Protocol Number: OP-104

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

NCT Number: NCT03481556

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Clinical Development Protocol

OP-104 Anchor Trial

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

Investigational Product	Melflufen
Study Sponsor	Oncopeptides AB Västra Trädgårdsgatan 15 SE-111 53 Stockholm, Sweden
Protocol Number	OP-104
EudraCT number	2017-002120-24
Investigational New Drug Number	116362
Clinical Research Organization (CRO)	[redacted]
Development phase	Phase 1/2
Document status	Version 1.0, June 22, 2017 Version 2.0, Amendment 1; November 13, 2017 Version 3.0, Amendment 3: May 17, 2018 Version 4.0, Amendment 4: November 16, 2018 Version 5.0, Amendment 5: February 14, 2019 Version 5.1, Amendment 6: March 18, 2020 Version 6.1, Amendment 7: April 10, 2020 Version 6.2, Amendment 8: May 05, 2021

Signature Page

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Date of Original Protocol:
Version 1.0, June 22, 2017
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Approved By:

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Signer Name: [redacted]
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Protocol Acceptance Page

Protocol Number: OP-104: ANCHOR TRIAL

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Version 6.1, Amendment 7: April 10, 2020
Version 6.2, Amendment 8: May 05, 2021

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

_____
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, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The study protocol and any amendments are to be reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before implementation.

Confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Oncopeptides AB.

Protocol Amendment Summary of Changes

Overall Rationale for Amendment 8, 05 May 2021:

Non-substantial amendment due to update of assigned safety CRO. SAE reporting email address updated to [redacted].

Changes Amendment 8 (non-substantial)

Section # and Name	Description of Change	Brief Rationale
Signature Page – Sponsor	Change of Sponsor Clinical Operations Director.	Administrative update.
Error! Reference source not found.	Assigned safety CRO changed. SAE reporting email address added: [redacted]	Safety CRO changed for the study.
Error! Reference source not found. 10.3 Pregnancy	Assigned safety CRO changed. SAE reporting email address added: [redacted]	Safety CRO changed for the study.

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Protocol Synopsis

Compound Name	Melflufen
Protocol Name	OP-104 ANCHOR Trial
Chemical Name	4-[Bis-(2-chloroethyl)amino]-L-phenylalanine-4-fluoro-L-phenylalanine ethyl ester hydrochloride
Study Protocol Title	An Open-Label Phase 1/2a Study of the Safety and Efficacy of Melflufen and Dexamethasone in Combination with either Bortezomib or Daratumumab in Patients with Relapsed or Relapsed-Refractory Multiple Myeloma
Study Sponsor	Oncopeptides AB
Site(s)	Approximately 17 sites in Europe and US.
Study Period	Enrollment from April 2018 – December 2021
Background and Rationale	Melflufen is a peptidase-potentiated alkylator. Melflufen is lipophilic and can thereby traverse the cell membrane passively and relatively freely. Once inside the cell, melflufen is cleaved by peptidases, which are over-represented in the cancer cells. Due to its lipophilicity and peptidase-dependent distribution profile, a strong increase of alkylator is achieved in cancer cells, without a corresponding increase in other cells (which determines the side effect profile (Gullbo et al. 2003c, Wickström et al. 2010). Consequently, melflufen has a different bio distribution and bioavailability profile compared to other alkylators. Melphalan is the most potent existing alkylator for the treatment of multiple myeloma. Cancer cells receive around 50 times higher exposure of alkylators after exposure to melflufen compared to melphalan. Via studies in animals and later clinical studies it has been established that this increase in exposure after treatment with melflufen does not lead to an increased number, or different types of, adverse effects. However, the cytotoxic effect on cancer cells increases and new efficacy qualities arise, such as increased effect on multi-resistant cancer cells and substantial anti-angiogenic effects (Gullbo et al. 2004, Wickström et al. 2007, Chauhan et al. 2013). An assessment of data from clinical trial O-12-M1 in relapsed-refractory multiple myeloma (RRMM) was performed after the data base lock November 09, 2017. Of the 45 patients treated with at least 1 dose of 40 mg melflufen in combination with weekly dexamethasone, 21 patients (47%) have reported a best response of minimal response (MR) or better and 14 patients (31%) have reported partial response (PR) or better. These 45 patients had a median of 4 prior lines of therapy, including immunomodulatory drugs (IMiD)s, proteasome inhibitors (PI)s and alkylators. The median progression free survival (PFS) was 5.7 months at the time of data-cut based on 41 events in 45 patients with ≥ 1 cycle. Median number of cycles completed was 5.0 (1 – 14). The safety profile of melflufen suggested by preclinical studies is supported by clinical data from 45 patients with solid tumors and from a total of 75 patients with RRMM in the completed Phase 1/2a clinical trial O-12-M1 (58 patients dosed at the MTD of 40 mg of melflufen and 17 patients dosed at other doses in Phase 1 part of the trial). Taken together, clinical and preclinical data support that melflufen provides peptidase potentiated alkylating metabolites to tumor cells such as MM and thereby exerts a higher anti-

	tumor activity compared with equimolar administration of melphalan but with a similar safety profile. In non-clinical in vitro studies, the combination of melflufen with bortezomib or dexamethasone triggered synergistic anti–multiple myeloma activity, evidenced by a significant decrease in viability of MM.1S cells. Importantly, a similar synergism was observed between melflufen and bortezomib or dexamethasone in melphalan-resistant LR5 multiple myeloma cells. Although definitive evidence of decreased toxicity of combination therapy awaits results of clinical trials, the synergy observed in vitro may allow for use of lower doses and decreased toxicity (Chauhan et al. 2013). A pharmacokinetic drug-drug interaction between melflufen and bortezomib is unlikely to occur. Melflufen is very rapidly distributed out of systemic circulation and metabolized to melphalan by peptidases and esterases. Hence, renal and hepatic elimination of melflufen and binding to drug metabolic enzymes is likely to be negligible. For melphalan the package insert states: Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant. The combination of melphalan, bortezomib and prednisone (VMP) is an established combination treatment in MM, and is part of the IMWG recommendations (Palumbo et al. 2014) for newly diagnosed patients who are not eligible for high dose therapy and stem cell transplant, as well as for patients with relapsed disease. A Phase 3 trial, with bortezomib-melphalan-prednisone-thalidomide followed by maintenance treatment with bortezomib-thalidomide evaluated a once weekly bortezomib dosing schedule and found no difference in efficacy, reduced peripheral neuropathy and reduced discontinuation due to this adverse event (Bringhen et al. 2010). Daratumumab is a first-in-class, human immunoglobulin G1 kappa (IgG1k) mAb that binds malignant cells expressing CD38 with high affinity and induces tumor cell death through several immune-mediated mechanisms. Daratumumab was initially studied in monotherapy setting in study GEN501 (Lokhorst et al. 2014, Usmani et al. 2016) and in the SIRIUS study (Lonial et al. 2016, Usmani et al. 2016). The combined results showed an overall response rate of 31% of daratumumab 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 month). Daratumumab has also been studied in combination with lenalidomide and dexamethasone (Dimopoulos et al, 2016), or bortezomib and dexamethasone (Palumbo 2016), for the treatment of patients with multiple myeloma who have received at least one prior therapy. These studies resulted in approval for daratumumab in these combinations. These studies reported that the addition of daratumumab to these therapies improved response rates but did not increase the toxicity of the backbone therapy other than daratumumab related infusion reactions, including when combined with the alkylating agent melphalan. Study MMY3007/Alcyone study is presently ongoing comparing daratumumab+VMP vs VMP. Although the incorporation of novel agents such as PIs and IMiDs,

	including retreatment, sequential and combination therapy approaches, has significantly improved outcomes in addition to autologous stem cell transplant (ASCT) (for those that are eligible), myeloma is not yet curable and additional treatment options are needed. Given the promising efficacy and unique mechanism, melflufen represents a reasonable option for evaluation in triple drug combinations.
Study Design	This is an open-label, Phase 1/2a, multicenter study which will enroll patients with relapsed or relapsed-refractory MM to combination regimens of melflufen with currently approved agents. The currently planned combinations include: • Regimen A: Melflufen plus bortezomib and dexamethasone • Regimen B: Melflufen plus daratumumab and dexamethasone Each combination will begin with a Phase 1 component which will follow the standard 3 + 3 Phase 1 design with 3 to 6 patients at each dose level, depending on dose limiting toxicity (DLT) observed in the first cycle of each patient. Patients who discontinue treatment during Cycle 1 due to reasons other than study drug related toxicity, and/or who are considered non-evaluable for DLT assessment, may be replaced at the discretion of the Data Safety Monitoring Committee (DSMC). Patient recruitment will continue until a full cohort of safety evaluable patients has been achieved. A DSMC will evaluate all treated patients in each cohort prior to dose level adjustment decisions. **Regimen A: Melflufen Plus Bortezomib and Dexamethasone** Up to 3 dose levels of melflufen will be tested; i.v. melflufen at 30 mg and 40 mg or 20 mg given on Day 1 of every 28-day cycle, in combination with subcutaneous (SQ) bortezomib at 1.3 mg/m^2 twice weekly on Days 1, 4, 8 and 11 of each 28-day cycle and a fixed dose of dexamethasone 20 mg orally (p.o.) (12 mg for patients ≥ 75 years of age) on Days 1, 4, 8, 11 and dexamethasone 40 mg (20 mg for patients ≥ 75 years of age) on Day 15 and 22, of each 28-day cycle. Alternate dose levels or schedules of melflufen, bortezomib or dexamethasone may be explored based on tolerability following review and recommendation of the DSMC. **Regimen B: Melflufen Plus Daratumumab and Dexamethasone** Up to 3 dose levels of melflufen will be tested; i.v. melflufen at 30 mg and 40 mg or 20 mg given on Day 1 of every 28-day cycle, in combination with daratumumab 16 mg/kg according to the following daratumumab schedule:

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

*Due to prolonged infusion time of the first dose of daratumumab, the

	Cycle 1 infusion of daratumumab will be given on Day 2 of Cycle 1. Dexamethasone 40 mg p.o. (20 mg p.o. for patients ≥ 75 years of age) will be given weekly. Due to the need for steroids to prevent infusion reactions with daratumumab, dexamethasone dosing may be split prior to daratumumab, and on the day after daratumumab on weeks when daratumumab is given. Refer to the dose and schedule of dexamethasone below in section Study Treatment, Regimen B of the synopsis and in Section 6.4.2, Table 6-2. Alternate dose levels or schedules of melflufen, daratumumab and dexamethasone may be explored based on tolerability following review and recommendation of the DSMC. **All Dosing Regimens** The primary objective is to determine the optimal dose of melflufen, up to 40 mg, in combination with partner drugs (drugs defined in a Regimen) in triple combinations. Once the optimal dose of melflufen in combination with the partner therapy is determined, alternate doses and/or schedules may be explored following review and recommendation of the DSMC. The objective of all dose adjustments is to find the best benefit/risk balance. Dose modifications may be made for individual patients based on toxicity during therapy. Once the optimal dose, up to 40 mg of melflufen has been determined to be safe for a given Regimen in Phase 1, approximately additional 20 efficacy evaluable patients will be enrolled in that Regimen and treated in a Phase 2a part of the study at the dose established in Phase 1. Patients will be assessed for response after each cycle according to the International Myeloma Working Group - uniform response criteria (IMWG-URC) (Rajkumar et al. 2011). Patients who have benefit from the therapy may continue treatment until disease progression or unacceptable toxicity. Dose modifications may be implemented to manage toxicity according to the protocol guidelines. Patients who discontinue treatment with one of the drugs in the Regimen (excluding dexamethasone) may continue on the other, at the investigator's discretion if in the best interest of the patient. Patients who discontinue melflufen and continue to be treated with the other drug in the Regimen will be followed for response, PFS and OS follow-up. **Regimen Selection** All patients meeting the required eligibility criteria may be eligible for one or both of the defined Regimens. For patients that are eligible for both Regimens, the Regimen selection may be determined by the investigator, given cohort availability for the selected Regimen at the time of screening. Only one cohort per patient will be reserved at a given time. If the patient fails screening for the reserved Regimen cohort, enrollment in a non-reserved Regimen cohort will be based on availability. Patients may be re-screened if appropriate. Both Regimens may enroll simultaneously to an available cohort. During Phase 2a, enrollment based on number of prior therapies and/or refractory status may be further explored to optimize the benefit/risk balance as recommended by the DSMC.

Objectives	**Primary Objective(s)** **Phase 1** To determine the optimal dose of melflufen, up to a maximum of 40 mg, given every 28 days, in triple drug combination therapy in patients with relapsed or relapsed-refractory MM. Each treatment regimen and dose will be evaluated separately. **Phase 2a** To evaluate the overall response rate (≥ PR) of melflufen, in each combination Regimen, at the dose levels and schedules determined in Phase 1 in efficacy evaluable patients as well as in all treated patients. Each treatment regimen and dose will be evaluated separately. **Secondary Objectives** • To evaluate the best response including the complete response/stringent complete response (CR/sCR), very good partial response (VGPR), partial response (PR) and clinical benefit rate (CBR: proportion of patients with ≥ minimal response (MR)), , time to response (TTR), duration of response (DOR; PR or better), duration of clinical benefit (CB), , progression free survival (PFS) and overall survival (OS) up to a minimum of 2 years in efficacy evaluable patients as well as in all treated patients. IMWG-URC guidelines will be used. Each treatment regimen and dose will be evaluated separately.To further explore the safety and tolerability of the combination regimens. Each treatment regimen and dose will be evaluated separately. **Exploratory Objectives** Pharmacokinetics will be evaluated in patients enrolled at selected sites only. To evaluate minimal residual disease (MRD) in patients achieving a CR.
Inclusion Criteria	Patients will be considered eligible for inclusion in this study if they meet all of the following criteria: 1. Male or female, age 18 years or older; 2. A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening; 3. One to four prior lines of therapy (Appendix D); 4. Measurable disease defined as any of the following: • Serum monoclonal protein ≥ 0.5g/dL by serum protein electrophoresis (SPEP) • ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour electrophoresis (UPEP) • Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain (FLC) ratio 5. Life expectancy of ≥ 6 months; 6. 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);

	7. Patient is a female of childbearing potential (FCBP)* with a negative serum or urine pregnancy test prior to initiation of therapy and agrees to practice appropriate methods of birth control, or is a female not of childbearing potential, or the patient is a male and agrees to practice appropriate methods of birth control (refer to Section 7.1); 8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent; 9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec (Appendix H); 10. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study drug 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 therapy) • Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without required 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), or 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 of ≥ 45 mL/min and serum creatinine ≤ 2.0 mg/dL (Appendix G); 11. Must have, or be willing to have an acceptable central catheter (port a cath, peripherally inserted central catheter [PICC] line, or central venous catheter). **Regimen Specific Inclusion criteria:** **Regimen A – Melflufen + Bortezomib and Dexamethasone** A1 Must be intolerant or refractory to a prior IMiD; refractory defined as failure to respond (MR or better) or progression while on therapy or within 60 days of last dose. **Regimen B – Melflufen + Daratumumab and Dexamethasone** B1 Must have had a prior IMiD and a proteasome inhibitor (PI); alone or in combination and must be refractory or intolerant to an IMiD, PI or both. *(FCBP) is any sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months.

Exclusion Criteria	Patients will be ineligible for this study if they meet any one of the following criteria: 1. Primary refractory disease (i.e. never responded with ≥ MR to any prior therapy); 2. Evidence of mucosal or internal bleeding and/or platelet transfusion refractory (i.e. platelet count fails to increase by > 10,000 cells/mm^3 after transfusion of an appropriate dose of platelets); 3. 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., myocardial infarction, significant cardiac conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months); 4. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of initiation of therapy; 5. 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; 6. Pregnant or breast-feeding females; 7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation; 8. Known human immunodeficiency virus or active hepatitis B or C viral infection (see criterion B5 for additional requirements for Regimen B); 9. Concurrent symptomatic amyloidosis or plasma cell leukemia; 10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes); 11. 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 antibodies (mAb) within 4 weeks of initiation of therapy. Prednisone up to but no more than 10 mg orally once daily (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; 12. 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); 13. Prior peripheral stem cell transplant within 12 weeks of initiation of therapy; 14. Prior allogeneic stem cell transplantation with active graft-versus-

host-disease);

15. Prior major surgical procedure or radiation therapy within 4 weeks of initiation of therapy (this does not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy);
16. Known intolerance to the required dose and schedule of steroid therapy, as determined by the investigator.
17. Prior treatment with melflufen.

Regimen specific exclusion criteria

Regimen A – Melflufen + Bortezomib and Dexamethasone

A1 Refractory to a PI in the last line of therapy prior to enrollment in this trial; refractory defined as failure to respond (MR or better) or progression while on therapy or within 60 days of last dose;

A2 History of allergic reaction/hypersensitivity attributed to compounds containing boron, mannitol, polysorbate 80 or sodium citrate dihydrate (See Appendix K).

Regimen B – Melflufen + Daratumumab and Dexamethasone

B1 Prior exposure to an antiCD-38 mAb;

B2 Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) less than 50% of predicted normal;

B3 Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification;

B4 ≥ Grade 3 conduction system abnormalities unless patient has a pacemaker.

B5 Active hepatitis B (defined as HBsAg+) or those at risk for reactivation (HBsAg-, Anti-HBs+, Anti-HBc+).

- Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-).
- Non-active hepatitis B (HBsAg-, Anti-HBs+, Anti-HBc+) may only be enrolled following approval by the sponsor after consideration of risk of reactivation (additional screening and monitoring for reactivation of hepatitis B and consultation with a liver disease specialist may be required) (see Table 8-1, footnote u).

Study Treatment(s)

For each Regimen, treatment may be given in an outpatient treatment setting in cycles. Each cycle is 28 days.

Dose levels to be tested:

Regimen A: Melflufen Plus Bortezomib and Dexamethasone
Phase 1

Dose Level	Melflufen dose (i.v.)	Bortezomib dose (SQ)*	Dexamethasone dose ## (p.o.)
Cycle = 28 days	Day 1	Days 1, 4, 8, 11	Days 1, 4, 8, 11, 15 and 22#

Level-1	20 mg	1.3 mg/m^2	20 mg**
Level 1	30 mg	1.3 mg/m^2	20 mg**
Level 2	40 mg	1.3 mg/m^2	20 mg**

*i.v. administration of bortezomib is acceptable only if SQ procedure is not tolerated. **12 mg for patients ≥ 75 years of age. #Day 15 and 22 dexamethasone 40 mg (20 mg for patients ≥ 75 years of age). ##Dexamethasone 40 mg (20 mg for patients ≥ 75 years of age) may be continued weekly during cycle delays.

