by the need for additional treatment of the disease.

Modification of drug doses or resuming therapy after holding will not be considered a new line of therapy provided that there was no evidence of progression of disease as defined in the IMWG-URC guidelines. The definition is further clarified by Rajkumar et al, 2015.

A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (e.g., 3-6 cycles of initial therapy with bortezomib-dexamethasone [VD] followed by stem cell transplantation [SCT], consolidation, and lenalidomide maintenance is considered as 1 line of therapy).

- New line of therapy
- A treatment is considered a new line of therapy if any 1 of the following 3 conditions are met:
- Start of a new line of treatment after discontinuation of a previous line: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. A regimen is considered to have been discontinued if all the drugs in that given regimen have been stopped. A regimen is not considered to have been discontinued if some of the drugs of the regimen, but not all, have been discontinued.
- The unplanned addition or substitution of 1 or more drugs in an existing regimen: Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.
- SCT: In patients undergoing >1 SCT, except in the case of a planned tandem SCT with a predefined interval (such as 3 months), each SCT (autologous or allogeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different. We recommend that data on type of SCT also to be captured.

10.10. Appendix 10: ISS and R-ISS Score

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

(Palumbo et al. 2015)

10.11. Appendix 11: Definition of Relapsed Disease per IMWG definitions

Refractory Myeloma:

- Refractory myeloma is defined as disease that is non-responsive (failure to achieve minimal response or develops PD while on therapy) while on primary or salvage therapy or progresses within 60 days of last therapy. There are 2 categories of refractory myeloma.
- Relapsed and refractory myeloma: Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously to then progressing in their disease course.
- Primary refractory myeloma: Refractory myeloma is defined as disease that is non-responsive in patients who have never achieved minimal response or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M-protein and no evidence of clinical progression; as well as primary refractory, progressive disease where patients meet criteria for true progressive disease.

Relapsed Myeloma:

Relapsed myeloma is defined as previously treated myeloma, which progresses and requires the initiation of salvage therapy but does not meet the criteria for either primary refractory myeloma or relapsed and refractory myeloma (Rajkumar et al 2011).

10.12. Appendix 12: Assessment of Q-Tc interval

Q-Tc Fridericia Formula:

$$QT_F = \frac{QT}{\sqrt[3]{RR}}$$

10.13. Appendix 13: Estimated Creatinine Clearance by Cockcroft-Gault Formula

For males:

Creatinine Clearance = $\frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})}$ OR $\frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$

For females:

Creatinine Clearance = $\frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})}$ OR $\frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$

Source: Cockcroft and Gault 1976

10.14. Appendix 14: EQ-5D-3L

https://euroqol.org/wp-content/uploads/2019/10/Sample_UK__English__EQ-5D-3L_Paper_Self_complete.pdf

10.15. Appendix 15: EORTC QLQ-C30

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf

10.16. Appendix 16: BPI-SF

http://www.npcrc.org/files/news/briefpain_short.pdf

10.17. Appendix 17: NRS for measure of bone pain

OP-108 NRS Version 2.0 Dated 12 May 2020 FINAL

Numeric Rating Scale

Patient Number _ _ _ _ - _ _ _ Completion Date: _ _ / _ _ _ / _ _ _ _ Time: _ _ : _ _
DD/MMM/YYYY HH : MM

1. Have you experienced bone pain during the last 24 hours?

Yes ☐

No ☐

If yes, please indicate the number that best describes your bone pain:

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

No pain — Moderate pain — Worst possible pain

2. Have you experienced muscle pain during the last 24 hours?

Yes ☐

No ☐

If yes, please indicate the number that best describes your muscle pain:

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

No pain — Moderate pain — Worst possible pain

10.18. Appendix 18: Use of health services and hospitalization

YOUR USE OF HEALTH SERVICES OVER THE LAST MONTH

1. Please could you tell us how many times you have used the following services for any problems (not just multiple myeloma) in the last month. If you cannot remember the exact number, please give an estimate. For example, if you think it was between 4 and 6 times, please put 5. If you haven't used the service, please enter 0.

SERVICE	Number of times used
Telephone health advice	
Primary care consultations	
Primary care home visits	
Nurse home visits	
Accident and emergency attendances	
Attendance at hospital as an outpatient	

2. Have you spent any nights as a hospital inpatient in the last month?

YES [ ] NO [ ]

If YES, how many nights were you in hospital for? _____

Oncopeptides questionnaire, modified from Health-care resource use questionnaire version 002, dated 11/07/2008. OP-108 version 1.0 dated 2 January 2020.

10.19. Appendix 19: Abbreviations

Abbreviation	Description
AE	Adverse Event
ADP	Adenosine diphosphate
ALP	Alkaline phosphatase
ALT	Alanine transaminase/Alanine aminotransferase, also known as glutamic pyruvic transaminase (SGPT)
ANC	Absolute Neutrophil Count
Anti-HBc-	Anti-hepatitis B core antibody negative
Anti-HBs-	Anti-hepatitis B surface antibody negative
Anti-HBc+	Anti-hepatitis B core antibody positive
Anti-HBs+	Anti-hepatitis B surface antibody positive
ASCT	Autologous Stem-Cell Transplantation
AST	Aspartate transaminase/Aspartate aminotransferase, also known as glutamic oxaloacetic transaminase (SGOT)
BMA	Bone Marrow Aspirate
BUN	Blood Urea Nitrogen
CA	Chromosomal Abnormalities
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CI	Confidence Interval
CMV	Cytomegalovirus
COVID-19	Coronavirus disease
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Contract Research Organization
CR	Complete Response
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events

DIRA	Daratumumab Interference Reflex Assay
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOCB	Duration of Clinical Benefit
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
H2	Histamine 2 receptor
HBV	Hepatitis B virus
HBsAg+	Hepatitis B surface antigen positive
HBsAg-	Hepatitis B surface antigen negative
IB	Investigator's Brochure
ICF	Informed Consent From
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
iFISH	interphase Fluorescence In Situ Hybridization
IFE	Immunofixation
Ig	Immunoglobulin
IL	Interleukin
IMiD	Immunomodulatory Drug

IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
IND	Investigational New Drug
IRC	Independent Review Committee
IRB	Institutional Review Board
IRR	Infusion Related Reaction
ISS	International Staging System
IUD	Intra Uterine Device
i.v.	Intravenously
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
mAb	monoclonal Antibody
MDSC	myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
MM	Multiple Myeloma
MR	Minimal Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NRS	Numeric Rating Scale
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFS-2	Progression Free Survival on next line of therapy

PI	Proteasome Inhibitor
PICC	Peripherally Inserted Central Catheter
PK	Pharmacokinetics
p.o.	Per oral
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein
PPIs	Proton Pump Inhibitors
PR	Partial Response
q.d.	Quaque die/ one a day
rHuPH20	Recombinant human hyaluronidase PH20
RBC	Red Blood Cell
REB	Regional Ethics Board
R-ISS	Revised International Staging System
RRMM	Relapsed Refractory Multiple Myeloma
SGOT	Serum Glutamic Oxaloacetic Transaminase, also known as AST
SGPT	Serum Glutamic Pyruvic Transaminase, also known as ALP
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
s.c.	Subcutaneous
SD	Stable Disease
SFLC	Serum Free Light Chain
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
SPEP	Serum Protein Electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event

TTNT	Time to Next Treatment
TTP	Time to Progression
TTR	Time to Response
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
VAS	Visual Analogue Scale
VGPR	Very Good Partial Response
WOCBP	Woman of Child Bearing Potential

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