Clinical Development Protocol

HORIZON TRIAL

A Single Arm, Open-Label, Phase 2 Study of Melflufen in Combination with Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Pomalidomide and/or an anti-CD38 Monoclonal Antibody

Investigational Product	**Melflufen**
Study Sponsor	**Oncopeptides AB** **Västra Trädgårdsgatan 15** **SE-111 53 Stockholm, Sweden**
Protocol Number	**OP-106**
EUDRACT Number	**2016-000965-21**
Investigational New Drug Number	**116362Precision Oncology**
Clinical Research Organization	**200 Route 31 North** **Suite 102** **Flemington, NJ 08822** **USA**
Development phase	**Phase 2**
Document status	**Version 1.0: May 4, 2016** **Version 2.0, Amendment 1: October 13, 2016** **Version 3.0, Amendment 2: December 19, 2016** **Version 4.0, Amendment 3: July 12, 2017** **Version 5.0, Amendment 4: May 31, 2018** **Version 6.0, Amendment 5: November 27, 2018** **Version 7.0, Amendment 6: March 4, 2019**

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Approved By:

Johan Harmenberg, MD
Chief Medical Officer

19 March 2019
Date

Paul Richardson, MD
Global Lead Investigator

Date

Eva Nordstrom, MSc Pharm
Head of Clinical Development

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Protocol Acceptance Page

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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 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.

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PROTOCOL SYNOPSIS:

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Protocol Name	OP-106
Chemical Name	4-[Bis-(2-chloroethyl)amino]-L-phenylalanine-4-fluoro-L-phenylalanine ethyl ester hydrochloride
Study Protocol Title	A Single Arm, Open-Label, Phase 2 Study of Melflufen in Combination with Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Pomalidomide and/or an Anti-CD38 Monoclonal Antibody
Study Sponsor	Oncopeptides AB
Global Lead Investigator	Paul Richardson, MD
Sites	Approximately 15-20 sites in Europe and the USA
Study Period	First patient in December 2016 with approximately 32 months of recruitment. Treatment may continue until disease progression or unacceptable toxicity, thereafter follow-up for overall survival.
Background and Rational	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 subsequent inflow of more melflufen (Gullbo et al. 2003c, Wickstrom 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 desethyl-melflufen) inside the cells and a less rapid disappearance of these molecules from the cells. The addition of melflufen to panels of primary cultures of human tumor cells, including multiple myeloma (MM), results in a similar pattern of activity as that of melphalan, but with 50 to 100-fold higher efficacy (Wickstrom et al. 2008), which is explained by the 50-fold higher intracellular exposure in MM cells of alkylating agents compared to that observed after an equimolar dose of melphalan (Chauhan et al. 2013a). Mechanistically oriented studies have shown that melflufen-induced apoptosis is associated with (i) activation of caspases and poly ADP ribose polymerase (PARP) cleavage; (ii) reactive oxygen species generation; (iii)

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	mitochondrial dysfunction and release of cytochrome c; and (iv) induction of DNA damage (Chauhan et al. 2013a). Moreover, melflufen inhibits MM cell migration and tumor associated angiogenesis. 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. 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, Wickstrom et al. 2007, Chauhan et al. 2013a). Melflufen is currently being evaluated in combination with low dose dexamethasone and as single agent in a Phase 1/2a clinical trial (O-12-M1) in relapsed refractory MM (RRMM). The Phase 1 part of the clinical trial, completed in September 2014, established the maximum tolerated dose (MTD) at 40 mg of melflufen every 21 days combined with 40 mg dexamethasone weekly (Paba-Prada et al. 2014). The schedule was later changed to 28 days in a Phase 2 amendment. The dose limiting toxicities consisted of dose-dependent neutropenia and thrombocytopenia manageable with dose delays and appropriate treatment, including dose reductions in subsequent cycles. A preliminary assessment of data from clinical trial O-12-M1 was performed on patients who were evaluable for efficacy by 11 Feb 2016. Of the 30 efficacy evaluable patients treated with 40 mg melflufen in combination with dexamethasone, 19 patients (63%) have reported a best response of minimal response (MR) or better and 12 patients (40%) have reported partial response (PR) or better. These 30 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 4.5 months at the time of data-cut based on 30 events in 40 patients with ≥1 cycle. Median number of cycles is 3.5 (range 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 57 patients with RRMM in the Phase 1/2a clinical trial O-12-M1 [40 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.

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	The present Phase 2 study will explore the use of melflufen plus dexamethasone in patients with pomalidomide and/or an anti-CD38 monoclonal antibody (mAb) refractory disease. In this population, there is a clear lack of treatment alternatives and a high unmet medical need. As of 22 October 2018, a total of 83 patients had been enrolled in the study: the population characteristics include a median number of 5 prior lines, with 60% of patients being refractory to pomalidomide and daratumumab, and 60% refractory to an IMiD, a PI and an anti-CD38 mAb. The preliminary ORR for the whole population (N=83) was 33%. (ASH 2018 oral presentation). The safety profile is acceptable, with primary adverse events being thrombocytopenia, neutropenia and anemia, and few grade 3/4 non-hematological adverse reactions. (ASH 2018 oral presentation, IB edition 8.0). As the study suggests a positive benefit-risk ratio for heavily pre-treated patients receiving melflufen, the sponsor expanded the study cohort for further collection of safety and efficacy data. Expansion of the study also allows for collection of functional status and well-being information.
Study Design	This is a single arm, open-label, Phase 2 multicenter study which will enroll patients with RRMM following at least 2 lines of prior therapy (Appendix D), including an IMiD and a PI, and who are refractory to pomalidomide and/or an anti-CD38 mAb defined as patients who relapse while on therapy or within 60 days of last dose. Patients will be treated with melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Patients ≥ 75 years of age will have a reduction of the starting dose of dexamethasone from 40 mg to 20 mg on the same schedule. In the event of cycle delay, in the absence of dexamethasone toxicity, it is recommended that dexamethasone continue weekly. Patients may receive treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician determine it is not in the patient's best interest to continue. Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol. A Schedule of Events for the study is outlined in Table 8-1 of the protocol.
Objectives	**Primary Objective** • To assess overall response rate (ORR), i.e. proportion of patients with ≥ partial response (PR) [stringent CR (sCR), complete response (CR), very good partial response (VGPR), and PR] as best response in

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	efficacy evaluable patients as assessed by the investigator according to IMWG Uniform Response Criteria (Rajkumar et al. 2011) (Appendix C). **Key Secondary Objectives** • To assess PFS according to IMWG Criteria (Rajkumar et al. 2011), • To assess duration of response (DOR) in efficacy evaluable patients with ≥ PR (sCR, CR, VGPR, PR) as best response according to IMWG Uniform Response Criteria (Rajkumar et al. 2011). • To assess overall survival (OS). **Other Secondary Objectives** • To assess clinical benefit rate (CBR, i.e. proportion of patients with ≥ MR) as best response in efficacy evaluable patients • Time to response (TTR) • Time to progression (TTP) • To assess the safety and tolerability • To assess functional status and well-being
Endpoints	**Primary Endpoint:** • Best response of PR or better, as assessed by the investigator according to IMWG-URC, from which ORR is calculated. **Secondary Endpoints** • PFS • DOR • OS • Best response of MR or better, from which CBR is calculated • TTR • TTP • Duration of SD • Frequency and grade of adverse events • Change from baseline in QLQ-C30 assessment Change from baseline in EQ-5D-3L assessment All tumor response and progression-depended endpoints are as assessed by the investigator assessment of response according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar et al. 2011, Appendix C).
Inclusion Criteria	**Patients will be considered 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

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	progression in need of treatment at time of screening. 3. Measurable disease defined as any of the following: • Serum monoclonal protein ≥ 0.5 g/dL (≥ 5g/L) by protein electrophoresis (SPEP) • ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis (UPEP) • Serum immunoglobulin free light chain ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda free light chain ratio 4. A minimum of 2 prior lines of therapy including an IMiD and a PI and is refractory to pomalidomide and/or an anti-CD38 mAb (Refractory is defined as patients who relapse while on therapy or within 60 days of last dose of pomalidomide and/or an anti-CD38 mAb in any line, regardless of response). 5. Life expectancy of ≥ 6 months; 6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. (Patients with worse performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the medical monitor) 7. Female of child bearing potential (FCBP)* and non-vasectomized male agree to practice appropriate methods of birth control (Section 7.6.1) 8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information 9. 12-lead electrocardiogram (ECG) with QTc interval calculated by Fridericia Formula QTcF interval of ≤ 470 msec (Appendix H) 10. The following laboratory results must be met during screening (within 21 days) and also prior to 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 prior to initiation of therapy) • Platelet count ≥ 75,000 cells/mm^3 (75 x 10^9/L) (without transfusions during 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 higher value in patients diagnosed with Gilberts syndrome after review and approval by the medical monitor.

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	• Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN • Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min. For women ≤ 155cm in height and with normal BMI (18.5 – 24.9 kg/m^2) the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method for calculation of glomerular filtration may be used (Appendix G). Cases with borderline values of creatinine clearance based on the Cockcroft-Gault formula may be discussed with the medical monitor. 11. Must have, or accept to have, an acceptable central catheter for infusion of melflufen prior to the first dose. (Port a cath, peripherally inserted central catheter (PICC) line, or central venous catheter) **(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. Evidence of mucosal or internal bleeding and/or is platelet transfusion refractory (i.e. platelet count fails to increase by > 10,000 cells/mm^3 after a transfusion of an appropriate dose of platelets). 2. 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 conduction system abnormalities, uncontrolled hypertension, ≥ grade 3 thromboembolic event in the last 6 months). 3. Active infection, treated with parenteral anti-infectives within 14 days, or oral anti-infectives within 7 days, prior to initiation of treatment (exceptions may be considered after review and approval by the medical monitor). 4. Primary refractory disease (i.e. never responded (≥ MR) to any prior 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, and very-low and low risk prostate cancer patients

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	in active surveillance as defined in NCCN version 3.2016. 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 HIV or active hepatitis B or C viral infection 9. Concurrent symptomatic amyloidosis or plasma cell leukemia 10. POEMS syndrome [plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-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. IMiDs, PIs and/or corticosteroids within 2 weeks prior to initiation of therapy. Prednisone up to but no more than 10 mg orally q.d. or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to initiation of therapy. Other investigational therapies and monoclonal antibodies or live vaccines within 4 weeks of initiation of therapy (other washout times may be considered following consultation with the medical monitor). 12. Residual side effects to previous therapy > grade 1 prior to initiation of therapy (Alopecia any grade and/or neuropathy grade 2 without pain are permitted) 13. Prior autologous or allogeneic stem cell transplant within 12 weeks of initiation of therapy 14. Prior allogeneic stem cell transplant with active graft-versus-host-disease (GVHD). 15. Prior major surgical procedure or radiation therapy within 4 weeks of the first dose of study treatment (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 steroid therapy
Study Treatment(s)	Treatment will be given in cycles in an outpatient treatment setting. Planned cycle length is 28 days. Melflufen 40 mg will be administered as a 30-minutes intravenous (iv) infusion on Day 1 of every 28-day cycle via acceptable central catheter. Dexamethasone 40 mg should be administered orally on Days 1, 8, 15 and 22 of each 28-day cycle. Dexamethasone starting dose will be reduced to 20 mg on the same schedule for patients ≥ 75 years of age.