Regimen B: Melflufen Plus Daratumumab and Dexamethasone Phase 1

:Dose Level	Melflufen dose (i.v.)	Daratumumab dose (i.v.)	Dexamethasone dose# (p.o.)*
Cycle = 28 days	Day 1	**Cycle 1 -** Days 2**, 8, 15 and 22 **Cycle 2 -** Days 1, 8, 15, 22 **Cycle 3 to 6 -** Days 1 and 15 **Cycle 7+ -** Day 1	On days when melflufen and daratumumab are given in combination (Day 1)**: Patients < 75 years old - Pre melflufen and daratumumab and the day after daratumumab Patients ≥ 75 years old - Pre melflufen and daratumumab
			All other daratumumab dosing days (see daratumumab schedule): Patients < 75 years old - Pre daratumumab and the day after daratumumab Patients ≥ 75 years old - Pre daratumumab
			On weeks when daratumumab is not given (not scheduled or dose held) on Days 8, 15, 22 (see daratumumab schedule)
Level-1	20 mg	16 mg/kg	**Melflufen and daratumumab in combination:** Patients < 75 years old - 20 mg Day 1** and 2 Patients ≥ 75 years old – 20 mg Day 1**
			All other daratumumab dosing days: Patients < 75 years old - 20 mg pre, and the day after daratumumab Patients ≥ 75 years old – 20 mg pre daratumumab
			During cycles when daratumumab is not given (not scheduled or dose held) on Days 8, 15 or 22:

			Patients < 75 years old - 40 mg p.o. Patients ≥ 75 years old – 20 mg p.o.
Level 1	30 mg	16 mg/kg	**Melflufen and daratumumab in combination:** Patients < 75 years old - 20 mg Day 1** and 2 Patients ≥ 75 years old – 20 mg Day 1**
			All other daratumumab dosing days: Patients < 75 years old - 20 mg pre, and the day after daratumumab Patients ≥ 75 years old – 20 mg pre daratumumab
			During cycles when daratumumab is not given (not scheduled or dose held) on Days 8, 15 or 22: Patients < 75 years old - 40 mg p.o. Patients ≥ 75 years old – 20 mg p.o.
Level 2	40 mg	16 mg/kg	**Melflufen and daratumumab in combination:** Patients < 75 years old - 20 mg Day 1** and 2 Patients ≥ 75 years old – 20 mg Day 1**
			All other daratumumab dosing days: Patients < 75 years old - 20 mg pre, and the day after daratumumab Patients ≥ 75 years old – 20 mg pre daratumumab
			During cycles when daratumumab is not given (not scheduled or dose held) on Days 8, 15 or 22: Patients < 75 years old - 40 mg p.o. Patients ≥ 75 years old – 20 mg p.o.

*Oral dexamethasone may be substituted with i.v. dexamethasone at the investigator's discretion, prior to daratumumab infusion only, if this is the standard of care of the site.

**Due to prolonged infusion time of the first dose of daratumumab, the Cycle 1 infusion of daratumumab will be given on Day 2 of Cycle 1. Therefore, the dexamethasone dose of 20 mg will be given on Day 1 prior to melflufen and on Day 2 prior to the daratumumab administration in

	Cycle 1 for patients < 75 years of age. For patients ≥ 75 years of age, the Cycle 1, Day 1 dexamethasone 20 mg dose may be split between Day 1 and Day 2 at the investigator's discretion (e.g. dexamethasone 12 mg p.o. on Day 1 prior to melflufen and 8 mg p.o. on Day 2 prior to daratumumab) or dexamethasone may also be given i.v. with a split dose (e.g. dexamethasone 10 mg i.v. on Day 1 prior to melflufen and 10 mg i.v. on Day 2 prior to daratumumab). No dexamethasone is required the day following daratumumab in Cycle 1. However, additional steroids may be given as needed to prevent or treat hypersensitivity reactions at the investigator's discretion and as per the SoC for the site.
	Phase 2 All Regimens Patients will be treated with the dose level of the combination regimen determined in Phase 1 for a given Regimen with the same schedule. All patients will follow the same procedures for drug administration as in Phase 1.
Dose Escalation Criteria	**All Regimens** The first cohort of patients enrolled in the Phase 1 portion of each Regimen will receive dose level 1 (melflufen 30 mg). A full safety evaluation will be conducted by a DSMC when the planned number of melflufen safety evaluable patients have completed the first cycle of combination therapy with DLT assessment. The optimal dose of melflufen in combination therapy will be defined as the highest of 20, 30 or 40 mg of melflufen that results in ≤ 1/6 patient with DLT during the first cycle of therapy. The minimum dose of melflufen is 20 mg. • If no DLT is reported in the first three patients at a dose level, that dose level will be considered safe and three patients will be enrolled at the next dose level. • If 1/3 patients in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable patients. • If 2/3 patients in a cohort at a dose level has a DLT, that dose level will not be considered safe and no further dose escalation will take place. • If there are < 2 patients with a DLT among the expanded cohort of six evaluable patients a cohort of three patients will be enrolled in the next higher dose level. • If there are 2 or more patients with a DLT among the expanded cohort of six evaluable patients, that dose level will not be considered safe and no further dose escalation will take place. • If less than 6 patients have been treated in the next lower dose level, additional patients will be entered into this dose level until there are 6 patients treated. If ≤ 1 of these 6 patients encountered DLT, then this dose level will be taken forward to Phase 2a. If 2 or more of the 6 patients encounter DLT, a lower dose will be considered. NOTE: If a patient discontinues treatment during Cycle 1 for reasons other than study drug related toxicity and is considered non-evaluable for DLT assessment, the patient may be replaced at the discretion of the DSMC. Patients who discontinue treatment with any drug in the Regimen (excluding dexamethasone) may continue treatment with the other drug in

	the Regimen at the investigator's discretion if in the patient's best interest. Patients who discontinue melflufen and continue to be treated with the other drug in the Regimen will be followed for response, PFS and OS follow-up. Further details are provided in section 6.7 and 6.8 of the protocol. **Definition of DLT** The following criteria will apply to all treatment Regimens. **Additional Regimen specific criteria are detailed in the protocol** Section 6.6.1 and 6.6.2. • Grade 3 non-hematologic toxicity preventing the administration of > 1 dose of the partner therapy* (excluding dexamethasone) during the 1st cycle • Grade 4 or greater non-hematologic toxicity • Grade 4 thrombocytopenia (platelet count < 25,000 cells/mm^3) preventing the administration of > 1 dose of the partner therapy* (excluding dexamethasone) or with clinically significant bleeding during the 1st cycle • Grade 4 neutropenia (ANC < 500 cells/mm^3), lasting more than 7 days during the 1st cycle. Greater than 14 days' delay to meet the criteria for the start of a new cycle (Cycle 2) due to toxicity. *Partner therapy includes the drugs defined in a Regimen excluding dexamethasone. Toxicity will be graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (AE) Version 4.03 (CTCAE 4.03) Appendix B.
Duration of Treatment	**Phase 1 and Phase 2a** Treatment will be administered in cycles of 28 days. Treatment may continue until progressive disease, unacceptable toxicity or if the patient/treating physician determines it is not in the patient's best interest to continue. Response will be evaluated every cycle according to the IMWG-URC guidelines.
Concomitant Drug/Therapy	All blood products and concomitant medications received from screening until the end of study treatment visit should be recorded. Refer to Section 7.0 for complete details on concomitant therapy. • Prophylactic treatment with anti-emetic(s) just prior to study treatment administration is recommended • Patients should receive full supportive care while on this study at the investigator's discretion, including red blood cell transfusions, antibiotics, anti-diarrheals, analgesics etc., and treatment of other concurrent medical conditions. • i.v. or p.o. bisphosphonate therapy, if indicated, is permitted. • Hematopoietic growth factors and platelet transfusions are allowed if neutropenia and/or thrombocytopenia occur but should not be used prophylactically during Cycle 1 of Phase 1. Also see Section 7.2 for additional limitations on use of growth factors and platelet

	transfusions. • No anticancer agents, other than the study medications administered as part of this study protocol, are permitted • Regimen specific required pre- and post-medication(s) are detailed in the protocol Section 6.5.
Number of Patients	**All Regimens** A maximum of 6 DLT evaluable patients will be enrolled in each dose level, melflufen 30 mg and 40 mg or 20 mg. For each Regimen tested, it is anticipated that up to 12 DLT evaluable patients will be enrolled in Phase 1. The 6 patients treated at the optimal dose of each Regimen in Phase 1, will be included in the Phase 2a assessment for each Regimen. Approximately 20 efficacy evaluable patients in each Regimen will be enrolled in the Phase 2a portion of the respective Regimen for a total of 26 efficacy evaluable patients at the optimal dose for each Regimen. Patients in Phase 1 who are not fully evaluable for assessment of DLT may be replaced and patients in Phase 2a who are not efficacy evaluable (received at least 2 doses of melflufen and ≥ 50% of the partner therapy (excluding dexamethasone) during Cycles 1 and 2 with appropriate assessments) may be replaced.

Assessments	All required study procedures are detailed in Table 8-1 Schedule of Events.
	Screening Disease Assessments
	• M-protein determination using the following procedures:
	  ○ Serum protein electrophoresis (SPEP) and serum protein immunofixation (IFE) with quantitative immunoglobulins (lg); and
	  ○ Urine protein electrophoresis (UPEP) and urine protein IFE (all using the same 24-hour urine collection); and
	  ○ Serum free light chains (SFLC) and SFLC ratio.
	• Bone marrow to quantify percent myeloma cell involvement and morphology, cytogenetics by Fluorescence In-Situ Hybridization (FISH) and a sample stored for possible MRD assessment. If cytogenetics by karyotype has been done according to institutional guidelines it should be recorded in the CRF.
	• Extramedullary plasmacytoma evaluation (by physical examination [PE] or imaging technique)
	• Skeletal survey and/or low dose computerized tomography (CT) scan
	• Beta2 microglobulin
	• Lactate dehydrogenase (LDH)
	• International staging system (ISS) Staging Score and Revised ISS (R-ISS)
	Efficacy Assessments
	• M-protein determination using the following procedures:

	○ SPEP and IFE with quantitative immunoglobulins (Ig) (quantitative Ig required only for patients with IgA or IgD myeloma); ○ As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive due to 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 Daratumumab Interference Reflex Assay (DIRA) test must be completed. ○ UPEP and urine protein immunofixation (all using the same 24-hour urine collection); and ○ SFLC and SFLC ratio • Bone marrow aspirate to quantify percent myeloma cell involvement and minimal residual disease (MRD) in patients achieving CR. • Extramedullary plasmacytoma evaluation (by PE or imaging technique) • Skeletal X-rays and/or low dose CT scan (same technique used at screening and each evaluation) • Serum calcium **Safety Assessments** • Assessment and grading of AEs • Physical examinations with vital signs, neurologic assessment and assessment of performance status • Routine safety laboratory tests, (complete blood count [CBC] with differential and platelets; clinical chemistry, coagulation tests and urinalysis) with calculation of glomerular filtration rate by the Cockcroft-Gault formula (Appendix G) • Pregnancy testing • Electrocardiograms • Chest X-ray • Additional Regimen specific evaluations are detailed in Table 8-1: Schedule of events AEs, including clinical laboratory and vital sign abnormalities, will be graded using the National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Appendix B).
	Pharmacokinetic Assessments The PK samples will be collected only at selected sites. Three plasma samples for determination of melphalan concentrations will be drawn in each of the first two melflufen treatment cycles, 10–15 minutes after the end of infusion, 1 hour after the end of infusion and the third sample 2 to 4 hours after the end of infusion (as late as possible within the time frame). For Regimen B, the third sample should be taken after the daratumumab infusion in cycle 2.
Statistical Methods	**Study Endpoints**

Primary Endpoint

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

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

Secondary Endpoints

- Best response during the study (sCR, CR, VGPR, PR, MR, stable disease [SD], PD or non-evaluable)
- CBR (≥ MR)
- DOR
- PFS
- OS
- Frequency and grade of AE's
- TTR
- TTP
- TTNT
- Duration of clinical benefit

Exploratory Endpoint

- PK parameters of melphalan at selected time points.
- Assessment of MRD status in patients that achieve a CR.

*All tumor response and progression-dependent endpoints are as assessed by the investigator according to the IMWG-URC (Rajkumar et al. 2011, Appendix C). Oncopeptides will implement an independent review of the response and progression assessments performed by the investigator. The investigator will be notified of any discrepancies in the form of a data query.

Each regimen and dose will be evaluated separately.

Analysis Sets

Safety Analysis Set
All patients that have initiated treatment (at least one dose or partial dose of any drug in the Regimen) will be considered evaluable for safety analysis. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

DLT Analysis Set
All patients in Phase 1 that complete one cycle of therapy or discontinue due to study drug related toxicity (other than exclusions as defined in the Regimen specific DLT criteria). Patients that have been replaced in the original assigned cohort will not be included in the DLT analysis set.

	Efficacy Analysis Set The efficacy population will be comprised of all patients who receive at least 2 doses of melflufen and ≥ 50% of the partner therapy (excluding dexamethasone) during Cycles 1 and 2, had a baseline disease assessment, and had at least 1 post-baseline disease assessment (≥ 28 days after first dose).
ICH and Ethics	This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. The study protocol will be reviewed and approved by local ethics committees or IRBs and patients will sign Informed Consent Forms before enrolling to the trial.

List of Abbreviations

AE	Adverse Event
ALT	Alanine transaminase/Alanine aminotransferase/glutamic pyruvic transaminase(SGPT)
ANC	Absolute neutrophil count
Anti-HBc-	Anti-hepatitis core antibody negative
Anti-HBs-	Anti-hepatitis surface antibody negative
Anti-HBc+	Anti-hepatitis core antibody positive
Anti-HBs+	Anti-hepatitis surface antibody positive
ASCT	Autologous stem-cell transplantation
AST	Aspartate transaminase/Aspartate aminotransferase/glutamic oxaloacetic transaminase(SGOT)
AUC	Area under the curve
BUN	Blood urea nitrogen
CA	Chromosomal abnormalities
CBC	Complete blood count
CBR	Clinical benefit rate
CI	Confidence interval
CMV	Cytomegalovirus
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
DNA	Deoxyribonucleic acid
DOR	Duration of response

DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EoT	End of Treatment
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HBsAg+	Hepatitis B surface antigen positive
HBsAg-	Hepatitis B surface antigen negative
IB	Investigator's brochure
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IFE	Immunofixation
Ig	Immunoglobulin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
IND	Investigational new drug
IRB	Institutional Review Board
ISS	International Staging System
i.v.	Intravenously
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
OS-FU	Overall survival follow-up
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Proteasome Inhibitor
PICC	Peripherally inserted central catheter
PK	Pharmacokinetics
p.o.	Per os/by mouth/orally
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein
PR	Partial response
q.d.	Quaque die/ one a day

RBC	Red blood cell
R-ISS	Revised international staging system
RRMM	Relapsed Refractory Multiple Myeloma
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent complete response
SD	Stable disease
SFLC	Serum free light chain
SmPC	Summary of product characteristics
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
VGPR	Very good partial response
VMP	Melphalan, bortezomib and prednisone

1 BACKGROUND

1.1 OVERVIEW OF MULTIPLE MYELOMA

Multiple myeloma (MM) is a malignancy of the differentiated plasma cells that affects the older patient 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 nearly 30,330 patients with myeloma are diagnosed in the United States in 2015 (SEER 2016).

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, hyperviscosity of the blood and renal function compromise (including renal failure). The disease course for MM varies with the disease stage at diagnosis, cytogenetic profile, as well as age and patient comorbidities. The median survival is approximately 5 to 7 years with some significant variation in survival depending on host factors, tumor burden, biology and response to treatment (Kumar et al. 2008). However, the disease remains ultimately fatal.

There are currently 6 classes of approved drugs available for the treatment of MM, including steroids (prednisone and dexamethasone), immunomodulatory drugs (IMiDs) (thalidomide, lenalidomide and pomalidomide), proteasome inhibitors (PIs) (bortezomib, carfilzomib and ixazomib), histone deacetylase inhibitors (panobinostat), conventional chemotherapy (melphalan, cyclophosphamide, doxorubicin), including high dose melphalan with autologous stem-cell transplantation (ASCT) and the most recent addition of monoclonal antibodies (elotuzumab and daratumumab). The selection of treatment in relapsed/refractory multiple myeloma (RRMM) is challenging. The National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2017) 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 lifespan.

Recent improvements in therapies have significantly increased the expected life span for these patients. 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 relapsed-refractory MM 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.

1.2 OVERVIEW OF MELFLUFEN

1.2.1 Melflufen Description

The chemical name for melflufen is 4-[Bis-(2-chloroethyl)amino]-L-phenylalanine-4-fluoro-L-phenylalanine ethyl ester hydrochloride and the chemical structure is provided in Figure 1-1. The molecular weight 498.4 as free base and 534.9 as the HCl salt.

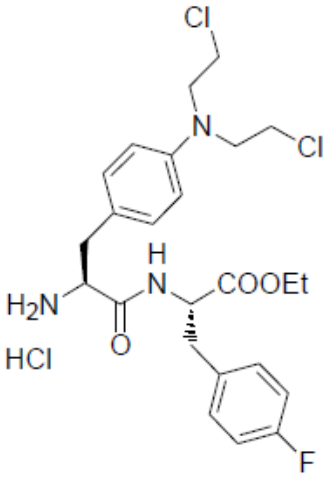

Figure 1-1: Structure of Melflufen

1.2.2 Melflufen Scientific Rationale

Melflufen is a peptidase-potentiated therapy designed for targeted delivery of alkylating moieties to tumor cells. In contrast to other alkylating agents that are hydrophilic, the lipophilicity of melflufen leads to rapid and extensive distribution into tissues and cells. Inside cells, melflufen may directly bind deoxyribonucleic acid (DNA) or is readily metabolized by intracellular peptidases into the well-known antitumor compound melphalan or by esterases into des-ethylmelflufen, which also has alkylating properties. Due to the high activity of peptidases and esterases in human tumor cells, the formation of melflufen's metabolites is rapid in these cells with continued inflow of more melflufen (Gullbo et al. 2003c, Wickström et al. 2010). Since des-ethylmelflufen and melphalan are relatively hydrophilic, there is a possibility for intracellular trapping of these alkylators. This can be explained by a more efficient transport of melflufen into these cells, an efficient conversion into other alkylating molecules (i.e. melphalan and des-ethylmelflufen) inside the cells and a less rapid disappearance of these molecules from the cells.

