Protocol OP-107
Version 6.0, April 30, 2021

Protocol Title: A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function

National Clinical Trial number: NCT03639610

Clinical Development Protocol

OP-107

BRIDGE TRIAL

A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function

Investigational Product	Melflufen
Study Sponsor	Oncopeptides AB Västra Trädgårdsgatan 15 SE-111 53 Stockholm, Sweden
Protocol Number	OP-107
EudraCT number	2018-000478-31
Investigational New Drug Number	116362
Clinical Research Organization (CRO)	PSI CRO AG, Baarerstrasse 113a, 6300 Zug, Switzerland
Development phase	Phase 2
Document status	Version 1.0: March 2, 2018 Amendment 1: Version 2.0: November 19, 2018 Amendment 2: Version 3.0: September 26, 2019 Amendment 3: Version 4.0: March 26, 2020 Amendment 4: Version 5.0: January 22, 2021 Amendment 5: Version 6.0: April 30, 2021

Signature Page

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Date of Original Protocol: **Version 1.0: March 2, 2018**
Amendment 1: **Version 2.0: November 19, 2018**
Amendment 2: **Version 3.0: September 26, 2019**
Amendment 3: **Version 4.0: March 26, 2020**
Amendment 4: **Version 5.0: January 22, 2021**
Amendment 5: **Version 6.0: April 30, 2021**

Approved By:

_____ _____
[redacted] Date
Clinical Study Physician
Oncopeptides AB
Luntmakargatan 46
111 37 Stockholm, Sweden
[redacted]

_____ _____
[redacted] Date
Global Lead Investigator
University Hospital Brno, Czech Republic

_____ _____
[redacted] Date
Clinical Operations Director

Protocol Acceptance Page

Protocol Number: OP-107

Protocol Title: A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function

Protocol Date: Version: 1.0: March 2, 2018
Amendment 1: Version 2.0: November 19, 2018
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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

Study Centre Name:

Study Center Address:

Study Center Phone number:

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

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

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Protocol Synopsis

Compound Name	Melflufen
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Chemical Name	4-[Bis-(2-chloroethyl)amino]-L-phenylalanine-4-fluoro-L-phenylalanine ethyl ester hydrochloride
International nonproprietary name (INN)	Melphalan flufenamide
Study Protocol Title	A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function.
Study Sponsor	Oncopeptides AB
Global Lead Investigator	[redacted]
Site(s)	Approximately 16 sites in Europe
Study Period	FPI September 2018
Background and Rationale	Melphalan flufenamide (hereinafter referred to as 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 desethyl-melflufen, 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, Wickström et al. 2010). Since des-ethylmelflufen and melphalan are relatively hydrophilic, there is a possibility for intracellular trapping of these alkylators. This can be explained by a more efficient transport of melflufen into these cells, an efficient conversion into other alkylating molecules (i.e. melphalan and desethyl-melflufen) inside the cells and a less rapid disappearance of these molecules from the cells. Melflufen has been evaluated in combination with low dose dexamethasone in a Phase 1/2a clinical trial (O-12-M1) in relapsed/refractory multiple myeloma (RRMM). The trial established the recommended dose at 40 mg of melflufen every 28 days combined with 40 mg dexamethasone weekly. As of November 9, 2017, clinical trial O-12-M1 in RRMM was evaluable for efficacy. There were 34 efficacy evaluable patients treated with at least 2 doses of 40 mg melflufen in combination with weekly dexamethasone, 22 patients (65%) have reported a best response of minimal response (MR) or better and 14 patients (41%) have reported partial response (PR) or better. These 34 patients had a median of 4 prior

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	lines of therapy, including immunomodulatory drugs (IMiD)s, proteasome inhibitors (PI)s and alkylators. The median progression free survival (PFS) was 5.7 months at the time of data-cut based on 41 events in 45 patients with ≥ 1 cycle. Median number of cycles completed was 5.0 (Range 1 – 14) (Palumbo et al. 2016). Taken together, clinical and preclinical data support that melflufen provides peptidase potentiated alkylating metabolites to tumor cells such as MM and thereby exerts a higher anti-tumor activity compared with equimolar administration of melphalan but with a similar safety profile. Renal impairment is a diagnostic feature of the end-organ damage of Multiple myeloma (MM) (Dimopoulos et al. 2016). Approximately 50% of MM patients will have some degree of renal impairment at diagnosis and/or during the course of disease (Knudsen et al. 2000). Reduction of tumor cell mass with therapy and with the use of supportive care, improvement or reversal of renal dysfunction is possible (Dimopoulos et al. 2008). However, renal impairment may affect the toxicity profile, as well as the disease response to treatment and it is therefore essential to establish the impact of melflufen in the context of renal impairment. During treatment with melflufen, the great majority of alkylating activity is expected to occur from melflufen instantly reaching cells and tissues outside of the plasma compartment (including any tumor cells present) and from the metabolite melphalan that is formed intracellularly from melflufen. Once formed, melphalan is distributed back to plasma from the cells, but melphalan in plasma is likely to have only a minor contribution to intra-cellular alkylating activity as the initial local concentrations when formed from melflufen in cells are much higher than those coming from redistributed melphalan in the circulation. Melphalan is eliminated from plasma primarily by spontaneous plasma hydrolysis to monohydroxy-melphalan and dihydroxy-melphalan, a process which is independent of renal function and hepatic metabolism. In addition, there is a minor contribution of direct renal elimination. Our expectation is that renal impairment will have no effect on melflufen pharmacokinetics (PK) and effects, and a minor effect on melphalan PK and effects. The OP-12-M1 trial as well as the ongoing Phase 3 OP-103 trial (melflufen and dexamethasone compared to pomalidomide and dexamethasone in RRMM) and OP-106 trial (melflufen and dexamethasone for RRMM patients' refractory to pomalidomide and/or daratumumab) required patients to have a baseline creatinine clearance (CrCl) of ≥ 45 mL/min based on Cockcroft Gault formula (Cockcroft 1976) combined with a serum creatinine of ≤ 2.0 mg/dL. In this OP-107 trial, we include RRMM patients with an estimated glomerular filtration rate (eGFR)of ≥ 30 mL/min/1.73m^2 to < 45 mL/min/1.73m^2 (cohort 1) corresponding to a moderate decrease in GFR. The trial will evaluate the relationship between renal function and the PK parameters for the metabolite melphalan during treatment with melflufen, and the safety and efficacy of the treatment in this patient population. Amendment 1 will include a potential cohort 2 of at least 6 patients with severe renal impairment. This cohort is added after recommendation by

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	the FDA, since it would be beneficial to allow clinical use of melflufen also in patients with severe renal impairment and since there are no unacceptable safety concerns with use of melphalan in patients with renal impairment, even after high dose treatment with melphalan 200 mg/m^2 (Sweiss 2016). Cohort 2 will only be initiated following DSMC review of the pharmacokinetic and safety profile of at least 6 patients in cohort 1. If the DSMC advises to proceed with Cohort 2, at least 6 patients with eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 will be enrolled and analyzed for safety and pharmacokinetics data. Since scientific data show that the Cockcroft-Gault formula is unreliable for patients with low CrCl (Michels 2010), guidelines advise not to use this formula for patients with CrCl of 30 mL/min or lower (Levey 2009, Tattersall 2011, KDIGO 2013). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula which estimates GFR, has better reliability especially at low CrCl value (Levey 2009, Michels 2010, KDIGO 2013, Levey 2017) and will therefore be used in the present study for all patients following approval of Amendment 1. The FDA also recommended to evaluate patients in later lines of therapy, limited to those who received 2-4 prior lines, as the treatment paradigm for multiple myeloma (MM) has shifted and there are approved therapies in the first 2 lines with known clinical benefit. Therefore, we will include only those patients with 2 – 4 prior lines of therapy. Amendment 2: Following PK evaluations from 9 patients enrolled in this study, 6 patients with eGFR ≥ 30 - < 45 mL/min/1.73m^2, and 3 patients with eGFR > 45 mL/min/1.73m^2 it was observed that Melphalan AUC increases with decreasing eGFR and this was linked to an increased myelotoxicity with lower nadir in platelets and neutrophils. DSMC recommended on 10 September 2019, further evaluation of melflufen 30 mg for patients with eGFR ≥ 30 - < 45 mL/min/1.73m^2 with a minimum of 6 additional patients in cohort 1 (Cohort 1b). Amendment 3: The current protocol requires all patients to have weekly CBC assessments. From cycle 3 onwards they can be done at a local laboratory close to the patient, and not necessarily at the clinic. Patients with good tolerability will no longer require all weekly CBC assessments. Specifically, if patient's tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (Granulocyte colony stimulating factor [G-CSF], blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded Day 8 and Day 22. For patients not visiting the site weekly they should still be contacted weekly by phone to follow up on AE/SAEs and dexamethasone compliance. Amendment 4, an amendment to update the CSP with the by DSMC confirmed starting dose for Cohort 2 of 20 mg, including dose reductions steps for this cohort, Table 6.1 updated. Cohort 2 will consist of two groups (a and b).

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	- Cohort 2a, evaluating patients with eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 with a starting dose of 20 mg melflufen. - Cohort 2b, evaluating patients with eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 with a starting dose of 30 mg melflufen. Cohort 2b will only open if recommended by DSMC after evaluating data from Cohort 1a, 1b and 2a. This amendment also includes adding an interim analysis for an interim clinical study report (iCSR), to conclude the results from Cohort 1, patients with eGFR ≥ 30 - < 45 mL/min/1.73m^2. As more cohorts are added the number of PK evaluable patients have increased from 25 to approximately 35. Amendment 5: Due to difficulties in recruiting eligible patients for Cohort 2a and b an updated feasibility assessment was performed alongside discussions with the investigators to identify potential eligibility hurdles in the current design of the protocol. The most frequent reasons for pre-screened patients not being eligible for screening was that they had received more than 4 prior lines of therapy (inclusion criteria no 3) or had deteriorating kidney function (inclusion criteria no 10). The protocol is therefore updated to allow at least 2 prior lines of therapy with no upper limit and a wider eGFR window for patients to proceed from Screening 1 to Screening 2. SAE reporting details have been updated to reflect the change of safety CRO from PSI PVG Unit to TFS. SAE reporting email address updated to [redacted].
Study Design	This multicenter study will enroll patients with RRMM who have received at least 2 lines of prior therapy. There are four Cohorts in the study 1a, 1b and 2a and 2b. • Cohort 1a (eGFR of ≥ 30 mL/min/1.73m^2 to < 45 mL/min/1.73m^2): 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. Following approval of Amendment 2, Cohort 1a will close for enrollment and Cohort 1b will open for a minimum of 6 additional patients. • Cohort 1b (eGFR of ≥ 30 mL/min/1.73m^2 to < 45 mL/min/1.73m^2): Patients will be treated with melflufen 30 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. After evaluating data from Cohort 1a and 1b the recommendation from DSMC was to open Cohort 2a for enrollment of a minimum of 6 additional patients. • Cohort 2a (eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2): Patients will be treated with melflufen 20 mg

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	(recommended dose by DSMC) on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Cohort 2b will only open if recommended by DSMC after evaluating data from Cohort 1a, 1b and 2a. • Cohort 2b (eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2): Patients will be treated with melflufen 30 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 reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22**.** Patients may receive treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician determines 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. In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly. A Schedule of Events for the study is outlined in Section 8, Table 8-1 of the protocol.
Objectives	**Primary Objectives** • To evaluate the relationship between renal function and the PK parameters for melphalan during treatment with melflufen • To assess the safety and tolerability of melflufen in patients with moderate (cohort 1a and 1b) and severe (cohort 2a and 2b) renal impairment **Secondary Objectives** • To assess the best tumor response as well as overall response rate (ORR) • To assess the PFS • To assess duration of response (DOR) in patients with ≥ PR (stringent complete response (sCR), complete response (CR), very good partial response (VGPR), PR) as best response • To assess clinical benefit rate (CBR) and duration of clinical benefit (i.e., proportion of patients with ≥ MR) as best response • To assess time to response (TTR) in patients with a PR or better and time to CB for patients with MR or better. • Overall survival (OS) All tumor response and progression-depended objectives are assessed by investigators according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar et al. 2011, Appendix C) unless otherwise specified. **Exploratory Objective** • To assess changes in renal function