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	Dose modifications and delays for both melflufen and dexamethasone may be implemented based on patient tolerance as detailed in Section 7.7. In the event of cycle delays, in the absence of dexamethasone toxicity, it is recommended that dexamethasone continue weekly.
Duration of treatment	Patients will receive treatment until there is documented progressive disease (PD) (PD 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.
Duration of follow-up	Follow up for progression free survival (PFS-FU): Patients who discontinue treatment for reasons other than disease progression will continue to be followed for disease response monthly until disease progression (PD to be confirmed on two consecutive assessments) or initiation of subsequent therapy, whichever comes first. Follow up for overall survival (OS-FU): Following disease progression or initiation of subsequent therapy, patients should be followed every three months, for 24 months for overall survival including recordings of first subsequent therapy and secondary malignancies. 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.
Concomitant Drug/Therapy	All blood products and concomitant medications received within 21 days of the initiation of therapy until the end of study visit should be recorded. Refer to Section 7.6 for a complete list of required, recommended and prohibited concomitant medications and therapies. Antibacterial, antifungal and antiviral prophylaxis should be given according to National Comprehensive Cancer Network (NCCN 2015) or institutional guidelines (See Section 7.6).
Number of Patients	A total number of approximately 150 patients are planned to be enrolled in the study, to achieve 130 patients evaluable for efficacy, including 50 patients evaluable for EQ-5D-3L. The study initially evaluated patients refractory to pomalidomide and patients refractory to daratumumab (an anti-CD38 mAb) separately to evaluate clinical benefit in both groups, with a target enrollment of approximately 39 efficacy evaluable patients per group. This original sample size was expanded in protocol amendment 4. Instead of calculating the sample size on the power to show superiority on ORR versus a fixed value, the sample size is now based on the precision of the estimates. As for the ORR, given a sample size of 130 evaluable patients and an observed ORR of 30%, the exact 95 % confidence interval would range from 22.3 % to 38.7 %.

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Sub-group of specific interest	Patients that are refractory to all three currently approved classes of drugs (IMiDs, PIs and anti-CD38 mAbs) have emerged as a sub-group of particular interest. All efficacy and safety analyses performed for the total population will be repeated in a similar way for this sub-population. In a retrospectively analysis as of 06 February 2019, this triple-class refractory sub-group represented 70% of the total population (67 of 95 patients). All triple-class refractory patients that are enrolled in the study on or after the date of the retrospective analysis will be followed prospectively. The ORR for patients of this sub-group accrued retrospectively before 06 February 2019 will be reported as well as patients prospectively enrolled after this date. If there is no substantial difference in ORR, the results will be presented for the total sub-group. Assuming a similar (or slightly higher) proportion of patients within the remaining approximately 55 patients, about 40 patients of the sub-group of specific interest can be followed prospectively.
Assessments	A complete list of study assessments and time lines can be found 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 (Ig); and – Urine protein electrophoresis (UPEP) and urine protein immunofixation (all using the same 24-hour urine collection) – Serum free light chains (SFLC) and SFLC ratio • Bone marrow to quantify percent myeloma cell involvement • Extramedullary plasmacytoma evaluation (by physical examination (PE) and/or imaging technique) • Skeletal survey or low dose computerized tomography (CT) scan. • Beta2 microglobulin • Lactate dehydrogenase (LDH) • Cytogenetics by fluorescence in situ hybridization (FISH) • International staging system (ISS) staging score and Revised-ISS (R-ISS) (Appendix I) **Efficacy Assessments:** • M-protein determination using the following procedures: – SPEP and serum protein IFE with quantitative Ig (quantitative Ig required only for patients with IgA and IgD myeloma); and

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	– UPEP and urine protein IFE (all using the same 24-hour urine collection) – SFLC and SFLC ratio • Bone marrow to quantify percent myeloma cell involvement • Extramedullary plasmacytoma evaluation • Skeletal x-rays or low dose CT scan (same technique used at screening and each evaluation). • Serum calcium (corrected calcium) M protein disease status (assessed by M-protein quantitation, IFE and free light chain from serum and 24-hour urine collection) should be assessed at screening and Cycle 1 Day 1. Starting with Cycle 2, M protein response to treatment should be assessed every cycle. Disease status, including skeletal x-rays or CT scan of bones and imaging assessment (i.e. CT, positron emission tomography (PET), magnetic resonance imaging [MRI] scan) of known or suspected extramedullary plasmacytomas will be performed at screening and if indicated according to the IMWG response criteria to evaluate response and/or progression. Bone marrow aspirate will be performed at screening and to confirm suspected CR in patients who have achieved a negative IFE. Additional skeletal x-rays and/or imaging assessments may be performed, at the investigator's discretion, at screening to further evaluate plasmacytomas. All imaging assessments should be documented in the eCRF. Repeat assessments if the patient has symptoms suggestive of progression of lesion(s) documented at screening or new lesions. If extramedullary plasmacytomas are present and measurable on physical examination, they will be assessed at every cycle. Extramedullary plasmacytomas documented and measurable only by imaging assessments will be assessed by the consistent relevant modality to confirm response or progression according to the IMWG response criteria. • Functional status and well-being Two different PROs will be used to evaluate functional status and well-being in the study; the EORTC QLQ-C30 and the EQ-5D-3L. – **EORTC QLQ-C30**, which includes 30 items resulting in 5 functional scales, 1 Global Health Status scale, 3 symptom scales, and 6 single items. The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients. Scores are transformed to a 0 to 100 scale. Administration time is approximately 11 minutes. QLQ-C30 domain scores will be

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	summarized at each time point and change from baseline will be derived. The relationship between clinical response and change in domain scores will be explored. – **EQ-5D-3L**, a generic measure of health status. For the purpose of this study the EQ-5D-3L will be used to generate utility scores for use in cost-effectiveness analyses. The EQ-5D-3L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale (EQ VAS) rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The 5 domains of EQ-5D-3L and the EQ VAS will be summarized at each time point and change from baseline will be derived. **Safety Assessments:** • Assessment and grading of adverse events • Physical examinations with vital signs, neurologic assessment and assessment of performance status • Routine safety laboratory tests (Complete blood count (CBC) with differential and platelets; serum chemistry and coagulation tests) with calculation of creatinine clearance by Cockcroft-Gault formula. For women ≤ 155cm in height and with normal BMI (18.5 – 24.9 kg/m2) the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method for calculation of glomerular filtration may be used (Appendix G). Cases with borderline values of creatinine clearance based on the Cockcroft-Gault formula may be discussed with the medical monitor. • Pregnancy testing • Electrocardiogram • Chest X-ray Adverse experiences, including clinical laboratory and vital sign abnormalities, will be graded using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events version 4.03.

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Analysis Sets & Statistical methods	**Efficacy Analysis Set:** The primary efficacy evaluable population will be comprised of all patients who received at least 2 doses of melflufen, had a baseline disease assessment and at least 1 post-baseline disease assessment. **All Treated Analysis Set:** All patients that receive any melflufen or dexamethasone treatment will be considered evaluable for safety analysis. **Statistical Methods:** The overall response rate (ORR) will be estimated as the proportion of patients who achieve a confirmed sCR, CR, VGPR, or PR as their best response as assessed by the investigator. At the end of the trial an exact two-sided 95% confidence interval for ORR will be determined. The distribution of PFS will be summarized using the Kaplan Meier (K-M) method (Kaplan et al. 1958). The median PFS will be estimated from the 50th percentile of the corresponding K-M estimates. Other time to events endpoints will be analyzed using the same method as for PFS. Clinical benefit rate (CBR), will be presented with its associated 95% exact two-sided confidence interval. The absolute values as well as change in EQ-5D-3L scores and QLQ-C30 scores will be described at each measured time point using descriptive statistics. The maximum grade (according to CTCAE v4.03) for each type of adverse event will be recorded for each patient, and frequency tables will be presented and reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

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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 Independent ethics committees (IEC) or Institutional Review Boards (IRBs) and patients will sign Informed Consent Forms before enrolling to the trial.

List of Abbreviations

ADCC	Antibody-dependent cellular-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem-cell transplantation
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CDC	Complement-dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CBR	Clinical benefit rate
CKD-EPI	The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
CMV	Cytomegalovirus
CRF(e)	Case report form (electronic)
CRO	Contract research organization
CR	Complete response
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
CXR	Chest-X-Ray
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data safety monitoring committee
eCCr	Estimated creatinine clearance rate
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EDC	Electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of therapy
EQ-5D-3L	EuroQol-5 Dimensions 3 Level
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FLC	Free light chain
GCP	Good clinical practice
GVHD	Graft-versus-host-disease
HDAC	Histone deacetylase
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International conference of harmonization
IEC	Independent ethics committee
IFE	Immunofixation
IgG	Immunoglobulin
IMiD	Immunomodulator drug
IMWG	International myeloma working group
IND	Investigational new drug

IRAC	Independent review and adjudication committee
IRB	Institutional review board
ISS	International staging system
iv	Intravenous
LDH	Lactate dehydrogenase
K-M	Kaplan Meier
mAb	Monoclonal antibodies
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MM	Multiple myeloma
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National comprehensive cancer network
NCI	National cancer institute
ORR	Overall response rate
OS	Overall survival
PARP	Poly ADP ribose polymerase
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 (M-protein) and skin changes
PR	Partial response
PRO	Patient Reported Outcome
q.d.	Quaque die/ one a day
QLQ-C30	Quality of Life Questionnaire Core 30
RBC	Red blood count
RRMM	Relapsed and refractory multiple myeloma
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	System organ class
SPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response

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 26,8500 patients with myeloma are diagnosed in the United States in 2015 (SEER 2014).

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 (HDAC) inhibitors (panobinostat), conventional chemotherapy (melphalan, cyclophosphamide, doxirubicin), including high dose melphalan with autologous stem-cell transplantation (ASCT) and the most recent addition of monoclonal antibodies (mAb) (elotuzumab and daratumumab). The selection of treatment in relapsed refractory multiple myeloma (RRMM) is challenging. The NCCN guidelines (NCCN 2015) and a recent overview published in the Mayo Clinic Proceedings (Rajkumar et al. 2016) detail an array of single agent, doublet and triplet combination regimens that can be considered. In many cases, the same agents used as induction therapy may be reinstituted for relapsed disease if the disease recurred more than 6 to 12 months after the last therapy ended. However, if the time to relapse is of shorter duration, the patient is refractory to initial therapy, or the disease is associated with severe symptoms like renal failure or hypercalcemia, a regimen with different mechanism of action (class switch) is often selected. 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, myeloma patients will receive an average of 4 to 8 different regimens during their lifespan.

1.1.1 Anti-CD38 mAbs

Daratumumab:

Daratumumab, a human anti-CD38 monoclonal antibody, received accelerated approval by the FDA on November 16, 2015 for myeloma patients who have received at least three prior lines of therapy, including both an IMiD and a PI, and for patients who are "double refractory", meaning their disease no longer responds to treatment with at least one IMiD and at least one PI. The efficacy was demonstrated in two open-label studies. In the Phase 2 MMY2002 (SIRIUS) study,

of the 106 participants receiving daratumumab, 29 percent of patients achieved a complete or partial reduction in their tumor burden, which lasted for an average of 7.4 months, and PFS was 3.7 months. In the Phase 1/2 GEN501 study, of the 42 participants receiving daratumumab, 36 percent had a complete or partial reduction in their tumor burden.

Isatuximab

Isatuximab (SAR650984) is a humanized anti-CD38 mAb that binds selectively to a unique epitope on the human surface antigen CD38. Isatuximab kills tumor cells via multiple biological mechanisms, antibody-dependent cellular-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), direct induction of apoptosis (pro-apoptosis) without crosslinking, and inhibition of CD38 enzymatic activity. CD38 is highly expressed on myeloma cells but is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic origin, making it a relevant target for the treatment of multiple myeloma.

Several clinical combination studies with isatuximab are ongoing, including phase 3 studies in RRMM patients such as one comparing carfilzomib/ dexamethasone with and without isatuximab (ICARIA-MM), and another in which isatuximab is combined with pomalidomide/ dexamethasone (IKEMA).