The properties of melflufen are supported by clinical pharmacokinetic data. Melflufen has a relatively low rate of hydrolysis in plasma according to in vitro studies. After intravenous infusion, melflufen shows a very rapid disappearance from plasma with no signs of redistribution back to the plasma, indicating that a complete metabolism occurs predominantly outside the plasma compartment. Following administration of melflufen, melphalan is found in plasma with a peak concentration at 5 to 10 minutes after the end of melflufen infusion (pharmacokinetics [PK] data from clinical trial O-12-M1). The total melphalan plasma exposure assessed as Area Under the Curve (AUC) after melflufen administration is similar to historical data on exposure after melphalan administration (Nath et al. 2010). However, the intracellular concentration in tumor cells could be considerably higher as discussed above. The metabolite des-ethylmelflufen reaches only very low concentrations in plasma with peak concentrations coinciding with end of melflufen infusion followed by a short elimination half-life.

The addition of melflufen to panels of primary cultures of human tumor cells, including MM, results in 50- to 100-fold higher efficacy to that of melphalan (Wickström et al. 2008), which is explained by the 50-fold higher intracellular exposure as AUC of alkylating agents compared to that observed after an equimolar dose of melphalan (Chauhan et al. 2013).

Mechanistically-oriented studies have shown that melflufen-induced apoptosis is associated with (i) activation of caspases and poly ADP ribose polymerase cleavage; (ii) reactive oxygen species generation; (iii) mitochondrial dysfunction and release of cytochrome c; and (iv) induction of DNA damage (Chauhan et al. 2013, Ray et al. 2016). Moreover, melflufen inhibits MM cell migration, tumor-associated angiogenesis and DNA repair. Importantly, in vitro studies in MM cell lines resistant to dexamethasone, bortezomib and melphalan have shown cytotoxic activities of melflufen at concentrations similar to those observed in the parental, non-resistant cell lines. Potent cytotoxic activity has also been demonstrated in primary MM cells from patients including those relapsing after multiple prior therapies with bortezomib, lenalidomide, and dexamethasone. These results suggest a different resistance mechanism for melflufen than for other agents used in MM. In efficacy studies conducted in mice and rats carrying different human tumors, including MM, superior antitumor activity of melflufen over equimolar dosage of melphalan was observed at seemingly comparable toxicity (Gullbo et al. 2004, Wickström et al. 2007, Chauhan et al. 2013).

The safety profile of melflufen suggested by preclinical studies is supported by clinical data from 45 patients with solid tumors (trial O-05-001) and from a total of 75 patients with RRMM in a Phase 1/2a clinical trial O-12-M1 (58 patients dosed at the maximum tolerated dose [MTD] of 40 mg of melflufen and 17 patients dosed at other doses in Phase 1 of the trial). Taken together, clinical and preclinical data support that melflufen provides peptidase-potentiated delivery of alkylating moieties to tumor cells (such as MM cells) and thereby exerts a higher anti-tumor activity compared with equimolar administration of melphalan but with a seemingly similar safety profile. The efficacy seems to be consistent across MM populations including patients who are double-refractory to IMiDs and PIs and refractory to alkylators.

Please see the Investigator's Brochure (IB) for additional information.

1.3 CLINICAL EXPERIENCE

1.3.1 Clinical Experience in RRMM

Melflufen was evaluated in combination with low dose dexamethasone, and as single agent, in a Phase 1/2a clinical trial O-12-M1 in RRMM. Adult patients with documented RRMM with at least 2 prior lines of therapy, including an IMiD and a PI, and who demonstrated disease progression on or within 60 days of last therapy, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, life expectancy of ≥ 6 months and preserved organ function were eligible to enter the study. Phase 1 followed the standard 3 + 3 Phase 1 design with 3 to 6 patients per dose cohort, depending on dose limiting toxicity observed, at each dose level that was tested.

The Phase 1 part of the clinical trial was completed in September 2014 (Paba-Prada et al. 2014). Based on data from 23 patients in four dose groups (15 mg, 25 mg, 40 mg and 55 mg), a MTD was established as 40 mg of melflufen in combination with 40 mg dexamethasone weekly. Following identification of the MTD, the Phase 2a part of the trial was initiated and all subsequently treated patients received a starting dose of 40 mg of melflufen. The Phase 2 part of the clinical trial was completed in November 2017 including data from 45 patients treated with melflufen in combination with dexamethasone and 13 patients treated with single agent melflufen.

1.3.1.1 Clinical Safety

As of November 9 , 2017, 58 patients had received 280 doses of melflufen 40 mg. The median number of completed cycles was 5.0 (Range 1 – 14).

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

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

Table 1-1 Summary of Melflufen Treatment-Related Grade 3 or 4 AE in ≥5% of 45 Patients Dosed with 40 mg Melflufen in combination with dexamethasone in 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	36 (80)	19 (42)
Thrombocytopenia	26 (58)	17 (38)
Neutropenia	26 (58)	11 (24)
Anemia	19 (42)	0 (0)
Lymphopenia	3 (7)	1 (2)

Continuous review of safety data in the Phase 2a part of the study led and the DSMC to include an additional week to the cycle length (i.e. to 28 days) to allow further recovery of platelet and neutrophil count and potentially allow the patients to stay on treatment longer and achieve more benefit.

Even though neutropenia and thrombocytopenia have been common in connection to melflufen treatment, few cases have been reported as serious adverse events (SAE)s as febrile neutropenia or bleeding (please see IB for details).

Since both the disease of MM as well as treatment with alkylators may cause neutropenia and neutropenia may be connected with both pneumonia, sepsis or other infections, it is important to follow institutional or NCCN guidelines (NCCN 2017) for antimicrobial prophylaxis for multiple myeloma patients.

Please refer to the current IB for further safety data on melflufen.

1.3.1.2 Evaluation of QTcF Intervals from Holter Recordings

Continuous 12-lead Holter recordings from before start of infusion to 120 minutes after start of the 30-minute infusion have been obtained on Day 1 of treatment cycles in a subset of patients in Study O-12 M1 for general screening purposes. No patient in the study has developed absolute QTcF values that are associated with a meaningful increased risk of arrhythmias. Please see IB for details.

1.3.2 Safety Summary

The clinical trials results, to date, indicate that the safety profile for melflufen is similar to that for other alkylators, where thrombocytopenia, neutropenia and anemia are the most common treatment-related AEs. The incidences of Grade 3 and 4 neutropenia and thrombocytopenia after 40 mg doses of melflufen are comparable to the incidences observed in studies with low dose melphalan regimens in combination with high dose steroids (Richardson et al. 2010). Even though neutropenia and thrombocytopenia have been common in connection to melflufen treatment, few cases have been reported as SAEs as febrile neutropenia or bleeding (please see current IB for details). There have been no reports of syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths in the clinical trials. The safety profile for melflufen is thus similar to that of other alkylators.

Since both the disease of MM as well as treatment with alkylators may cause neutropenia and neutropenia may be connected with both pneumonia, sepsis or other infections, it is important to follow institutional or NCCN guidelines (NCCN 2017) for antimicrobial prophylaxis for multiple myeloma patients.

1.4 CLINICAL EFFICACY

The Phase 2 part of the clinical trial was completed in November 2017 including data from 45 patients treated with melflufen in combination with dexamethasone and 13 patients treated with single agent melflufen. ORR among the 45 patients treated with 40 mg melflufen and dexamethasone was 31.1%, median DOR was 8.4 months based on 13 events in 14 patients (95% CI: 4.6-9.6), median PFS was 5.7 months based on 41 events in 45 patients (95% CI: 3.7-9.2) and median OS was 20.7 months based on 23 events in 45 patients (95% CI: 11.8-∞).

Please refer to the current IB for further details on clinical data on melflufen.

1.4.1 Clinical Pharmacokinetics

In humans, melflufen is metabolized to des-ethyl-melflufen, melphalan and the non-alkylating para-fluoro-phenylalanin ethyl ester. PK data for melflufen and melphalan are available from the completed clinical trial O-05-001 in patients with solid tumors and from 10 MM patients in the ongoing clinical trial O-12-M1.

In clinical trial O-12-M1 in MM patients, PK data from 12 patients covering the dose range 15 mg to 55 mg were available as of 30 November 2017. In all patients, melflufen plasma concentration reached a peak before end of infusion and was eliminated with a half-life of 1 to 5 minutes as measured from end of infusion. Melphalan PK parameters were similar to those observed in clinical trial O-05-001. Des-ethyl-melflufen reached only very low concentrations in plasma and was eliminated with a half-life of approximately 15 minutes.

The combined results from the two clinical trials demonstrate that the PK of melflufen is characterized by low plasma concentrations and a very rapid disappearance from plasma after end of the intravenous infusion. The PK of melphalan after administration of melflufen is characterized by a rapid formation where plasma concentrations exceed those of melflufen within 15 minutes after start of melflufen infusion, and where peak plasma concentrations are lower and AUC similar compared with equimolar infusions of melphalan at a similar rate (Mougenot et al. 2004, Nath et al. 2010). Peak plasma concentrations of melphalan appear with a delay by up to 10 minutes after the end of melflufen infusion. The elimination phase of melphalan is similar after melflufen and melphalan infusions, according to published data for melphalan administration (Mougenot et al. 2004, Nath et al. 2010).

Overall, the observations suggest a mechanism where melflufen is rapidly and widely distributed to tissues (including any tumor cells present) outside of the blood compartment. Melphalan is predominately formed in these tissues and thereafter distributed back to plasma and eliminated primarily by spontaneous hydrolysis to non-alkylating metabolites and with a small contribution of direct renal elimination. There is no appreciable active metabolism of melphalan mediated by drug metabolic enzymes. Please see IB for details.

1.5 OVERVIEW OF BORTEZOMIB

Bortezomib is a PI that inhibits NFKB, induces caspase-8/9 mediated apoptosis, and disrupts IL-6 induced intracellular signaling pathways (Hideshima et al. 2003). In a landmark Phase 3 trial, bortezomib was superior to high dose dexamethasone in relapsed MM (Richardson et al. 2005). The agent has also been associated with promising results in patients with newly diagnosed disease. In this setting the combination of bortezomib plus melphalan and prednisone was superior to melphalan and prednisone alone with respect to response, remission duration, and overall survival (San Miguel et al. 2008). Bortezomib was approved by US FDA 2003.

In non-clinical in vitro studies, the combination of melflufen with bortezomib or dexamethasone triggered synergistic anti–multiple myeloma activity, evidenced by a significant decrease in viability of MM.1S cells. Importantly, a similar synergism was observed between melflufen and bortezomib or dexamethasone in melphalan-resistant LR5 multiple myeloma cells. The synergy observed in vitro may allow for use of lower doses and decreased toxicity (Chauhan et al. 2013).

A pharmacokinetic drug-drug interaction between melflufen and bortezomib is unlikely to occur. Melflufen is very rapidly distributed out of systemic circulation and metabolized to melphalan by peptidases and esterases. Hence, renal and hepatic elimination of melflufen and binding to drug metabolic enzymes is likely to be negligible. For melphalan the package insert states: Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

The combination of melphalan, bortezomib and prednisone (VMP) is an established combination treatment in MM, and is part of the International Myeloma Working Group (IMWG) recommendations (Palumbo et al. 2014) for newly diagnosed patients who are not eligible for high dose therapy and stem cell transplant, as well as for patients with relapsed disease.

A Phase 3 trial, bortezomib-melphalan-prednisone-thalidomide followed by maintenance treatment with bortezomib-thalidomide evaluated a once weekly bortezomib dosing schedule and found no difference in efficacy, reduced peripheral neuropathy and reduced discontinuation due to this adverse event (Bringhen et al. 2010).

Additional details regarding bortezomib can be found in the US prescribing information or EU Summary of Product Characteristics (SmPC).

1.6 OVERVIEW OF DARATUMUMAB

Daratumumab is a first-in-class, human immunoglobulin G1 kappa (IgG1k) (mAb) that binds malignant cells expressing CD38 with high affinity and induces tumor cell death through several immune-mediated mechanisms of action, including complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, antibody-dependent cell-mediated cytotoxicity, induction of apoptosis, and modulation of CD38 enzyme activities (De Weers et al. 2011, Lammerts van Bueren et al. 2014). Although normal lymphoid, myeloid, and some

nonhematopoietic cells or tissues express low levels of CD38, (Deaglio et al. 2001) myeloma cells overexpress the protein, (Lin et al. 2004, Santonocito et al. 2004) thus providing a clinical rationale or the protein as a therapeutic target in MM. In addition to these immune mediated killing mechanisms, daratumumab may also have an immunomodulatory role via T-cell activation and expansion as well as mitigation of immunosuppression in patients with MM (Krejcik et al. 2016).

Daratumumab was initially studied in monotherapy setting in study GEN501 (Lokhorst et al. 2015, Usmani et al. 2016) and in the SIRIUS study (Lonial et al. 2016, Usmani et al. 2016). The combined results showed an overall response rate of 31% of daratumumab 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 month). Daratumumab has also been studied 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. These studies resulted in approval for daratumumab in these combinations.

Daratumumab has been studied in several combination trials and is approved in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy (Dimopoulos et al, 2016, Palumbo et al. 2016). An additional Phase 1/2 study explored daratumumab in combination with other backbone regimens in patients with ND and RRMM included a combination of daratumumab plus bortezomib, dexamethasone and melphalan (Moreau et al. 2015). This study reported that the addition of daratumumab to these therapies improved response rates but did not increase the toxicity of the backbone therapy other than daratumumab related infusion reactions, including when combined with the alkylating agent melphalan. Study MMY3007/Alcyone study is presently ongoing comparing daratumumab and VMP vs VMP.

Daratumumab was approved by US FDA 2015. Additional details regarding daratumumab can be found in the US prescribing information or EU Summary of Product Characteristics (SmPC).

As of 15 Nov 2018, daratumumab has been administered to approximately 4,407 patients in the setting of clinical trials, and an estimated world-wide post-marketing exposure of 34,316 person-years. Hepatitis B (HBV) reactivation, including fatal cases, has been observed in association with daratumumab. Janssen determined HBV reactivation is an important identified risk and an adverse drug reaction associated with daratumumab. The overall frequency of HBV reactivation in daratumumab clinical trials, including serious and non-serious reports, is uncommon (0.2%). The protocol was updated to exclude patients with active hepatitis B or at risk for reactivation.

2 RATIONALE

2.1 STUDY RATIONALE

Recent improvements in therapies have significantly increased the expected life span for MM patients. 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 relapsed-refractory MM 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.

Melflufen has a different bio distribution and bioavailability profile compared to other alkylators. Melphalan is the most potent existing alkylator for the treatment of multiple myeloma. Cancer cells receive approximately 50 times higher exposure of alkylators after exposure to melflufen compared to melphalan. In the Phase 2a potion of protocol O-12-M1 the median PFS was 5.1 months (95% confidence interval 3.7 to 8.5 months) based on 40 events in 45 patients with available data. Of the 34 heavily pretreated (median 4 lines of therapy) efficacy evaluable patients the overall response rate (ORR) was 41% and 62% reported a best response of minimal response (MR) or better. Given the promising efficacy, melflufen represents a reasonable option for evaluation in triple drug combinations.

2.2 RATIONALE FOR THE SELECTED PATIENT POPULATION

The proposed trial will be conducted in relapsed or RRMM patients who have received 1 to 4 prior lines of therapy

Many triple drug combinations include the use of IMiDs; however, not all patients are candidates for IMiD based therapy, such as those who are refractory, or with co-morbid conditions. Only 20 to 30% of the relapsed-refractory MM 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.

During Phase 2a, enrollment based on number of prior therapies and/or refractory status may be further explored to optimize the benefit/risk balance as recommended by the DSMC.

2.3 RATIONALE FOR DOSE SELECTION

The dose and schedule of melflufen was established in the Phase 1/2 trial (O-12-M1) with melflufen in combination with weekly dexamethasone in RRMM patients as 40 mg on Day 1 of a 28-day cycle. The goal of this trial is to determine the optimal dose, up to 40 mg of melflufen, in triple combination regimens. In study O-12-M1 and in an ongoing trial (OP-106 Horizon of melflufen and dexamethasone in pomalidomide- and/or daratumumab-refractory patients), hematologic toxicity is the most common adverse event (AE) reported, with thrombocytopenia being the most clinically important AE.

Bortezomib is approved in the present US FDA label (09/2015) at 1.3 mg/m^2 twice weekly with one week rest period in combination with melphalan and prednisone in 6-week cycles in previously untreated multiple myeloma patients for the first 4 cycles and once weekly beyond Cycle 4. In relapsed multiple myeloma, 1.3 mg/m^2 bortezomib is administrated twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, bortezomib may be administered on a maintenance schedule of once every 28 days (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). No guidance is provided in the US FDA label for schedule adjustments in relapsed multiple myeloma patients when combined with other medications and for cycle lengths that are not multiples of 3 weeks.

The Phase 1 part of the present study will explore the triple combination of melflufen, dexamethasone and bortezomib in a step-wise fashion. In the initial cohort, 30 mg melflufen (once every 4 weeks) will be given in combination with subcutaneous (SQ) bortezomib at 1.3 mg/m^2 twice weekly on Days 1, 4, 8 and 11 of each 28-day cycle and a fixed dose of dexamethasone 20 mg orally (p.o.) (12 mg for patients ≥ 75 years of age) on Days 1, 4, 8, 11, and 40 mg (20 mg for patients ≥ 75 years of age) on Days 15 and 22. If the side effect profile is acceptable in the first cohort, the melflufen dose will be increased to 40 mg every 28 days with the other components of the triple combination being unchanged.