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Endpoints	**Primary Endpoints** • PK parameters of melphalan • Frequency and grade of Adverse Events (AE) **Secondary Endpoints** • ORR • CBR • PFS • DOR and duration of clinical benefit • TTR • Best response during the study (sCR, CR, VGPR, PR, MR, stable disease [SD] or progressive disease [PD]) • Overall survival (OS) **Exploratory Endpoint** • The changes in eGFR over time.
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 at the time of signing the informed consent 2. A prior diagnosis of MM with documented disease progression requiring further treatment at time of screening 3. Received at least 2 prior lines of therapy. (Appendix D) 4. Measurable disease defined as any of the following: • Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP). • ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis (UPEP) • Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain ratio 5. Life expectancy of ≥ 6 months 6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to MM may be eligible following consultation and approval of the medical monitor) (Appendix A) 7. Patient is a female of childbearing potential (FCBP)* with a negative serum or urine pregnancy test prior to initiation of therapy and agrees to practice appropriate methods of birth control, or the patient is male and agrees to practice appropriate methods of birth control (Section 7.1) 8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent. 9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec (Appendix H). 10. **Renal function:** Estimated GFR by CKD-EPI formula (Appendix G) on 2 consecutive screening evaluations. Patients meeting criteria for Screening 1, must also meet criteria for Screening 2 following

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	optimal hydration (as determined by the investigator). Screening 2 must be on or as close as possible to treatment start date (preferably < 24-48 hours) but cannot exceed 72 hours. **Cohort 1 (a and b):** **Screening 1:** eGFR between ≥25mL/min/1.73 m^2 to <45 mL/min/1.73m^2 **Screening 2:** eGFR between ≥30 mL/min/1.73m^2 to <45 mL/min/1.73m^2. **Cohort 2 (a and b):** **Screening 1:** eGFR between ≥ 10 mL/min/1.73m^2 to < 35 mL/min/1.73m^2. **Screening 2:** eGFR between ≥15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2. Enrollment into Cohort 2b will only be initiated following approval from the DSMC. Patients with fluctuating values of eGFR may be eligible following consideration of additional assessments in consultation with the medical monitor. 11. The following laboratory results must be met during screening and immediately before study drug administration on Cycle 1 Day 1: • Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] prior to initiation of study therapy) • Platelet count ≥ 75,000 cells/mm^3 (75 x 10^9/L) (without transfusions during the 10 days prior to initiation of study 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 in patients diagnosed with Gilberts syndrome that have been reviewed and approved by the medical monitor. • Aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) ≤ 3.0 x ULN. 12. Must have, or be willing to have, an acceptable central catheter. (Port a cath, peripherally inserted central catheter [PICC] line, or central venous catheter) *(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:**

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	1. Primary refractory disease (i.e. never responded with ≥ MR to any prior therapy) 2. Evidence of mucosal or internal bleeding and/or platelet transfusion refractory (platelet count fails to increase by > 10,000 cells/mm^3 [10.0 x 10^9/L] after a transfusion of an appropriate dose of platelets) 3. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months), 4. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of initiation of therapy. 5. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance. 6. Pregnant or breast-feeding females 7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation 8. Known human immunodeficiency virus or active hepatitis B or C viral infection 9. Concurrent symptomatic amyloidosis or plasma cell leukemia 10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) 11. Previous cytotoxic therapies, including cytotoxic investigational agents, for MM within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy. The use of live vaccines within 30 days before initiation of therapy. IMiDs, PIs and corticosteroids within 14 days prior to initiation of study therapy. Other investigational therapies and monoclonal antibodies within 4 weeks of initiation of study 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 study therapy. Plasmapheresis is not permitted within 14 days of initiation of therapy. 12. Residual side effects to previous therapy > Grade 1 prior to enrollment (Alopecia any grade and/or neuropathy Grade 2 without pain are permitted) 13. Prior peripheral stem cell transplant within 12 weeks of initiation of study therapy 14. Prior allogeneic stem cell transplantation with active graft-versus-host-disease. 15. Prior major surgical procedure or radiation therapy within 4 weeks of the initiation of study therapy (this does not include limited course of radiation used for management of bone pain to be completed within 7 days of initiation of study therapy).

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	16. Known intolerance to steroid therapy 17. Prior renal transplant 18. Currently in need of renal dialysis
Study Treatment(s)	Treatment will be given in an outpatient treatment setting in cycles. Each cycle is 28 days. Melflufen 10-40 mg will be administered as a 30-minutes intravenous infusion on Day 1 of every 28-day cycle via acceptable central catheter. Dexamethasone 40 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient < 75 years of age. **OR** Dexamethasone 20 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient ≥ 75 years of age. In the event of cycle delays, it is recommended that dexamethasone continue weekly. Dose modifications and delays may be implemented based on patient tolerance as detailed in the protocol.
Duration of treatment	Patients will receive treatment until there is documented disease progression according to IMWG criteria (Rajkumar et al.2011, Appendix C) (to be confirmed on two consecutive assessments of the applicable disease parameters), unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue.
Duration of follow-up	Patients who discontinue treatment for reasons other than disease progression will continue to be followed for disease response monthly until progression (PD to be confirmed on two consecutive assessments) or initiation of subsequent therapy. Patients with Grade 3 or 4 neutropenia or thrombocytopenia at the end of treatment (EoT) visit will continue to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. OS will be followed in all patients until the last patient completes progression free survival follow-up (PFS-FU), after which time, an OS assessment at a future date may be done if requested by the sponsor.
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 the protocol 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 2018) or institutional guidelines.
Number of Patients	Approximately 35 PK evaluable patients given at least one dose of melflufen with acceptable PK sampling, at least 6 PK evaluable patients per Cohort.
Assessments	**Screening Disease Assessments** • M-protein determination using the following procedures: – SPEP and serum protein immunofixation (IFE) with quantitative immunoglobulins (Ig); and

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	– Urine protein electrophoresis (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 (by physical examination or imaging technique) • Skeletal survey and/or low dose computerized tomography (CT) scan • Beta2 microglobulin • Cytogenetics/ Fluorescence In Situ Hybridization (FISH) • Lactate dehydrogenase (LDH) • International staging system (ISS) Staging Score and Revised ISS (R-ISS) (Appendix I) **Pharmacokinetic sampling** Three plasma samples for determination of melphalan concentrations will be drawn in connection to the first two melflufen treatment cycles (Cycle 1 and 2); 5-10 minutes after the end of infusion, 2 - 3 hours after the end of infusion and 5-7 hours after the end of infusion. For enrolled patients with moderate renal impairment one repeat set of three PK samples, will be collected in one cycle if during the treatment period of the study, the patient's eGFR falls below 30 mL/min/1.73m^2. For enrolled patients with severe renal impairment one repeat set of three PK samples, will be collected in one cycle if during the treatment period of the study, the patient's eGFR falls below 15 mL/min/1.73m^2 and the patients is approved for dosing by MM. All PK samples must be drawn peripherally and not from the central catheter. Refer to the Laboratory Manual for details on specimen collection and processing. **Safety Assessments:** • Assessment and grading of AEs • Physical examinations with vital signs, neurologic assessment and assessment of performance status • Routine safety laboratory tests, (complete blood count [CBC] with differential and platelets and clinical chemistry) with calculation of eGFR by CKD-EPI equation (Appendix G) • Pregnancy testing • ECGs • Chest X-ray AEs, including clinical laboratory and vital sign abnormalities, will be graded using the National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 **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 or IgD myeloma); and

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	– UPEP and urine protein IFE (all using the same 24-hour urine collection); and – SFLC and SFLC ratio • Bone marrow to quantify percent myeloma cell involvement • Extramedullary plasmacytoma evaluation (by PE or imaging technique) • Skeletal X-rays and/or low dose CT scan (same technique used at screening and each evaluation) Serum calcium (corrected calcium)
Analysis Sets & Statistical methods	**Definition of Analysis Sets:** **PK Analysis Set** All patients that have received at least one melflufen dose and have sufficient PK samples taken after Cycle 1 or 2 infusion. **Efficacy Analysis** All patients that complete 2 doses of melflufen and have relevant baseline and follow-up disease assessments after the second dose of melflufen. **Safety Analysis Set** All patients that receive at least one or partial dose of melflufen or dexamethasone. **Statistical Methods:** **Primary Endpoints:** **PK Analysis** Melphalan concentration data will be pooled across patients and all melflufen studies providing data and evaluated using a population approach with nonlinear mixed-effect modeling. Actual time points for drug administration and plasma sampling will be used. Details on the modeling approach will be described in a separate population PK-PD plan which will be developed in parallel with the ongoing Phase 3 study OP-103 (OCEAN TRIAL). The relationship between melphalan PK parameters and patient factors will be assessed, as well as the inter-occasion variability in melphalan exposure. **Safety Analysis** The number (%) of patients experiencing treatment emergent adverse events (TEAEs) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The denominator for the percentage will be based on the number of patients at in the Safety analysis set. No formal statistical analysis will be performed for the safety endpoints.

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	Secondary Endpoints: The ORR will be estimated as the proportion of patients with ≥ PR (sCR, CR, VGPR and PR) as best response. Clinical benefit response will also be assessed in patients who achieve ≥ MR. PFS, DOR, duration of clinical benefit, TTR and OS will be analyzed using the method by Kaplan-Maier. **Interim analysis** An interim analysis for an interim clinical study report (iCSR) is planned when patients enrolled in Cohort 1a and 1b have been followed until progression or up to at least 6 months after first dose. The objective of this interim analysis is to evaluate PK, safety and efficacy in Cohort 1, moderately impaired patients, to support regulatory submissions.
ICH and Ethics	This clinical study was designed and shall be implemented and reported in accordance with the International Conference Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. The study protocol will be reviewed and approved by local ethics committees or Institutional Review Boards (IRBs) and patients will sign Informed Consent Forms (ICFs) before enrolling to the trial.

List of Abbreviations

AE	Adverse Event
ALT	Alanine transaminase/Alanine aminotransferase/glutamic pyruvic transaminase (SGPT)
ANC	Absolute neutrophil count
ASCT	Autologous stem-cell transplantation
AST	Aspartate transaminase/Aspartate aminotransferase/glutamic oxaloacetic transaminase (SGOT)
AUC	Area under the curve
BMA	Bone marrow aspiration
CB	Clinical benefit
CBC	Complete blood count
CBR	Clinical benefit rate
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eCRF	electronic Case Report Form
CRO	Clinical Research Organization
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
DNA	Deoxyribonucleic acid

DOR	Duration of response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoT	End of Treatment
FCBP	Female of childbearing potential
FISH	Fluorescence In Situ Hybridization
FLC	Free light chain
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
iCSR	Interim Clinical Study Report
IEC	Independent Ethics Committee
IFE	Immunofixation
Ig	Immunoglobulin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
IND	Investigational new drug
IRB	Institutional Review Board
ISF	Investigator Site File
ISS	International Staging System
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal response
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
OS-FU	Overall survival follow-up
PD	Progressive disease
PFS	Progression free survival
PFS-FU	Progression free survival follow-up
PI	Proteasome Inhibitor
PICC	Peripherally inserted central catheter
PK	Pharmacokinetics
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein
PR	Partial response
PT	Preferred term
q.d.	Quaque die/ one a day

RBC	Red blood cell
R-ISS	Revised international staging system
RRMM	Relapsed Refractory Multiple Myeloma
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent complete response
S-Cr	Serum Creatinine
SD	Stable disease
SFLC	Serum free light chain
SOC	System organ class
SPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TTR	Time to response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WHO	World Health Organization

1 BACKGROUND

1.1 OVERVIEW OF MULTIPLE MYELOMA

Multiple myeloma (MM) is a malignancy of the differentiated plasma cells that affects the older patient with a median age at onset of 65 to 70 years and a slight male predominance. MM is the second most common hematologic malignancy and nearly 30,330 patients with myeloma were diagnosed in the United States in 2015 (SEER 2016).

The disease is characterized by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal Ig (usually of the IgG or IgA type or free urinary light chain [paraprotein, M-protein or M-component]). Patients with MM may experience significant decrement to quality of life, including bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia, hyperviscosity of the blood and renal function compromise (including renal failure). The disease course for MM varies with the disease stage at diagnosis, cytogenetic profile, as well as age and patient comorbidities. The median survival is approximately 5 to 7 years with some significant variation in survival depending on host factors, tumor burden, biology and response to treatment (Kumar et al. 2008). However, the disease remains ultimately fatal.

There are currently 6 classes of approved drugs available for the treatment of MM, including steroids (prednisone and dexamethasone), immunomodulatory drugs (IMiDs) (thalidomide, lenalidomide and pomalidomide), proteasome inhibitors (PIs) (bortezomib, carfilzomib and ixazomib), histone deacetylase inhibitors (panobinostat), conventional chemotherapy (melphalan, cyclophosphamide, doxorubicin), including high dose melphalan with autologous stem-cell transplantation (ASCT) and the most recent addition of monoclonal antibodies (elotuzumab and daratumumab). The selection of treatment in relapsed/refractory multiple myeloma (RRMM) is challenging. The National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2018) and a recent overview published in the Mayo Clinic Proceedings (Kumar et al. 2016) detail an array of single agent, doublet and triplet combination regimens that can be considered. Patients for whom stem cells were cryopreserved early in the disease course, and who are transplant candidates, may benefit from ASCT as salvage therapy (Cavo et al. 2011). In general, MM patients will receive an average of 4 to 8 different treatment regimens during their lifespan.