1.1.2 Pomalidomide

Pomalidomide (in combination with dexamethasone) is approved for the treatment of patients with MM who have received at least two prior therapies, including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. The FDA accelerated approval of pomalidomide was based on the results in the Phase 2 trial (MM 002), where 113 patients in the pomalidomide + dexamethasone trial arm had an ORR of 29.2% (FDA Pomalyst precribing information 2016). An updated analysis demonstrated a median progression free survival (PFS) of 4.2 months (primary endpoint) and an overall response rate (ORR) of 33% and a clinical benefit response (CBR) of 45% (Richardson et al. 2014). In the subsequent pomalidomide Phase 3 clinical trial (MM-003) patients were randomized to either pomalidomide plus dexamethasone or high-dose dexamethasone and evaluated with PFS as primary endpoint. Based on a median follow-up of 4.2 months (data cutoff of 7 September 2012), the 302 patients randomized to pomalidomide plus dexamethasone showed a median PFS of 3.6 months. A later data cutoff on 1 March 2013 with median follow-up of 10 months, showed an ORR of 23.5% (Independent Review and Adjudication Committee (IRAC) assessed data), and these data supported the regular FDA approval of pomalidomide in 2015. This Phase 3 study was also published as investigator assessed data with the same 1 March 2013 cutoff (San Miguel et al. 2013). The authors showed a median PFS of 4.0 months and ORR of 31%. The CHMP approval of pomalidomide in European Union (EU) in 2013 was based on the IRAC assessed data from the 7 September 2102 data cut-off in trial MM-003 (with a median of 4.2 months follow-up) with support from trial MM-002 (Imnovid EPAR 2013).

Recent improvements in therapies have significantly increased both the expected life span and the quality of life 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. The molecular weight is 498.4 as free base and 534.9 as the HCl salt.

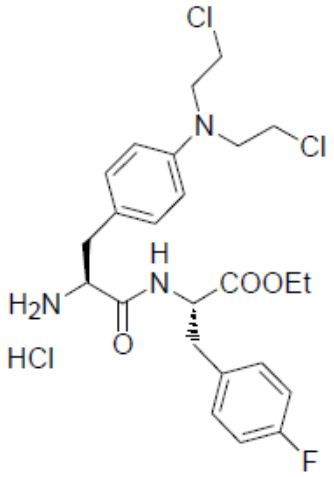

Figure 1-1: Structure of Melflufen

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 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, Wickstrom 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 AUC after melflufen administration is similar to historical data on exposure after melphalan administration (Mougenot et al. 2004, 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 (Wickstrom et al. 2008), which is explained by the 50-fold higher intracellular exposure as Area Under the Curve (AUC) of alkylating agents compared to that observed after an equimolar dose of melphalan (Chauhan et al. 2013a). Mechanistically-oriented studies have shown that melflufen-induced apoptosis is associated with (i) activation of caspases and poly ADP ribose polymerase (PARP) cleavage; (ii) reactive oxygen species generation; (iii) mitochondrial dysfunction and release of cytochrome c; and (iv) induction of DNA damage (Chauhan et al. 2013a). 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 parenteral, 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, Wickstrom et al. 2007, Chauhan et al. 2013a).

A preliminary assessment of data from clinical trial O-12-M1 was performed on patients who were evaluable for efficacy by 11 Feb 2016. Of the 30 efficacy evaluable patients with late stage relapsed and relapsed-refractory MM treated with 40 mg melflufen in combination with dexamethasone, 19 patients (63%) have reported a best response of minimal response (MR) or better and 12 patients (40%) have reported partial response (PR) or better. These 30 patients had a median of 4 prior lines of therapy, including IMiDs, PIs and alkylators.

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 57 patients with RRMM in the Phase 1/2a clinical trial O-12-M1 [40 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 for additional information.

1.2.3 Clinical Experience

Please refer to the IB for further details.

The preclinical properties are supported by clinical data from 45 patients with solid tumors (data not presented, refer to the IB for details) and 57 patients (as of 11 February, 2016) with advanced relapsed and RRMM including patients that are refractory to IMiDs, PIs and alkylators.

1.2.3.1 Clinical Experience in RRMM

Please refer to the IB for further details.

Melflufen is currently being 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 modified Fibonacci design with 3 to 6 patients per dose cohort, depending on dose limiting toxicities (DLTs) 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 given every 3 weeks in combination with 40 mg dexamethasone weekly. Following identification of the MTD, the Phase 2 part of the trial was initiated and all subsequently treated patients received a starting dose of 40 mg of melflufen.

The O-12-M1 study is complete as per 09 November 2017. Please refer to the IB for further details.

Clinical Safety

As of 11 February 2016, 40 patients had received 183 doses of melflufen 40 mg. The median number of cycles is 3.5 (range 1 – 14).

The most common treatment emergent adverse events (TEAE) to date 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 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 AEs were reported in 34 patients out of 40 patients (85%). Those related to melflufen and occurring in ≥5% of the patients are presented in Table 1-1.

Table 1-1 Summary of Melflufen Treatment Related Grade 3 or 4 AE in ≥ 5% of 40 Patients Dosed with 40 mg Melflufen in Clinical Trial O-12-M1

System Organ Class (Preferred Term)	Patients with Grade 3 or 4 AEs n (%)	Patients with Grade 4 AEs n (%)
Any treatment-related event	34 (85)	20 (50)
Blood and lymphatic system disorders	33 (83)	20 (50)
Thrombocytopenia	25 (63)	16 (40)
Neutropenia	23 (58)	12 (30)
Anemia	17 (43)	0 (0)
Febrile neutropenia	2 (5)	0 (0)
General disorders and administration site conditions	7 (18)	0 (0)
Fatigue	2 (5)	0 (0)
Pyrexia	2 (5)	0 (0)
Asthenia	2 (5)	0 (0)
Investigations	5 (13)	0 (0)
Neutrophil count decreased	4 (10)	0 (0)
White blood cell count decreased	2 (5)	0 (0)
Infections and infestations	2 (5)	0 (0)
Pneumonia	2 (5)	0 (0)

Continuous review of safety data in the Phase 2 part of the study lead the data safety monitoring committee (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.

After a fatal pneumonia case occurred during the summer of 2015, a thorough evaluation of all cases of pneumonia and sepsis in the study was conducted.

A total of 7 cases of pneumonia (2 associated with sepsis) and 2 other cases of sepsis in various dose cohorts were reported as SAEs (5 patients [12%] in the 40 mg cohort). Four cases resulted in death, both cases of sepsis and 2 cases of pneumonia (1 associated with sepsis and one diagnosed as pneumocystis carinii). Three of the fatal events were in the 40 mg cohort.

As of 23 October 2015, 53% (20 patients) of the 40 mg melflufen (+dexamethasone) treated patients had reported grade 3/4 neutropenia, 16% pneumonia, 3% (1 patient) upper respiratory infection and 0% sepsis regardless of relationship to study treatment. Comparative data from the pomalidomide+dexamethasone arm in the pomalidomide Phase 3 study (FDA US label) showed 48% neutropenia, 16% pneumonia, 3% upper respiratory infections and 1% neutropenic sepsis as

grade 3/4 events. The Grade 3/4 AE rate with respect to neutropenia, pneumonia, upper respiratory infections and neutropenic sepsis were similar between the two studies.

All 9 infections cases were reviewed in detail by DSMC on November 9th 2015. The overall rate of infections was similar to that expected. With respect to the 4 fatal infectious events, the DSMC concluded: "even though there are likely alternative explanations for each individual case, such as rapid tumor progression, it cannot be excluded that treatment with melflufen may have contributed to the outcome of the events".

The DSMC therefore recommended:

- Future pneumonia cases should be followed closely
- Study guidelines for antimicrobial prophylaxis treatment in patients with intermediate and high infection risk should be issued (NCCN guidelines) or institutional guidelines.
- The study could continue as planned

The O-12-M1 study is complete as of 09 November 2017. Please refer to the IB for further details.

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 for general screening purposes. Data for in total 37 treatment cycles in 19 patients were available by 2 Nov 2015 for a preliminary analysis of the change in QTcF from baseline over the melflufen dose range 15 mg to 55 mg. No changes in QTcF during or after infusion of melflufen up to 25 mg have been observed. After 40 mg and 55 mg small mean increases by up to approximately 7 msec have been observed. The 90% confidence interval for the mean change ranges up to 11.1 msec for the 40 mg dose which is well below the limit of 20 msec which is commonly assessed as acceptable for anticancer drugs.

No patient in the study has developed absolute QTcF values that are associated with a meaningful increased risk of arrhythmias

Safety Summary

Please refer to the IB for further details. There is no change to the overall safety evaluation of melflufen.

The clinical trials results, to date, indicate that the safety profile for melflufen is similar to that for other alkylators, where thrombocytopenia, anemia and neutropenia are the most common AEs, followed by leukopenia and pyrexia. The DSMC investigated the 9 infectious SAEs in November 2015. The DSMC recommended that the international NCCN or institutional guidelines for infectious prophylaxis in MM should be followed. 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). 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. Final data from O-12-M1 study are available since 09 November 2017.

Clinical Efficacy

Please refer to the IB for further details.

As of 11 February 2016, 30 patients were evaluable for efficacy (patients receiving at least two doses of 40 mg melflufen with appropriate follow-up). Of these 30 patients, 3 achieved very good partial response (VGPR), 9 partial response (PR) and 7 minimal response (MR). Ten patients maintained stable disease (SD) and one progressive disease (PD). Median time from initial diagnosis to first dose of melflufen was 5.0 years (1-15). Median number of prior therapies was 4 (2-9). All patients but two had been exposed to (IMiD compounds), PIs and alkylators. Refractory status was available for 29 patients (missing data for 1 patient) at the time of the data cut-off. Of these 29 patients, 24 patients (83%) patients were IMiD-refractory, 19 (66%) were PI-refractory and 15 (52%) were alkylator refractory. Seventeen out of the 29 patients (59%) were double-refractory (IMiDs+PIs) and 9 (31%) were double- and alkylator-refractory. Twenty-three patients (78%) were refractory to last line of treatment.

The median PFS in the trial has been evaluated both for the protocol efficacy evaluable patients (PP), [i.e. treated with ≥2 doses of melflufen (n=30)] and all patients [those evaluable after ≥1 dose of melflufen (N=40)] with baseline and appropriate follow-up assessments. The median PFS for the efficacy evaluable population was at the time of data cut-off 8.0 months (95% confidence interval 4.1 to 14 months) based on 21 events in 30 patients with available data. Nine patients were still alive, had not progressed and were therefore censored at the latest time of tumor assessment. For all treated patients, the median PFS was 4.5 months (95% confidence interval 3.7 to 11 months) based on 30 events in 40 patients with available data. Ten patients were still alive, had not progressed and were therefore censored at the latest time of tumor assessment. These preliminary data suggest that the responses could be of considerable duration and that also the MR and SD patients may have a benefit of considerable duration until progression.

Final data from O-12-M1 study are available as of 09 November 2017, showing a median PFS of 5.7 months, and a median OS of 20.7 months in the 45 patients treated with 40 mg melflufen in combination with dexamethasone. Please refer to the IB for further details.

1.2.3.2 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 six MM patients in the clinical trial O-12-M1. The elimination phase for melflufen could not be followed in clinical trial O-05-001 since the plasma concentrations were generally below the limit of quantitation during this phase. Subsequent improvements of the bioanalytical method and sampling schedule have allowed estimation of the melflufen elimination phase in clinical trial O-12-M1. Further, the metabolite des-ethyl-melflufen is quantified in clinical trial O-12-M1, while it was not measured in clinical trial O-05-001.

In clinical trial O-05-001 (patients with solid tumors), melflufen plasma concentrations could be followed only up to end of infusion or very shortly thereafter. Melphalan concentrations were generally higher than those of melflufen both during and after the infusion. Melflufen and melphalan exposures increased slightly less than proportional to dose and the intra-patient variability in exposure between treatment cycles was low after administration of the same dose amount. Gender and body weight had no significant influence on the PK parameters of melflufen or melphalan.

In the clinical trial O-12-M1 in MM patients, PK data from eight patients covering the dose range 15 mg to 55 mg were available as of 10 February, 2015. Preliminary analysis showed that the melflufen plasma concentration reached a peak before end of infusion and is thereafter eliminated with a half-life of 3 to 5 minutes. 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 is 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 iv infusion. The reasons for the decrease in melflufen concentrations during the ongoing infusion, frequently observed in both studies, are not known. 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, but 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 or blood components outside of the plasma compartment in which melphalan is predominantly formed. Melphalan is thereafter distributed back to the plasma.