It is anticipated that the combination of melflufen with bortezomib and dexamethasone will also contribute to hematologic toxicity, thus the initial starting dose of melflufen will be 30 mg on Day 1 of each cycle with the goal to increase to 40 mg if feasible or to drop down to 20 mg if needed. The twice weekly dosing of bortezomib (Days 1, 4, 8 and 11), was selected based on the transient duration and differing mechanism of thrombocytopenia related to bortezomib compared to melflufen. With this schedule, it may be possible to deliver the full anti-tumor effect of bortezomib to a patient by front loading the administration of this compound in each cycle while the transient and limited anti-thrombocyte count effect has passed before the full anti-tumor count effect from melflufen becomes apparent in most patients.

The once weekly schedule of bortezomib has been shown to have similar antitumor efficacy combined with reduced peripheral neuropathy (Bringhen et al. 2010, Mateos et al, 2014). In the event that twice weekly bortezomib is not tolerable, once weekly dosing may be explored.

Changes in the standard doses or schedule of the partner drug, may only be adjusted following review and recommendation by the DSMC. Dose modifications may be made for individual patients based on toxicity during therapy.

The toxicity profile of daratumumab is mainly related to infusion related reactions (Lonial et al. 2016). A study conducted by Moreau and colleagues concluded that daratumumab added little additional toxicity to the combination therapies tested (Moreau et al. 2014). However, hematologic toxicity was noted in single agent studies (Lonial et al. 2016, Usmani et al. 2016) and increased rates of thrombocytopenia were noted in the combination of daratumumab with bortezomib and dexamethasone compared to bortezomib and dexamethasone without daratumumab, (Palumbo et al. 2016). For this reason, the same dose levels of melflufen as proposed for the combination of melflufen with bortezomib will be implemented in the combination of melflufen with the approved dose of daratumumab with the 4-week dosing schedule. The first dose of daratumumab will be administered on Day 2 of Cycle 1 due to prolonged infusion times if both melflufen and daratumumab were to be given on Day 1.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

3.1.1 Phase 1 Primary Objective

- The primary objective of the Phase 1 portion of the study is to determine the optimal dose of melflufen, up to a maximum of 40 mg, given every 28 days in triple drug combination therapy in patients with relapsed or RRMM. Each treatment regimen will be evaluated separately.

3.1.2 Phase 2a Primary Objective

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

3.2 SECONDARY OBJECTIVES

- To evaluate the best response including complete response/stringent complete response (CR/sCR), very good partial response (VGPR), PR and clinical benefit rate (CBR: proportion of patients with ≥ MR), time to response (TTR), duration of response (PR or better), duration of CB, progression free survival (PFS) and overall survival (OS)

up to a minimum of 2 years as defined in the SAP.. International Myeloma Working Group Uniform Response Criteria (IMWG-URC) guidelines will be used (Rajkumar et al. 2011, Appendix C). Each treatment regimen and dose will be evaluated separately.

- To further explore the safety and tolerability of the combination regimens. Each treatment regimen and dose will be evaluated separately.

3.3 EXPLORATORY OBJECTIVES

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

4 STUDY DESIGN

4.1 DESCRIPTION OF STUDY DESIGN

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

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

All patients meeting the required eligibility criteria may be eligible for one or both of the defined Regimens. For patients that are eligible for both Regimens, the Regimen selection may be determined by the investigator, given cohort availability for the selected Regimen at the time of screening. Only one cohort per patient will be reserved at a given time. If the patient fails screening for the reserved Regimen cohort, enrollment in a non-reserved Regimen cohort will be based on availability. Both regimens may enroll simultaneously to an available cohort.

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

Patients who discontinue treatment with one drug in the Regimen (excluding dexamethasone) for any reason, may continue treatment with the other drug in the Regimen at the investigator discretion if in the patients' best interest. Patients who discontinue melflufen and continue on treatment with the other dug in the Regimen will be followed for response, PFS and OS follow-up.

Regimen A: Melflufen plus Bortezomib and Dexamethasone

Up to 3 dose levels will be tested; i.v. melflufen at 30 mg and 40 mg or 20 mg given on Day 1 of every 28-day cycle, in combination with subcutaneous (SQ) bortezomib at 1.3 mg/m2 twice weekly on Days 1, 4, 8 and 11 of each 28-day cycle and a fixed dose of dexamethasone 20 mg orally (p.o.) on Days 1, 4, 8, and 11, and 40 mg on Days 15 and 22. For patients ≥ 75 years of age, 12 mg will be given on Days 1, 4, 8 and 11 and 20 mg on Days 15 and 22.

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

Regimen B: Melflufen plus Daratumumab and Dexamethasone

Up to 3 dose levels of melflufen will be tested; i.v. melflufen at 30 mg and 40 mg or 20 mg given on Day 1 of every 28-day cycle, in combination with daratumumab 16 mg/kg according to the following daratumumab schedule: in Table 4-1.

Table 4-1 Daratumumab Schedule

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

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

Dexamethasone 40 mg p.o. (20 mg p.o. for patients ≥ 75 years of age) will be given weekly. Due to the need for steroids to prevent infusion reactions with daratumumab, dexamethasone dosing may be split prior to the daratumumab infusion, and the day after daratumumab on weeks when daratumumab is given. Refer to the dose and schedule of dexamethasone in Table 6-2.

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

All Dosing Regimens:

Once the optimal dose of melflufen has been determined for each combination regimen in Phase 1, approximately 20 additional efficacy evaluable patients will be enrolled in each combination regimen and treated at the dose determined in the Phase 1 part of the study.

Patients will be assessed for response after each cycle according to the IMWG-URC. Patients who have benefit from the therapy may continue treatment until disease progression or unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue. Dose modifications may be implemented to manage toxicity according to the protocol guidelines in for each Regimen in Section 6.8.

Patients who discontinue treatment with any drug in the Regimen (excluding dexamethasone) for any reason may continue treatment with the other drug in the Regimen at the investigator discretion if in the patients' best interest. Patients who discontinue melflufen and continue treatment with the other drug in the Regimen will be followed for response, PFS and OS follow-up.

A Schedule of Events for the study is outlined in Section 8, Table 8-1.

5 PATIENT POPULATION

5.1 PATIENT SCREENING

Written informed consent must be obtained before any protocol-specific screening tests or procedures are performed. Patients must meet all the entry criteria detailed in Section 5.2.1 and Section 5.2.2. After informed consent is obtained, the screening assessments will be performed as detailed in Section 8 of the protocol. Table 8-1, Schedule of Events, lists all of the screening assessments including frequency and time lines of when assessments are to be performed.

Assessments performed as part of the patient's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to enrollment.

All patients meeting the required eligibility criteria may be eligible for one or both of the defined Regimens. For patients that are eligible for both Regimens, the Regimen selection may be determined by the investigator, given cohort availability for the selected Regimen at the time of screening. Only one cohort per patient will be reserved at a given time. If the patient fails screening for the reserved Regimen cohort, but is eligible for enrollment in a non-reserved Regimen cohort, assignment of that cohort will be based on availability. Patients may be re-screened if appropriate.

5.1.1 Screening Failures

Patients who sign an informed consent but fail to be enrolled for any reason, e.g. do not fulfill eligibility criteria below, will be considered screen failures. Patients may be re-screened following all the same criteria in the event a screening evaluation changes.

5.2 PATIENT ELIGIBILITY

The Investigator must ensure that patients meet all the following inclusion and exclusion criteria.

5.2.1 Inclusion Criteria

Patients will be considered eligible for inclusion in this study if they meet all of the following criteria:

1. Male or female, age 18 years or older;
2. A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening;
3. One to four prior lines of therapy (Appendix D);
4. Measurable disease defined as any of the following:
   - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
   - ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis (UPEP)
   - Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain ratio;
5. Life expectancy of ≥ 6 months;

6. 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) (Appendix A);
7. Patient is a female of childbearing potential (FCBP)* with a negative serum or urine pregnancy test prior to initiation of therapy and agrees to practice appropriate methods of birth control, or is a female not of childbearing potential, or the patient is a male and agrees to practice appropriate methods of birth control (Section 7.1);
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent;
9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec (Appendix H);
10. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study drug 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 therapy)
    - Platelet count ≥ 75,000 cells/mm3 (75 x 10^9/L) (without required 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), or 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 and serum creatinine ≤ 2 mg/dL (Appendix G);
11. Must have, or be willing to have, an acceptable central catheter. (port a cath, peripherally inserted central catheter [PICC] line, or central venous catheter);

Regimen Specific Inclusion criteria:

Regimen A – Melflufen + Bortezomib and Dexamethasone

A1 Must be intolerant or refractory to a prior IMiD; refractory defined as failure to respond (MR or better) or progression while on therapy or within 60 days of last dose.

Regimen B – Melflufen + Daratumumab and Dexamethasone

B1 Must have had a prior IMiD and a proteasome inhibitor (PI); alone or in combination and must be refractory or intolerant to an IMiD, PI or both.

During Phase 2a, enrollment based on number of prior therapies and/or refractory status may be further explored to optimize the benefit/risk balance as recommended by the DSMC.

*(FCBP) is any sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months.

5.2.2 Exclusion Criteria

Patients will be ineligible for this study if they meet any one of the following criteria:

1. Primary refractory disease (i.e. never responded with ≥ MR to any prior therapy);
2. Evidence of mucosal or internal bleeding and/or platelet transfusion refractory (i.e. platelet count fails to increase by > 10,000 cells/mm^3 after transfusion of an appropriate dose of platelets);
3. 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., myocardial infarction, significant cardiac conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months);
4. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of initiation of therapy;
5. 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;
6. Pregnant or breast-feeding females;
7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation;
8. Known human immunodeficiency virus or active hepatitis B or C viral infection (see criterion B5 additional requirements for Regimen B);
9. Concurrent symptomatic amyloidosis or plasma cell leukemia;
10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);
11. 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 antibodies (mAb) within 4 weeks of initiation of therapy Prednisone up to but no more than 10 mg orally once daily (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;
12. 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);
13. Prior peripheral stem cell transplant within 12 weeks of initiation of therapy;
14. Prior allogeneic stem cell transplantation with active graft-versus-host- disease;

15. Prior major surgical procedure or radiation therapy within 4 weeks of initiation of therapy (this does not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy);
16. Known intolerance to the required dose and schedule of steroid therapy as determined by the investigator.
17. Prior treatment with melflufen

Regimen specific exclusion criteria

Regimen A – Melflufen + Bortezomib and Dexamethasone

A1 Refractory to a PI in the last line of therapy prior to enrollment in this trial; refractory defined as failure to respond (MR or better) or progression while on therapy or within 60 days of last dose.

A2 History of allergic reaction/hypersensitivity attributed to compounds containing boron, mannitol, polysorbate 80 or sodium citrate dihydrate (see Appendix K).

Regimen B – Melflufen + Daratumumab and Dexamethasone

B1 Prior exposure to an antiCD-38 mAb;

B2 Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) less than 50% of predicted normal;

B3 Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification;

B4 ≥ Grade 3 conduction system abnormalities unless patient has a pacemaker.

B5 Active hepatitis B (defined as HBsAg+) or those at risk for reactivation (HBsAg-, Anti-HBs+, Anti-HBc+).

- Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-).
- Non-active hepatitis B (HBsAg-, Anti-HBs+, Anti-HBc+) may only be enrolled after approval of the sponsor and consideration of risk of reactivation (additional screening and monitoring for reactivation of Hepatitis B and consultation with a liver disease specialist may be required) (see Table 8-1 footnote u).

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 regimens 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.

5.3 PATIENT ENROLLMENT

5.3.1 Enrollment Procedure

Sites must be formally notified of activation before patients can be consented at that site. An IRB/EC approved Informed consent form (ICF) must be signed by the patient before any study-specific tests may be performed.

Complete details on patient enrollment procedures are provided in the Investigator Site File (ISF) at each site. Following completion of the ICF process and Screening activities the site will complete a patient enrollment form and submit along with the required documentation to the Medical Monitor for approval. Once eligibility is confirmed by the medical monitor, the

patient will be considered enrolled into the study and the site will be notified of the Regimen and cohort assignment for patients enrolled in Phase 1 or the established dose and schedule of the Regimen for patients enrolled in Phase 2a. Further details will be provided in the Investigator Site File (ISF) at each site.

Patients that do not meet all the eligibility criteria will be considered screen failures and will not be enrolled.

5.3.2 Patient Numbering

A unique patient number will be assigned at the time of signing of consent.

5.3.3 Replacement Policy

Patients in Phase 1 who are not fully evaluable for assessment of DLT may be replaced and patients in Phase 2a who are not efficacy evaluable may be replaced. Efficacy evaluable patients are those who receive at least 2 doses of melflufen and ≥ 50% of the partner therapy (excluding dexamethasone) during Cycles 1 and 2, had a baseline disease assessment, and had at least 1 post-baseline disease assessment ≥ 28 days after first dose.

6 STUDY TREATMENT

Treatment may be given in an outpatient treatment setting in cycles. Each cycle is 28 days. Pretreatment tests/procedures and timelines are detailed in Table 8-1, Schedule of Events. All evaluations must be complete prior to enrollment and initiation of treatment.

6.1 REGIMEN A AND B: DOSE LEVEL SELECTION

6.1.1 Phase 1

The first cohort of patients (3 - 6) enrolled in the Phase 1 portion of each Regimen will receive dose level 1. A full safety evaluation will be conducted by the DSMC when the planned number of melflufen safety evaluable patients have completed the first cycle of combination therapy with DLT assessment. Subsequent patients will be enrolled in the dose level based on the dose escalation schema. The optimal dose of melflufen in combination therapy will be defined as the highest dose of 20, 30 or 40 mg of melflufen that results in ≤ 1/6 patients with DLT during the first cycle of therapy (See Section 6.3). The dose of melflufen can never be reduced to lower than 20 mg. Patients who discontinue treatment for reasons other than study drug related toxicity and/or are considered non-evaluable for DLT assessment may be replaced at the discretion of the DSMC.

6.1.2 Phase 2a

Patients in Phase 2a will be enrolled in the optimal dose and schedule determined in Phase 1.

6.2 REGIMEN A AND B: INITIATION OF THERAPY (CYCLE 1 DAY 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/ mm3 (1.0 x 109/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] of initiation of therapy)

- Platelet count ≥ 75,000 cells/ mm3 (75 x 109/L) (without transfusion during the previous 10 days to initiation of therapy)
- 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 glomerular filtration rate by Cockcroft-Gault formula ≥ 45 mL/min (Appendix G)

6.3 REGIMEN A AND B: DOSE ESCALATION SCHEMA

- If no DLT is reported in the first three patients at a dose level, that dose level will be considered safe and three patients will be enrolled at the next dose level.
- If 1/3 patients in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable patients.
- If 2/3 patients in a cohort at a dose level has a DLT, that dose level will not be considered safe and no further dose escalation will take place.
- If there are < 2 patients with a DLT among the expanded cohort of six evaluable patients a cohort of three patients will be enrolled in the next higher dose level.
- If there are 2 or more patients with a DLT among the expanded cohort of six evaluable patients, that dose level will not be considered safe and no further dose escalation will take place.

If less than 6 patients have been treated in the next lower dose level, additional patients will be entered into this dose level until there are 6 patients treated. If ≤ 1 of these 6 patients encountered DLT, then this dose level will be taken forward to Phase 2a. If 2 or more of the 6 patients encounter DLT, a lower dose will be considered.

NOTE: If a patient discontinues therapy during Cycle 1 for reasons other than treatment related toxicity and is considered non-evaluable for DLT assessment, the patient may be replaced at the discretion of the DSMC.

The 6 patients treated in Phase 1 with the dose taken forward to Phase 2a will be the first 6 patients of the Phase 2a component of the study.

Patients who discontinue treatment with any drug in the Regimen (excluding dexamethasone) for any reason may continue treatment with the other drug in the Regimen at the investigator discretion if in the patients' best interest. Patients who discontinue melflufen and continue on treatment with the other drug in the Regimen will be followed for response, PFS and OS follow-up.

Patients starting on 30 mg of melflufen in Phase 1, that did not experience a DLT in Cycle 1 and did not required a dose reduction in any cycle may be considered for increase in the dose of melflufen to 40 mg, following consultation with the medical monitor and sponsor if in the best interest of the patient to optimize risk/benefit balance. In addition, the 40 mg melflufen dose cohort must be completed and considered well tolerated.

6.4 REGIMEN A AND B: DOSE LEVELS TO BE TESTED

6.4.1 Regimen A Dose levels

Up to 3 dose levels will be tested; i.v. melflufen at 30 mg and 40 mg or 20 mg given on Day 1 of every 28-day cycle, in combination with subcutaneous (SQ) bortezomib at 1.3 mg/m2 twice weekly on Days 1, 4, 8 and 11 of each 28-day cycle and a fixed dose of dexamethasone 20 mg orally (p.o.)(12 mg for patients ≥ 75 years of age) on Days 1, 4, 8, 11, and 40 mg (20 mg for patients ≥ 75 years of age) on Days 15 and 22 of each 28-day cycle

Table 6-1 Dose Levels to be Tested

Dose level	Melflufen dose (i.v.)	Bortezomib dose (SQ)*	Dexamethasone dose## (p.o.)
Days of Cycle	Day 1	Days 1, 4, 8, 11	Day of bortezomib on Days 1, 4, 8, 11, and on Days 15** and 22**
Level - 1	20 mg	1.3 mg/m^2	20 mg**
Level 1 Starting dose	30 mg	1.3 mg/m^2	20 mg**
Level 2	40 mg	1.3 mg/m^2	20 mg**

*i.v. administration of bortezomib is acceptable only if the SQ procedure is not tolerated.

**Dexamethasone dose will be decreased to 12 mg for patients ≥75 years of age on Days 1, 4, 8 and 11. Dexamethasone 40 mg (20 mg for patients ≥ 75 years of age) will be given on Days 15 and 22. See Section 6.5.2.3 for dexamethasone administration during cycle delays. ##Dexamethasone 40 mg (20 mg for patients ≥ 75 years of age) may be continued weekly during cycle delays

Dose modifications and delays may be implemented based on patient tolerance as detailed in Section 6.8. Alternate dose levels or schedules of melflufen, bortezomib or dexamethasone may be explored based on tolerability following review and recommendation of the DSMC.