1.2 RENAL IMPAIRMENT IN MULTIPLE MYELOMA

Renal impairment is a diagnostic feature of the end-organ damage of MM (Dimopoulos et al. 2016) and one of the most common complications of MM. Approximately 50% of MM patients will have some degree of renal impairment at diagnosis and/or during the course of disease (Knudsen et al. 2000). The incidence of renal impairment is defined either as serum creatinine (S-Cr) above the upper normal limit or > 2 mg/dL or as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (Riccardi et al. 1991; Abbott et al. 2001; Tsakiris et al. 2010)

Renal impairment in patients with MM is caused mainly by the toxic effects of the monoclonal light chains on basement membranes of the glomeruli and/or the renal tubule (Dimopoulos et al. 2008). The most common form of renal injury in patients with MM is cast nephropathy which often leads to acute kidney injury (Dimopoulos et al. 2008; Hutchison et al. 2012; Kastritis et al. 2013). Cast nephropathy develops when light chain production overcomes the capacity of tubular cells to endocytose and to catabolize the filtered free light chains. As a result, excess light chains form aggregates and casts with uromodulin in the

distal nephron, leading to tubular obstruction and concomitant inflammation (Kastritis et al. 2013; Huang et al. 1995; Sengul et al. 2002). Hypercalcemia, dehydration, nephrotoxic drugs (aminoglycoside antibiotics and/ or nonsteroidal anti-inflammatory agents), infection and contrast agents contribute to the development of or exacerbate existing renal impairment by aggravating the toxic effect of light chains (Dimopoulos M. et al. 2008; Hutchison C. et al. 2012; From et al. 2008) In a study evaluating renal impairment in patients with MM, renal biopsy indicated in 15% of patients that the renal impairment had no association with the monoclonal gammopathy. Alternate reasons included arterionephrosclerosis (6%), diabetic glomerulosclerosis (5%), post infectious glomerulonephritis (2%), or even smoking related glomerulopathy (0.5%) (Nasr et al, 2012). The presence of monoclonal immunoglobulin deposition disease (MIDD) or amyloidosis may also contribute to renal impairment. All patients with symptomatic myeloma should have in their diagnostic work-up serum creatinine, electrolytes measurements, and eGFR and also serum free light chain (SFLC) measurement and electrophoresis of a sample from a 24-hour urine collection. A 24-hour urine protein electrophoresis (UPEP) may reveal patterns of protein excretion that may provide clues to the etiology of renal impairment. Predominantly selective proteinuria, consisting of light chains, with limited albumin excretion is most likely a result of cast nephropathy, whereas larger amounts of albumin or nonselective patterns of proteinuria suggest an alternative pathology. (Leung et al. 2012; Dimopoulos et al. 2016).

Rapid intervention to reverse renal dysfunction is critical for the management of patients with renal impairment especially for those with light chain cast nephropathy. Reversal of renal dysfunction is possible (Dimopoulos et al, 2008) with reduction of tumor cell mass with therapy and with the use of supportive care.

1.3 OVERVIEW OF MELFLUFEN

1.3.1 Melflufen Description

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

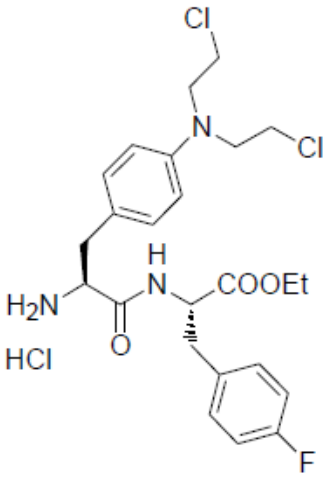

Figure 1-1: Structure of Melflufen

1.3.2 Melflufen Scientific Rational

Melphalan flufenamide (hereinafter referred to as 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 desethylmelflufen, which also has alkylating properties. Due to the high activity of peptidases and esterases in human tumor cells, the formation of melflufen's metabolites is rapid in these cells with continued inflow of more melflufen (Gullbo et al. 2003c; Wickström et al. 2010). Since des-ethylmelflufen and melphalan are relatively hydrophilic, there is a possibility for intracellular trapping of these alkylators. This can be explained by a more efficient transport of melflufen into these cells, an efficient conversion into other alkylating molecules (i.e. melphalan and des-ethylmelflufen) inside the cells and a less rapid disappearance of these molecules from the cells.

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

The addition of melflufen to panels of primary cultures of human tumor cells, including MM, results in 50- to 100-fold higher efficacy to that of melphalan (Wickström et al. 2008), which is explained by the 50-fold higher intracellular exposure as AUC of alkylating agents compared to that observed after an equimolar dose of melphalan (Chauhan et al. 2013). Mechanistically-oriented studies have shown that melflufen-induced apoptosis is associated with (i) activation of caspases and poly Adenosine diphosphate ribose polymerase cleavage; (ii) reactive oxygen species generation; (iii) mitochondrial dysfunction and release of cytochrome c; and (iv) induction of DNA damage (Chauhan et al. 2013; Ray et al. 2016). Moreover, melflufen inhibits MM cell migration, tumor-associated angiogenesis and DNA repair. Importantly, in vitro studies in MM cell lines resistant to dexamethasone, bortezomib and melphalan have shown cytotoxic activities of melflufen at concentrations similar to those observed in the parental, non-resistant cell lines. Potent cytotoxic activity has also been demonstrated in primary MM cells from patients including those relapsing after multiple prior therapies with bortezomib, lenalidomide, and dexamethasone. These results suggest a different resistance mechanism for melflufen than for other agents used in MM. In efficacy studies conducted in mice and rats carrying different human tumors, including MM, superior antitumor activity of melflufen over equimolar dosage of melphalan was observed at seemingly comparable toxicity (Gullbo et al. 2004; Wickström et al. 2007; Chauhan et al. 2013).

1.4 CLINICAL EXPERIENCE

1.4.1 Clinical Experience in RRMM

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

The Phase 1 part of the clinical trial was completed in September 2014 (Paba-Prada et al. 2014). Based on data from 23 patients in four dose groups (15 mg, 25 mg, 40 mg and 55 mg), a maximum tolerated dose (MTD) was established as 40 mg of melflufen in combination with 40 mg dexamethasone weekly. Following identification of the MTD, the Phase 2a part of the trial was initiated and all subsequently treated patients received a starting dose of 40 mg of melflufen (Palumbo et al, 2016).

1.4.1.1 Clinical Safety

As of November 9, 2017, 58 patients had received 284 doses of melflufen 40 mg in trial O-12-M1. The median number of completed cycles was 5.0 (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 the disease of MM and of treatment with alkylators. These events were assessed to be dose-related, reversible, monitorable and mechanism-driven.

Treatment related Grade 3 or 4 adverse events (AEs) were reported in 37 out of 45 patients (82%) treated with 40 mg melflufen in combination with 40 mg weekly dexamethasone. Those related to melflufen and occurring in ≥ 2 patients are presented in Table 1-1.

Table 1-1 Summary of Melflufen Treatment-Related Grade 3 or 4 AE in ≥ 2 Patients

System Organ Class (Preferred Term)	Patients with Grade 3 or 4 AEs n (%)	Patients with Grade 4 AEs n (%)
Any treatment-related event	37 (82)	19 (42)
Blood and lymphatic system disorders	36 (80)	19 (42)
Thrombocytopenia	26 (58)	17 (38)
Neutropenia	26 (58)	11 (24)
Anemia	19 (42)	0 (0)
Lymphopenia	3 (7)	1 (2)
Febrile neutropenia	2 (4)	0 (0)
General disorders and administration site conditions	7 (16)	0 (0)
Asthenia	2 (4)	0 (0)
Fatigue	2 (4)	0 (0)
Pyrexia	2 (4)	0 (0)

Investigations *White blood cell count decreased*	5 (11) 2 (4)	0 (0)0 (0)
Infections and infestations *Pneumonia*	2 (4) 2 (4)	0 (0) 0 (0)

Continuous review of safety data in the Phase 2a part of the study led 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.

Even though neutropenia and thrombocytopenia have been common in connection to melflufen treatment, few cases have been reported as serious adverse events (SAEs) such as febrile neutropenia or bleeding. Please see the current investigator's brochure (IB) for details.

1.4.1.2 Evaluation of QTcF Intervals from Holter Recordings

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

1.4.2 Safety Summary

The clinical trials results, to date, indicate that the safety profile for melflufen is similar to that for other alkylators, where thrombocytopenia, anemia and neutropenia are the most common AEs, followed by pyrexia and asthenia. The incidence of Grade 3 and 4 neutropenia and thrombocytopenia after 40 mg doses of melflufen are comparable to the incidence observed in studies with low dose melphalan regimens in combination with steroids (Richardson et al. 2010). Even though neutropenia and thrombocytopenia have been common in connection to melflufen treatment, few cases have been reported as SAEs, as febrile neutropenias, or thrombocytopenia associated bleedings.

Since both the disease of MM as well as treatment with alkylators may cause neutropenia and neutropenia may be connected with pneumonia, sepsis or other infections, it is important to follow institutional or NCCN guidelines (NCCN 2018) Prevention and treatment of cancer-related infection for antimicrobial prophylaxis for MM patients.

Please see the IB for additional information.

1.5 CLINICAL EFFICACY

As of Nov 9, 2017, 34 patients were evaluable for efficacy (patients receiving at least two doses of 40 mg melflufen with appropriate follow-up). Of these 34 patients, 5 achieved very good partial response (VGPR), 9 achieved PR and 8 achieved minimal response (MR). Eleven patients maintained stable disease (SD) and one had progressive disease (PD) (Richardson 2017).

A total of 45 patients had received at least one dose of melflufen. Median time since initial diagnosis was 5.0 years (1-21). Median number of prior therapies was 4.0 (2-14). All patients had been exposed to IMiDs, 44 had been exposed to PIs and 42 of the 45 patients

had been exposed to alkylators. Of these 45 patients, 39 patients (87%) patients were IMiD-refractory, 32 (71%) were PI-refractory and 24 (53%) were alkylator refractory. Thirty out of the 45 patients (67%) were double-refractory (IMiDs and PIs) and 18 (40%) were double- and alkylator-refractory. Thirty-nine (87%) were refractory to last line of treatment.

The median progression free survival (PFS) in the trial has been evaluated both for the protocol defined efficacy evaluable patients, (i.e. treated with ≥ 2 doses of melflufen [n=34]) and all patients (those evaluable after ≥ 1 dose) of melflufen [N=45]) with baseline and appropriate follow-up assessments. The median PFS for the efficacy evaluable population was at the time of data cut-off 8.3 months (95% confidence interval [CI] 4.5 to 9.8 months) based on 30 events in 34 patients with available data. Four 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 5.7 months (95% CI 3.7 to 9.3 months) based on 41 events in 45 patients with available data. 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.

1.5.1 Clinical Pharmacokinetics

In humans, melflufen is metabolized to desethyl-melflufen, melphalan and the non-alkylating para-fluoro-phenylalanin ethyl ester, and this metabolism appears to occur primarily outside of the plasma compartment. PK data for melflufen and melphalan are available from the completed clinical trial O-05-001 in patients with solid tumors and from ten MM patients in the ongoing clinical trial O-12-M1.

In clinical trial O-12-M1 in MM patients, PK data from ten patients covering the dose range 15 mg to 55 mg were available as of 6 February 2017. In all patients, melflufen plasma concentration reached a peak before end of infusion and was eliminated with a half-life of 1 to 5 minutes as measured from end of infusion. Melphalan PK parameters were similar to those observed in clinical trial O-05-001. Des-ethyl-melflufen reached only very low concentrations in plasma and was eliminated with a half-life of approximately 15 minutes.

The combined results from the two clinical trials demonstrate that the PK of melflufen is characterized by low plasma concentrations and a very rapid disappearance from plasma after end of the intravenous infusion. The PK of melphalan after administration of melflufen is characterized by a rapid formation where plasma concentrations exceed those of melflufen within 15 minutes after start of melflufen infusion, and where peak plasma concentrations are lower and AUC similar compared with equimolar infusions of melphalan at a similar rate (Mougenot et al. 2004; Nath et al. 2010). Following administration of melflufen, melphalan is found in plasma with a peak concentration at 5 to 10 minutes after the end of melflufen infusion (PK data from clinical trial O-12-M1). The elimination phase of melphalan is similar after melflufen and melphalan infusions, according to published data for melphalan administration (Mougenot et al. 2004; Nath et al. 2010).

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

1.5.2 Melflufen and Renal Function

During treatment with melflufen, the great majority of alkylating activity is expected to occur from melflufen instantly reaching cells and tissues outside of the plasma compartment (including any tumor cells present) and from the metabolite melphalan that is formed intracellularly from melflufen and subsequently is distributed back to plasma. The contribution to alkylating activity from melphalan that is again distributed back to cells from the bloodstream is therefore likely to be small. Once formed, melphalan is distributed back to plasma from the cells, but melphalan in plasma is likely to have only a minor contribution to intra-cellular alkylating activity as the initial local concentrations when formed from melflufen in cells are much higher than those coming from redistributed melphalan in the circulation. Melphalan is eliminated from plasma primarily by spontaneous plasma hydrolysis to monohydroxy-melphalan and dihydroxy-melphalan, a process which is independent of renal function and hepatic metabolism. In addition, there is a minor contribution of direct renal elimination.