2 STUDY RATIONALE

2.1 RATIONALE FOR THE SELECTED PATIENT POPULATION

The proposed initial target patient population for melflufen is a heavily pre-treated and highly refractory population, consisting of MM patients who have received at least two prior lines of therapy including a PI and an IMiD compound, and are refractory to pomalidomide and/or daratumumab. In this population, there is a clear lack of treatment alternatives and a high unmet medical need. Early preliminary efficacy data suggest considerable clinical benefit in terms of PFS, tumor response as well as response duration in patients regardless of refractory status to available treatments (IMiDs, PIs, alkylators and/or MAb) as described above and in the Investigator's Brochure (IB). The side effect profile in heavily pretreated patients with MM has

been reported to be similar to that expected after treatment with alkylators. Melflufen may therefore offer a meaningful benefit with acceptable toxicity profile for patients with heavily pre-treated disease and refractory to pomalidomide and/or daratumumab.

The purpose for Amendment 6 is to expand the drug class of anti-CD38 mAbs from daratumumab to include also isatuximab, currently in Phase 3 clinical trials, and other anti-CD38 mAbs in development. Given the broad patient exposure to these alternate monoclonal antibodies in clinical trials, the late stage development of isatuximab and the rapidly evolving landscape of approved drugs for the treatment of MM, it is adequate to evaluate the activity of melflufen following failure of the drug class rather than just the specific drug (daratumumab). In addition, a targeted sub-group of patients who are triple-class refractory (i.e. refractory to an IMiD, a PI and an anti-CD38 mAb) has been identified as a subgroup of particular interest. All efficacy and safety analyses will be performed both in the total population and the subgroup in the clinical study report.

2.2 RATIONALE FOR DOSE SELECTION

Patients will be treated with melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. The starting dexamethasone dose will be reduced to 20 mg/day in all patients equal to or older than 75 years in line with previous studies (San Miguel et al. 2013).

The dose and schedule of melflufen is based on data from the Phase 1/2 trial with melflufen in combination with dexamethasone in RRMM patients. The Phase 1 portion of the trial established the MTD to be 40 mg melflufen iv every 21 days with 40 mg oral dexamethasone weekly. In the Phase 2 part of the trial, the DSMC decided to increase the cycle length to 28 days to improve tolerability by allowing additional time for hematologic recovery, and enable patients to stay on therapy longer. It was found that this increase resulted in a higher proportion of cycle lengths according to the protocol default. Thus the 28-day schedule will be implemented in this trial. Melflufen may be given until disease progression or unacceptable toxicity, and dose and schedule should be adjusted based on tolerability.

2.3 RATIONALE FOR STUDY EXPANSION

The patients in OP-106 Horizon study are heavily pre-treated with a median of 5.5 prior treatment lines. Of the 62 patients treated in the study by 10 May 2018, 90% were pomalidomide-refractory and 65% were daratumumab-refractory. Six of the 62 treated patients were not evaluable at the time of the cut-off: 5 patients had recently started treatment, and 1 patient experienced a fatal SAE during first cycle. The preliminary efficacy data are promising with an ORR for the whole population (N=56) of 32.1%. In the 56 patients, 12 patients had achieved PR, 5 patients had achieved VGPR and 1 patient had achieved CR, with 22 patients still actively on treatment at the time of the cut off. In addition, 4 patients achieved an MR as their best response.

Preliminary data show higher response rates in some subgroups – e.g. ORR of 40.0% among patients refractory to pomalidomide without being refractory to daratumumab (N=20), and ORR of 66.7% in patients refractory to daratumumab without being refractory to pomalidomide (N=6).

The safety profile continues to be acceptable, with primary adverse events being thrombocytopenia, neutropenia and anemia, and few grade 3/4 non-hematological adverse reactions (EHA 2018 poster, IB edition 8.0).

On 21 December 2017, following the protocol defined futility analysis, the DSMC assessed the benefit/risk balance for both of the predefined groups of the study (pomalidomide-refractory and daratumumab-refractory, respectively) and rejected futility. Due to the overall positive benefit/risk balance, the DSMC recommended the study to be continued.

Based on the preliminary safety and efficacy data available to date, the sponsor believes the benefit-risk ratio to be positive for the OP-106 study patient population. The population treated in this study is heavily pre-treated patients (median prior lines 5,5) with almost no remaining treatment alternatives. It is therefore considered justified to enroll additional patients to obtain further efficacy and safety data in this population. In addition, the sponsor would like to initiate the collection of preliminary functional status and well-being information. No such data has been collected in melflufen clinical trials to date.

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE

- To assess ORR, i.e. proportion of patients with ≥ partial response (PR) [stringent CR (sCR), complete response (CR), very good partial response (VGPR), and PR] as best response in efficacy evaluable patients as assessed by the investigator according to International Myeloma Working Group (IMWG) Uniform Response Criteria (URC) (Rajkumar et al. 2011) (Appendix C).

3.1.1 Key Secondary Objectives

- To assess PFS according to IMWG (Rajkumar et al. 2011),
- To assess duration of response (DOR) in efficacy evaluable patients with ≥ PR (sCR, CR, VGPR, PR) as best response according to IMWG-URC (Rajkumar et al. 2011), (Appendix C).
- To assess Overall Survival (OS).

3.1.2 Other Secondary Objectives

- To assess CBR (i.e. proportion of patients with ≥ MR), as best response in efficacy evaluable patients),
- To assess Time to Response (TTR)
- To assess time to Progression (TTP)
- To assess the safety and tolerability
- To assess functional status and well-being

3.2 PRIMARY ENDPOINT

- Best response of PR or better, as assessed by the investigator according to IMWG-URC. ORR will be estimated as the proportion of patients who achieve a confirmed sCR, CR, VGPR, or PR as their best response as assessed by the investigator.

3.2.1 Secondary Endpoints

- PFS
- DOR
- OS
- Best response of MR or better. CBR will be estimated as the proportion of patients who achieve a best response of MR or better.
- TTR
- TTP
- Duration of SD
- Frequency and grade of AEs
- Change from baseline in QLQ-C30 assessment
- Change from baseline in EQ-5D-3L assessment

* All tumor response and progression-depended objectives are as assessed by the investigator's assessment of response according to the IMWG-URC (Rajkumar et al. 2011), (Appendix C).

4 STUDY DESIGN

4.1 DESCRIPTION OF STUDY DESIGN

This is a single arm, open-label, Phase 2 multicenter study which will enroll patients with RRMM following at least 2 lines of prior therapy (Appendix D), including an IMiD and a PI, and who are refractory to pomalidomide and/or an anti-CD38 antibody defined as patients who relapse while on therapy or within 60 days of last dose.

Patients will be treated with melflufen 40 mg infusion on Day 1 and dexamethasone 40 mg orally on Days 1, 8, 15 and 22 of each 28-day cycle. Patients ≥ 75 years of age will have a reduction of the starting dose of dexamethasone from 40 mg to 20 mg on the same schedule. In the event of cycle delays, in the absence of dexamethasone toxicity, it is recommended that dexamethasone continue weekly.

Patients may receive treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician determine it is not in the patient's best interest to continue.

Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol (Section 7.7).

A Schedule of Events for the study is outlined in Section 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. After informed consent is obtained, the screening assessments will be performed as detailed in Section 8 of the protocol. Table 8-1, Schedule of Event, 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. Laboratory results noted in the inclusion criteria must remain within the limits specified prior to first dose of study drug on Cycle 1 Day 1.

5.1.1 Screening Failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered screen failures.

5.2 PATIENT ELIGIBILITY

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

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 this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. The planned analysis will explore differences in treatment effect based on racial and gender groupings, but the sample size is not increased in order to provide additional power for such subset analyses. Investigators are encouraged to recruit a diverse population.

5.3 INCLUSION CRITERIA

Eligible patients will be considered 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. Measurable disease defined as any of the following:
   - Serum monoclonal protein ≥ 0.5 g/dL (≥ 5 g/L) by serum protein electrophoresis (SPEP)
   - ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine protein electrophoresis (UPEP)

- Serum immunoglobulin free light chain ≥10 mg/dL (≥ 100 mg/L) AND abnormal serum immunoglobulin kappa to lambda free light chain ratio

4. A minimum of 2 prior lines of therapy, including an IMiD and a PI, and is refractory to pomalidomide and/or an anti-CD38 mAb. (Refractory status includes patients who relapse while on therapy or within 60 days of last dose of pomalidomide and/or an anti-CD38 mAb in any line, regardless of response).
5. Life expectancy of ≥ 6 months.
6. ECOG performance status ≤ 2 (Patients with worse performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the medical monitor).
7. Female of child bearing potential (FCBP)* and non-vasectomized male agree to practice appropriate methods of birth control (See Section 7.6.1).
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.
9. 12-lead ECG with QTcF interval of ≤ 470 msec calculated by Fridericia Formula (Appendix H).
10. The following laboratory results must be met during screening (within 21 days) and also prior to 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 prior to initiation of therapy)
    - Platelet count ≥ 75,000 cells/mm^3 (75 x 10^9/L) (without transfusions required 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 higher value in patients diagnosed with Gilberts syndrome after review and approval by the medical monitor
    - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN
    - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min. For women ≤ 155 cm in height and with normal BMI (18.5 – 24.9 kg/m^2) the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method for calculation of glomerular filtration may be used. (Appendix G). Cases with borderline values of creatinine clearance based on the Cockcroft-Gault formula may be discussed with the medical monitor.
11. Must have, or accept to have, an acceptable central catheter for infusion of melflufen (Port a cath, PICC line, or central venous catheter).

**(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.*

5.4 EXCLUSION CRITERIA

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

1. Evidence of mucosal or internal bleeding and/or is platelet transfusion refractory (i.e. platelet count fails to increase by > 10,000 cells/mm^3 after a transfusion of an appropriate dose of platelets).
2. 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 (MI), significant conduction system abnormalities, uncontrolled hypertension, ≥ grade 3 thromboembolic event in the last 6 months)
3. Active infection, treated with parenteral anti-infectives within 14 days, or oral anti-infectives within 7 days, prior to initiation of treatment (exceptions may be considered after review and approval by the medical monitor).
4. Primary refractory (never responded (≥ MR) to any prior 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, and very-low and low risk prostate cancer patients in active surveillance as defined in NCCN version 3, 2016.
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 HIV or active hepatitis B or C viral infection
9. Concurrent symptomatic amyloidosis or plasma cell leukemia
10. POEMS syndrome [plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-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. IMiDs, PIs and/or corticosteroids within 2 weeks prior to initiation of therapy. Prednisone up to but no more than 10 mg orally q.d. or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to initiation of therapy. Other investigational therapies and monoclonal antibodies or live vaccines within 4 weeks prior to initiation of therapy (other washout times may be considered following consultation with the medical monitor).
12. Residual side effects to previous therapy > grade 1 prior to initiation of therapy (Alopecia

any grade and/or neuropathy grade 2 without pain are permitted)

13. Prior autologous or allogeneic stem cell transplant within 12 weeks of initiation of therapy
14. Prior allogeneic stem cell transplant with active graft-versus-host- disease (GVHD)
15. Prior major surgical procedure or radiation therapy within 4 weeks of the initiation of therapy (this does not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy).
16. Known intolerance to steroid therapy

6 PATIENT ENROLLMENT

6.1 ENROLLMENT PROCEDURE

Site initiation visits must be complete at each site before patients can be screened at that site. Informed consent must be signed before any study-specific tests may be performed.

Patients must meet all the entry criteria detailed in Section 5.3 and Section 5.4 in order to be enrolled. The medical monitor must verify entry criteria are met and provide approval for enrollment. Documentation of the enrollment process is filed in the Investigator Site File.

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

6.2 PATIENT NUMBERING

A unique patient number will be assigned by the site, at the time of screening that will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient.

6.3 REPLACEMENT POLICY

Patients will not be replaced unless they fail to start treatment or if they are considered non-evaluable for response. The response data will be assessed in efficacy evaluable patients (all patients who receive at least 2 doses of melflufen, had a baseline disease assessment, and had at least 1 post-baseline disease assessment).