6.4.2 Regimen B Dose Levels

Up to 3 dose levels will be tested; i.v. melflufen at 30 mg and 40 mg or 20 mg given on Day 1 of every 28-day cycle, in combination with daratumumab 16 mg/kg weekly for 8 doses, every 2 weeks for 8 doses and then every 4 weeks (Table 6-2) with dexamethasone 20 mg pre daratumumab infusion and 20 mg the day after the infusion. For patients ≥ 75 years of age 20 mg of dexamethasone will be given only prior to each daratumumab infusion.

Table 6-2 Regimen B Dose Levels

Dose Level	Melflufen dose (i.v.)	Daratumumab dose (i.v.)	Dexamethasone dose (p.o.*)
Cycle = 28 days	Day 1	**Cycle 1 -**Days 2**, 8, 15 and 22 **Cycle 2** - Days 1, 8, 15, 22 **Cycle 3 to 6 -** Days 1 and 15 **Cycle 7 + -** Day 1	**On days when melflufen and daratumumab are given in combination (Day 1)**:** Patients < 75 years old - Pre melflufen and daratumumab and the day after daratumumab Patients ≥ 75 years old- Pre melflufen and daratumumab
			All other daratumumab dosing days (see daratumumab schedule):

			Patients < 75 years old - Pre daratumumab and the day after daratumumab Patients ≥ 75 years old - Pre daratumumab
			On weeks when daratumumab is not given (not scheduled or dose held) on Days 8, 15, 22 (see daratumumab schedule)
Level – 1	20 mg	16 mg/kg	**Melflufen and daratumumab in combination:** Patients < 75 years old - 20 mg Day 1** and 2 Patients ≥ 75 years old – 20 mg Day 1**
			All other daratumumab dosing days: Patients < 75 years old - 20 mg pre, and the day after daratumumab Patients ≥ 75 years old – 20 mg pre daratumumab
			During cycles when daratumumab is not given (not scheduled or dose held) on Days 8, 15 or 22: Patients < 75 years old - 40 mg p.o. Patients ≥ 75 years old – 20 mg p.o.
Level 1 Starting dose	30 mg	16 mg/kg	**Melflufen and daratumumab in combination:** Patients < 75 years old - 20 mg Day 1** and 2 Patients ≥ 75 years old – 20 mg Day 1**
			All other daratumumab dosing days: Patients < 75 years old - 20 mg pre, and the day after daratumumab Patients ≥ 75 years old – 20 mg pre daratumumab
			During cycles when daratumumab is not given (not scheduled or dose held) on Days 8, 15 or 22: Patients < 75 years old - 40 mg p.o. Patients ≥ 75 years old – 20 mg p.o.
Level 2	40 mg	16 mg/kg	**Melflufen and daratumumab in combination:**

			Patients < 75 years old - 20 mg Day 1** and 2 Patients ≥ 75 years old – 20 mg Day 1**
			All other daratumumab dosing days: Patients < 75 years old –20 mg pre, and the day after daratumumab Patients ≥ 75 years old – 20 mg pre daratumumab
			During cycles when daratumumab is not given (not scheduled or dose held) on Days 8, 15 or 22: Patients < 75 years old – 40 mg p.o. Patients ≥ 75 years old – 20 mg p.o.

*Oral dexamethasone may be substituted with i.v. dexamethasone at the investigators discretion, prior to daratumumab infusion only, if this is the standard of care of the site.

**Due to prolonged infusion time of the first dose of daratumumab, the Cycle 1 infusion of daratumumab will be given on Day 2 of Cycle 1. Therefore, the dexamethasone dose of 20 mg will be given on Day 1 prior to melflufen and on Day 2 prior to the daratumumab administration in Cycle 1, for patients < 75 years of age. For patients ≥ 75 years of age, the Cycle 1, Day 1 dexamethasone 20 mg dose may be split between Day 1 and Day 2 at the investigators discretion (e.g dexamethasone 12 mg p.o. on Day 1 prior to melflufen and 8 mg p.o. on Day 2 prior to daratumumab) or dexamethasone may also be given i.v. with a split dose (e.g. dexamethasone 10 mg i.v. on Day 1 prior to melflufen and 10 mg i.v. on Day 2 prior to daratumumab). No dexamethasone is required the day following daratumumab in Cycle 1. However, additional steroids may be given as needed to prevent or treat hypersensitivity reactions at the investigators discretion and as per the SoC for the site. See Section 6.5.2.3 for dexamethasone administration when drug is held or cycle delays.

6.5 STUDY DRUG ADMINISTRATION

Refer to Section 9 for supply, storage, preparation and accountability of study drugs used in each Regimen.

6.5.1 Regimen A and B: Melflufen Administration

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 bortezomib (Regimen A) or daratumumab (Regimen B) are scheduled on the same day melflufen should be administered first.

The study treatment should be administered through a central 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. (Port A Cath, PICC line or central venous catheter).

Before infusion:

- Document vital signs prior to start of infusion

- Prepare the central catheter by flushing with approximately 20 mL of the same type of solution (5% glucose or 0.9% saline) that is used for dilution of the melflufen in the 250 mL bag.

Infusion:

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

After infusion:

- Document vital signs at the end of the infusion
- First flush the central catheter with approximately 20 mL of the same type of solution (5% glucose or 0.9% saline) that is used for dilution of the melflufen in the 250 mL bag. 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. Refer to Section 9 for melflufen supply, storage and accountability. Refer to the Pharmacy Manual for details on melflufen preparation and administration.

6.5.2 Regimen A and B: Dexamethasone Administration

6.5.2.1 Regimen A

Dexamethasone 20 mg (12 mg for patients ≥ 75 years of age) should be administered orally on the day of bortezomib on Days 1, 4, 8, and 11. Dexamethasone 40 mg (20 mg for patients ≥ 75 years of age) should be administered orally on Day 15 and 22. Dexamethasone is best administered prior to melflufen and prior to melflufen and bortezomib on days when both drugs are given on the same day (Day 1 of each cycle).

6.5.2.2 Regimen B

Dexamethasone 40 mg p.o. (20 mg p.o. for patients ≥ 75 years of age) will be given weekly. Due to the need for steroids to prevent infusion reactions with daratumumab, dexamethasone dosing may be split to give a dose prior to daratumumab, and the day after daratumumab on weeks when daratumumab is given. Refer to the dose and schedule of dexamethasone in Table 6-2. Oral dexamethasone may be substituted with i.v. dexamethasone, at the investigator's discretion, prior to daratumumab infusion only, if this is the standard of care of the site.

Due to prolonged infusion time of the first dose of daratumumab, the Cycle 1 infusion of daratumumab will be given on Day 2 of Cycle 1. Therefore, the dexamethasone dose will be given on Day 1 prior to melflufen and on Day 2 prior to the daratumumab administration in Cycle 1 for patients < 75 years of age. For patients ≥ 75 years of age, the Cycle 1, Day 1 dexamethasone 20 mg dose may be split between Day 1 and Day 2 at the investigators discretion (e.g dexamethasone 12 mg p.o. on Day 1 prior to melflufen and 8 mg p.o. on Day 2 prior to daratumumab) or dexamethasone may also be given i.v. with a split dose (e.g. dexamethasone 10 mg i.v. on Day 1 prior to melflufen and 10 mg i.v. on Day 2 prior to daratumumab). No dexamethasone is required the day following daratumumab in Cycle 1. However, additional steroids may be given as needed to prevent or treat hypersensitivity reactions at the investigator's discretion and as per the SoC for the site.

Dexamethasone is best administered prior to melflufen and prior to melflufen and daratumumab on days when both drugs are given on the same day (Day 1 of each cycle following Cycle 1 as noted above).

6.5.2.3 Regimen A and B

During cycles when daratumumab (Regimen B) is not administered each week (following week 9), dexamethasone 40 mg (20 mg for patients ≥ 75 years of age), should be administered p.o. weekly. Resulting in the patient receiving weekly dexamethasone regardless of the bortezomib or daratumumab administration schedule. Dexamethasone may be given if the partner drug is held or continued weekly during cycle delays, at the investigator's discretion.

6.5.3 Regimen A: Bortezomib Administration

The amount (in mg) of bortezomib to be administered will be determined based on body surface area (BSA). The BSA is to be calculated based on body weight using the DuBois formula (Appendix J). The dose should be calculated on Day 1 of the cycle, and should be recalculated at the start of the next cycle; the dose administered should remain the same throughout the cycle. If a patient experiences a notable change in weight (i.e., loss or gain of 5% body weight) within the cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time. Bortezomib should not be administered to patients who have a known allergy to bortezomib, boron or mannitol.

Bortezomib should be administered SQ. Sites for injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous or indurated. Refer to Section 9 and the bortezomib Prescribing Information or SmPC for complete drug preparation and administration guidelines for SQ administration. In the event that SQ administration procedure is not tolerated, bortezomib may be given i.v. at the investigator's discretion.

6.5.4 Regimen B: Daratumumab Administration

Table 6-3 Daratumumab Dosing Schedule

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

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

6.5.4.1 Pre-infusion Medications

Prior to each infusion of daratumumab, administer pre-infusion medications to reduce the risk of infusion reactions approximately 1 – 3 hours prior to the infusion of daratumumab as follows:

- Dexamethasone: See Table 6-2 for dexamethasone dose and schedule
- Antipyretics: (oral or i.v. acetaminophen 650 – 1000 mg)
- Antihistamine: (oral or i.v. diphenhydramine 25 – 50 mg or equivalent)

Alternate and or additional medications to reduce the risk of infusion related reactions such as montelukast 10 mg may be given at the investigator's discretion.

On days when melflufen and daratumumab are scheduled on the same day, dexamethasone should be given first (1-3 hours prior to the daratumumab infusion), followed by melflufen then followed by the pre-medication for daratumumab approximately 30 minutes prior to the start of the daratumumab administration. Dexamethasone should be given prior to melflufen, 1 – 3 hours prior to the infusion of daratumumab, when both drugs are given on the same day.

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.

6.5.4.2 Infusion Rates

Administer daratumumab infusion intravenously at the infusion rate described below in Table 6-4. Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

Table 6-4 Infusion Rates for Daratumumab Administration

	Dilution volume	Initial rate (first hour)	Rate increment[a]	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion	500 mL[b]	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

a) Consider incremental escalation of the infusion rate only in the absence of infusion reactions. Escalation not required and may be at the discretion of the investigator.

b) Use a dilution volume of 500 mL only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.

c) Use a modified initial rate for subsequent infusions (i.e. third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hour in the first two infusions. Otherwise, continue to use instructions for the second infusion.

6.5.4.3 Post-infusion Medications

For patients with a history of chronic obstructive pulmonary disease, consider prescribing post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids. Following the first four infusions, if the patient experiences no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

6.5.4.4 Management of Infusion Reactions

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab as outlined below.

- **Grade 1-2 (mild to moderate):** Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at

increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour.

- **Grade 3 (severe):** Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 6-4. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.
- **Grade 4 (life threatening):** Permanently discontinue daratumumab treatment.

6.6 PHASE 1 DOSE LIMITING TOXICITY

Toxicity will be graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03). The following criteria will apply to each cohort to be evaluated in Phase 1, Cycle 1 only. Each cohort will be assessed by the DSMC prior to changes in cohort assignment. Patients who discontinue therapy during cycle 1 for reasons other the study drug related toxicity and are considered non-evaluable for DLT assessment may be replaced at the discretion of the DSMC. Events that are clearly and incontrovertibly due to extraneous causes should not be counted as DLTs.

6.6.1 Regimen A: Dose Limiting Toxicity

The prophylactic use of growth factors and platelet transfusions is not permitted in Cycle 1 of the dose escalation cohorts in Phase 1.

- Grade 3 non-hematologic toxicity preventing the administration of > 1 dose of bortezomib during the 1st cycle
    - Grade 3 peripheral neuropathy in patients with a baseline neuropathy due to prior PI exposure will not be considered a DLT. These patients may be replaced at the discretion of the DSMC.
- Grade 4 or greater non-hematologic toxicity
- Grade 4 thrombocytopenia (platelet count < 25,000 cells/ mm3) preventing the administration of > 1 dose of bortezomib during the 1st cycle or with clinically significant bleeding during the 1st cycle
- Grade 4 neutropenia (ANC < 500 cells/mm3), lasting more than 7 days during the 1st cycle
- Greater than 14 days' delay to meet the criteria for the start of a new cycle (Cycle 2) due to toxicity

6.6.2 Regimen B: Dose Limiting Toxicity

Toxicity will be graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03).

The prophylactic use of growth factors and platelet transfusions is not permitted in Cycle 1 of the dose escalation cohorts in Phase 1.

The following DLT criteria will apply to Regimen B in Phase 1, Cycle 1 only:

- Grade 3 non-hematologic toxicity preventing the administration of > 1 dose of daratumumab during the 1st cycle
- Grade 4 or greater non-hematologic toxicity
- infusion related reactions are not considered DLT. Patients requiring discontinuation of daratumumab (Grade 4 or Grade 3 on 3 occasions [see Section 6.5.4.4]) may be replaced at the discretion of the DSMC
- Grade 4 thrombocytopenia (platelet count < 25,000 cells/ mm3) preventing the administration of > 1 dose of daratumumab during the 1st cycle or with clinically significant bleeding during the 1st cycle
- Grade 4 neutropenia (ANC < 500 cells/mm3), lasting more than 7 days during the 1st cycle.
- Greater than 14 days' delay to meet the criteria for the start of a new cycle (Cycle 2) due to toxicity

6.7 REGIMEN A AND B: INITIATION OF A NEW CYCLE OF THERAPY

The following guidelines apply to all cycles following Cycle 1. Patients should be assessed at the beginning of each cycle according to the tests and evaluations outlined on Day 1 of each cycle in Table 8-1: Schedule of Events. Refer to Section 6.8 for dose modifications related to toxicity. To begin a new cycle of treatment, the following criteria must be met.

Regimen A and B: Criteria for Initiation of a New Cycle of Therapy

- ANC must be ≥ 1,000 cells/mm^3 (1.0 x10^9/L)
- Platelet count must be ≥ 50,000 cells/mm^3 (50.0 x 10^9/L) (platelet transfusions not recommended within ≤ 5 days of dosing [See Section 7.2]). This is applicable for patients in both arms as well as for patients in arm A that have discontinued melflufen but remain on bortezomib and dexamethasone. For patients in arm B that have discontinued melflufen but remain on daratumumab and dexamethasone the platelet count must be ≥ 25,000 cells/mm^3 (25.0 x 10^9/L)
- All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except peripheral neuropathy Grade 1 without pain, alopecia and fatigue ≤ Grade 2)
- **(Regimen B only)** Absence of daratumumab infusion reactions that require discontinuation (Grade 4 or Grade 3 on three occurrences in the previous cycle see Section 6.5.4.4)

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 6.8 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 drug is held for more than 28 days due to drug related toxicity the patient will be removed from the study treatment and enter progression free survival follow-up (PFS-FU). If, however the patient was clearly benefiting from therapy, the patient may be able to continue treatment at the Investigator discretion and in consultation with the medical monitor, after resolution of the AE.

6.8 DOSE MODIFICATIONS

No dose modifications are permitted in Phase 1 during Cycle 1, unless the patient experiences DLT. Patients experiencing DLT during Cycle 1 may continue on therapy if the toxicity can be managed according to the dose modification guidelines outlined below. However, the DLT event will contribute to the assessment of toxicity for that given cohort.

Dose modifications are permitted following Cycle 1 in Phase 1 and in all cycles of Phase 2a according to guidelines described in this section. Toxicity should be assessed using the common terminology criteria for adverse events (CTCAE) version 4.03 (Appendix B). 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. Reduction of one agent and not the other 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.

6.8.1 Dose Reduction Steps

6.8.1.1 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 20 mg. If a patient is unable to tolerate the lowest dose of melflufen due to drug related toxicity the patient must be withdrawn from treatment. Prior to each cycle of melflufen the criteria for initiation of therapy must be met (See Section 6.7). Patients who discontinue treatment with any drug in the Regimen (excluding dexamethasone) for any reason may continue treatment with the other drug in the Regimen at the investigator discretion if in the patients' best interest. Patients who discontinue melflufen and continue on treatment with the other drug in the Regimen will be followed for response, PFS and OS follow-up.

Patients in Phase 1, starting on 30 mg melflufen, may have the dose increased to 40 mg following consultation with the medical monitor and sponsor, for patients who have not had a DLT in Cycle 1 and have not required a dose reduction in any cycle, if in the best interest of the patient. In addition, the 40 mg melflufen dose cohort must be completed and well tolerated.

Table 6-5 describes the dose reduction depending on the starting dose of melflufen.

Table 6-5 Dose Reduction Steps for Melflufen

Starting dose	Dose reduction Step - 1	Dose reduction Step – 2
40 mg	30 mg	20 mg
30 mg	20 mg	Discontinue
20 mg	Discontinue	Discontinue

6.8.1.2 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 6-7 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
12 mg	4mg	Discontinue

*40 mg dose (20 mg for patients ≥ 75 years of age) on scheduled days when bortezomib or daratumumab are not administered. Note when bortezomib dosing schedule changes to Days 1, 8, 15 and 22, dexamethasone will also be dosed on these days, 40 mg for patients < 75 years of age and 20 mg for patients ≥ 75 years of age. See Table 6-7.

6.8.1.3 Dose Reduction Steps for Bortezomib (Regimen A)

Dose modifications of bortezomib for drug related toxicity are permitted. Multiple dose reductions are permitted however, the lowest dose permitted is 0.7 mg/m2. If a patient is unable to tolerate the lowest dose of bortezomib due to drug related toxicity the patient must be withdrawn from treatment. Prior to each cycle of bortezomib the criteria for initiation of therapy must be met (See Section 6.7). If bortezomib is discontinued for any reason, the patient may continue on therapy with melflufen and dexamethasone.

Table 6-7 Dose Reduction Steps for Bortezomib

Starting dose of bortezomib	1st Dose reduction	2nd Dose reduction	3rd Dose reduction
Days 1,4,8,11	Days 1,4,8,11	Days 1,8,15,22	Days 1,8,15,22
1.3 mg/m^2	1.0 mg/m^2	1.0 mg/m^2	0.7 mg/m^2 OR Days 1, 8, 15 and maintain 1.0 mg/m^2

Alternate dose and schedules may be considered following consultation with the Medical Monitor to best manage the timing of hematologic toxicity. Note when bortezomib dosing schedule changes to Days 1, 8, 15 and 22, dexamethasone will also be dosed on these days 40 mg for patients < 75 (20 mg or patients ≥ 75 years of age).