Melflufen is cleared very rapidly from the plasma compartment and completely metabolized to melphalan in tissues. Renal function is therefore assessed not to contribute to melflufen total clearance. The relationship between glomerular filtration rate (GFR) and melphalan PK after administration of melphalan has been evaluated in two studies including 11 and 15 patients, respectively (Adair et al. 1986; Osterborg et al. 1989), and in a population PK study with 100 patients (Nath et al. 2010). The results were consistent across studies and demonstrated a slightly less than two-fold increase in melphalan total exposure (AUC) for a defined melphalan dose when comparing a GFR of 120 mL/min (normal function) with a GFR of 30 mL/min (threshold to severe renal impairment). To date there have been no reports of renal toxicity related to melflufen in completed or ongoing clinical trials evaluating melflufen.

In an investigation in 272 patients with newly diagnosed MM, cycles of melphalan 0.25 mg/kg once daily orally for four days with no adjustment for renal function were given as palliative treatment (Carlson et al. 2005). Patients were categorized according to estimated creatinine clearance (CrCl) of >50, 30 to 50, and <30 mL/min and hematological toxicity World health organization (WHO) Grades 3-4 after the first course was seen in 18%, 28% and 36%, respectively. WHO Grades 3-4 infections occurred in 6% of the total population and were not significantly related to renal function.

A modest prolongation of the melphalan elimination half-life with no change in peak concentrations in patients with renal impairment down to a GFR of 30 mL/min is assessed to have negligible impact on the efficacy and safety of the melflufen treatment. The long dosing intervals will prevent any drug accumulation.

2 RATIONALE

2.1 STUDY RATIONALE

Recent improvements in therapies have significantly increased the expected life span for MM patients. However, despite the availability of effective therapies, the optimal combinations and sequencing of these agents with other therapies and with one another is still unclear. Only 20 to 30% of the RRMM patients typically respond to any particular treatment and ultimately patients relapse from all available options. In addition, many therapies are not well tolerated due to compromise in renal function associated with MM and some drugs have restrictions in relation to renal function. Renal impairment has significant implications in

both the toxicity profile, as well as the disease response to treatment and it is therefore essential to establish the impact of renal impairment with melflufen therapy. Patients with decreased renal function have poorer prognosis compared with patients with normal renal function and thus the medical need for these patients is high.

Melflufen has a different bio distribution and bioavailability profile compared to other alkylators. Melphalan is the most potent existing alkylator for the treatment of MM. Cancer cells receive approximately 50 times higher exposure of alkylating moieties after exposure to melflufen compared to melphalan. In the Phase 2a portion of protocol O-12-M1 in heavily pretreated RRMM patients (median 4 prior lines of therapy) the median PFS was 5.7 months (95% confidence interval 3.7 to 8.5 months) based on 40 events in 45 patients with available data. Of the 34 efficacy evaluable patients the ORR was 41% and 62% of the patients reported a best response of MR or better.

The safety profile of melflufen suggested by preclinical studies is supported by clinical data from 45 patients with solid tumors (trial O-05-001) and from a total of 75 patients with RRMM in a Phase 1/2a clinical trial O 12 M1 (58 patients dosed at the 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 antitumor 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.

This trial will evaluate the relationship between renal function and the PK parameters for the metabolite melphalan during treatment with melflufen, as well as the safety and efficacy of melflufen treatment in patients with impaired renal function.

2.2 RATIONALE FOR PATIENT SELECTION AND PK SAMPLING SCHEDULE

The proposed trial will be conducted in relapsed or RRMM patients who have received 2 to 4 prior lines of therapy, and with moderate and severe renal impairment. In the previous melflufen study O-12-M1 with rich PK sampling the evaluation demonstrated a consistent delay in the achievement of peak concentrations for melphalan by 5-10 minutes after end of melflufen infusion. Thereafter the decrease in melphalan plasma concentrations followed a first-order process. Using non-compartmental methods, a comparison was performed between the results in O-12-M1 with rich sampling and an assumed reduced sampling according to the schedule planned for the present OP-107 study. The average deviation for AUCinf and Cmax did not exceed 5% and the highest individual deviation was 11%. It was therefore demonstrated that the reduced sampling in OP-107 (3 samples collected after the start of infusion) will provide PK estimates of sufficient accuracy. A separate population PK-PD plan will be developed for a combined analysis from this study and the OP-103 Ocean study, where patients with normal or limited renal impairment are included. The OP-12-M1 trial as well as the ongoing OP-103 and OP-106 trials required patients to have a baseline CrCl of ≥ 45 mL/min based on Cockcroft Gault formula (Cockcroft 1976) combined with a S-Cr of ≤ 2.0 mg/dL. In this trial, by using the CKD-EPI formula (Appendix G) we will include one cohort of MM patients with an eGFR of ≥ 30 mL/min/1.73m^2 to < 45 mL/min/1.73m^2 corresponding to a moderate decrease in GFR and a second cohort with an eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 corresponding to a severe decrease in GFR.

2.3 RATIONALE FOR DOSE SELECTION

The dose and schedule of melflufen was established in the Phase 1/2 trial (O-12-M1) with melflufen in combination with weekly dexamethasone in RRMM patients as 40 mg on Day 1 of a 28-day cycle. In study O-12-M1 and in the ongoing trial OP-106 (melflufen and dexamethasone in pomalidomide- and/or daratumumab-refractory patients), hematologic toxicity is the most common AE reported, with thrombocytopenia being the most clinically important AE. This trial will establish the safety of melflufen given at the established recommended Phase 2 dose (RP2D) of 40 mg on Day 1 of a 28-day cycle in patients with moderate or severe renal dysfunction. Available data indicate that renal impairment with GFR down to 45 mL/min will not have a clinically meaningful effect on melflufen or melphalan PK.

Following PK evaluations from 9 patients enrolled in this study, 6 patients with eGFR ≥ 30 - < 45 mL/min/1.73m^2, and 3 patients with eGFR > 45 mL/min/1.73m^2, it was observed that Melphalan AUC increases with decreasing eGFR and this was linked to an increased myelotoxicity with lower nadir in platelets and neutrophils. DSMC recommended on 10 September 2019 further evaluation of melflufen 30 mg as the starting dose for patients with eGFR ≥ 30 - < 45 with a minimum of 6 additional patients in cohort 1 (Cohort 1b).

Following PK evaluation from 19 patients enrolled in this study, DSMC recommended on 15 December 2020 melflufen 20 mg as the starting dose for patients with eGFR ≥ 15 - < 30. A melflufen dose of 20 mg is predicted to be adequate for an eGFR of 15-29 mL/min/1.73 m^2 based on melphalan AUC.

2.4 RATIONALE FOR AMENDMENT 1

Amendment 1 will include a potential cohort of at least 6 patients with severe renal impairment. This cohort is added after recommendation by the FDA since it would be beneficial to allow clinical use of melflufen also in patients with severe renal impairment and since there are no unacceptable safety concerns with use of melphalan in patients with renal impairment, even after high dose treatment with melphalan 200 mg/m^2 (Sweiss 2016). Cohort 2 will only be initiated following DSMC review of the pharmacokinetic and safety profile of at least 6 patients in cohort 1. If the DSMC advises to proceed with Cohort 2, at least 6 patients with eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 will be enrolled and analyzed for safety and pharmacokinetics data.

Since scientific data show that the Cockcroft-Gault formula is unreliable for patients with low CrCl (Michels 2010), guidelines advise not to use the Cockcroft-Gault formula for patients with CrCl of 30 mL/min or lower (Levey 2009, Tattersall 2011, KDIGO 2013). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Appendix G), which estimates GFR, has better reliability especially at low CrCl value (Levey 2009, Michels 2010, KDIGO 2013, Levey 2017) and will therefore be used in the present study for all patients following approval of Amendment 1.

The FDA also recommended evaluating patients in later lines of therapy limited to those who have received 2 – 4 prior lines, as the treatment paradigm for multiple myeloma (MM) has shifted as there are approved therapies with known clinical benefit in the first 2 lines of therapy. Therefore, we will enroll only those patients that have received 2 – 4 lines of therapy.

2.5 RATIONALE FOR AMENDMENT 2

The current protocol does not allow Cycle 1 Day 1 to start at any other dose than 40 mg of melflufen. Data from the PK and safety analysis of the first 9 patients indicates that the AUC increases with decreasing eGFR and that this was linked to an increased myelotoxicity with lower nadir in platelets and neutrophils. However, there was no increased incidence of clinically important bleedings or infections. As a result, the DSMC recommends further evaluation of melflufen with a reduced starting dose of 30 mg in 6 additional patients in Cohort 1. Cohort 1 will then consist of two groups: cohort 1a with a starting dose of 40 mg and 1b with a starting dose of 30 mg melflufen. Following approval of amendment 2, cohort 1a will close for enrollment and cohort 1b will open.

The opening and starting dose for Cohort 2 will be decided following review of available data from cohort 1a+1b and recommendation of the DSMC.

2.6 RATIONALE FOR AMENDMENT 3

The current protocol requires all patients to have weekly CBC assessments. From cycle 3 onwards they can be done at a local laboratory close to the patient, and not necessarily at the clinic. Patients with good tolerability will no longer require all weekly CBC assessments. Specifically, if patient's tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (Granulocyte colony stimulating factor [G-CSF], blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded Day 8 and Day 22.

For patients not visiting the site weekly, they should still be contacted weekly by phone to follow up on AE/SAEs and dexamethasone compliance.

2.7 RATIONAL FOR AMENDMENT 4

To update the CSP with the by DSMC confirmed starting dose for Cohort 2a of 20 mg melflufen, including dose reductions steps for this cohort, Table 6.1 updated.

Cohort 2 will consist of two groups.

- Cohort 2a, evaluating patients with eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 with a starting dose of 20 mg melflufen.
- Cohort 2b, evaluating patients with eGFR of ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 with a starting dose of 30 mg melflufen.

Cohort 2b will only open if recommended by DSMC after evaluating data from Cohort 1a, 1b and Cohort 2a.

This amendment also includes adding an interim analysis for an iCSR, to conclude the results from Cohort 1, patients with eGFR ≥ 30 - < 45 mL/min/1.73m^2.

As more cohorts are added the number of PK evaluable patients have increased from 25 to approximately 35.

2.8 RATIONAL FOR AMENDMENT 5

Due to difficulties in recruiting eligible patients for Cohort 2a and b an updated feasibility assessment was performed alongside discussions with the investigators to identify potential eligibility hurdles in the current design of the protocol. The most frequent reasons for pre-screened patients not being eligible for screening was that they had received more than 4 prior lines of therapy (inclusion criteria no 3) or had deteriorating kidney function (inclusion criteria no 10). The protocol is therefore updated

to allow at least 2 prior lines of therapy with no upper limit and a wider eGFR window for patients to proceed from Screening 1 to Screening 2.

SAE reporting details have been updated to reflect the change of safety CRO from PSI PVG Unit to TFS. SAE reporting email address updated to [redacted].

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

3.1.1 Primary Objectives

- To evaluate the relationship between renal function and the PK parameters for melphalan during treatment with melflufen
- To assess the safety and tolerability of melflufen in patients with moderate (Cohort 1a and 1b) and severe (Cohort 2a and 2b) renal impairment

3.2 SECONDARY OBJECTIVES

- To assess the best tumor response as well as overall response rate (ORR)
- To assess the PFS
- To assess duration of response (DOR) in patients with ≥ PR (stringent complete response (sCR), CR, VGPR, PR) as best response
- To assess clinical benefit rate (CBR) and duration of clinical benefit (i.e., proportion of patients with ≥ MR) as best response
- To assess time to response (TTR) in patients with a PR or better and time to CB for patients with MR or better.
- Overall Survival (OS)

All tumor response and progression-depended objectives are assessed by investigators according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar et al. 2011, Appendix C) unless otherwise specified.

3.3 EXPLORATORY OBJECTIVE

- To assess changes in renal function

4 STUDY DESIGN

4.1 DESCRIPTION OF STUDY DESIGN

This multicenter study will enroll patients with RRMM who have received at least 2 lines of prior therapy.

Patients will be treated with melflufen 10-40 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 reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22.

Patients will be assessed for response after each cycle according to the IMWG-URC (Rajkumar et al. 2011, Appendix C). Patients may continue treatment until there is

documented disease progression, unacceptable toxicity or the patient/treating physician determines 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. In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

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

5 PATIENT POPULATION

5.1 PATIENT SCREENING

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

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

Patients who complete the screening process for study OP-103 (OCEAN) but fail to meet the required estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min for OP-103 may consent for OP-107. In this case, the screening assessments performed for OP-103 that are required in OP-107 do not need to be repeated provided that the assessments are performed as required and within the specified timeframe required for OP-107.