7 TREATMENT

7.1 STUDY TREATMENT

Patients must begin treatment ≤ 5 calendar days of enrollment. Pretreatment tests/procedures must remain within the screening timelines specified in Table 8-1: Schedule of Events.

Treatment will be given in an outpatient treatment setting. Patients will receive the following treatment:

- Melflufen 40 mg will be administered as a 30-minutes intravenous (iv) infusion on Day 1 of every 28-day cycle via an acceptable central catheter *.
- Dexamethasone will be administered orally on Days 1, 8, 15 and 22 of each 28-day cycle at the following dose based on age:
  - Dexamethasone 40 mg for patient < 75 years of age
    OR
  - Dexamethasone 20 mg orally for patient ≥ 75 years of age.

Oral dexamethasone may be substituted with iv dexamethasone at the investigator's discretion (USA only).

**All patients must have a central catheter prior to the initiation of the first dose of melflufen. (Port A Cath, PICC line or central venous catheter).*

Dose modifications and delays may be implemented based on patient tolerance as detailed in Section 7.7. In the event of cycle delay, in the absence of dexamethasone toxicity, it is recommended that dexamethasone continue weekly.

7.2 INITIATION OF THERAPY

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 meet the entry criteria as follows:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days of initiation of therapy).
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusion during the previous 10 days to initiation of therapy).
- Hemoglobin ≥ 8.0 g/dl (RBC transfusions are permitted).
- Total Bilirubin ≤ 1.5 x upper limit of normal (ULN) except patients diagnosed with Gilberts syndrome that have been reviewed and approved by the medical monitor.
- AST and ALT ≤ 3.0 x ULN.
- Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min. For women below 155 cm in height and with normal BMI (18.5 – 24.9 kg/m^2) the CKD-EPI method for calculation of glomerular filtration may be used (Appendix G). Cases with borderline values of creatinine clearance based on the Cockcroft-Gault formula may be discussed with the medical monitor.

7.3 MELFLUFEN

7.3.1 Melflufen Packaging and Labeling

The drug product, melflufen powder for solution for infusion, is filled in 50 mL glass vials with grey rubber stoppers and flip-off seals. Please refer to the Pharmacy Manual for further details on packaging and labeling.

7.3.2 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 - 8°C (refrigerated).

7.3.3 Preparation of Melflufen Solution for Infusion

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 (cold). The iv 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 rapidly degrades in solution.

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 until the start of iv infusion is 45 minutes.
- 250 ml bag of 0.9% saline
  - Pre-cooled: the 250 ml bag of 0.9% 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. Use of ambient saline is not permitted.

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.

7.3.4 Melflufen Administration

Prophylactic treatment with anti-emetic drug(s) prior to melflufen solution administration is recommended. Subsequent anti-emetic drugs against delayed emesis will be administered at the discretion of the investigator. Concomitant medication shall be documented in the concomitant medication page in the eCRF.

The study treatment will be administered via an acceptable central catheter, which will 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).
Refer to Pharmacy Manual for complete instructions on melflufen preparation for infusion.

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 of 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.

7.4 DEXAMETHASONE

7.4.1 Dexamethasone Packaging and Labeling

Oral dexamethasone will be supplied by Oncopeptides AB to sites located in Europe. Oral dexamethasone may be substituted with iv dexamethasone at the investigator's discretion (USA only). Only oral dexamethasone will be supplied to sites outside of USA. USA sites will use commercially available dexamethasone supplies.

7.4.2 Dexamethasone Storage

Dexamethasone is to be stored at controlled room temperature. Consult the package insert or Summary of Product Characteristics (SmPC) for dexamethasone for additional storage and usage instructions.

7.4.3 Dexamethasone Administration

Dexamethasone should be administered orally. Sites are responsible to record administration and patient compliance regarding dexamethasone dosing in the source documents and eCRF. Consult the package insert or SmPC for the respective product for additional instructions for

dexamethasone administration. Dexamethasone is best taken prior to melflufen on days when both drugs are given on the same day (Day 1 of each cycle).

7.5 STUDY DRUG COMPLIANCE AND ACCOUNTABILITY

7.5.1 Study Drug Compliance

Compliance should be assured by administration of the study treatment under the supervision of the investigator or his/her designee, and should be documented in the study drug administration and accountability records. Compliance with weekly dexamethasone will be verified by patient inquiry and documented in the source documents and eCRF.

7.5.2 Study Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the 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 dexamethasone, melflufen and drug labels should be discarded according to a CRO approved site drug destruction policy. A copy of the drug destruction policy and completed drug accountability log should be provided to the monitor.

7.6 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 blood products, physical therapy and herbal/natural medications) administered during the study must be listed on the Concomitant Medications section of the eCRF.

7.6.1 Required Concomitant Therapy

- Contraceptive measures

  Male patients, and female patients of child-bearing potential, shall be required to use effective contraceptive methods (or abstinence) prior to initiation of melflufen, while on therapy and for 28 days after the last dose for women and 3 months after the last dose for men. The best method should be determined in consultation with the Investigator.

  Females:

  Birth control methods that can are considered as highly effective include: tubal ligation, intra uterine device, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy.

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

  Males:

Males must use a latex or synthetic condom during any sexual contact with females of child-bearing potential 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.

7.6.2 Recommended Concomitant Therapy

- Pneumocystis prophylaxis
  - All patients are recommended to receive pneumocystis prophylaxis concomitant with treatment according to the NCCN or institutional guidelines. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf or NCCN.org
  - 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 delayed emesis should be administered at the discretion of the investigator.
- Patients should receive full supportive care, including transfusions of blood and blood products (including platelets), antibiotics, anti-diarrheals, analgesics, etc. and prophylactic treatment for tumor lysis syndrome when appropriate.
  - Melflufen is a potent myelosuppressive agent, it is essential that careful attention 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 discretion, that platelet transfusion should be avoided less than 5 days of the next dose of melflufen 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 7.2 for use of growth factors and platelet transfusions prior to the first dose of melflufen).
- Bisphosphonate therapy iv or p.o. should be administered if indicated in accordance with institutional guidelines.
- 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 entry criteria.
- Recommended Antimicrobial prophylaxis
  - For patients with history of 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

- Antiviral and antifungal prophylaxis should be considered.

7.6.3 Contraindicated Concomitant Therapy

- Concurrent therapy with any approved or investigative anticancer therapeutic drug with activity against multiple myeloma is not allowed.
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) > prednisone 10 mg/day (or its equivalent) are not permitted.
- Other investigative agents must not be used during the study.
- The use of live vaccines is prohibited during the study and for 30 days after last dose of study drug
- 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.
- Limitations on the use of growth factors and platelet transfusions are detailed in Section 7.6.2.

7.7 DOSE MODIFICATIONS

Dose adjustments are permitted for drug related toxicity according to guidelines described in this section. Toxicity should be assessed using the CTCAE version 4.03 (Appendix B). All dose modifications should be based on the worst preceding toxicity. 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.

7.7.1 Dose Reduction Steps for Melflufen

Table 7-2 outlines the dose reduction steps for melflufen based on the starting dose for Cycle 1 or subsequent cycles.

Table 7-2 Dose Reduction Steps for Melflufen

Starting Dose	Dose reduction Step - 1	Dose reduction Step - 2
40 mg	30 mg	20 mg

7.7.2 Dose Modification Guidelines for Melflufen

Dose modifications of melflufen for drug related toxicity are permitted. Multiple dose reductions are permitted down to 20 mg. If a patient is unable to tolerate the 20 mg dose of melflufen due to drug related toxicity, the patient should discontinue study treatment. However, if in the opinion of the investigator it is in the patient's best interest to continue treatment on a lower dose (15 mg or 10 mg), this may be considered after review and approval of the medical monitor.

Prior to each cycle of melflufen the criteria for initiation of therapy must be met. (See Section 7.7.5).

7.7.2.1 Hematologic Toxicity

Melflufen is a potent myelosuppressive agent, it is essential that careful attention 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 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 following guidelines for dose modification due to drug related hematologic toxicity should be followed (see also Table 7-3). Criteria for a new cycle is detailed in (Section 7.7.5).

Please note: The guidelines in Table 7-3 are based on the laboratory values obtained at each cycle on Day 29 (scheduled day 1) or subsequent weekly evaluations as noted below (not the blood counts during the cycle on days 8, 15 or 22). Patients that experience a grade 4 thrombocytopenia or neutropenia on Day 29 **in more than one consecutive cycle** on the same dose level **will require a one level dose reduction when the criteria for initiation of a new cycle are met.**

Table 7-3 Dose Modifications of Melflufen for Hematologic Toxicity:

Hematologic criteria for initiation of a new cycle • ANC ≥ 1,000 cell/mm^3 (1.0 x10^9/L) • Platelet count ≥ 50,000 cell/mm^3 (50.0 x 10^9/L)		
Day	**Criteria met for new cycle**	**Criteria not met for new cycle**
Day 29	Continue at same dose level Investigator discretion: • Optional to hold one week (to Day 36)	Hold dose. Evaluate in one week (to Day 36)

Day 36	Continue at same dose level* Investigator discretion: • Optional one level dose reduction • Optional to hold one week (to Day 43)	Hold dose. Evaluate in one week (to Day 43)
Day 43	Continue at same dose level* Investigator discretion: (consultation with medical monitor is encouraged) • Optional one level dose reduction • Optional to hold one week (to Day 50)	Hold dose. Evaluate in one week (to Day 50)
	NOTE: The cycle length may not exceed 43 days if criteria are met on Day 29 or 36	
Day 50	Continue with required one level dose reduction	Hold dose. Evaluate in one week (to Day 57)
Day 57	Continue with required one level dose reduction	Discontinue from therapy**
*Second failure to recover from treatment related Grade 4 neutropenia or thrombocytopenia on Day 29 in a subsequent cycle within the same dose level will result in a one-step dose reduction once recovered. Optional dose delays to allow for further recovery are permitted as detailed in this table above.		
** If the criteria for initiation of a new cycle of therapy **are not met** by Day 57 due to drug related toxicity, then the patient must be discontinued from therapy, unless in the investigator's opinion the patient is benefitting from therapy. Continuation must be discussed with the medical monitor or Sponsor on a case by case basis.		

Alternate dose modification (prolongations/reductions) 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 adverse event including abnormal laboratory value must be followed as described in Section 8.2.5 and 8.2.6.

7.7.2.2 Non-hematologic Toxicity

The resolution of all non-hematologic drug related toxicity must be to ≤ Grade 1 or baseline (except alopecia any grade and fatigue ≤ Grade 2) on Day 1 of each cycle.

The following guidelines should be followed:

- If the criteria for initiation of a new cycle of therapy are not met on Day 29 (the next scheduled Day 1 of any given cycle), the dose should be held and the patient should be re-evaluated weekly.
- If cycle prolongation, due to non-hematologic toxicity, of more than 14 days is needed to meet the criteria for initiation of a new cycle, a one-step dose reduction is necessary
- The option to "hold one week" for further resolution of toxicity is permitted at the investigator's discretion based on the time lines in Table 7-3 above.
- If cycle prolongation of more than 28 days (beyond Day 57) is needed, study treatment is to be discontinued unless in the investigator's opinion the patient is benefitting from therapy. Continuation must be discussed with the medical monitor or sponsor on a case by case basis.
- Grade 3 or 4 treatment related non-hematologic toxicity that occurs or persists on Day 29 (scheduled Day 1) of any cycle requires a one-step dose reduction when the criteria for a new cycle are met with the following exceptions:
    - 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)

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

7.7.3 Dose Reduction Steps for Dexamethasone

Table 7-4 outlines the dose reduction steps for dexamethasone. Dose reductions of dexamethasone other than those listed in Table 7-4 or discontinuation may be considered in consultation with the medical monitor.