6.8.1.4 Dose Reductions for Daratumumab (Regimen B)

No dose reductions of daratumumab are recommended. Refer to Table 6-4 for changes in the rate of infusion for daratumumab infusion related reactions.

6.8.2 Regimen A: Dose Modification Guidelines Based on Toxicity

Melflufen is a potent myelosuppressive agent, and bortezomib may contribute to hematologic toxicity, therefore 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 as necessary. It is recommended, at the investigator 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.

The guidelines for dose modification for both melflufen and bortezomib based on toxicity experienced on Day 1 of a cycle and during a cycle are detailed in Table 6-8. If the criteria for initiation of a new cycle of therapy, as detailed in Section 6.7, are not met on Day 29 (the next scheduled Day 1 of any given cycle), treatment should be held and the patient should be re-evaluated weekly.

Table 6-8 Regimen A: Dose Modification Guidelines for Melflufen and Bortezomib Related Toxicity

Toxicity	Cycle Day	Action with Melflufen	Action with Bortezomib*
Hematologic Toxicity – Supportive therapy with platelets and growth factors is permitted according to the guidelines in Section 7.2			
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 6.7).	Hold, evaluate weekly* and resume therapy when criteria for initiation of a new cycle are met (Section 6.7).
		First occurrence – if resolved in ≤ 14 days same dose may be resumed. Dose reduction or delay may be considered.	First occurrence – if resolved in ≤ 14 days same dose may be resumed. If resolved in > 14 days dose reduction of bortezomib in addition to melflufen is optional.
		If resolved in > 14 days dose reduction is required.	
		For subsequent episodes of hematologic toxicity, melflufen or bortezomib may be dose reduced together or independently at the investigators discretion to manage toxicity. Consultation with the Medical Monitor is encouraged.	
ANC < 500 mm^3 (0.5 X 10^9/L) **Platelet count** <25,000 mm^3 (<25.0 x 10^9 /L)	Any day during the cycle		Hold and evaluate with next scheduled administration. Resume therapy within the cycle if resolved to ≤ Grade 2 within the cycle.
Non-hematologic Toxicity Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly.**			
Grade 3 drug related non-hematologic toxicity	Day 1	Hold, evaluate weekly* and resume therapy when criteria for initiation of a new cycle are met (Section 6.7).	Hold, evaluate weekly* and resume therapy when criteria for initiation of a new cycle are met (Section 6.7).

		Assess attribution if possible and reduce responsible drug***	Assess attribution if possible and reduce responsible drug***
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***	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 reduce by one dose level when the criteria for a new cycle are met***
Grade 4 drug related non-hematologic toxicity	Any day	Discontinue therapy	Discontinue therapy

*If cycle prolongation due to study drug related toxicity of more than 28 days (beyond Day 57) is needed, study treatment is to be discontinued unless in the investigators opinion the patient is benefitting from therapy. Continuation must be discussed with the medical monitor or Sponsor on a case-by-case basis.

**For bortezomib related peripheral neuropathy please refer to Table 6-9.

*** 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, transient abnormal laboratory value, fatigue). This must be discussed with the Medical Monitor on a case by case basis.

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

Patients who discontinue treatment for a study related AE including abnormal laboratory value must be followed as described in Section 8.2.6 and 8.2.7.

Regimen A - Dose Modifications for Bortezomib Related Peripheral Neuropathy

Patients experiencing new or worsening peripheral neuropathy during bortezomib therapy may require a decrease in the dose and/or a less dose-intense schedule (see Table 6-7). For dose or schedule modification guidelines for patients who experience bortezomib related neuropathic pain and/or peripheral neuropathy see Table 6-9.

Table 6-9 Dose Modification for Bortezomib Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of peripheral neuropathy signs and symptoms	Modification of dose and regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce bortezomib by one dose level (Table 6-7)**

Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL ***)	Withhold bortezomib therapy until toxicity resolves to ≤ Grade 2 without pain. When toxicity resolves reinitiate with a reduced dose of bortezomib (if already dosing at 0.7 mg/m^2, discontinue therapy).
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib

*Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc;

**A weekly schedule of bortezomib maybe considered based on the current dose and schedule being tested or as determined to be safe by the DSMC. Consultation with the medical monitor is required.

***Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

6.8.3 Regimen B: Dose Modification Guidelines Based on Toxicity

6.8.3.1 Regimen B: Dose Modifications for Daratumumab

There are no dose reductions for daratumumab. Refer to Table 6-4 for changes in the rate of infusion for daratumumab hypersensitivity infusion related reactions.

6.8.3.2 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 a patient has received daratumumab. Type and screen patients prior to starting daratumumab.

Management of Hepatitis B Virus Reactivation

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted 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. Primary antiviral prophylaxis is permitted as per local standard of care.

6.8.3.3 Melflufen precautions

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 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 6-10 Dose Modifications for Melflufen and Daratumumab Drug Related Toxicity

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 7.2			

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 6.7).	Hold, evaluate weekly and resume therapy when criteria for initiation of a new cycle are met. (Section 6.7). For patients that have discontinued melflufen, dosing may continue if platelets are >25,000 mm^3 (>25.0 x 10^9 /L) (Section 6.7)
		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 (Refer to Table 6-3 for daratumumab schedule)		Hold until resolved to ≤ Grade 2 within the cycle (Refer to Table 6-3 for daratumumab scheduled) For patients that have discontinued melflufen, see Section 6.7
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* and resume therapy when criteria for initiation of a new cycle are met (Section 6.7). Reduce dose if attributed to melflufen***	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 (Section 6.7).

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***	**No dose reduction, refer to Section 6.4 for rate changes for related hypersensitivity reactions
Grade 4 drug related non-hematologic toxicity	Any day	Discontinue therapy	Discontinue therapy

*If cycle prolongation of more than 28 days (beyond Day 57) is needed, study treatment is to be discontinued unless in the investigators opinion the patient is benefitting from therapy. Continuation must be discussed with the medical monitor or Sponsor on a case by case basis.

**For daratumumab related infusion reactions please refer to Section 6.5.4.4

*** 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.

Alternate dose modification may be considered in discussion with the medical monitor or the Sponsor. 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).

Patients who discontinue treatment for a study related AE including abnormal laboratory value must be followed as described in Section 8.2.6 and 8.2.7.

6.8.4 Regimen A and B: Dose Modifications for Dexamethasone

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. However, alternate steroids may be required for prevention of daratumumab infusion related reactions. Refer to the daratumumab Prescribing Information or SmPC for further information. In the event of a cycle delay, unrelated to dexamethasone toxicity, dexamethasone may be continued weekly at the investigators discretion.

Table 6-11 Dose Modifications 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 H2 blockers, sucralfate, or omeprazole. 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 omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures,

Body System	Symptom	Recommended Action
	≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	decrease dose 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 or the Sponsor.

6.9 TREATMENT DURATION

Patients will receive treatment until there is documented PD, according to the IMWG-URC guidelines (Rajkumar et al. 2011, Appendix C), to be confirmed on two consecutive assessments, unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue. Confirmed PD (on 2 consecutive assessments) should be verified by the medical monitor prior to treatment discontinuation.

7 CONCOMITANT THERAPY

All blood products and baseline medications that the patient is taking within 21 days prior to the initiation of therapy must be recorded. All additional medications (other than study drug) or changes in baseline medications and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications page of the eCRF.

7.1 REQUIRED CONCOMITANT THERAPY

- **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.

  Females:

  - Birth control methods that are considered as highly effective include: tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or

implants), or partner's vasectomy. Microdose progesterone analogues should be avoided.

- Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.

Males:

Males must use a condom during any sexual contact with females of child-bearing potential during therapy and for three months after the last dose of study drug, even if they have had a successful vasectomy. Males should not donate sperm during the study and for 3 months after treatment has been stopped. 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.

- **Anti-viral prophylaxis**

  It is required that patients receive prophylaxis against herpes zoster using oral acyclovir (400 mgs twice daily) or valacyclovir (500 mgs twice daily) or equivalent antiviral therapy per institutional guidelines and at the discretion of the site investigator, unless the participant develops a hypersensitivity to the agents.

  Reactivation of Hepatitis B: See Section 6.8.3.2, regarding management of patients at risk for, or diagnosed with, reactivation of hepatitis B.

- **Regimen specific requirements**

  Refer to the specific subsection of each drug for any additional required concomitant medications associated with the respective drug in each Regimen.

7.2 RECOMMENDED CONCOMITANT THERAPY

- Pneumocystis prophylaxis
  - All patients are recommended 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 x per week. 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
- 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.
- Patients should receive full supportive care, including transfusions of blood and blood products (with the limitations of prophylactic use noted below), antibiotics, anti-diarrheals, analgesics, etc. and prophylactic treatment for tumor lysis syndrome when appropriate.
- Other prophylactic treatment for patient related concomitant conditions or risks may be considered.

- Bisphosphonate therapy i.v. or p.o. should be administered if indicated in accordance with institutional guidelines.
- Thrombocytopenia and neutropenia are known consequences of MM but also the most common expected adverse event (AE)s 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 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 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 6.2 for use of growth factors and platelet transfusions prior to the first dose of therapy).
- Recommended 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 or NCCN.org
    - 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 or NCCN.org
- Regimen specific recommendations
    - Refer to the drug administration section of each drug for any additional recommended concomitant medications associated with the respective drug in each Regimen.

7.3 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
- Other investigative agents should not be used during the study
- Radiation therapy to a limited area for bone pain to a pre-existing lesion may be considered in consultation with and approval of the medical monitor
- The use of live vaccines is prohibited during the study and for 30 days after last dose of study drug

- The prophylactic use of growth factors and platelet transfusions are not permitted to render the patient eligible for trial participation except as described within the inclusion criteria Section 5.2.1. Other limitations are detailed in Section 6.7 and Section 7.2.
- The prophylactic use of growth factors and platelet transfusions is not permitted in Cycle 1 of the dose escalation cohorts in Phase 1.

8 VISIT SCHEDULE AND ASSESSMENTS

8.1 STUDY FLOW AND VISIT SCHEDULE

Table 8-1 lists all of the assessments required in the study and marked with an "X", indicating when they are to be performed. Evaluations marked with (X) are only required if indicated. All data obtained from these assessments must be supported in the patient's source documentation.

Table 8-1 Schedule of Events

Evaluation	Screening Days -21 to -1	Regimen A and B (except where specified) All Cycles [t] Day 1	Day 8	Day 15	Day 22	End of Treatment [q]	PFS - FU[r]	OS-FU[s]
Informed consent [a]	X							
Inclusion/exclusion criteria and review on day 1	X	X						
Medical and disease history [b]	X							
Physical examination/symptom assessment [c]	X	X	(X)	(X)	(X)	X		
Vital signs and BSA [d]	X	X	(X)	(X)	(X)	X		
ECOG performance status	X	X				X		
Pregnancy test [e]	X	X				X		
Blood type and screen for **Regimen B only** prior to first dose of daratumumab	X							
Electrocardiogram [f]	X					X		
Chest X-ray	X							
Hematology [g]	X	X D1 and 4 for Reg A	(X)* D8 and 11 for Reg A	X	(X)*	X		
Coagulation [h]	X							
Blood chemistries [i]	X	X				X	(X)[r]	
Pulmonary Function Tests **Regimen B only**	X							
Hepatitis B screen (HBsAg, Anti-HBs, Anti-HBc) **Regimen B only [u]**	X	(X)				(X)	(X)	(X)
Urinalysis	X							
Bone marrow aspiration [j]	X	(X)				(X)	(X)[r]	
M protein assessments (SPEP/UPEP, IFE, SFLC) [k]	X	X				X	(X)[r]	
Serum β2-microglobulin	X							
Assessment of extramedullary plasmacytoma [l]	X	(X)				(X)	(X)[r]	
Skeletal survey or CT scan [m]	X	(X)				(X)	(X)[r]	
Pharmacokinetic samples [n]		(X)[n]						
Dexamethasone administration [o] and review of patient compliance*		Refer to the assigned Regimen for the required days of dexamethasone administration.						
Melflufen administration [o]		X						

Evaluation	**Screening Days -21 to -1**	**Regimen A and B (except where specified) All Cycles [t]**				**End of Treatment [q]**	**PFS - FU[r]**	**OS-FU[s]**
		Day 1	Day 8	Day 15	Day 22			
Bortezomib administration [o] **Regimen A only**		X D1 and 4	X D8 and 11	(X)	(X)			
Daratumumab administration [o] **Regimen B only**		X Day 2 C1 only	(X) (week 1 – 8)	(X) (week 1 – 24)	(X) (week 1-8)			
Concomitant medications [p]	X	→				X		
AE monitoring		→				X		
Follow-up (PFS, OS)							X[r]	X

(X) Only if indicated

a) All patients must sign an (IRB/IEC/REB)-approved informed consent document prior to enrollment and prior to any study related procedures.

b) Medical History including demographics, prior and current medical illness and conditions, prior surgical procedures. Disease history includes date of initial diagnosis, ISS, R-ISS and cytogenetics at diagnosis (if previously evaluated). ISS and R-ISS stage (Appendix I) at time of study entry. Prior surgery and/or radiation and anticancer therapy, including start and stop dates, documentation of best response, date of progressive disease and relapsed or refractory status (Appendix E).

c) A complete physical exam, including height (screening only) and weight, neurologic assessment and assessment for extramedullary myeloma (if present on PE) will be conducted at screening, Day 1 of each cycle and End of Treatment visit. A symptom directed physical examination will be conducted as needed during a cycle. Plasmacytomas that can be followed by physical exam are to be evaluated on Day 1 of each cycle. Baseline symptoms and residual toxicity from previous therapy is to be assessed within 21 days prior to initiation of therapy.

d) Vital signs including blood pressure, pulse, respiration rate, temperature, to be assessed at screening and pre and post melflufen infusion and pre and post each daratumumab infusion and as clinically indicated. Regimen A: BSA should be calculated on Day1 of each cycle prior to bortezomib administration. (See Section 6.5.3 and Appendix J).

e) All FCBP must have a medically supervised negative serum or urine pregnancy test prior to the initiation of therapy. A FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

f) A12-lead ECG assessment will be performed on all patients at screening and End of Treatment visit and as clinically indicated. Q-Tc interval to be assessed by Fridericia formula (Appendix H).

g) Hematology: CBC with differential, and platelet count. Patients are required to have all laboratory evaluations completed at the study center during Cycles 1 and 2. Following Cycle 2, CBC 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. Repeat CBC is required on Day 4 and 11 only for patients on twice weekly bortezomib (Regimen A). Exceptions and reduced frequency of CBC evaluations may be made only in consultation with the medical monitor. All CBC values collected in addition to protocol specified time points must be recorded in the eCRF. See Section 10.1.5 for reporting requirements of scheduled and unscheduled results of thrombocytopenia and neutropenia. 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 bortezomib administration on day 8 in each cycle and before each dose of daratumumab.

h) Coagulation: prothrombin time (PT), international normalized ratio (INR).

i) Blood chemistry: sodium, chloride, potassium, magnesium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), glucose (fasting at baseline), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine, and estimated glomerular filtration rate by Cockcroft-Gault Formula (Appendix G) calcium and lactate dehydrogenase (LDH). Patients are required to have all evaluations completed at the treatment center during Cycles 1 and 2. Following Cycle 2, Chemistry 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..

j) Bone marrow aspirate (BMA) to be collected at screening for % plasma cells, morphology, and cytogenetics by Fluorescence In-Situ Hybridization (FISH). Minimum FISH probes include t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q)(Sonneveld et al 2016). In addition, If cytogenetics by karyotype has been done according to institutional guidelines it should be recorded in the CRF. A BMA sample is to be collected at screening and stored for possible MRD assessment. If a bone marrow aspirate and/or biopsy has been collected within 28 days, with the appropriate evaluations, prior to initiation of therapy, it does not need to be repeated. A repeat BMA is required to confirm a suspected CR and to assess MRD status. Stored BMA samples may be used for optional future testing if requested by Oncopeptides in consenting patients and where regionally acceptable. Refer to Laboratory manual.

k) SPEP and UPEP and serum and urine IFE (if SPEP or UPEP are not detectable and to confirm a CR), quantitative immunoglobulins per routine lab practice 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, Cycle 1 Day 1 and prior to each cycle even if treatment is delayed. Quantitative immunoglobulins only need to be repeated for patients with IgA or IgD myeloma. All assessment of SPEP, UPEP, IFE and FLC must be completed in the same laboratory for a given patient. In the event treatment is delayed, ≥ 6 weeks (beyond Day 43), MM disease response assessments are required to be repeated on the day the new cycle starts (Day 50 or 57 of the previous cycle). If treatment is discontinued beyond Day 43 the response assessments should be repeated on the day of that determination (or as soon as possible ≥ 30 days after last dose of study drug) as part of the end of treatment (EoT) visit. As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive due to 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 (refer to the lab guidance document for details).

l) Known or suspected extramedullary plasmacytomas are to be assessed at screening (perform necessary imaging to obtain measurements), as clinically indicated and to confirm response identified by M protein or suspected progression. The same method of evaluation should be used throughout the study (e.g., Computerized tomography [CT]/ magnetic resonance imaging [MRI]/ positron emission tomography [PET]). All imaging assessments with measurements should be documented in the eCRF.

m) 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 or in place of conventional X-ray with the same technique to be used with each evaluation. Required if previous survey > 6 weeks from initiation of therapy and at any time when clinically indicated. Limited X-rays may be performed as clinically indicated to confirm PD.