5.1.1 Screening Failures

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

A minimal set of screen failure information is required to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) that occurs during the screening period.

5.2 PATIENT ELIGIBILITY

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

5.2.1 Inclusion Criteria

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

1. Male or female, age 18 years or older, at the time of signing the informed consent;
2. A prior diagnosis of MM with documented disease progression in need of treatment at time of screening;

3. Received at least 2 prior lines of therapy. (Appendix D);
4. Measurable disease defined as any of the following:
    a. Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
    b. ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis (UPEP)
    c. SFLC ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain ratio;
5. Life expectancy of ≥ 6 months;
6. ECOG performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to MM may be eligible following consultation and approval of the medical monitor) (Appendix A);
7. Patient is a female of childbearing potential (FCBP)* with a negative serum or urine pregnancy test prior to initiation of therapy and agrees to practice appropriate methods of birth control, or the patient is male and agrees to practice appropriate methods of birth control (Section 7.1);
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent;
9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec (Appendix H);
10. Renal function: Estimated GFR by CKD-EPI formula (Appendix G) on 2 consecutive screening evaluations. Patients meeting criteria for Screening 1, must also meet criteria for Screening 2 following optimal hydration (as determined by the investigator). Screening 2 must be on or as close as possible to treatment start date (preferably < 24-48 hours) but cannot exceed 72 hours.
    Cohort 1 (a and b):
    Screening 1: eGFR between ≥25mL/min/1.73m^2 to <45 mL/min/1.73m^2.
    Screening 2: eGFR between ≥30 mL/min/1.73m^2 to < 45 mL/min/1.73m^2.

    Cohort 2 (a and b):
    Screening 1: eGFR between ≥10 mL/min/1.73m^2 to < 35 mL/min/1.73m^2.
    Screening 2: eGFR between ≥15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2.

    Cohort 2b will only be enrolled following approval of DSMC after evaluating data from Cohort 1a, 1b and 2a.

    Patients with fluctuating values of eGFR may be eligible following consideration of additional assessments in consultation with the medical monitor.

11. The following laboratory results must be met during screening (within 21 days) and immediately before study drug administration on Cycle 1 Day 1:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] prior to initiation of therapy)
- Platelet count ≥ 75,000 cells/mm^3 (75 x 10^9/L) (without required transfusions during the 10 days prior to initiation of therapy)
- Hemoglobin ≥ 8.0 g/dl (red blood cell [RBC] transfusions are permitted)
- Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), or higher in patients diagnosed with Gilbert's syndrome, that have been reviewed and approved by the medical monitor
- Aspartate transaminase / Serum glutamic oxaloacetic transaminase (AST / SGOT) and alanine transaminase / Serum glutamic pyruvic transaminase (ALT / SGPT) ≤ 3.0 x ULN;

12. Must have, or be willing to have, an acceptable central catheter. (Port a cath, peripherally inserted central catheter [PICC] line, or central venous catheter);

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

5.2.2 Exclusion Criteria

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

1. Primary refractory disease (i.e. never responded with ≥ MR to any prior therapy);
2. Evidence of mucosal or internal bleeding and/or are platelet transfusion refractory (platelet count fails to increase by > 10,000 cells/mm^3 [10.0 x 10^9/L] after transfusion of an appropriate dose of platelets);
3. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months);
4. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of initiation of therapy;
5. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance;
6. Pregnant or breast-feeding females;
7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation;
8. Known human immunodeficiency virus or active hepatitis B or C viral infection;
9. Concurrent symptomatic amyloidosis or plasma cell leukemia;

10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);
11. Previous cytotoxic therapies, including cytotoxic investigational agents, for MM within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy. The use of live vaccines within 30 days before initiation of therapy. IMiDs, PIs and or corticosteroids within 2 weeks prior to initiation of therapy. Other investigational therapies and monoclonal antibodies (mAb) within 4 weeks of initiation of therapy. Prednisone up to but no more than 10 mg orally once daily (q.d.) or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to initiation of therapy;
12. Residual side effects to previous therapy > Grade 1 prior to initiation of therapy (Alopecia any grade and/or neuropathy Grade 2 without pain are permitted);
13. Prior peripheral stem cell transplant within 12 weeks of initiation of therapy;
14. Prior allogeneic stem cell transplantation with active **graft**-versus-host- disease;
15. Prior major surgical procedure or radiation therapy within 4 weeks of initiation of study therapy this does not include limited course of radiation used for management of bone pain to be completed within 7 days of initiation of study therapy. Plasmapheresis is not permitted within 14 days of initiation of therapy;
16. Known intolerance to steroid therapy;
17. Prior renal transplant;
18. Currently in need of renal dialysis.

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

5.3 PATIENT ENROLLMENT

5.3.1 Enrollment Procedure

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

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

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

5.3.2 Patient Numbering

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

5.3.3 Replacement Policy

If a patient discontinues therapy prior to completing sufficient PK sampling and is not evaluable for PK analysis the patient may be replaced. (See Section 12.4.1.2)

6 STUDY TREATMENT

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

6.1 INITIATION OF THERAPY (CYCLE 1 DAY 1)

Prior to initiation of therapy, patients must continue to meet eligibility criteria including ECOG performance status of ≤ 2 and the Cycle 1 Day 1 laboratory results must also meet the entry criteria noted below: Screening 2 must be on or as close as possible to treatment start date (preferably < 24-48 hours) but cannot exceed 72 hours.

- ANC ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] prior to initiation of therapy)
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusion during the previous 10 days prior to initiation of therapy)
- Hemoglobin ≥ 8.0 g/dl (RBC transfusions are permitted)
- Total Bilirubin ≤ 1.5 x ULN, except patients diagnosed with Gilbert's syndrome that have been reviewed and approved by the medical monitor
- AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN

See Section 7 for required, recommended and prohibited concomitant medications. Dose modifications and delays may be implemented based on patient tolerance as detailed in Section 6.4.

6.2 STUDY DRUG ADMINISTRATION

Refer to Section 9 and Pharmacy Manual for supply, storage, preparation and accountability of study drugs.

6.2.1 Melflufen Administration

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

The study treatment should be administered through a central catheter, which should be inserted according to standard local practice. All patients must have an acceptable central catheter for infusion prior to the initiation of the first dose of melflufen (Port A Cath, PICC line or central venous catheter). Refer to Section 9.1.5 and the 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. The maximum time from dilution to infusion is obtained if the final dilution is performed with 0.9% saline (cold). See the Pharmacy Manual for recommended storage times.

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 clock time for the infusion, should be documented in the source documents and on the appropriate eCRF page. Refer to Section 9 for melflufen supply, storage and accountability. Refer to the Pharmacy Manual for details on melflufen preparation and administration and a Pharmacy Worksheet for recording drug preparation times.

6.2.2 Dexamethasone Administration

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

Dexamethasone may be given even if the melflufen is held (continued weekly during cycle delays, at the investigator's discretion).

6.3 INITIATION OF A NEW CYCLE OF THERAPY

The following guidelines apply to all cycles following Cycle 1. Patients should be assessed at the beginning of each cycle according to the tests and evaluations outlined on Day 1 of each cycle in Table 8-1: Schedule of Events. Refer to Section 6.4 for dose modifications related to toxicity. To begin a new cycle of treatment, the following criteria must be met.

Criteria for Initiation of a New Cycle of Therapy

- 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 within ≤ 5 days of dosing [See Section 7.3)
- eGFR ≥ 15 mL/min/1.73m^2. Melflufen dosing of patients with eGFR below 15 mL/min/1.73m^2 is not acceptable, unless in the best interest of the patient as assessed by the investigator and in consultation with the medical monitor. Melflufen dosing in patients in need of dialysis is also not acceptable and may only be considered in required consultation with the medical monitor on a case-by-case basis (Also see section 7.3).

All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except peripheral neuropathy Grade 2 without pain, 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. Refer to Section 6.4 for guidelines on dose modification due to drug related toxicity.

The maximum amount of time for which study therapy may be held due to drug related toxicity is 28 days from a scheduled Day 1 (Day 57). If study drug is held for more than 28 days due to drug related toxicity the patient will be removed from the study treatment and enter progression free survival follow-up (PFS-FU). If, however the patient was clearly benefiting from therapy, the patient may be able to continue treatment at the Investigator's discretion and in consultation with the medical monitor, after resolution of the AE.

6.4 DOSE MODIFICATIONS

Dose modifications are permitted according to guidelines described in this section. Toxicity should be assessed using the common terminology criteria for adverse events (CTCAE) version 4.03 (Appendix B). All dose modifications should be based on the worst preceding toxicity. Each AE should be attributed to a specific drug (melflufen or dexamethasone), if possible, so that the dose modifications can be made accordingly. No dose escalations are permitted in any given patient once a dose level has been reduced.

Dose modifications different from those stated in the protocol should only be made in consultation with the medical monitor or Sponsor; unless required for immediate patient safety.

Administration of the study treatment should be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the investigator, warrants discontinuation. All interruptions or changes to study treatment administration must be recorded in the eCRF. In case of dose reduction of any study therapy, the dose should not be re-escalated to the higher dose once the AE resolves.

6.4.1 Dose Reduction Steps

6.4.1.1 Dose Reduction Steps for Melflufen

Dose modifications of melflufen for drug related toxicity are permitted. Multiple dose reductions are permitted, however, the lowest dose permitted is 10 mg. If a patient is unable to tolerate the lowest dose of melflufen due to drug related toxicity the patient must be withdrawn from treatment. Prior to each cycle of melflufen the criteria for initiation of therapy must be met (See Section 6.3). Table 6-1 describes the dose reduction steps for melflufen.

Table 6-1 Dose Reduction Steps for Melflufen

Cohort	Starting dose	Dose reduction Step - 1	Dose reduction Step - 2	Dose reduction Step - 3
Cohort 1a	40 mg	30 mg	20 mg	15mg
Cohort 1b	30 mg	20 mg	15 mg	10 mg
Cohort 2a	20 mg	15 mg	10 mg	N/A
Cohort 2b	30 mg	20 mg	15 mg	10 mg

6.4.1.2 Dose Reduction Steps for Dexamethasone

Table 6-2 outlines the dose reduction steps for dexamethasone. Dose reductions of dexamethasone other than those listed in Table 6-2 or discontinuation may be considered in consultation with the medical monitor.

Table 6-2 Dose Reduction Steps for Dexamethasone

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

* (20 mg is the starting dose for patients ≥ 75 years). **If dexamethasone is not tolerated, alternate steroids may be considered at the at the investigator's discretion in consultation with medical monitor.

6.4.2 Dose Modification Guidelines Based on Toxicity

Melflufen is a potent myelosuppressive agent, therefore it is essential that careful attention be paid to the monitoring of blood counts. General supportive measures, together with appropriate RBC and platelet transfusions and hematological growth factors, should be instituted as necessary (See Section 7.0). It is recommended, at the investigator's discretion, that platelet transfusion should be avoided ≤ 5 days of the next dose of melflufen in order to assess endogenous platelet recovery and avoid the possibility of excessive myelosuppression.

Please note: The guidelines in Table 6-3 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 sequential 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 6-3 Dose Modification Guidelines 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 one level dose reduction • 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 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 investigators 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, such as directly to 20 mg) may be considered in discussion with the medical monitor or the Sponsor. Continued dosing with or without dose reduction may be considered after contact with the medical monitor in case of non-study drug related cycle prolongations (for example: influenza).

Patients who discontinue treatment for a study related AE including abnormal laboratory value must be followed as described in Section 8.2.5 and 8.2.6.

6.4.2.1 Dose Modifications for Non-Hematologic Toxicity

In order to start a new cycle of therapy the resolution of all non-hematologic toxicity must be to ≤ Grade 1 or baseline except peripheral neuropathy Grade 2 without pain, alopecia any grade and fatigue ≤ Grade 2. Melflufen dosing of patients with eGFR below 15 mL/min/1.73m^2 is not acceptable, unless in the best interest of the patient as assessed by the investigator and in consultation with the medical monitor. Melflufen dosing in patients in need of dialysis is also not acceptable and may only be considered in required consultation with the medical monitor on a case-by-case basis (Also see section 6.3). 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), dose should not be given, and the patient should be re-evaluated weekly.
- If cycle prolongation 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 timelines in Table 6-3 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.

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

Patients who discontinue treatment for a study related AE including abnormal laboratory value must be followed as described in Section 8.2.5 and 8.2.6.

6.4.3 Dose Modifications for Dexamethasone

Dose modifications for dexamethasone are permitted. If a patient is unable to tolerate dexamethasone due to dexamethasone related toxicity, dexamethasone may be further reduced or discontinued following consultation with the medical monitor. In the event of a cycle delay, unrelated to dexamethasone toxicity, dexamethasone may be continued weekly at the investigators' discretion.