Table 7-4 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	8 mg

7.7.4 Dose Modification Guidelines for Dexamethasone

Multiple dose reductions of dexamethasone are permitted. If a patient is unable to tolerate dexamethasone due to dexamethasone related toxicity, dexamethasone may be discontinued in consultation with the medical monitor. However, the patient may continue on treatment with melflufen at the investigator's discretion. In the event of a cycle delay, in the absence of dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

Table 7-5 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 ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, 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.

7.7.5 Initiation of a New Cycle of Treatment

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. To begin a new cycle of treatment the following criteria must be met:

- ANC must be ≥ 1,000 cell/mm^3 (1.0 x10^9/L)
- Platelet count must be ≥ 50,000 cell/mm^3 (50.0 x 10^9/L) (platelet transfusions not recommended less than 5 days of subsequent melflufen dose (see Section 7.6.2)
- All non-hematologic study drug related toxicities must be ≤ Grade 1 or returned to baseline (except alopecia any grade and fatigue ≤ grade 2).

If these criteria are not met on the scheduled Day 1, the new cycle should be held and patients should be re-evaluated weekly following the guidelines in Section 7.7.2.1, 7.7.2.2 and Table 7-3. A new cycle can only be initiated when the criteria are met.

The maximum amount of time for which melflufen 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 benefitting 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.

7.7.6 Treatment Duration

Patients will receive treatment until there is documented disease progression according to the IMWG guidelines (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.

8 VISIT SCHEDULE AND ASSESSMENTS

8.1 SCHEDULE OF EVENTS

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 clinically 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	All Cycles[s, u]				End of Treatment [p]	PFS-FU[q,s]	OS-FU[r,s]
		Day 1	Day 8	Day 15	Day 22			
Informed consent [a]	X							
Inclusion/exclusion criteria	X							
Medical and disease history [b]	X							
Physical examination and symptom assessment [c]	X	X	(X)	(X)	(X)	X		
Vital signs [d]	X	X				X		
ECOG performance status	X	X				X		
Pregnancy test [e]	(X)	(X)				(X)		
Electrocardiogram [f]	X					X		
Chest X-ray	X							
Hematology [g]	X	X	X	X	X	X		
Coagulation [h]	X							
Blood chemistries [i]	X	X				X	(X)[q]	
Bone marrow aspiration [j]	X	(X)				(X)	(X)[q]	
M- protein assessments (SPEP/UPEP, IFE, SFLC) [k]	X	X				X	X[q]	
Serum β2-microglobulin	X							
Assessment of extramedullary plasmacytoma [l]	X	(X)				(X)	(X)[q]	
Assessment of lytic bone lesions [m]	X	(X)				(X)	(X)[q]	
PRO assessment[t]		(X)[t]				X	X	(X)
Dexamethasone administration [n]		X	X	X	X			
Melflufen administration [n]		X						
Concomitant medications [o]	X	→				X		
Adverse event monitoring		→				X		
Follow-up PFS							X[q]	
Follow-up-OS								X[r]

(X) Only if clinically indicated

a) All patients must sign an IRB/IEC-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 and R-ISS stage at diagnosis and cytogenetics (if previously evaluated). 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 examination (PE), 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. A site visit is required for Cycle 1 and 2 for weekly symptom assessment. Plasmacytomas that can be followed by PE 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.

e) All FCBP must have a negative pregnancy test (urine or serum) documented prior to start of therapy with melflufen, repeat pregnancy test on Day 1 of each cycle and at End of Treatment visit. 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) A 12-lead ECG assessment will be performed on all patients at baseline and End of Treatment visit and as clinically indicated. Q-Tc interval to be assessed by Fridericia formula (Appendix H).

g) Hematology: Complete blood count (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. Exceptions 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 9.1.2).

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

i) Blood chemistry: sodium, chloride, potassium, magnesium, phosphate, uric acid, carbon dioxide, blood urea nitrogen (BUN), glucose (fasting at baseline), AST, ALT, alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine, calcium and lactate dehydrogenase (LDH), and estimated creatinine clearance by Cockroft-Gault Equations (or by CKD-EPI method for calculation of glomerular filtration for women below 155 cm in height and with normal BMI (18.5 – 24.9 kg/m^2) (Appendix G). 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) BMA to be collected at screening for % plasma cells, morphology, cytogenetics by FISH. Minimum FISH probes include 17p, 4;14, 14;16. Repeat for % plasma cells at the time of suspected CR (negative IFE). If a bone marrow aspirate and/or biopsy has been collected within 6 weeks prior to initiation of therapy, it does not need to be repeated.

k) SPEP, UPEP, serum and urine protein IFE (IFE if SPEP or UPEP are not detectable at screening, and subsequently if not detected in both SPEP and UPEP, as well as to confirm CR), with quantitative immunoglobulins per routine laboratory practice (quantitative Ig required to be repeated for patients with IgA or IgD myeloma) and serum free light chain (SFLC) assay (only required if SPEP and UPEP are not measurable [UPEP is < 200 mg/24 hrs and SPEP is < 0.5 g/dL] and to confirm a sCR). To be conducted at screening, Cycle 1 Day 1 and Day 1 of each additional cycle even if treatment is delayed. All assessment of SPEP, UPEP, IFE and FLC must be completed in the same laboratory for a given patient (see also footnote q). In the event of cycle delay beyond day 43, M protein disease assessment are required to be repeated on the day the new cycle starts i.e., Day 1 of the new cycle. If treatment is discontinued beyond day 43, the assessments should be repeated on the day of that determination (or as soon as possible 30 days after the last dose of study drug) as part of the EoT visit. Refer to Laboratory Guidance Document for details. All response assessments require 2 consecutive evaluations according to the IMWG criteria. Confirmed PD should be verified by the medical monitor prior to discontinuation of treatment.

l) Known or suspected extramedullary plasmacytomas are to be assessed and measured at screening (within 28 days), as clinically indicated, and to confirm a response obtained by M protein assessment or a suspected progression according to IMWG-UCR. The same method of evaluation should be used throughout the study (e.g. CT/MRI/PET), and bi-dimensional measurements must be obtainable. All imaging assessments should be documented in the eCRF.

m) Assessment of lytic bone lesions can be done either by skeletal survey, or low dose CT scan. Assessment includes: lateral radiograph of the skull, and anterioposterior views of femur and humeri, aterioposterior and lateral views of the spine, and anterioposterior views of the pelvis and ribs or low dose CT scan. Required ≤ 6 weeks prior to study entry. Additional imaging assessments may be performed at the investigator's discretion and should be documented in the eCRF. Repeat imaging assessments (same technique as used at screening) at any time when clinically indicated or to confirm PD. Limited X-rays or scans may be performed as clinically indicated if able to confirm PD.

n) See Section 7 in the protocol for complete details on study drug administration, dose modifications and start of a new cycle of therapy.

o) Concomitant medications: All blood products and medications within 21 days prior to first dose of study drug until the End of Treatment Visit

p) End of Treatment visit should be scheduled 30 days (accepted time window ±3 days) after last dose of melflufen 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 unresolved toxicity), with evaluation of safety variables including recording of new and ongoing adverse events, review of concomitant medications and any other new disease related therapy. If a new treatment for multiple myeloma 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 stabilization or initiation of subsequent therapy. Serious Adverse Events should be followed until resolution or stabilization with no expected resolution.

q) Follow-up for Disease Progression: 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. (Confirmed PD should be verified by medical monitor prior to discontinuation of therapy). If the patient enters PFS-FU, the first PFS M protein disease assessment should be scheduled 30 days +/- 7 days after the EoT visit. Patients unwilling or unable to return to the site for PFS evaluations may have the laboratory assessments done locally following approval by the medical monitor. 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 date and regimen of the first subsequent therapy is required. M-protein assessments required monthly, imaging of lytic lesions and/or plasmacytomas and serum calcium (corrected calcium) required only if suspected as evidence of PD.

r) Follow-up for overall survival: Following confirmed disease progression or initiation of subsequent therapy, follow-up for overall survival status, second primary malignancies and (documentation of the date and regimen of first) subsequent therapy, if not done during PFS-FU, will take place every three months +/- 7 days for 24 months. The first OS follow-up should be scheduled 3 months after the last PFS-FU or EOT visit. 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.

s) Follow-up may be completed by phone contact. Serious Adverse Events 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) PRO: the QLQ-C30 and EQ-5D-3L questionnaires should be administered to the patient before any other study procedures are performed and before the administration of study drug. To be completed at C1D1, C2D1, C4D1, C6D1, C8D1, EOT, PFS-FU and at OS-FU (only if patient conducts the follow up visit onsite). If the patient wishes to have the questions read aloud and then answer orally and the study personnel write the answer on the questionnaires, this is acceptable.

u) +/- 3-day window permitted for all visits (except Cycle 1 Day 1 [no leeway].

8.2 STUDY ASSESSMENTS

All assessments should be done according to the timelines outlined in Table 8-1; Schedule of Events.

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 SPEP 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
- Extramedullary plasmacytoma evaluation of known or suspected lesions (by PE and/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 or low dose CT scan may be used (with the same technique to be used at screening and each evaluation).
- Beta2 microglobulin
- LDH
- Cytogenetics by FISH
- ISS staging score and revised R-ISS (Appendix I)

8.2.2 Efficacy Assessments

Efficacy Assessments

- M-protein determination using the following procedures:
  - SPEP and serum protein IFE with quantitative Ig (quantitative Ig required only for patients

for patients with IgA and IgD myeloma);

- Immunofixation of serum is required at any time when M protein by both SPEP and UPEP becomes non-detectable and to confirm a CR.

o UPEP and urine protein IFE (all using the same 24-hour urine collection);

- Immunofixation of urine is required at any time when M protein by both UPEP and SPEP becomes not detectable and to confirm a CR.

o 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. Bi-dimensional measurements must be obtainable by the selected imaging technique.
- Bone marrow aspirate to quantify percent myeloma cell involvement
- Assessment of lytic bone lesions: skeletal X-rays or CT scan (with the same technique at screening and each evaluation).
- Serum calcium (corrected calcium)

M protein disease status (assessed by M-protein quantitation and IFE and free light chain from serum and 24-hour urine collection), should be assessed at screening and Cycle 1 Day 1, and on planned Day 1 (i.e. Day 29 of the previous cycle) of each cycle even if treatment is delayed. In the event treatment for a new cycle is delayed beyond Day 43 of the previous cycle, M protein disease status is required to be repeated on the day the new cycle starts, i.e. Day 1 of the new cycle (e.g. Day 50 or 57 of the previous cycle). If treatment is discontinued beyond Day 43, the assessment should be repeated on the day of that determination (or as soon as possible 30 days after the last dose of study drug) as part of end of treatment (EoT) visit. If the patient enters PFS-FU, the first PFS M protein disease status assessment should be scheduled 4 weeks after the EoT visit. If the patient is discontinued mid-cycle, prior to Day 28, the EoT visit should be scheduled 30 days (+/- 3 days) after the last dose of study drug.

Starting with Cycle 2, M protein response to treatment should be assessed every cycle. Disease status, including skeletal x-rays of bones or low dose CT scan and imaging assessment (i.e. CT/ positron emission tomography [PET]/ magnetic resonance imaging [MRI] scan) of known or suspected extramedullary plasmacytomas, will be performed at screening and if indicated according to the IMWG response criteria. Bone marrow aspirate will be performed at screening

and to confirm suspected CR in patients who have achieved a negative IFE. Additional skeletal x-rays and/or imaging assessments may be performed at the investigator's discretion at screening to further evaluate plasmacytomas. All imaging assessments should be documented in the eCRF. Repeat assessments if the patient has symptoms suggestive of progression of lesion(s) documented at screening or new lesions. If extramedullary plasmacytomas are present at screening and measurable on physical examination, they will be assessed at every cycle. Extramedullary plasmacytomas documented and measurable only by imaging assessments will be assessed by the same relevant modality to confirm response or progression according to the IMWG response criteria.

- Functional status and well-being

  Two different PROs will be used to evaluate functional status and well-being in the study; the EORTC QLQ-C30 and the EQ-5D-3L.