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

o) See Section 6 in the protocol for complete details on study drug administration, dose modifications, start of a new cycle of therapy and study drug compliance. See Section 9 for study drug supply, storage, preparation and accountability.

p) Concomitant medications and procedures: - all blood products and medications within 21 days prior to first dose until the End of Treatment Visit.

q) End of Treatment 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) with evaluation of safety variables including recording of new and ongoing AEs, review of concomitant medications and any other new disease related therapy. 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. Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EoT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. SAEs should be followed until resolution or stabilization with no expected resolution.

r) Progression Free Survival Follow-Up (PFS-FU): Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until documented progression (confirmed on 2 consecutive assessments) or initiation of subsequent therapy. Schedule the first assessment 4 weeks after the EoT visit. Confirmed PD should be verified by medical monitor prior to discontinuation of therapy. If PD has not been confirmed prior to the initiation of subsequent therapy the reason for the subsequent therapy should be documented. Documentation of the start date and regimen of the first subsequent therapy is required. Serum calcium and albumin (corrected calcium) required only if evidence of PD.

s) Overall Survival Follow-up (OS-FU): 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 24 months. In the event that Oncopeptides AB would like to determine the OS status of patients following 24 months, future inquiries about their health status may be conducted. This information may be recorded outside of the eCRF established for this study. Documentation of the start date and regimen of the first subsequent therapy should be done if it occurs during OS -FU. Follow-up may be completed by phone contact. SAEs should be followed until resolution or stabilization with no expected resolution. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable.

t) +/- 3 day window permitted (Except Cycle 1 Day 1) for holidays/administrative reasons.

u) Hepatitis B assessments required for Regimen B screening. Patients with active hepatitis B (defined as HBsAg+) are excluded. Patients with non-active hepatitis B (HBsAg-, Anti-HBs+, Anti-HBc+) may only be enrolled after approval of the sponsor and consideration of risk of reactivation. If approved, additional screening

and monitoring will include HBV-DNA testing by PCR performed locally at screening, every 12 weeks during treatment, at the EoT Visit, then 3 and 6 months after the last dose of daratumumab. Consultation with a liver disease specialist may be required.

* If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (Granulocyte colony stimulating factor (G-CSF), blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded as the following; Regimen A Day 22; Regimen B Day 8 and Day 22. Patients should still be contacted weekly to follow up on AE/SAEs and Dexamethasone compliance.

8.2 STUDY ASSESSMENTS

Refer to the Table 8-1; Schedule of Events. For details and timelines and explanation of all study assessments. Refer to the Laboratory Guidance Document for details on lab testing requirements.

8.2.1 Screening Disease Assessments

- M-protein determination using the following procedures
    - SPEP and serum protein IFE with quantitative Ig;
        - Quantitative immunoglobulin evaluation may be based on regional availability of the test.
        - Immunofixation of serum is required at screening if M protein by SPEP is not detectable
    - UPEP and urine protein IFE (all using the same 24-hour urine collection)
        - Immunofixation of urine is required at screening if M protein by UPEP is not detectable
    - SFLC and SFLC ratio
        - FLC assessment is not required at screening in the presence of measurable SPEP and/or UPEP (SPEP ≥ 0.5 g/dL and/or UPEP ≥ 200 mg/24 hours),
        - If the M protein is non-measurable in SPEP and UPEP at screening or Cycle 1, Day 1, the FLC is required
- BMA to quantify percent myeloma cell involvement and morphology, cytogenetics by FISH and a sample stored for possible MRD assessment. If cytogenetics by karyotype has been done according to institutional guidelines it should be recorded in the CRF.
- Extramedullary plasmacytoma evaluation of known or suspected lesions (by PE or imaging procedures)
- Skeletal survey: 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 or in place of conventional X-ray (with the same technique to be used with each evaluation)
- Beta2 microglobulin
- Lactate dehydrogenase (LDH)
- ISS staging score and revised R-ISS (Appendix I)

8.2.2 Efficacy Assessments

M-protein determination using the following procedures (also refer to footnote k on Table 8-1):

- SPEP and serum protein IFE with quantitative immunoglobulins (For patients with IgA and IgD myeloma);

- As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive due to 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.
- Immunofixation of serum is required at any time when M protein by SPEP becomes non-detectable and to confirm a CR.

- UPEP and urine protein IFE (all using the same 24-hour urine collection); and
  - Immunofixation of urine is required at any time when M protein by UPEP becomes not detectable and to confirm a CR.
- SFLC and SFLC ratio
  - 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.
  - It is up to the site to work with the laboratory that performs the response analyses to ensure that the laboratory completes the immunofixation and FLC evaluations when required, to enable response assessments according to IMWG criteria.
- Extramedullary plasmacytoma evaluation with the same technique to be used with each evaluation
- Bone marrow aspirate to quantify percent myeloma cell involvement
- Skeletal X-rays and/or CT scans
- Serum calcium (corrected calcium)

8.2.3 Safety and Tolerability Assessments

- Assessment and grading of AE(s)
- Physical examination with vital signs, neurologic assessment and assessment of performance status
- Routine safety laboratory tests (CBC with differential and platelets; clinical chemistry, coagulation tests and urinalysis) with calculation of the glomerular filtration rate according to the Cockcroft-Gault formula. (Appendix G)
- Chest X-ray (postero-anterior/lateral)
- Pulmonary function tests (Regimen B only)
- Hepatitis Screen (Regimen B only)
- Pregnancy testing (FCBP)
- Electrocardiogram - Q-Tc interval to be assessed by Fridericia formula (Appendix H)

AEs, including clinical laboratory and vital sign abnormalities, will be graded using the CTCAE version 4.03 (Appendix B). Patients are evaluable for toxicity if they receive any dose of study treatment.

8.2.4 Pharmacokinetic Assessments

Plasma samples for determination of melphalan concentrations will be drawn in connection to 2 melflufen treatment cycles, 10 – 15 minutes after the end of the infusion, 1 hour after the end of infusion and 2 – 4 hours after the end of infusion (as late as possible within the time frame). Refer to the Laboratory Manual for details on collecting and processing specimens.

8.2.5 Assessments 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. 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 bortezomib administration on Day 8 in each cycle and before each dose of daratumumab. Patients who discontinue melflufen and continue to be treated with the other drug in the Regimen should also be followed for response, PFS and OS.

8.2.6 End of Treatment

The End of Treatment (EoT) visit should be scheduled 30 days (accepted time window ±3 days) after last dose of study drug or as soon as possible if the decision to remove the patient from therapy occurs later than 30 days after last dose (e.g. in the case of prolonged cycle). At the EoT visit evaluation of safety including recording of new and ongoing AEs, review of concomitant medications and any other new disease related therapy should be done. Patients with PD as the reason for EoT should have the PD confirmed with 2 consecutive assessments and verified by the medical monitor prior to discontinuation of therapy. 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. If PD has not been confirmed prior to the initiation of subsequent therapy the reason for the subsequent therapy should be documented. Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EoT visit are to be followed until resolution (≤ Grade 2), or initiation of subsequent therapy. Ongoing SAE's should be followed until resolution or stabilization with no expected resolution. The date and regimen of the first subsequent therapy should be recorded in the eCRF.

8.2.7 Follow Up Assessments

PFS-FU and OS-FU assessments should be completed on all patients unless due to death, lost to follow-up or the patient specifically has withdrawn consent for follow-up. Discontinuation from treatment does not preclude the need to complete follow-up assessments.

8.2.7.1 Progression Free Survival Follow-up

Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done for PFS-FU until progression or initiation of subsequent therapy. Schedule the first assessment 4 weeks after the EoT visit. If PD has not been confirmed prior to initiation of subsequent therapy the reason for the subsequent therapy should be documented. The start date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during PFS-FU.

8.2.7.2 Overall Survival Follow-up

Following confirmed disease progression, patients will be followed for OS-FU. Follow-up for overall survival status, second primary malignancies and first subsequent therapy will take place every three months +/- 7 days for 24 months. In the event that Oncopeptides AB would like to determine the OS statusf patients following 24 months, future inquiries about their health status may be conducted. This information may be recorded outside of the eCRF established for this study. OS-FU may be completed by phone contact. Death information from public sources, (e.g. death registry, obituary listing, etc.), can also be used when it is available and verifiable. The start date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during OS-FU.

8.2.7.3 Lost to Follow-Up

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient (e.g., dates of telephone calls, registered letters, etc.).

8.2.8 Criteria for Premature Patient Withdrawal

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

- Documented confirmed disease progression verified by the medical monitor (2 consecutive evaluations)
- Patients may choose to withdraw from the study treatment at any time and continue in follow-up
- AEs that, in the judgment of the investigator, may cause severe or permanent harm or which require study drug discontinuation (See Sections 6.8.2 and 6.8.3)
- Clinical judgment of the investigator: A patient may be withdrawn from the study treatment, if in the opinion of the investigator, it is not in the patient's best interest to continue
- Requiring other anti-neoplastic therapies
- Major deviation of the study protocol (i.e., unable to adhere to study schedule)
- Confirmed pregnancy
- Lost to follow-up

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

- Withdrawal of consent for study participation
- Death
- Lost to follow-up
- Discontinuation of the study by Oncopeptides AB
- Completed OS follow-up per protocol

The reason(s) for withdrawal of study treatment or study participation 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.

9 STUDY DRUG SUPPLY AND HANDLING

9.1 MELFLUFEN

9.1.1 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.

9.1.2 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 to +8°C (refrigerated).

9.1.3 Melflufen Supply

Melflufen will be provided by Oncopeptides free of charge.

9.1.4 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.

9.1.5 Melflufen Drug Preparation

Melflufen powder for solution for infusion is prepared by reconstitution with 5% glucose solution and then further diluted in a 250 mL infusion bag of either 5% glucose solution (ambient or cold) or 0.9% saline solution (cold). The i.v. tubing must be primed with the same solution either before or after the dilution of melflufen in the 250 mL bag. Careful attention and documentation of the preparation procedures and time frames are required since melflufen degrades in solutions*.

Time to infusion requirements:

- 250 mL bag of 5% glucose:

- **Ambient:** the 250 mL bag of 5% glucose should be at room temperature prior to adding melflufen. The maximum allowed time from start of reconstitution until the start of iv infusion is 30 minutes.
- **Pre-cooled:** the 250 mL bag of 5% glucose should be pre-cooled prior to adding melflufen. The maximum allowed time from start of reconstitution to start of infusion is 45 minutes.

- 250 mL bag of 0.9% saline:
  - The 250 mL bag of 0.9% saline should be pre-cooled prior to adding melflufen. The maximum allowed time from start of reconstitution until the start of iv infusion is 3.5 hours.

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. (See Pharmacy Manual for details).

9.2 DEXAMETHASONE

9.2.1 Dexamethasone Packaging and Labeling

No additional labeling is required for the use of commercial dexamethasone in the USA. Dexamethasone will be labeled for investigational use for sites outside of the USA.

9.2.2 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.

9.2.3 Dexamethasone Supply

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

9.3 BORTEZOMIB

9.3.1 Bortezomib Packaging and Labeling

Bortezomib for injection is a sterile lyophilized powder for reconstitution and is supplied in sterile, single use vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of bortezomib contain 35 mg of mannitol.

Bortezomib will be labeled for investigational use according to local regulations.

9.3.2 Bortezomib Storage

Vials containing lyophilized bortezomib for injection should be stored according to label requirements. Store at USP controlled room temperature which is 25°C (77°F); excursions permitted from 15 to 30°C (59 to 86°F). Upon receipt, the temperature log should be checked and notice given to supplier of the condition of the shipment.

9.3.3 Bortezomib Supply

Commercial supplies of bortezomib should be used for patients enrolling at sites in the USA. Bortezomib will be supplied by Oncopeptides to sites other than USA. Please refer to the Pharmacy Manual for complete details on drug supply and ordering procedures.

9.3.4 Bortezomib Special Handling

Bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling bortezomib 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.

9.3.5 Bortezomib Drug Preparation

Please refer to the Prescribing Information or the SmPC for instructions on drug preparation of bortezomib for SQ or i.v. administration.

9.4 DARATUMUMAB

9.4.1 Daratumumab Packaging and Labeling

Daratumumab is a colorless to yellow, preservative-free solution available as Injection:

- 100 mg/5 mL (20 mg/mL) in a single-dose vial
- 400 mg/20 mL (20 mg/mL) in a single-dose vial

Daratumumab will be labeled for investigational use for sites according to local regulations.

9.4.2 Daratumumab Storage

Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze or shake. Protect from light. This product contains no preservative. Upon receipt, the temperature log should be checked, and notice given to supplier of the condition of the shipment.

Since daratumumab does not contain a preservative, administer the diluted solution immediately at room temperature 15°C–25°C (59°F–77°F) and in room light. Diluted solution may be kept at room temperature for a maximum of 15 hours (including infusion time).

If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions 2°C – 8°C (36°F–46°F) and protected from light. Do not freeze.

If stored in the refrigerator, allow the solution to come to room temperature. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP or PE.

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

9.4.3 Daratumumab Supply

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

9.4.4 Daratumumab Drug Preparation

Refer to the Prescribing Information or the SMPC for instructions on daratumumab preparation and requirements for administration. Also refer to Section 6.5.4.

9.5 STUDY DRUG COMPLIANCE AND ACCOUNTABILITY

9.5.1 Study Drug Compliance

Compliance 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.

9.5.2 Study Drug Accountability

All study drug must be stored by the sites in a secure facility with limited access. The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment supplied to the site by the Sponsor in a drug accountability log. Drug accountability will be reviewed by the Clinical Research Organization (CRO) monitor during site visits and at the completion of the study.

At study close-out, and as appropriate during the course of 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.

10 SAFETY MONITORING AND REPORTING

10.1 ADVERSE EVENTS

10.1.1 Definitions

An AE is any untoward medical occurrence in a study patient administered an investigational product and that does not necessarily have a causal relationship with this treatment.

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

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the melflufen IB or partner therapy Package Insert would be considered "unexpected".

10.1.2 Grading of Severity

Whenever possible, the CTCAE version 4.03 should be used to describe the event and for assessing the severity of AEs (See Appendix B). 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 (Section 10.1.5).

For AEs not adequately addressed in the CTCAE, the severity in Table 10-1 may be used:

Table 10-1 Adverse Event Severity

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

10.1.3 Causality

The assessment of causality should be based on the information available, and may be changed upon receipt of additional information.

Causality should be assessed using the following categories:

- 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.

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 10.1.5.1).

10.1.4 Adverse Event Reporting

All AEs that are spontaneously reported by the patient or detected during or between visits by non-directive questioning, through physical examination, laboratory test, or other assessments should be reported in the eCRF. As far as possible, each AE should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5);
2. Its duration (Start and end dates);
3. Its relationship to the study treatment (causality);
4. Action taken with study drug (e.g., none, dose reduced, dose held, permanently discontinued);
5. Whether medication or therapy was given (e.g., concomitant medication or procedure);
6. Outcome (e.g., not resolved, resolved, resolved with sequalae, fatal, unknown);
7. Whether it is a SAE as defined in Section 10.2.1.

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the eCRF.

Any AE (e.g., a new event or an exacerbation of a pre-existing condition) that occurs after the first dose of study medication up to 30 days after the last study drug administration must be recorded as an AE on the appropriate page(s) of the eCRF. Should a patient discontinue from treatment and commence subsequent anticancer therapy within 30 days of the last study drug administration, AEs attributable to this subsequent therapy should not be recorded.

10.1.5 Laboratory Test Abnormalities

10.1.5.1 Definitions and Reporting

Laboratory abnormalities are usually not recorded as AEs; however, signs and/or symptoms that are associated with laboratory findings requiring treatment discontinuation, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as AE's (or serious AE's) if they meet the definition of an AE (or serious AE) as described in Section 10.1 or 10.2. In addition, laboratory abnormalities assessed as clinically significant should also be recorded as AEs. 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).

Clinically significant laboratory abnormalities are those that:

- Induce clinical signs and symptoms
- Require concomitant therapy
- Require change in study treatment
- Investigator considers clinically significant for any reason

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 protocol participation, 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 in the SAE report;
- All ANC and platelet counts associated with a 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 AE or prophylactic reasons must be reported in the eCRF and if applicable also in the SAE report.

10.2 SERIOUS ADVERSE EVENTS

10.2.1 Definitions

A SAE is defined as any AE, occurring at any dose that meets any one or more of the following criteria:

- Is fatal or immediately life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant; defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or if the patient may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Note that hospitalizations for the following reasons should not be reported as SAE's:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition including
    - Hospitalization that is needed to complete a daratumumab infusion or due to an infusion related reaction (not due to melflufen)
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
- Disease progression: In instances of SAE's due to "disease progression" the event or condition that met the criteria for the SAE should be indicated as the event term or condition rather than disease progression to the extent possible (e.g. "respiratory failure" or "renal failure" due to progressive MM)

10.2.2 Serious Adverse Event Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has signed informed consent and until 30 days after the last administration of any study drug must be reported to the Oncopeptides AB designated CRO and reported in the EDC system , within 24 hours of the onset or after the investigator became aware of the SAE.

An SAE reporting form must be filled out and sent via email to designated CRO. Fax can be used as a back-up method for transmission of information only if emailing reports is not possible (fax number is provided in the Investigator Site File).

- Email: [redacted]

The initial SAE report form should have the following data elements, at a minimum, to constitute a valid report: a patient identifier (patient number), an identifiable investigational agent (study drug), an identifiable reporting source (investigator's name or site number) as well as an identifiable serious adverse event. The investigator's initial causality assessment must also be included if available.

Each re-occurrence, change in grade, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAE that occurs after the above defined regular SAE reporting period, should also be reported if the investigator suspects a causal relationship to the study treatment. All deaths occurring during the regular SAE reporting period must be reported, regardless of cause (See Section 10.2.2.1).

SAEs should be followed until resolution, or stabilization with no anticipation of resolution regardless of 30-days reporting time line unless deemed by the investigator as not expected to resolve at the last study visit or patient is lost to follow-up and this is documented in the study file.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the Health Competent Authorities and concerned Independent Ethics Committees (IECs/Institutional Review Boards (IRBs) in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. For the purpose of SUSAR reporting, only possibly or probably related SAEs (i.e. there is a reasonable possibility of causality) will be considered serious adverse drug reactions.

10.2.2.1 Reporting of Death

- 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.

10.3 PREGNANCY

All instances of pregnancy occurring in a patient or partner of a patient taking study therapy must be reported within 24 hours of awareness of the pregnancy.

The pregnancy should be followed-up to determine its outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications and possible relationship to the study treatment.

A pregnancy reporting form must be filled out and sent via email to designated CRO. Fax can be used as a back-up method for transmission of information only if emailing reports is not possible (fax number is provided in the Investigator Site File.

- Email: [redacted]

Any SAE experienced during pregnancy (such as congenital anomaly/birth defect/spontaneous abortions) must be reported as noted above.