Table 6-4 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 one 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 one dose level; if edema persists despite above measures, decrease dose another dose level.

Body System	Symptom	Recommended Action
		Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration ≥ Grade 3 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness ≥ Grade 3 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

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

6.5 TREATMENT DURATION

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

7 CONCOMITANT THERAPY

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

7.1 REQUIRED CONCOMITANT THERAPY

- **Contraceptive measures**

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

  Females:

  Birth control methods that are considered as highly effective include: tubal ligation, Intrauterine device (IUD), 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.

Males:

Males must use a condom during any sexual contact with females of child-bearing potential during therapy and for three months after the last dose of study drug, even if they have had a successful vasectomy. Males should not donate sperm during the study and for 3 months after treatment has been stopped. It is not known if melflufen may cause permanent sterility, therefore, male patients may wish to consider cryo-preservation of semen before initiating therapy with melflufen.

7.2 RECOMMENDED CONCOMITANT THERAPY

- Pneumocystis prophylaxis
  - All patients are recommended to receive pneumocystis prophylaxis concomitant treatment according to the NCCN or institutional guidelines:
  - http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
  - Trimethoprim/sulfamethoxazole – Prophylaxis: single or double strength daily or double strength 3 x per week. May require adjustment for renal insufficiency.
  - Patients who are found to be intolerant of pneumocystis prophylaxis while on study may continue on study at the discretion of the investigator.
- Patients enrolled in the trial may be vaccinated in accordance with the advice of their treating physician and continue study participation, and allowed vaccines must have local approval and not be live vaccines.
- 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 (with the limitations of prophylactic use noted below), antibiotics, antidiarrheals, analgesics, etc. and prophylactic treatment for tumor lysis syndrome when appropriate.
- Other prophylactic treatment for patient related concomitant conditions or risks may be considered.
- Bisphosphonate therapy intravenously or oral should be administered if indicated in accordance with institutional guidelines.
- Thrombocytopenia and neutropenia are known consequences of MM but also the most common expected AEs associated with melflufen. Careful attention is to be paid to the monitoring of blood counts. General supportive measures, together with appropriate blood and platelet transfusions and hematological growth factors should be instituted if necessary. It is recommended, at the investigator's discretion, that platelet transfusion should be avoided within ≤ 5 days of the next dose in order to assess endogenous platelet recovery and avoid the possibility of excessive myelosuppression (Excluding Cycle 1, Day 1 which adheres to the guidelines in Section 6.1 for use of growth factors and platelet transfusions prior to the first dose of therapy).

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

7.3 PROHIBITED CONCOMITANT THERAPY

- Concurrent therapy with any approved or investigative anticancer therapeutic drug with activity against MM, including alpha interferon and/or chronic use of clarithromycin, is not allowed.
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) prednisone > 10 mg/day (or its equivalent) are not permitted.
- Other investigative agents should not be used during the study
- Radiation therapy to a limited area for bone pain to a pre-existing lesion may be considered in consultation with the medical monitor and approval of the sponsor.
- The use of live vaccines is prohibited during the study and for 30 days after last dose of study drug.
- The prophylactic use of growth factors and platelet transfusions are not permitted to render the patient eligible for trial participation except as described within the inclusion criteria Section 5.2.1. Other limitations are detailed in Section 6.3 and Section 7.2.
- Plasmapheresis is not permitted on study or within 14 days of initiation of therapy.
- Patients on renal dialysis are not permitted to enter the study, however, if renal dialysis is needed during the course of therapy in a patient that is benefitting from therapy, it must be discussed with the medical monitor and approved by the sponsor.

8 VISIT SCHEDULE AND ASSESSMENTS

8.1 STUDY FLOW AND VISIT SCHEDULE

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

Table 8-1 Schedule of Events

Evaluation	Screening Days -21 to -1	All Cycles [s] Day 1	Day 8	Day 15	Day 22	End of Treatment [p]	PFS - FU[q]	OS-FU[r]
Informed consent [a]	X							
Inclusion/exclusion criteria and review on day 1	X	X						
Medical and disease history [b]	X							
Physical examination/symptom assessment [c]	X	X	(X)	(X)	(X)	X		
Vital signs[d] and weight	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)[t]	X	(X)[t]	X		
Blood chemistries [h]	X/X	X				X	(X) [r]	
Urinalysis	X							
Bone marrow aspiration [i]	X	(X)				(X)	(X)[r]	
M protein assessments (SPEP/UPEP, IFE, SFLC) [j]	X	X				X	(X)[r]	
Serum β2-microglobulin	X							
Assessment of extramedullary plasmacytoma [k]	X	(X)				(X)	(X)[r]	
Skeletal survey or CT scan [l]	X	(X)				(X)	(X)[r]	
Pharmacokinetic samples [m]		(X)						
Melflufen administration [n]		X						
Dexamethasone administration [n] and review of patient compliance		X	X[t]	X	X[t]			
Concomitant medications [o]	X	→				X		
AE monitoring [u]		→				X		
Follow-up (PFS, OS)							X[q,]	X

(X) Only if indicated

a) All patients must sign an Independent Ethics Committee (IEC)-approved ICF within 28 days 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, International staging system (ISS) and cytogenetics at diagnosis (if previously evaluated). ISS and revised international staging system (R-ISS) stage (Appendix I) at time of study entry. Prior surgery and/or radiation and anticancer therapy, including start and stop dates, documentation of best response, date of PD and relapsed or refractory status (Appendix E).

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

d) Vital signs including blood pressure, pulse, respiration rate, temperature, to be assessed at screening and pre-and post melflufen infusion and as clinically indicated and at End of treatment visit. Weight to be recorded on Day 1 of each cycle.

e) All FCBP must have a medically supervised negative serum or urine pregnancy test prior to the initiation of therapy and on day 1 of each cycle. 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 will be performed on all patients at screening and at end of treatment, 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. CBC required at screening and may need to be repeated prior to enrollment for patients with borderline evaluations if requested by the medical monitor. Patients are required to have all laboratory evaluations completed at the study center during Cycles 1 and 2. Starting with Cycle 3, 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 and reduced frequency of CBC evaluations may be made only in consultation with the medical monitor. All CBC values collected in addition to protocol specified time points must be recorded in the eCRF. See Section 10.1.5 for reporting requirements of scheduled and unscheduled results of thrombocytopenia and neutropenia.

h) Blood chemistry: sodium, chloride, potassium, blood urea nitrogen [BUN] or urea, glucose (fasting at baseline), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine, and eGFR by CKD-EPI Formula (two consecutive screening evaluations for eGFR) (Appendix G) calcium and lactate dehydrogenase (LDH). Patients are required to have all evaluations completed at the treatment center during Cycles 1 and 2. Starting with Cycle 3, 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.

i) BMA to be collected at screening for % plasma cells, morphology, and cytogenetics by Fluorescence In Situ Hybridization (FISH). Minimum FISH probes include t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q). (Sonneveld et al. 2016). If a BMA and/or biopsy has been collected within 28 days, with the appropriate evaluations, prior to initiation of therapy, it does not need to be repeated. A repeat BMA is required to confirm a suspected CR. Refer to Laboratory manual.

j) SPEP and UPEP and serum and urine IFE (if SPEP and UPEP are not detectable and to confirm a CR), quantitative immunoglobulins (Ig) per routine lab practice and SFLC assay (only required if SPEP and UPEP are not measurable [UPEP is < 200 mg/24 hours and SPEP is < 0.5 g/dL]) are to be conducted at screening, Cycle 1 Day 1 and prior to each cycle even if treatment is delayed and to confirm sCR. Quantitative Ig only need to be repeated for patients with IgA or IgD myeloma. All assessment of SPEP, UPEP, IFE and free light chain (FLC) must be completed in the same laboratory for a given patient. In the event treatment is delayed, ≥ 6 weeks (beyond Day 43), MM disease response assessments are required to be repeated on the day the new cycle starts (Day 50 or 57 of the previous cycle). If treatment is discontinued beyond Day 43 the response assessments should be repeated on the day of that determination (or as soon as possible) after last dose of melflufen as part of the EoT visit.

k) Known or suspected extramedullary plasmacytomas are to be assessed at screening, as clinically indicated and to confirm response or progression. The same method of evaluation should be used throughout the study (e.g., Computerized tomography [CT]/ magnetic resonance imaging [MRI]/ positron emission tomography [PET]). All imaging assessments should be documented in the eCRF. Imaging assessments at screening do not need to be repeated if completed within 28 days of initiation of therapy.

l) Skeletal survey includes x-rays of lateral radiograph of the skull, and anterioposterior views of femur and humeri, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis and ribs. Low dose CT scan may be used in addition or in place of conventional X-ray with the same technique to be used with each evaluation. Bone imaging assessments at screening do not need to be repeated if completed within 6 weeks of initiation of therapy. Required at any time when clinically indicated. Limited X-rays may be performed as clinically indicated to confirm PD.

m) PK samples: Three plasma samples for determination of melphalan concentrations will be drawn in connection to the first two melflufen treatment cycles (Cycle 1 and 2); 5-10 minutes after the end of infusion, 2 - 3 hours after the end of infusion and 5-7 hours after the end of infusion, if PK sampling is missed during Cycle 1 or 2 it may be taken at a later cycle. For enrolled patients with moderate renal impairment one repeat set of three PK samples, will be drawn in one cycle, if during the treatment period, the patient's eGFR falls below 30 mL/min/1.73m^2. For enrolled patients with severe renal impairment one repeat set of three PK samples, will be drawn in one cycle, if during the treatment period, the patient's eGFR falls below 15 mL/min/1.73m^2 and dosing is approved by MM. All PK samples must be drawn peripherally and not from the central catheter. Refer to the Laboratory Manual for details on specimen collection and processing.

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

o) Concomitant medications and procedures: - all blood products and medications within 21 days prior to first dose until the EoT Visit.

p) 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 (such as in the case of a prolonged cycle) with evaluation of safety variables including recording of new and ongoing AEs, review of concomitant medications and any other new disease related therapy. If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug the EoT visit should occur as close as possible before the first dose of the new drug. **Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EoT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy.** SAEs should be followed until resolution or stabilization with no expected resolution.

q) PFS-FU: Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until documented progression (confirmed on 2 consecutive assessments) or initiation of subsequent therapy. Schedule the first assessment 4 weeks after the EoT visit. Confirmed PD should be verified by medical monitor prior to discontinuation of therapy. If PD has not been confirmed prior to the initiation of subsequent therapy the reason for the subsequent therapy should be documented. Documentation of the date and regimen of the first subsequent therapy is required. Serum calcium and albumin (corrected calcium) required only if evidence of PD. *Patients unwilling or unable to return to the site for PFS evaluations may have the lab evaluations done locally following approval by the medical monitor.

r) Overall Survival Follow-up (OS-FU): Following confirmed disease progression or initiation of subsequent therapy, FU for OS status and second primary malignancies will take place every three months +/- 7 days. Following completion of the last patient in PFS-FU, OS-FU will end. However, in the event that Oncopeptides AB would like to determine the status of patients following this time point, patients will consent to one or more inquiries to their health status. This information may be collected

outside of the eCRF established for this study. Documentation of the date and regimen of the first subsequent therapy should be done if it occurs during OS -FU. Follow-up may be completed by phone contact. SAEs should be followed until resolution or stabilization with no expected resolution. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable.

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

t) If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (Granulocyte colony stimulating factor (G-CSF), blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded Day 8 and Day 22.
For patients not visiting the site weekly they should still be contacted weekly by phone to follow up on AE/SAEs and dexamethasone compliance.

u) SAEs will be collected from signing of the ICF until 30 days after last dose of study treatment. Any SAE that occurs after this timepoint and is considered related to melflufen or study participation in the opinion of the investigator will also be collected.

8.2 STUDY ASSESSMENTS

Refer to the Table 8-1; Schedule of Events for details and timelines and explanation of all study assessments. Adherence to the study design requirements, including those specified in Table 8-1, is essential and required for study conduct. Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 8-1.

Refer to the Laboratory Guidance Document for details on lab testing requirements.

8.2.1 Screening Disease Assessments

- M-protein determination using the following procedures
  - SPEP and serum protein IFE with quantitative Ig;
    - Quantitative Ig evaluation may be based on regional availability of the test.
    - IFE 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)
    - IFE of urine is required at screening if M protein by UPEP is not detectable
  - SFLC and SFLC ratio
    - FLC assessment is not required at screening in the presence of measurable SPEP and/or UPEP (SPEP $\geq$ 0.5 g/dL and/or UPEP $\geq$ 200 mg/24 hours),
    - If the M protein is non-measurable in SPEP and UPEP at screening or Cycle 1, Day 1, the FLC is required
- BMA to quantify percent myeloma cell involvement and morphology, cytogenetics by FISH.
- Extramedullary plasmacytoma evaluation of known or suspected lesions (by physical examination or imaging procedures)
- Skeletal survey: lateral radiograph of the skull, and anterioposterior views of femur and humeri, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis and ribs. Low dose CT scan may be used in addition or in place of conventional X-ray (with the same technique to be used with each evaluation)
- Beta2 microglobulin
- LDH
- ISS staging score and revised R-ISS (Appendix I)

8.2.2 Efficacy Assessments

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

- SPEP and serum protein IFE with quantitative Ig (For patients with IgA and IgD

myeloma);

- Immunofixation (IFE) of serum is required at any time when M protein by SPEP becomes non-detectable* and to confirm a CR.