  - **EORTC QLQ-C30,** which includes 30 items resulting in 5 functional scales, 1 Global Health Status scale, 3 symptom scales, and 6 single items. The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients. Scores are transformed to a 0 to 100 scale. Administration time is approximately 11 minutes. QLQ-C30 domain scores will be summarized at each time point and change from baseline will be derived. The relationship between clinical response and change in domain scores will be explored.
  - **EQ-5D-3L**, a generic measure of health status. For the purpose of this study the EQ-5D-3L will be used to generate utility scores for use in cost-effectiveness analyses. The EQ-5D-3L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale (EQ VAS) rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and are cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The 5 domains of EQ-5D-3L and the EQ VAS will be summarized at each time point and change from baseline will be derived. Functional status and well-being.
  - The patient should complete the questionnaires prior to any procedures on the day of the visit and prior to being told anything related to health. If the patient wishes to have the questions read aloud and then answer orally and the study personnel write the answer on the questionnaires, this is acceptable.

8.2.3 Safety and Tolerability Assessments

Safety Assessments:

- Serial physical examinations with vital signs and assessment of performance status and neurological status.
- Routine safety laboratory tests (CBC with differential and platelets; serum chemistry, coagulation tests) with calculation of creatinine clearance according to the Cockcroft-Gault equation. For women below 155 cm in height and with normal BMI (18.5 – 24.9 kg/m^2) the CKD-EPI method for calculation of glomerular filtration may be used (Appendix G). Cases with borderline values of creatinine clearance based on the Cockcroft-Gault formula may be discussed with the medical monitor.
- Chest X-ray (postero-anterior/lateral).
- Grade 3 and 4 thrombocytopenia and neutropenia (See Section 9.1.5).
- Pregnancy testing.
- ECG.
- Assessment and grading of adverse events.

Adverse experiences, 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 one dose of study treatment.

8.2.4 Electrocardiogram Assessments

At screening and End of Treatment (EoT) visit, a 12-lead ECG assessment will be performed on all patients and as clinically indicated. QTc interval to be assessed by Fridericia formula (Appendix H).

8.2.5 End of Treatment

The EoT visit should be scheduled 30 days (accepted time window ±3 days) after last dose of melflufen or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (e.g. in the case of prolonged toxicity). At the EoT visit, evaluation of safety variables including recording of new and ongoing AEs, review of concomitant medications and any other new disease related therapy should be performed. 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 multiple myeloma 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 stabilization, or initiation of subsequent therapy. Serious Adverse Events 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.

8.2.6 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. Treatment discontinuation alone does not preclude the need to complete follow-up assessments.

8.2.6.1 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. If PD has not been confirmed prior to initiation of subsequent therapy, the reason for the subsequent therapy should be documented. The date and regimen of the first subsequent therapy should be recorded in the eCRF if occurs during PFS-FU.

8.2.6.2 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 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. 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 date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during OS-FU.

8.2.6.3 Assessment of Functional Status and Well-being during Follow up

Patients should complete PROs for the assessment of functional status and well-being at each follow up visit (PFS-FU and OS-FU) that the patient performs onsite. The completion of PROs is to be done first in the day, prior to any other procedures.

8.2.6.4 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.

8.2.7 Criteria for Premature Patient Withdrawal

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

1. Documented confirmed disease progression (2 consecutive evaluations) verified by the medical monitor.
2. Patients may choose to discontinue from the study treatment at any time and continue in follow-up.
3. AEs that, in the judgment of the investigator, may cause severe or permanent harm or which require study drug discontinuation (See section 7.7).

4. 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.
5. Requiring other anti-neoplastic therapies.
6. Major violation of the study protocol (i.e., unable to adhere to study schedule).
7. Confirmed pregnancy.
8. Lost to follow-up

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

1. Withdrawal of consent for study participation.
2. Death.
3. Lost to follow-up.
4. Discontinuation of the study by Oncopeptides AB.
5. Completed OS follow up as per protocol

The reason(s) for withdrawal of 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 SAFETY MONITORING AND REPORTING

9.1 ADVERSE EVENTS

9.1.1 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 participation in an investigational study, 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 adverse reactions, 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 of melflufen or prescribing information for dexamethasone. 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 would be considered “unexpected”.

9.1.2 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

needs to be reported on the AE eCRF. This includes any abnormal laboratory values that the investigator considers clinically significant (Section 9.1.5).

For AEs not adequately addressed in the CTCAE, the severity table below may be used:

Table 9-1 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 related to AE

9.1.3 Causality

The assessment of causality will 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. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome (Section 9.1.5.1).

9.1.4 Adverse Event Reporting

All adverse events 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 adverse event 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, other).
5. Whether medication or therapy was given (concomitant medication or procedure).
6. Outcome (e.g. not resolved, resolved, resolved with sequalae, fatal, unknown).
7. Whether it is a serious adverse event (SAE) as defined in Section 9.2.

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

Any adverse event (i.e. 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 adverse event on the appropriate page(s) of the CRF. Should a patient discontinue from treatment or complete the study and commence subsequent anticancer therapy within 30 days of the last study drug administration, adverse events attributable to this subsequent therapy should not be recorded.

9.1.5 Laboratory Test Abnormalities

9.1.5.1 Definitions and Reporting

Laboratory abnormalities are usually not recorded as adverse events; 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 adverse events (or serious adverse events) if they meet the definition of a serious adverse event as described in Section 9.2. In addition, laboratory abnormalities assessed as clinically significant should also be recorded as adverse events. The Investigator will record the grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition. Adverse events as a result of laboratory abnormalities 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 thrombocytopenia and neutropenia events. They must be:

- Collected and reported during the study period and the EoT visit.
- Ongoing grade 3 and 4 thrombocytopenia and neutropenia 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 adverse events or prophylactic reasons must be reported in the eCRF and if applicable also in the SAE report.

9.2 SERIOUS ADVERSE EVENTS

9.2.1 Definitions

A Serious Adverse Event (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, i.e., 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.
- (AEs requiring hospitalization of less than 24 hours, will not be reported as SAEs unless another seriousness criteria is fulfilled)

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 serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- 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).

9.2.2 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, 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 fax or email to:

- SAE Fax line (United States): 1-877-853-3275
- SAE Fax line (Europe): +34 91 307 60 47
- Email: drugsafety@pivotal.es

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. A 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 9.2.2.1).

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 expecting 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 Ethics Committees (ECs)/Institutional Review Boards (IRBs) in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. For the purpose of SUSARs reporting, only possibly or probably related SAEs (i.e. there is a reasonable possibility of causality) will be considered serious adverse drug reactions. See Section 9.1.3 for further information.

9.2.2.1 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.

9.3 PREGNANCY

To ensure patient safety, any pregnancy occurring while the patient is on study treatment must be reported by the investigator to the designated CRO, within 24 hours of learning of its occurrence. 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 fax or email to:

- SAE Fax line (United States): 1-877-853-3275
- SAE Fax line (Europe): +34 91 307 60 47
- Email: drugsafety@pivotal.es

Any SAE experienced during pregnancy (such as congenital anomaly/birth defect/spontaneous abortions) must be reported via fax or email 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.

9.4 DATA SAFETY MONITORING COMMITTEE

An independent data and safety monitoring committee (DSMC) will perform surveillance of efficacy/safety balance at regular intervals and on an as needed basis during the study, to safeguard the interest of study participants. The DSMC will consist of key investigator(s) and Sponsor representative(s) and headed by an independent chairperson. All activities and processes surrounding the DSMC will be outlined in the DSMC Charter.

10 DATA COLLECTION AND MANAGEMENT

10.1 DATA CONFIDENTIALITY

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

- What protected health information (PHI) 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 PHI.

In the event that a patient revokes authorization to collect or use PHI, 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 PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

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

10.2 SITE MONITORING

Before study initiation, at a site initiation visit or at an investigator's meeting, Oncopeptides AB personnel (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 copy of the signed form 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.

10.3 DATA COLLECTION

An electronic Case Report Form (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.

10.4 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 corrections to the data.

11 STATISTICAL METHODS AND DATA ANALYSIS

11.1 STUDY ENDPOINTS

11.1.1 Primary Endpoint

The primary endpoint is a best response of PR or better, as assessed by the investigator according to IMWG-URC, from which overall response rate (ORR) is calculated. ORR is defined as the proportion of patients with a best confirmed response of sCR, CR, VGPR, or PR according to the IMWG-URC (Rajkumar et al. 2011), (Appendix C), as assessed by the Investigator and reported in the eCRF using the study center laboratory evaluation.

11.1.2 Secondary Endpoints

PFS: is defined as time (months) from date of first dose to the earlier of confirmed disease progression or death due to any cause. The conventions for censoring of PFS are described in Table 11-1.

Progression status will be assessed by the investigator using the IMWG-URC, (Rajkumar et al. 2011).

Best response of MR or better, from which clinical benefit rate will be calculated. CBR, i.e. proportion of patients with ≥ MR): is the rate of efficacy evaluable patients that achieve a confirmed minimal response or better.

TTR: is defined as the time from the date of first dose to the date of the first documented confirmed response in a patient that has responded with ≥ PR.

TTP: is defined as the time from the first date of first dose to the date of the first documented confirmed PD.

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

Duration of stable disease: is defined as the date of first dose to the first documented PD in patients who fail to achieve response (≥ MR)

OS: is defined as time (months) from date of first dose 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.

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

Functional status and well-being: The PROs QLQ-C30 and EQ-5D-3L will be used to evaluate functional status and well-being. The derivation of summary scores as well as subscales will be performed at each measured time point following the guidelines related to the Questionnaire. Observed results will be presented at each measured time point as well as change from baseline.

11.2 SAMPLE SIZE CALCULATION

A total number of approximately 150 patients are planned to be enrolled in the study, to achieve 130 patients evaluable for efficacy, and 50 patients evaluable for EQ-5D-3L.

Initially, one group of approximately 39 efficacy evaluable patients that are refractory to pomalidomide and one group of approximately 39 efficacy evaluable patients that are refractory to daratumumab were planned to be enrolled (see interim analysis Section 11.3.4).

Based on the positive benefit-risk ratio in this patient population to date, as well as the objective to obtain functional status and well-being data in this patient population, this was changed to allow an increased sample size.

Instead of calculating the sample size on the power to show superiority on ORR versus a fixed value, the sample size is now based on the precision of the estimates. As for the ORR, given a sample size of 130 evaluable patients and an observed ORR of 30%, the exact 95 % confidence interval would range from 22.3 % to 38.7 %.

Further enrollment to each group may continue to establish a sufficient dataset if deemed appropriate at the discretion of the Sponsor regardless of the number of patients recruited at that time.

11.3 SUB-GROUP OF SPECIFIC INTEREST

Patients that are refractory to all three currently approved classes of drugs (IMiDs, PIs and anti-CD38 mAbs) have emerged as a sub-group of particular interest.

All efficacy and safety analyses performed for the total population will be repeated in a similar way for this sub-population. In a retrospectively analysis as of 06 February 2019, this triple-class refractory sub-group represented 70% of the total population (67 of 95 patients). All triple-class refractory patients that are enrolled in the study on or after the date of the retrospective analysis will be followed prospectively. The ORR for patients of this sub-group accrued retrospectively before 06 February 2019 will be reported as well as patients prospectively enrolled after this date. If there is no substantial difference in ORR, the results will be presented for the total sub-group. Assuming a similar (or slightly higher) proportion of patients within the remaining approximately 55 patients, about 40 patients of the sub-group of specific interest can be followed prospectively.

11.4 STATISTICAL METHODS

11.4.1 General Considerations for the Statistical Analysis

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. 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 (SD), 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 electronic case report forms (eCRFs) and any derived data will be presented by in data listings.

11.4.2 Analysis populations

11.4.2.1 Efficacy Analysis Set

The primary efficacy population will be comprised of all patients who received at least 2 doses of melflufen, had a baseline disease assessment and at least 1 post-baseline disease assessment (efficacy evaluable patients).

To be evaluable for functional and well-being analysis, patients must be evaluable for efficacy and have a completed baseline (C1D1) and at least one post baseline (C2D1 and/or later) assessment.