Male patients, who impregnate their female partners during study participation, should be requested to provide the outcome and details of the pregnancy, with details completed as above.

11 DATA COLLECTION AND MANAGEMENT

11.1 DATA CONFIDENTIALITY

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization form informing the patient of the following:

- What personal identifying and health information will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their personal and health information

In the event that a patient revokes authorization to collect or use personal identifying and health information, the Sponsor and its agents, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use personal identifying and health information, attempts should be made to obtain permission to collect follow-up safety information.

Access to the data collection system will be controlled by user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

11.2 SITE MONITORING

Before study initiation, at a site initiation visit or at an investigator's meeting, Oncopeptides AB staff (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Oncopeptides AB (or CRO) monitoring standards require full source data verification for the presence of signed and dated informed consent, adherence to the inclusion/exclusion criteria and documentation of AE/SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

11.3 DATA COLLECTION

An eCRF is required and should be completed for each patient. The patient's identity should always remain confidential. 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.

The designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs will check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff.

The study Investigators are responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

11.4 DATABASE MANAGEMENT AND QUALITY CONTROL

Oncopeptides AB personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

12 STATISTICAL METHODS AND DATA ANALYSIS

12.1 STUDY ENDPOINTS

12.1.1 Primary Endpoints

Phase 1

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

Phase 2a

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

12.1.2 Secondary Endpoints

Phase 1 and 2a

Best response during the study (CR/sCR, VGPR, PR, MR, SD, PD or non-evaluable),

Clinical benefit rate ≥ MR,

TTP: Time from first dose to first documented confirmed progression, death from causes other than progression will be censored,

TTR: Time from first dose or therapy to first documented confirmed response.

TTNT: Time from date of initiation of therapy to start of next line of therapy.

DOR: Time (months) from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. DOR is defined only for patients with a confirmed PR or better.

Duration of clinical benefit: time (months) from the first evidence of confirmed assessment of sCR, CR, VGPR, PR or MR to first confirmed disease progression, or to death due to any cause. Duration of clinical benefit is defined only for patients with a confirmed MR or better.

PFS: Time (months) from date of initiation of therapy to the earlier of confirmed disease progression or death due to any cause or last known assessment.

Oncopeptides will implement an ongoing review of the response and progression assessments performed by the investigator. The investigator will be notified of any discrepancies in the form of a data query.

OS: Time (months) from date of initiation of therapy to death due to any cause. Patients still alive at end of study, or lost to follow up, will be censored at last day known alive.

To further evaluate the frequency and grade of all AE's of the combination including the rate and type of second primary malignancies. Each regimen and dose will be evaluated separately.

The maximum grade (according to CTCAE v4.03) for each type of AE will be recorded for each patient, and frequency tables will be presented and reviewed to determine patterns. Additionally, the relationship of the AE(s) to the study treatment will be taken into consideration.

Laboratory abnormalities will be presented and reviewed.

Each regimen and dose will be evaluated separately.

12.1.3 Exploratory Endpoints

- PK parameters of melphalan
- The rate of MRD negative or positive status for patients achieving a CR

12.2 SAMPLE SIZE CALCULATION

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

Phase 2a sample size will include approximately 20 additional efficacy evaluable patients in order to reach a total of 26 efficacy evaluable patients per Regimen.

12.3 GENERAL CONSIDERATIONS FOR THE STATISTICAL ANALYSES

The statistical analyses as outlined in this section will be further described in the statistical analysis plan (SAP), which will be finalized prior to locking the database. In general, summaries of all data will be provided for each Regimen. Statistical analyses will be reported using summary tables, inferential analyses, 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.

12.3.1 Analysis Populations

Patients will be summarized according to the treatment Regimen actually received.

12.3.1.1 Dose Limiting Toxicity Analysis Set

The DLT analysis set is defined as all patients in Phase 1 that complete Cycle 1 of therapy or are discontinued due to a DLT event defined in Section 6.6.1 and Section 6.6.2. Patients that have been replaced in the original assigned cohort will not be included in the DLT analysis set.

12.3.1.2 Safety Analysis Set

The Safety analysis set is defined as all patients who received at least one or partial dose of melflufen, dexamethasone or partner therapy (drugs defined in the Regimen). The Safety analysis set will be the primary population for the summaries of all efficacy, exposure and safety data. The analysis (PFS) will be performed using the Safety analysis set with each regimen and dose evaluated separately.

12.3.1.3 Efficacy Analysis Set

The efficacy analysis set will be comprised of all patients who receive at least 2 doses of melflufen and ≥ 50% of the partner therapy (excluding dexamethasone) during Cycles 1 and 2, had a baseline disease assessment, and had at least 1 post-baseline disease assessment (≥28 days after first dose). Each regimen and dose will be evaluated separately.

12.4 ANALYSIS OF PRIMARY ENDPOINTS

12.4.1 Phase 1

The frequency and grade of AE's and defined DLT's occurring in each cohort will be determined.

Dose escalation study will follow fixed dose schedule with 3-6 DLT evaluable patients at each dose level. Depending on the dose level at which DLT is observed, approximately 12 eligible patients may be enrolled in Phase 1. The first cohort of patients enrolled in the Phase 1 portion of each Regimen will receive dose level 1 (melflufen 30 mg). A full safety evaluation will be conducted by a DSMC when these patients have completed the first cycle of combination therapy with DLT assessment. The optimal dose of melflufen in combination therapy will be defined as the highest of 20, 30 or 40 mg of melflufen that results in ≤ 1/6 patient with DLT during the first cycle of therapy.

12.4.2 Phase 2a

Following determination of the optimal dose of melflufen for each Regimen, approximately 20 additional efficacy evaluable patients will be enrolled at that level for a total of 26 efficacy evaluable patients treated at the dose defined in the Phase 1 part of the study per Regimen.

For patients with more than one post-baseline efficacy assessment, the best response of all measurements will be used in the Phase 2a primary endpoint analysis. Patients with incomplete disease assessments at screening will not be admitted into the study.

12.5 ANALYSIS OF SECONDARY ENDPOINTS

12.5.1 Analysis of efficacy endpoints

12.5.1.1 Overall Response Rate

The ORR will be estimated as the proportion of patients in each treatment group who achieve a confirmed response of sCR, CR, VGPR, or PR as their best response in efficacy evaluable as well as all treated patients. The exact binomial 95% confidence interval (CI) for ORR will be calculated for each treatment regimen.

12.5.1.2 Progression Free Survival

PFS is measured from the date of initiation of therapy to the date of documented disease progression or death in efficacy analysis set as well as the safety analysis set. PFS will be right-censored for patients who meet one of the following conditions:

- No post baseline disease assessments
- Non-protocol systemic anticancer treatment started before documentation of disease progression or death
- Death or disease progression after more than 1 missed disease assessment visit, or
- Death or PD between planned disease assessments
- Death before first disease assessment
- Alive without documentation of disease progression before a data analysis cutoff date

These conventions are based on the May 2007 Food and Drug Administration (FDA) Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics'.

(http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071590.pdf)

For such patients, the primary analysis of PFS will be right-censored according to the conventions described in Table 12-1.

Table 12-1 Conventions for Censoring for PFS

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

The distribution of PFS will be summarized for each Regimen using the Kaplan-Meier (K-M) method. The median PFS will be estimated for each treatment regimen from the 50th percentile of the corresponding K-M estimates. The 95% CI for median PFS will be constructed using the method of Brookmeyer (Brookmeyer and Crowley, 1982). Duration of follow-up for PFS will be summarized according to the K-M estimate of potential follow-up also termed "reverse Kaplan-Meier" (Schemper and Smith, 1996).

12.5.1.3 Other efficacy endpoints

The DOR will be calculated for patients who achieve a confirmed response of PR or better. The DOR is defined as the time from first documentation of response to disease progression or death due to any cause. Dates of progression and censoring will be determined as described for the analysis of PFS.

The duration of clinical benefit is defined as the time from first documentation of response to disease progression or death due to any cause. Dates of progression and censoring will be determined as described for the analysis of PFS.

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

Best response (sCR, CR, VGPR, PR, MR, SD or PR) will be summarized without analysis. The exact 95% CIs for sCR, CR, VGPR and PR, will be calculated for each treatment regimen and dose.

CBR will be summarized without analysis. The exact 95% CI for CBR will be calculated for each treatment regimen.

TTR is defined as the time (months) from initiation of therapy to the date of the first confirmed response (≥ PR).

TTP is defined as the time (months) from initiation of therapy to the date of the first documented confirmed progression.

TTNT is defined as the time (months) from initiation of therapy to the date of the first documented next treatment.

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

12.5.2 Analysis of Safety Endpoints

All safety results will be presented for the safety analysis set. No formal statistical analysis will be performed for the safety endpoints. Each Regimen and dose will be reported separately.

Study treatment administration, including duration of exposure, total dose, and dose modifications will be summarized for each group separately.

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 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 to any study drug, 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, SAEs, 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, associated clinical consequences/medical management and associated significant AEs.

During the Phase 2a portion of the study a DSMC will assess the non-hematologic toxicity according to the following study stopping rules:

Phase 2a (includes all Phase 2a patients, including Phase 1 patients treated at the MTD). Previous bortezomib data show that Grade 4 adverse events occurred in 28% of the patients treated with bortezomib in combination with melphalan and dexamethasone (San Miguel et al, 2008) with the majority being hematological events. Current information shows that Grade 4 non-hematological toxicity is rare in connection to daratumumab treatment (Daratumumab label). The most common Grade 4 events were thrombocytopenia and neutropenia occurring in 5.4% and 2.7% of the daratumumab treated patients (Usmani et al, 2016). Grade ≥ 4 non-hematologic melflufen-related toxicity occurred in 6.7 % of RRMM patients treated with melflufen (at the MTD of 40 mg/28 days) and dexamethasone in the Phase 2a study. Non-hematological treatment-related Grade 4 toxicity is therefore expected to occur at a frequency of less than 10% in the present study.

The DSMC will meet regularly to assess the benefit/risk profile in the Phase 2a portion of the study. All reported Grade 3-4 treatment-related non-hematological AEs, as well as all SAEs, and any treatment-related deaths due to hematologic or non-hematologic AEs will then be presented to the DSMC. If the DSMC considers the AE patterns differ from the Reference Safety Information for the individual drugs in the combination, the DSMC may recommend additional safety monitoring or stopping further recruitment. A recommended stopping rule is if three non-hematological treatment-related Grade 4 events occur among the first 10 patients or in 20% of the patients at any time thereafter, or if any treatment-related deaths due to hematologic or non-hematologic AEs occur at any time. This stopping rule would suspend accrual to the study pending DSMC investigation of the benefit/risk profile.

12.6 ANALYSIS OF EXPLORATORY ENDPOINTS

12.6.1 Pharmacokinetic Analysis

The pharmacokinetic (PK) evaluation will be performed only at selected centers in a sub-group of patients.

Three plasma samples for determination of melphalan concentrations should be drawn at each of the first two melflufen treatment cycles. The first sample should be taken 10-15 minutes after end of infusion, the second sample 1 hour after end of infusion and the third sample 2 to 4 hours (as late as possible within the time frame) after end of infusion.

The relationship between melphalan PK parameters and patient factors, will be assessed, as well as the inter-occasion variability in melphalan exposure when comparing data for treatment Cycles 1 and 2.

The melphalan concentration data will be pooled across patients and evaluated using a population approach with nonlinear mixed-effect modeling. Actual time points for drug administration and plasma sampling will be used.

Details on the modeling approach will be described in a separate population PK-PD plan which will be developed in parallel with the ongoing Phase 3 study OP-103 (OCEAN TRIAL). Data from other melflufen studies may be included in this analysis as appropriate.

12.6.2 Minimal Residual Disease

The rate of positive and negative MRD evaluations will be summarized without analysis.

12.7 HANDLING OF DROP-OUTS AND MISSING DATA

The SAP describes how drop-outs 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, time since most recent relapse, determination of whether a medication is concomitant or an AE is treatment-emergent), the date will be imputed. Detail of the methods of imputation will be provided in the SAP.

13 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1 REGULATORY AND ETHICAL COMPLIANCE

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, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 DATA SAFETY MONITORING COMMITTEE

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

13.3 INDEPENDENT RESPONSE ADJUDICATION

Oncopeptides will implement an independent adjudication review of the response and progression assessments performed by the investigator for the purpose of quality monitoring. The investigator will be notified of any discrepancies in the form of a data query.

13.4 RESPONSIBILITIES OF THE INVESTIGATOR AND IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB, IEC or REB before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Oncopeptides AB (or designated CRO) before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Oncopeptides AB (or designated CRO) monitors, auditors, Clinical Quality Assurance representatives, designated agents of Oncopeptides AB, IRBs/IECs/REBs and regulatory authorities as required.

13.5 INFORMED CONSENT PROCEDURES

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures. The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent is obtained will be captured in the eCRFs.

Oncopeptides AB (or designated CRO) will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH Good Clinical Practice (GCP) guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Oncopeptides AB before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Oncopeptides AB (or designated CRO) monitor after IRB/IEC/REB approval.

13.6 DISCONTINUATION OF THE STUDY

Oncopeptides AB reserves the right to discontinue this study under the conditions specified in the clinical study agreement at a single study center or the study as a whole. Specific conditions for terminating the study at any time for reasonable medical or administrative reasons in any single center could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol
- 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

13.7 PUBLICATION OF STUDY PROTOCOL AND RESULTS

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. Any publication will be a joint publication between Oncopeptides AB and the investigators and authorship will be determined by mutual agreement.

13.8 STUDY DOCUMENTATION, RECORD KEEPING AND RETENTION OF DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in an Oncopeptides AB sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

The Investigator must retain the study records for a minimum of 2 years after the last marketing application for the indication is approved in an ICH region or for 2 years after the Investigational new drug (IND) is withdrawn. For IND studies conducted outside the US, the investigator must retain study records for the time period described above or according to local laws or requirements, whichever is longer.

13.9 CONFIDENTIALITY OF STUDY DOCUMENTS AND PATIENT RECORDS

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Oncopeptides AB, their agents or Health Authorities. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable

patient identification at the site. Refer to Section 11.1 for additional details regarding patient confidentiality.

13.10 AUDITS AND INSPECTIONS

Source data/documents must be available to inspections by Oncopeptides AB or designee or Health Authorities.

13.11 FINANCIAL DISCLOSURES

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site prior to study start.

14 PROTOCOL ADHERENCE

Investigators ascertain they will apply due diligence to avoid protocol deviations. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Oncopeptides AB or designated CRO should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

14.1 AMENDMENTS TO THE PROTOCOL

Any change or addition to the protocol can only be made in a written protocol amendment by Oncopeptides AB. The amendment must be approved by the Health Authorities where required, and the IRB/IEC/REB before it may be implemented. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval.

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16 APPENDICES

Appendix A. 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

Source: Oken MM, et al. 1982.

Appendix B. National Cancer Institute CTCAE Version 4.03

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) v4.03

Publish Date: (v4.03: June 14, 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix C. IMWG Uniform Response Criteria

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.

Response	***IMWG criteria*** (Rajkumar, et al. 2011)
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 h. • 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 h • 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) EBMT Criteria	• ≥ 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 • 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-component (the absolute increase must be ≥ 0.5 g/dL) and/or • Urine M-component (the absolute increase must be > 200 mg/24 h) 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 (CR, sCR, VGPR, PR, MR, SD and PD) require two consecutive assessments made at any time before the institution of any new therapy; all response categories and SD 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 be confirmed. For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 0.5 g/dL.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 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.

Appendix D. 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 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.

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 (eg, 3-6 cycles of initial therapy with bortezomib-dexamethasone [VD] followed by stem cell transplantation [SCT], consolidation, and lenalidomide maintenance is considered 1 line).

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 be captured.

Appendix E. Definition of Relapsed Disease

This study will use the 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).

Appendix F. Declaration of Helsinki

http://www.wma.net/en/30publications/10policies/b3/

Appendix G. Estimated Creatinine Clearance by Cockcroft- Gault Formula

For males:

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

For females:

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

Source: Cockcroft 1976

Appendix H. Assessment of QTC Interval

QTc Fridericia Formula

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

Appendix I. 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 B 2-microglobulin ≥ 5.5 mg/L
Chromosomal abnormalities (CA) by interphase by florescent in situ hybridization (iFISH)	
High Risk	Presence of del(17p) and/or translocation of t(4:14) and/or translocation of t(14:16)
Standard Risk	No high risk CA
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 of III
Stage III	ISS stage III and either high risk CA by iFISH or high LDH

(Palumbo et al. 2015)

Appendix J BSA DuBois Formula

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ X\ Weight\ (kg)}{3600}}$$

Appendix K Products containing boron, mannitol, sodium citrate and polysorbate-80

The following lists may not be all inclusive and product information should be referenced if necessary.

Boron:

- Bortezomib
- Tavaborole

Mannitol:

- Buprenorphine Hydrochloride (Sublingual)
- Naloxone Hydrochloride (Sublingual)
- Clonazepam (dispersible)
- Gabapentin
- Hydrochlorothiazide and lisinopril
- Lisinopril 20 mg
- Omeprazole Delayed Release
- Ondansetron Hydrochloride (Orally Disintegrating)
- Pantoprazole Sodium Delayed-Release
- Pramipexole Dihydrochloride
- Tramadol Hydrochloride

Sodium citrate dihydrate: Sodium citrate is the natural salt of citric acid and is often used as a food additive. The following is a list of medications that contain sodium citrate.

- Alka-Seltzer Heartburn Relief
- Bicitra, Cytra-2
- Citra pH
- Citrate-Phos-Dex
- Citrocarbonate
- Citrolith
- Liqui-Dual Citra
- Oracit
- Polycitra
- Polycitra-LC

- Scot-Tussin Original (old formulation)
- Tricitrasol
- Tricitrates
- Tussirex
- Tussirex Sugar Free
- Virtrate-3

Polysorbate -80: Polysorbate 80 is commonly used in foods, vitamins, medicines, and vaccines, soaps and cosmetics. Drugs containing polysorbate-80 include:

- Amitriptyline Hydrochloride
- Amoxicillin and Clavulanate Potassium
- Cyclobenzaprine Hydrochloride
- Escitalopram Oxalate
- Gabapentin
- Hydroxychloroquine Sulfate
- Hydroxyzine Hydrochloride
- OxyContin
- Sertraline Hydrochloride