- UPEP and urine protein IFE (all using the same 24-hour urine collection); and
  - IFE of urine is required at any time when M protein by UPEP becomes not detectable* and to confirm a CR.

*IFE is not required on one (serum or urine) if the other remains detectable.

- 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 IFE and FLC evaluations when required, to enable response assessments according to IMWG criteria (Rajkumar et al. 2011, Appendix C).

- Extramedullary plasmacytoma evaluation with the same technique to be used with each evaluation
- BMA to quantify percent myeloma cell involvement
- Skeletal X-rays and/or CT scans
- Serum calcium (corrected calcium)

BMA to be collected at screening for % plasma cells, morphology, and cytogenetics by Fluorescence In Situ Hybridization (FISH). Minimum FISH probes include t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q). (Sonneveld et al. 2016). If a BMA and/or biopsy has been collected within 28 days, with the appropriate evaluations, prior to initiation of therapy, it does not need to be repeated. A repeat BMA is required to confirm a suspected CR. Refer to Laboratory manual.

SPEP and UPEP and serum and urine IFE (if SPEP and UPEP are not detectable and to confirm a CR), quantitative immunoglobulins (Ig) per routine lab practice and SFLC assay (only required if SPEP and UPEP are not measurable [UPEP is < 200 mg/24 hours and SPEP is < 0.5 g/dL]) are to be conducted at screening, Cycle 1 Day 1 and prior to each cycle even if treatment is delayed and to confirm sCR. Quantitative Ig only need to be repeated for patients with IgA or IgD myeloma. All assessment of SPEP, UPEP, IFE and SFLC must be completed in the same laboratory for a given patient. In the event treatment is delayed, ≥ 6 weeks (beyond Day 43), MM disease response assessments are required to be repeated on the day the new cycle starts (Day 50 or 57 of the previous cycle). If treatment is discontinued beyond Day 43 the response assessments should be repeated on the day of that determination (or as soon as possible) after last dose of melflufen as part of the EoT visit.

Known or suspected extramedullary plasmacytomas are to be assessed at screening, as clinically indicated and to confirm response or progression. The same method of evaluation should be used throughout the study (e.g., Computerized tomography [CT]/ magnetic

resonance imaging [MRI]/ positron emission tomography [PET]). All imaging assessments should be documented in the eCRF. Imaging assessments at screening do not need to be repeated if completed within 28 days of initiation of therapy.

Skeletal survey includes x-rays of lateral radiograph of the skull, and anterioposterior views of femur and humeri, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis and ribs. Low dose CT scan may be used in addition or in place of conventional X-ray with the same technique to be used with each evaluation. Bone imaging assessments at screening do not need to be repeated if completed within 6 weeks of initiation of therapy. Required at any time when clinically indicated. Limited X-rays may be performed as clinically indicated to confirm PD.

8.2.3 Safety and Tolerability Assessments

Safety Assessments:

- Assessment and grading of AE
- Physical examination with vital signs, weight, neurologic assessment and assessment of performance status
- Routine safety laboratory tests (CBC with differential and platelets; clinical chemistry, and urinalysis) with calculation of the eGFR according to the CKD-EPI formula. (Appendix G)
- Chest X-ray (postero-anterior/lateral)
- Pregnancy testing
- ECG - Q-Tc interval to be assessed by Fridericia formula (Appendix H)

AEs, including clinical laboratory and vital sign abnormalities, will be graded using the CTCAE version 4.03 (Appendix B). Patients are evaluable for toxicity if they receive any dose of study treatment.
The investigator must review the laboratory report and document abnormal laboratory results as an AE according to the guidelines in Section 10.1.5. The laboratory reports must be filed with the source documents.

8.2.4 Pharmacokinetic Assessments

Three plasma samples for determination of melphalan concentrations will be drawn in connection to the first two melflufen treatment cycles (Cycle 1 and 2); 5-10 minutes after the end of infusion, 2 - 3 hours after the end of infusion and 5-7 hours after the end of infusion. If PK sampling is missed during Cycle 1 or 2 it may be taken at a later cycle. For enrolled patients with moderate renal impairment one repeat set of three PK samples, will be drawn in one cycle if during the treatment period the patient's eGFR falls below 30 mL/min/1.73m^2. For enrolled patients with severe renal impairment one repeat set of three PK samples, will be collected in one cycle if during the treatment period of the study, the patient's eGFR falls below 15 mL/min/1.73m^2 and the patients is approved for dosing by MM. All PK samples must be drawn peripherally and not from the central catheter. Refer to the Laboratory Manual for details on specimen collection and processing.

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

8.2.6 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. Discontinuation from treatment 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. Schedule the first assessment 4 weeks after the EoT visit. If PD has not been confirmed prior to initiation of subsequent therapy the reason for the subsequent therapy should be documented. The date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during PFS-FU.

8.2.6.2 Overall Survival Follow-up

Following confirmed disease progression, or initiation of subsequent therapy, patients will be followed for OS-FU. Follow-up for overall survival (OS) status, second primary malignancies and first subsequent therapy will take place every three months +/- 7 days. Following completion of the last patient in PFS-FU OS-FU will end. However, in the event that Oncopeptides AB would like to determine the status of patients following this time point, patients will consent to one or more inquiries to their health status. This information may be collected 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 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:

- Documented confirmed disease progression verified by the medical monitor (2 consecutive evaluations)
- Patients may choose to withdraw from the study treatment at any time and continue in follow-up
- AEs that, in the judgment of the investigator, may cause severe or permanent harm or which require study drug discontinuation (See Sections 6.4.2 and 6.4.3).
- Clinical judgment of the investigator: A patient may be withdrawn from the study treatment, if in the opinion of the investigator, it is not in the patient's best interest to continue
- Requiring other anti-neoplastic therapies
- Requiring renal dialysis not approved by the sponsor
- Major deviation of the study protocol (i.e., unable to adhere to study schedule)
- Confirmed pregnancy
- Lost to follow-up

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

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

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

9 STUDY DRUG SUPPLY AND HANDLING

9.1 MELFLUFEN

9.1.1 Melflufen Packaging and Labeling

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

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

9.1.2 Melflufen Storage

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

9.1.3 Melflufen Supply

Melflufen will be provided by Oncopeptides AB free of charge.

9.1.4 Melflufen Special Handling

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

9.1.5 Melflufen Drug Preparation

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

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
  - The 250 mL bag of saline 0.9% should be pre-cooled prior to adding melflufen. The infusion bag may be stored at 2-8º C before use (See the Pharmacy Manual for recommended storage times).

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 a Pharmacy Worksheet to record drug preparation time points).

9.2 DEXAMETHASONE

9.2.1 Dexamethasone Packaging and Labeling

Dexamethasone will be labeled for investigational use for sites.

9.2.2 Dexamethasone Storage

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

9.2.3 Dexamethasone Supply

Oral dexamethasone will be supplied by Oncopeptides AB.

9.3 STUDY DRUG COMPLIANCE AND ACCOUNTABILITY

9.3.1 Study Drug Compliance

Compliance will be assured by administration of the study treatment under the supervision of the investigator or his/her designee and should be documented in the study drug administration and accountability records.

9.3.2 Study Drug Accountability

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

At study close-out, and as appropriate during the course of the study, all unused study drug packaging and any associated supplies should be discarded according to the site drug destruction policy following review and approval of the site CRO monitor. A copy of the drug destruction policy and the completed drug accountability log should be provided to the CRO monitor.

10 SAFETY MONITORING AND REPORTING

10.1 ADVERSE EVENTS

10.1.1 Definitions

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

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not

considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the patient begins study therapy is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

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

10.1.2 Grading of Severity

Whenever possible, the CTCAE version 4.03 should be used to describe the event and for assessing the severity of AEs (See Appendix B). Any event representing a change in the CTCAE Grade need to be reported on the AE eCRF. This includes any abnormal laboratory values that the investigator considers clinically significant (Section 10.1.5).

For AEs not adequately addressed in the CTCAE, the severity in Table10-1 may be used:

Table 10-1 Adverse Event Severity

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

10.1.3 Causality

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

Causality should be assessed using the following categories:

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

agent administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

The investigator must appraise all abnormal laboratory results for their clinical significance. Only if an abnormal laboratory result is considered clinically significant, should it be reported as a TEAE. (See Section 10.1.5.1).

10.1.4 Adverse Event Reporting

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

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

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

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

10.1.5 Laboratory Test Abnormalities

10.1.5.1 Definitions and Reporting

Laboratory abnormalities are usually not recorded as AEs; however, signs and/or symptoms that are associated with laboratory findings requiring treatment discontinuation, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as AE's (or serious AE's) if they meet the definition of an AE as described in Section 10.1 or 10.2. In addition, laboratory abnormalities assessed as clinically significant should also be recorded as AEs. The Investigator will record the grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition. Laboratory AEs should be recorded using only one event term per event such as thrombocytopenia for low platelet count but not as both (thrombocytopenia and low platelet count).

Clinically significant laboratory abnormalities are those that:

- Induce clinical signs and symptoms (Note: The sign/symptom should be recorded as an AE, not the lab abnormality)
- Require concomitant therapy
- Require change in study treatment
- Investigator considers clinically significant for any reason
- **Additional Laboratory Reporting Guidelines** All platelet and neutrophil laboratory values collected during the course of the study should be reported including protocol specified time points and any additional time points (unscheduled assessment).
- Ongoing Grade 3 and 4 platelet and ANC values at the time of the EoT visit are to be followed until resolution (≤ Grade 2), or stabilization, or initiation of a subsequent therapy;
- All neutrophil and platelet laboratory values associated with an SAE, regardless of the nature of the event, must be reported in the details of the SAE report;
- Supportive care such as platelet transfusions and Granulocyte colony-stimulating factor (G-CSF) given for AEs or prophylactic reasons must be reported in the eCRF and if applicable also in the SAE report.

10.2 SERIOUS ADVERSE EVENTS

10.2.1 Definitions

A SAE is defined as any AE, occurring at any dose that meets any one or more of the following criteria (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting):

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

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

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)

Note that in-patient hospitalizations for the following reasons should not be reported as SAE’s:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition including
- 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 and/or administrative 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 SAE

10.2.2 Serious Adverse Event Reporting

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

An SAE reporting form must be filled out and emailed to Oncopeptides safety report mailbox: [redacted].

A fax number can be found in the Investigator Site File and is **only** to be used as a back-up if emailing report is not possible.

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 SAE. The investigator’s initial causality assessment must also be included if available.

Each recurrence, 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 10.2.2.1).

SAEs should be followed until resolution, or stabilization with no anticipation of resolution regardless of 30-days reporting timeline 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 IECs in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. For the purpose of SUSAR reporting, only possibly or probably related SAEs (i.e. there is a reasonable possibility of causality) will be considered serious adverse drug reactions.

10.2.2.1 Reporting of Death

- Death is an outcome of a SAE and not a SAE 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);
- Adverse events resulting in death that occur later than 30 days after the last study drug administration should be reported as SAEs only if assessed as related to the study treatment.

10.3 PREGNANCY

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

The pregnancy should be followed-up to determine its outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications and possible relationship to the study treatment.
A pregnancy reporting form must be filled out and emailed to Oncopeptides safety report mailbox:

[redacted]

A fax number can be found in the Investigator Site File and is **only** to be used as a back-up if emailing reports is not possible.

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.

10.4 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 lead investigator, the CRO global medical monitor, Sponsor representative(s) and headed by an independent chairperson. All activities and processes surrounding the DSMC will be outlined in the DSMC Charter. Refer also to Section 12.5.2.

11 DATA COLLECTION AND MANAGEMENT

11.1 DATA CONFIDENTIALITY

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

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

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

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

11.2 SITE MONITORING

Before study initiation, at a site initiation visit and/or at an investigator's meeting, Oncopeptides AB staff (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, 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, ECGs, 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 ICF (a signed copy is given to the patient).

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

11.3 DATA COLLECTION

An eCRF is required and should be completed for each patient. The patient's identity should always remain confidential. The completed original eCRF is the sole property of the Sponsor and should not be made available in any form to third parties (except to authorized representatives of appropriate regulatory authorities) without written permission from the Sponsor.

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

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

11.4 DATABASE MANAGEMENT AND QUALITY CONTROL

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

12 STATISTICAL METHODS AND DATA ANALYSIS

12.1 STUDY ENDPOINTS

12.1.1 Primary Endpoints

- PK parameters of melphalan
- Frequency and grade of AE's.