11.4.2.2 Safety (All Treated) Analysis Set

The safety (all treated) analysis set will be comprised of all patients that receive any study treatment (melflufen or dexamethasone).

11.4.3 Analysis of Efficacy Endpoints

11.4.3.1 Primary Endpoint

The ORR will be estimated as the proportion of patients who achieve a confirmed response of sCR, CR, VGPR, or PR as their best response as assessed by the investigator. At the end of the trial an exact two-sided 95% confidence interval for ORR will be determined. The ORR will primarily be based on the efficacy evaluable analysis set.

11.4.3.2 Analyses of Secondary Endpoints

PFS is measured from the date of first study drug to the date of documented disease progression or death. PFS will be right-censored for patients who met 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 FDA Guidance for Industry, (FDA 2007). For such patients, the primary analysis of PFS will be right-censored according to the conventions described in Table 11-1.

Table 11-1 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 first dose	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
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 using the Kaplan Meier method. The median PFS will be estimated from the 50th percentile of the corresponding Kaplan Meier estimates. The 95% CI for median PFS will be constructed using the method of Brookmeyer (Brookmeyer et al. 1982). Duration of follow-up for PFS will be estimated by the reverse Kaplan-Meier method of Schemper (Schemper et al. 1996). PFS will be based on both the All Treated and the Efficacy analysis set.

Other time to events endpoints will be described in the same way as PFS.

CBR, will be estimated with its associated 95% confidence interval assuming binomial proportions.

Functional status and well-being:

QLQ-C30: The observed value, as well as change from C1D1 (baseline), in the QLQ-C30 summary score as well as all subscales will be summarized.

EQ-5D-3L will be summarized both for the descriptive system as well as for the EQ VAS scores at each measured time point. Furthermore the results from the EQ-5D-3L will be used in the evaluation of cost effectiveness of melflufen.

11.4.3.3 Independent review of primary and secondary endpoints

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.

11.4.4 Interim Analysis

An interim analysis for futility (according to the Simon two-stage design) for each group (pomalidomide-refractory and daratumumab-refractory patients) was planned and conducted after 19 patients had been enrolled and were evaluable for the primary endpoint (ORR) (Simon 1989). Following the futility analysis, on 21 December 2017, the study DSMC assessed the benefit/risk balance, and found this balance to be positive in both of the groups as well as for the total study

population. Due to the overall positive benefit/risk balance, the DSMC recommended that the study recruitment would proceed without changes or limitations.

11.4.5 Analysis of Safety Data

All safety results will be presented for the All Treated analysis set. No formal statistical analysis will be performed for the safety endpoints.

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

Each reported AE term will be mapped to a preferred term (PT) and a system organ class (SOC) using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The summaries of adverse events (AEs) will be based on TEAEs. TEAEs are defined as AEs that start on or after the first day of study treatment is administered and within 30 days of the last administration of study treatment or before start of subsequent anticancer treatment (whichever occurs first) or that worsen on or after the first day of study treatment.

The number (%) of patients experiencing TEAEs will be summarized by MedDRA SOC and PT. The denominator for the percentage will be based on the number of patients at in the All Treated analysis set. A patient reporting the same AE more than once will be counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination. For such cases, the maximum CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. Treatment-related AEs, defined as AEs with a relationship of possibly or probably related will be summarized in the same way.

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

Actual value and change from baseline for all hematology, serum chemistry, and coagulation parameters will be summarized at each scheduled visit. Selected laboratory test results will be assigned toxicity grades using CTCAE 4.03. Shift tables assessing the

toxicity grade at baseline versus worst toxicity recorded on study will be presented. A listing of all grade 3 or higher laboratory values will be provided.

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

11.5 HANDLING OF DROP-OUTS AND MISSING DATA

The SAP describes how dropouts and missing data impact the calculation of the time to event variables. Missing data will not be estimated or carried forward for any of the other summaries or analyses. If only a partial date is available and is required for a calculation (e.g., time since diagnosis, 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.

Handling of partial missing data for the PRO measurements will be done in accordance with the instructions for the QLQ-C30 questionnaire and EQ-5D-3L and described in the SAP.

12 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

12.1 REGULATORY AND ETHICAL COMPLIANCE

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.

12.2 RESPONSIBILITIES OF THE INVESTIGATOR AND IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC 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 and regulatory authorities as required.

12.3 INFORMED CONSENT PROCEDURES

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-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 form (ICF) was actually obtained will be captured in the eCRFs.

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

12.4 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. A study group may be discontinued at interim futility analysis as described in Section 11.3.4. Specific conditions for terminating the study at any time for reasonable medical or administrative reasons in any single center could include 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.

12.5 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.

12.6 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 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.

12.7 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 10.1 for additional details regarding patient confidentiality.

12.8 AUDITS AND INSPECTIONS

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

12.9 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.

12.10 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.

12.11 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 before it may be implemented. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval.

13 REFERENCES

American Society of Hematology Annual Meeting San Diego 2018, oral presentation of abstract #600

Brookmeyer, R. and J. Crowley (1982). "A Confidence Interval for the Median Survival Time."

Cavo, M., S. V. Rajkumar, A. Palumbo, et al. (2011). "International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation." Blood **117**(23): 6063-6073.

Chauhan, D., A. Ray, K. Viktorsson, et al. (2013). "In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells." Clin Cancer Res **19**(11): 3019-3031.

FDA (2007). "Guidance for Industry Clinical Trail Endpoints the Approval of Cancer Drugs and Biologics." US Food and Drug Administration.

FDA Pomalyst Prescribing Information (2013).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204026s012s014lbl.pdf

Gullbo, J., E. Lindhagen, S. Bashir-Hassan, et al. (2004). "Antitumor efficacy and acute toxicity of the novel dipeptide melphalanyl-p-L-fluorophenylalanine ethyl ester (J1) in vivo." Invest New Drugs **22**(4): 411-420.

Gullbo, J., M. Wickstrom, M. Tullberg, et al. (2003c). "Activity of hydrolytic enzymes in tumour cells is a determinant for anti-tumour efficacy of the melphalan containing prodrug J1." J Drug Target **11**(6): 355-363.

Investigator Brochure, Melflufen Oncopeptides AB (2018), Edition 8

Kaplan, E. L. and P. Meier (1958). "Nonparametric estimation from incomplete observations." Journal of the American Statistical Association **53**: 457-485.

Koyama, T. and H. Chen (2008). "Proper inference from Simon's two-stage designs." Stat Med **27**(16): 3145-3154.

Kumar, S. K., S. V. Rajkumar, A. Dispenzieri, et al. (2008). "Improved survival in multiple myeloma and the impact of novel therapies." Blood **111**(5): 2516-2520.

Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006 Aug 15;145(4):247-54.

Mateos, M., Oriol, A., Larocca, A. et al (2018). The Horizon: a preliminary report on efficacy and safety of melflufen in late stage relapsed-refractory myeloma (RRMM) patients refractory to

pomalidomide and/or daratumumab. 23rd Congress of the European Hematology Association (EHA), poster number PF581.

Mougenot, P., F. Pinguet, M. Fabbro, et al. (2004). "Population pharmacokinetics of melphalan, infused over a 24-hour period, in patients with advanced malignancies." Cancer Chemother Pharmacol **53**(6): 503-512.

Nath, C. E., P. J. Shaw, J. Trotman, et al. (2010). "Population pharmacokinetics of melphalan in patients with multiple myeloma undergoing high dose therapy." Br J Clin Pharmacol **69**(5): 484-497.

NCCN (2016). "National Comprehensive Cancer Network: Clinical Practice Guidelines Multiple Myeloma Version 1.2017. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

NCCN (2016). "National Comprehensive Cancer Network: Clinical Practice Guidelines Prostate Cancer Version 3.2016. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Oken, M. M., R. H. Creech, D. C. Tormey, et al. (1982). "Toxicity and response criteria of the Eastern Cooperative Oncology Group." Am J Clin Oncol **5**(6): 649-655.

Paba-Prada, C., A. Palumbo, U. H. Mellqvist, et al. (2014). "Determination of the MTD and Preliminary Results in an Ongoing Open-Label Phase I/IIa Study of the Safety and Efficacy of Melflufen and Dexamethasone in Combination for Patients with Relapsed and Relapsed-Refractory Multiple Myeloma (RRMM)." Blood **124**:2123.

Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. Journal of Clinical Oncology. 2015 33:26, 2863-2869

Pomalidomide Celgene EPAR (2013). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Public_assessment_report/human/002682/WC500147721.pdf.

Rajkumar, S. V., J. L. Harousseau, B. Durie, et al. (2011). "Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1." Blood **117**(18): 4691-4695.

Rajkumar S.V. Richardson P, San Miguel, J. (2015). "Guidelines for determination of the number of prior lines of therapy in multiple myeloma." Blood 126:921-922.

Rajkumar, S. V. and S. Kumar (2016). "Multiple Myeloma: Diagnosis and Treatment." Mayo Clinic Proceedings **91**(1): 101-119.

Richardson, P. G., J. Laubach, C. Mitsiades, et al. (2010). "Tailoring treatment for multiple myeloma patients with relapsed and refractory disease." Oncology (Williston Park) **24**(3 Suppl 2): 22-29.

Richardson, P. G., D. S. Siegel, R. Vij, et al. (2014). "Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study." Blood **123**(12): 1826-1832.

San Miguel, J., K. Weisel, P. Moreau, et al. (2013). "Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial." Lancet Oncol **14**(11): 1055-1066.

Schemper, M. and T. L. Smith (1996). "A note on quantifying follow-up in studies of failure time." Control Clin Trials **17**(4): 343-346.

SEER (2015). "Surveillance, Epidemiology, and End Results Program Cancer statistics Stat Fact Sheets: Myeloma." National Cancer Institute; http://www.seer.cancer.gov/statfacts/html/mulmy.html.

Simon, R. (1989). "Optimal two-stage designs for phase II clinical trials." Control Clin Trials **10**(1): 1-10.

Wickstrom, M., C. Haglund, H. Lindman, et al. (2008). "The novel alkylating prodrug J1: diagnosis directed activity profile ex vivo and combination analyses in vitro." Invest New Drugs **26**(3): 195-204.

Wickstrom, M., J. I. Johnsen, F. Ponthan, et al. (2007). "The novel melphalan prodrug J1 inhibits neuroblastoma growth in vitro and in vivo." Mol Cancer Ther **6**(9): 2409-2417.

Wickstrom, M., K. Viktorsson, L. Lundholm, et al. (2010). "The alkylating prodrug J1 can be activated by aminopeptidase N, leading to a possible target directed release of melphalan." Biochem Pharmacol **79**(9): 1281-1290.

Wisloff, F., Eika, S., Hippe E., et al. (1996). “Measurement of health-related quality of life in multiple myeloma. Nordic Myeloma Study Group.” Br J Haematol. 1996;92:604–613

Wisloff F, Hjorth M. (1996). “Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma” Br J Haematol. 1997;97:29–37

14 APPENDICES

Appendix A. 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

(Oken et al. 1982)

Appendix B. NCI 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 Response Criteria

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,[3] 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 measureable, ≥ 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	• ≥ 25% but < 49% reduction of serum M protein and reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs. • 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 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)[4] 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 and PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ 1 g/dl are sufficient to define relapse if starting M-component is ≥ 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 et al. 2011).

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 Response Criteria.

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 Refractory 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

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Appendix G. Renal Function Calculations

Cockcroft-Gault formula

For males:

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

For females:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Chronic Kidney Disease Epidemiology Collaboration equation

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for women below 155cm in height and with normal BMI (18.5 – 24.9 kg/m^2)

The CKD-EPI equation, expressed as a single equation, is:

$$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018\ [\text{if female}] * 1.159\ [\text{if black}]$$

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

(Levey 2006)

Appendix H. QTc Fridericia Formula

Assessment of QTC Interval using 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 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 or III
Stage III	ISS stage III and either high risk CA by iFISH or LDH

(Palumbo et al. 2015)

Appendix J. QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix K. EQ-5D-3L

Health Questionnaire

English version for the UK

(Validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today