12.1.2 Secondary Endpoints

ORR: Proportion of patients with ≥ PR (sCR, CR, VGPR and PR) as best response

CBR: Proportion of patients with ≥ MR (sCR, CR, VGPR, PR and MR) as best response

PFS: defined as time (months) from date of initiation of therapy to the earlier of confirmed disease progression or death due to any cause.

DOR: defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. DOR is defined only for patients with a confirmed PR or better. Duration of clinical benefit, for patients with a confirmed MR, or better will also be evaluated.

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

Best response during the study (sCR, CR, VGPR, PR, MR, SD or PD).

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

12.2 EXPLORATORY ENDPOINT

Renal function: The level of eGFR determined at baseline and the start of each cycle.

12.3 SAMPLE SIZE

Enrollment of approximately 35 PK evaluable patients is considered sufficient for a reliable assessment of the PK parameters, at least 6 patients per cohort.

12.4 GENERAL CONSIDERATIONS FOR THE STATISTICAL ANALYSES

The statistical analyses as outlined in this section will be further described in the statistical analysis plan (SAP), which will be finalized prior to locking the database. Statistical analyses will be reported using summary tables, inferential analyses, figures, and data listings.

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

12.4.1 Analysis Populations

12.4.1.1 Safety Analysis Set

The Safety analysis set is defined as all patients who received at least one or partial dose of melflufen or dexamethasone. The Safety analysis set will be the primary population for the summaries of all exposure, efficacy and safety data.

12.4.1.2 PK Analysis Set

All patients that have received at least one melflufen dose and have sufficient PK samples taken after this infusion (three samples as scheduled post infusion). This analysis set will be used for the PK analysis.

12.4.1.3 Efficacy Analysis Set

All patients that complete 2 doses of melflufen and have relevant baseline and follow-up disease assessments after the second dose of melflufen. This population may be used for assessment of select secondary analysis endpoints as defined in the SAP.

12.5 ANALYSIS OF PRIMARY ENDPOINTS

12.5.1 Pharmacokinetic Analysis

12.5.1.1 Pharmacokinetic methods

Three plasma samples for determination of melphalan concentrations will be drawn in connection to the first two melflufen treatment cycles (Cycle 1 and 2), 5 – 10 minutes after the end of infusion, 2 - 3 hours after the end of infusion and 5-7 hours after the end of infusion.

For enrolled patients with moderate renal impairment one repeat set of three PK samples, will be drawn in one cycle if during the treatment period the patient's eGFR falls below 30 mL/min/1.73m^2.

For enrolled patients with severe renal impairment one repeat set of three PK samples will be drawn in one cycle, if during the treatment period of the study the patient's eGFR falls below 15 mL/min/1.73m^2 and the patients is approved for dosing by MM.

In the previous melflufen study O-12-M1 with rich PK sampling the evaluation demonstrated a consistent delay in the achievement of peak concentrations for melphalan by 5-10 minutes after end of melflufen infusion. Thereafter the decrease in melphalan plasma concentrations followed a first-order process. Using non-compartmental methods, a comparison was performed between the results in O-12-M1 with rich sampling and an assumed reduced sampling according to the schedule planned for the present OP-107 study. The average deviation for AUCinf and Cmax did not exceed 5% and the highest individual deviation was 11%. It was therefore demonstrated that the reduced sampling in OP-107 will provide PK estimates of sufficient accuracy.

12.5.1.2 Individual PK modeling

For all concentration-time profiles with 3 measurable melphalan concentrations PK parameters will be evaluated by non-compartmental methods using the software WinNonlin Professional Version 7.0 (Pharsight Corporation). Actual time points for drug administration and plasma sampling will be used.

The following PK parameters will be assessed:

- Time of maximum observed concentration (tmax)
- Maximum observed concentration (Cmax)
- Area under the concentration versus time curve between 0h and time of last measured concentration (AUC0-t)
- Area under the concentration versus time curve from 0h to infinity (AUCinf)
- Elimination phase half-life (t½)

12.5.1.3 Population PK modeling

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

Details on the modeling approach will be described in a separate population pharmacokinetics-Pharmacodynamic plan which will be developed in parallel with the ongoing Phase 3 study OP-103 (OCEAN TRIAL).

The relationship between melphalan PK parameters and patient factors will be assessed on the pooled data, as well as the inter-occasion variability in melphalan exposure.

12.5.1.4 Statistical methods for PK parameters from the individual modeling

Descriptive statistics including mean, geometric mean, median, minimum, maximum, standard deviation, and percent coefficient of variation (CV%) for the obtained PK parameters will be calculated.

Results for estimated PK parameters will be tabulated using 3 significant figures. Exceptions are values 1000 or higher where no rounding will be performed. For descriptive statistics mean, geometric mean and median values are shown with 4 significant figures, and standard deviation and CV% with 3 significant figures. In the statistical calculations data will be used as provided by the input files and by the PK modeling software, without rounding.

12.5.2 Analysis of Safety Endpoints

The number (%) of patients experiencing TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The denominator for the percentage will be based on the number of patients at in the Safety analysis set.

No formal statistical analysis will be performed for the safety endpoints. The summaries of AEs will be based on TEAEs. TEAEs are defined as AEs that start on or after the first day of study treatment is administered and within 30 days of the last administration of study treatment or before start of subsequent anticancer treatment (whichever occurs first) or that worsen on or after the first day of study treatment.

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

Summaries of TEAEs and treatment-related AEs will be provided according to maximum toxicity grade. Grade 3 or higher TEAEs and treatment-related AEs, SAEs, and TEAEs resulting in permanent discontinuation of study treatment will be provided. Grade 3 and 4 thrombocytopenia and neutropenia will be evaluated to determine their frequency, duration, relationship to treatment, associated clinical consequences/medical management and associated significant AEs.

A DSMC will assess the benefit/risk profile of the study. All reported Grade 3-4 treatment-related non-hematological AEs, as well as all SAEs, and any treatment-related deaths due to

hematologic or non-hematologic AEs as well as efficacy and PK data will then be presented to the DSMC.

Cohort 2 was initiated following DSMC review of the pharmacokinetic and safety profile of 31 patients in Cohort 1, of which 19 patients were evaluable for PK. The DSMC advised that Cohort 2 should continue as planned and recommended the starting dose to be 20 mg melflufen with dose modifications according to Table 6-1. At least 6 patients with eGFR ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 will be enrolled and analyzed for safety and pharmacokinetics data.

Cohort 2 will have two parts, Cohort 2a and 2b. After at least 6 patients in Cohort 2a with eGFR ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2 have been evaluated, the DSMC may advise if a higher starting dose (Cohort 2b, 30 mg melflufen) should be investigated.

If the DSMC considers the benefit/risk profile different from previous knowledge of efficacy and safety the DSMC may recommend change to the protocol, additional safety monitoring or stopping further recruitment.

12.6 ANALYSIS OF SECONDARY ENDPOINTS

ORR: The ORR will be estimated as the proportion of patients who achieve a confirmed response of sCR, CR, VGPR, or PR as their best response in the safety evaluable population. The exact binomial 95% CI for ORR will be calculated.

CBR: The CBR will be estimated as the proportion of patients who achieve a confirmed response of sCR, CR, VGPR, PR, or MR as their best response in the safety population. The exact binomial 95% CI for CBR will be calculated.

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

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

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

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

Table 12-1 Conventions for Censoring for PFS

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

The distribution of PFS will be summarized using the Kaplan-Meier (K-M) method. The median PFS will be estimated from the 50th percentile of the corresponding K-M estimates. The 95% CI for median PFS will be constructed using the method of Brookmeyer (Brookmeyer and Crowley, 1982).

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

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

TTR: TTR will be presented using descriptive statistics. TTR is defined as time from first dose of study drug until documentation of a disease response. The TTR will be calculated for patients who achieve a confirmed response of PR or better. Time to CB will be presented for confirmed response of MR or better.

12.7 ANALYSIS OF EXPLORATORY OBJECTIVES

Renal function will be assessed over the duration of the trial to observe patterns and potential correlation with various parameters such as co-morbid conditions, concomitant medications, tolerability and MM disease status.

12.8 HANDLING OF DROP-OUTS AND MISSING DATA

The SAP describes how drop-outs and missing data impact the calculation of the time to event variables. Missing data will not be estimated or carried forward for any of the other summaries or analyses. If only a partial date is available and is required for a calculation

(e.g., time since diagnosis, time since most recent relapse, determination of whether a medication is concomitant, or an AE is treatment-emergent), the date will be imputed. Detail of the methods of imputation will be provided in the SAP.

12.9 INTERIM ANALYSIS

An interim analysis for an interim clinical study report (iCSR) is planned when patients enrolled in Cohort 1a and 1b have been followed until progression or up to at least 6 months after first dose. The objective of this interim analysis is to evaluate PK, safety and efficacy in Cohort 1, moderately impaired patients, to support regulatory submissions.

As no inferential statistical analyses are planned at the interim analysis, the interim has no impact on the statistical methods or presentation of data for the final report.

13 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1 REGULATORY AND ETHICAL COMPLIANCE

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 RESPONSIBILITIES OF THE INVESTIGATOR AND IEC

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IEC before study start. A signed and dated statement that the protocol and informed consent have been approved by the 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, IECs and regulatory authorities as required.

13.3 INFORMED CONSENT PROCEDURES

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), 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 is obtained will be captured in the eCRFs.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date.

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 before submission to the IEC, and a copy of the approved version must be provided to the Oncopeptides AB (or designated CRO) monitor after IEC approval.

13.4 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. Specific conditions for terminating the study at any time for reasonable medical or administrative reasons in any single center could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol
- An incidence or a seriousness of SAEs in this study or other studies indicating a potential danger for the patient's health caused by the study treatment

13.5 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.

13.6 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 harmonization requirements for the protection of confidentiality of patients. As part of participating in an Oncopeptides AB sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

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

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

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

13.7 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 ICFs and patient enrollment log must be kept strictly confidential to enable patient identification at the site. Refer to Section 11.1 for additional details regarding patient confidentiality.

13.8 AUDITS AND INSPECTIONS

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

13.9 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.

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

14 PROTOCOL ADHERENCE

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

14.1 AMENDMENTS TO THE PROTOCOL

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

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16 APPENDICES

Appendix A. Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

Source: Oken MM, et al. 1982.

Appendix B. National Cancer Institute CTCAE Version 4.03

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

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

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

Appendix C. IMWG Uniform Response Criteria

Response	IMWG criteria (Rajkumar 2011)
Stringent Complete Response (sCR)	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
Complete Response (CR)	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, > 90% decrease in the difference between involved and uninvolved FLC levels is required.
Partial Response (PR)	• ≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥ 90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minimal Response (MR) EBMT Criteria	• ≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50 – 89%, which still exceeds 200 mg/24 hours. • In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required

	• No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease
Progressive Disease (PD)	Increase of ≥ 25% from lowest response value in any one or more of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL) and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein levels 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; all response categories and SD also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 0.5 g/dL.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

Appendix D. Line of Therapy Definition

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

Modification of drug doses or resuming therapy after holding will not be considered a new line of therapy provided that there was no evidence of progression of disease as defined in the IMWG-URC.

The definition is further clarified by Rajkumar et al, 2015.

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

New line of therapy

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

Appendix E. Definition of Relapsed Disease

This study will use the IMWG definitions:

Refractory Myeloma:

Refractory myeloma is defined as disease that is non-responsive (failure to achieve minimal response or develops PD while on therapy) while on primary or salvage therapy or, progresses within 60 days of last therapy. There are 2 categories of refractory myeloma.

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

Relapsed myeloma:

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

(Rajkumar et al. 2011).

Appendix F. Declaration of Helsinki

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

Appendix G. Estimated Glomerular Filtration Rate (eGFR) by CKD-EPI equation

CKD-EPI equation calculator:
An online calculator for estimating eGFR may be accessed at the following link:

https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr

CKD-EPI equation:

$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [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, et al 2017)

Appendix H. Assessment of QTC Interval

QTc Fridericia Formula

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

(Fridericia, 1920)

Appendix I. ISS and R-ISS Score

Standard Risk Factors for MM and the Revised -ISS (R-ISS)	
Prognostic Factor	Criteria
ISS Stage	
Stage I	Serum B2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
Stage II	Not ISS stage I or III
Stage III	Serum B 2-microglobulin ≥ 5.5 mg/L
Chromosomal abnormalities (CA) by interphase by florescent in situ hybridization (iFISH)	
High Risk	Presence of del(17p) and/or translocation of t(4:14) and/or translocation of t(14:16)
Standard Risk	No high risk CA
LDH	
Normal	Serum LDH < upper limit of normal
High	Serum LDH > upper limit of normal
A new model for risk stratification of MM R-ISS	
Stage I	ISS stage I and standard risk CA by iFISH and normal LDH
Stage II	Not R-ISS stage I of III
Stage III	ISS stage III and either high risk CA by iFISH or high LDH

(Palumbo et al. 2015)